INNOVATIONS IN CARDIO-THORACIC SURGERY

PREDICTING AND OPTIMISING OUTCOME
WITH STATE OF THE HEART TECHNOLOGY

Frank Ruben Halfwerk

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PROEFSCHRIFT

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Summary

Cardio-thoracic surgery envelops surgery of the heart, lungs, mediastinum, large intrathoracic vessels, diaphragm and the thoracic wall. Many operative techniques introduced from 1950 to 1980 are still used today. Cardio-thoracic (cardiac) surgery is still superior in long-term clinical outcome compared to cardiological interventions. However, a perceived drawback is its invasiveness and procedural complications. As a result, the number of surgeries is dropping and innovations are mainly focused and funded for less invasive approaches like interventional cardiology.

To further improve clinical outcomes of cardiac surgery, several themes can be defined to make cardiac surgery sustainable for the future.

This thesis focuses on minimally invasive cardiac surgery, technological innovations and multidisciplinary approaches to improve surgical outcome for patients. The hypothesis is that cardiac surgery remains a first time right strategy for patients when these themes are adopted in clinical practice.

PART I: Minimally invasive cardiac surgery

Minimising effects of the heart lung machine during heart surgery

A heart lung machine (cardiopulmonary bypass, CPB) takes over the heart's pumping function and gas transfer of the lungs during open heart surgery. Major drawbacks however are the systemic inflammatory response syndrome, acute kidney injury or cerebrovascular accidents. Minimally invasive extracorporeal circulation (MiECC) aims to reduce the systemic inflammatory response by reducing blood-air contact and priming volume, as well as having inert blood contact surfaces.

In **Chapter 2** systemic effects of cardiopulmonary bypass were reduced by using a MiECC approach for isolated aortic valve replacement. In a randomised controlled trial with 125 patients MiECC was compared to an advanced standard extracorporeal circulation (AdECC). Although a significant difference in blood loss after 12 hours was found between AdECC and MiECC of 58 mL (288 vs 230 mL), this difference has no major clinical impact for a general population. There was no difference in blood product use or other clinical endpoints.

Some centres prefer a conventional ECC system due to perceived safety concerns and training of dedicated teams. Using an AdECC system can be an alternative for these centres, with benefits from fully coated lines, a centrifugal pump and arterial filters.

Improving intraoperative measurements during coronary artery bypass grafting

The coronary arteries supply the heart itself with oxygen and nutrients. Narrowing of these coronaries (stenosis) might lead to chest pain or myocardial infarction. To improve symptoms, quality of life and survival in these patients, myocardial revascularisation by percutaneous coronary intervention or coronary artery bypass graft (CABG) is an effective strategy. Unfortunately, the degree of coronary stenosis can easily be misjudged and impacts short and long-term outcomes of CABG.

Intraoperative evaluation of graft flow can be performed through transit time flow measurements (TTFM), yet clinically relevant cut-off values for graft failure vary between

studies and are still debated. In **Chapter 3** preoperative angiography findings were combined with intraoperative TTFM in 50 CABG patients without the use of CPB (off-pump CABG, OPCAB). This study investigates the impact of left anterior descending artery (LAD) stenosis on competitive flow measured in left internal mammary artery (LIMA) grafts.

Competitive flow is coronary bypass graft flow impaired by native coronary flow. A new parameter was developed: the competitive flow index (CFI) as ratio of bypass mean graft flow (MGF) with the native coronary artery open and temporarily closed.

MGF increased from 20 mL/min with open LAD to 30 mL/min with snared LAD and differed between severity of coronary stenosis groups. In 26 patients (52%) MGF was below clinical relevant TTFM cut-off values with LAD open and increased in 16 patients after snaring the LAD. The CFI in patients with a >70% stenosis was much lower compared to patients with a <50% stenosis.

Routine use of CFI can be useful to identify competitive flow in case of intraoperative borderline TTFM parameters. Further studies are needed to establish definitive evidence regarding the role of Competitive Flow Index and routine snaring of coronary arteries in off-pump CABG.

The radial artery: A reusable blood vessel or only suitable for single use?

Cardiac catheterisation is used to identify coronary stenosis and predominantly use the radial artery for vascular access. However, the radial artery is also recommended by European guidelines for use as a conduit for CABG. Transradial coronary procedures expose the artery to some degree of vascular trauma and may reduce bypass graft patency.

Yet, it is unknown (1) how often a percutaneous intervention via the left radial approach precedes CABG, (2) how cardiologists deal with the problem of having multiple options for use of the radial artery that mutually exclude each other, and (3) to what extent cardiologists are aware of the new 2018 European guidelines for myocardial revascularisation.

In **Chapter 4** a retrospective study and semi-structured interviews were performed with 50 Dutch cardiologists to investigate their awareness of the outlined potential 'dilemma'.

In 3100 CABG patients, left or bilateral transradial access prior to CABG increased from 0.3% in 2008 – 2015 to 2.4% in 2016 – 2018. One out of nine patients who received a radial artery conduit during CABG surgery with prior transradial access experienced radial graft dysfunction and resulted in repeating CABG.

All 50 cardiologists indicated familiarity with the guidelines, yet 56% said not to be familiar with the aforementioned dilemma, and 18% stated there was no dilemma at all. Interventional cardiologists preferred access via the left radial artery more often (64%) than non-interventional cardiologists (23%) when the right radial artery was unavailable.

While only 10% of all participants indicated that they had personal experience with the aforementioned dilemma, 36% said that they would change vascular access after this interview in order to preserve the (left) radial artery for CABG in selected patients.

Therefore, a flowchart was created for Cath lab use to illustrate how to consider preserving the radial artery as a bypass conduit when deciding on a vascular access route for percutaneous coronary procedures.

PART II: Technological innovations in cardio-thoracic surgery

Supercritical carbon dioxide treated pericardium for applications in cardio-thoracic surgery

Many biomaterials are used in cardio-thoracic surgery with good short-term results. However, calcification, structural prosthetic valve degradation, and formation of scar tissue are reported. The aim of the research described in **Chapter 5** is to characterize porcine and bovine pericardium after supercritical carbon dioxide (scCO₂) decellularisation as an alternative biological material for uses in cardio-thoracic surgery. Untreated and commercially available glutaraldehyde treated bovine pericardium were used as gold standards for comparison.

Mechanical properties and ultrastructure were determined. scCO₂ decellularised porcine and bovine pericardium maintained their tensile strength compared to untreated native pericardium. Tensile strength of glutaraldehyde treated pericardium was significantly higher compared to untreated pericardium.

scCO₂ processing preserves initial mechanical and structural properties of porcine and bovine pericardium, while glutaraldehyde processing damages the extracellular matrix of bovine pericardium. Initial mechanical properties of pericardium are of great interest for surgical use and with preservation of these properties using scCO₂ decellularisation promising scaffolds for applications in cardio-thoracic surgery are expected.

Increasing the pump function of the heart with smart materials

Heart Failure is characterised by the “inability of the heart to pump blood at an adequate volume” and results in marked limitation of physical activity. Unfortunately, heart failure is incurable and 5-year mortality is as high as 50%, exceeding many types of cancer. Recently, the use of smart memory alloys (SMA) in the treatment for heart failure in bench models generated considerable attention.

In the demonstrator study in **Chapter 6**, we investigate which SMA designs, and which pulse width modification techniques are able to increase ejection fraction of a mono-chamber static heart model by at least 5%. SMA wires were applied onto the resuscitation balloon in spiral, band, cross and oblique configurations. A 380 µm SMA wire configured in a spiral oriented shape activated with a duty cycle of 80%, a frequency of 50/min gave the highest volume displacement (stroke volume, 6.2 mL). A maximum ejection fraction of 3.5% was achieved.

Our current setup is not yet likely to reduce dyspnoea symptoms. Future research should focus on evaluation of spiral shaped configurations around the heart in dynamic bench models or an ex vivo porcine cadaver model.

PART III: Multidisciplinary approaches to improve outcome of heart surgery

Moving is improving!

Chapter 7 describes a prospective study to improve early mobilisation after heart surgery with a mobilisation poster and to increase patient self-control over their rehabilitation. Patients were asked to reflect on this approach. Patient activities like lying in bed, sitting in a chair, walking to the toilet in the patient's private hospital room, walking at the ward corridor, cycling on a home trainer and walking the stairs were aggregated in a composite score from the American College of Sports Medicine (ACSM) and a newly deducted Thoraxcentrum Twente (TCT) score.

ACSM functional score measured day-to-day improvement in mobilisation of patients at a cardiac surgery ward, yet no difference in ACSM score between a mobilisation poster and usual care group was observed. TCT scores chair, toilet, corridor and home trainer did increase in the poster group. However, there was no difference in length of stay or survival. Surprisingly, men had higher ACSM scores than women. Patients found this poster to be clear, motivating and not pushy and family members were more involved in patients' recovery.

Functional activities might increase faster with persuasive technology focusing on the actual daily activity level. Future work should focus on patient-specific information and exercises that match the current functional level of patients recovering from cardiac surgery. Differences between gender should be quantified using objective data from activity trackers.

Proficiency before clinical practice

This thesis ends where (technical) medicine students start their clinical career.

In **Chapter 8** we developed and evaluated a proficiency-based, simulation-based course for basic surgical skills at graduate level for Technical Medicine students. Learning outcomes were measured at the level of knowledge and skills and students' reactions to the course during their clinical rotations.

The surgical skills curriculum was anchored to surgical patient route. The course focuses on anatomical and physiological knowledge, technical skills and non-technical skills like situational awareness and decision making. Also, assessors were trained to prevent biased judgments before they assessed students on basic surgical skills. Students often performed sterile instrument handling, scrubbing and donning, and suturing skills during clinical rotations. The majority of students felt confident during their clinical rotations to attend a surgery and stated they could show a professional attitude in the operating room.

Based on this study, we recommend that proficiency-based training using simulation should be standard in surgical curricula before students are allowed to practice on patients.

Conclusion and future perspectives

Minimally invasive cardiac surgery can improve outcomes for large groups of patients by reducing the impact of the heart-lung machine. Here patient and procedural characteristics determine decision making for a (minimally invasive) surgical, percutaneous or conservative treatment. Technological innovations in cardio-thoracic surgery such as improved biomaterials for reconstructive surgery and effective devices are necessary to further improve surgical outcome.

Many factors that are associated with adverse outcomes for OPCAB are related to training. Unfortunately OPCAB training in a simulated environment is not available or used by residents or junior surgeons. Strong proficiency-based, simulation-based courses on all aspects of cardiac surgery should be standard before practice on patients.

Finally, a multidisciplinary approach with teamwork and shared decision making from patients, (technical) medical specialists, nurses, physiotherapists and other professionals will optimise treatments in cardio-thoracic surgery.

Samenvatting

Cardio-thoracale chirurgie of hartchirurgie focust zich op de chirurgische behandeling van hart, longen, mediastinum, grote intra thoracale bloedvaten, het diafragma en de thoraxwand. Veel operatietechnieken stammen nog uit de periode 1950 tot 1980 en worden nog steeds veel gebruikt. Desalniettemin zijn lange termijn uitkomsten van hartchirurgie ongeëvenaard t.o.v. cardiologische behandelingen. Een groot ervaren nadeel van hartchirurgie is de omvang van de ingreep. Daardoor daalt het aantal ingrepen en wordt er voornamelijk geld en aandacht aan andere disciplines zoals de interventiecardiologie geïnvesteerd.

Om de uitkomsten van hartchirurgie te verbeteren en te voorkomen dat hartchirurgie een tweederangs behandeling wordt zijn diverse thema's geïdentificeerd. Dit proefschrift richt zich op minimaal invasieve chirurgie, technologische innovaties en een multidisciplinaire aanpak om de uitkomsten voor patiënten te verbeteren. De hypothese is dat hartchirurgie, met slechts één interventie, een goede behandeloptie voor patiënten blijft als deze thema's worden toegepast in de klinische praktijk.

DEEL I: Minimaal invasieve hartchirurgie

Verminderen van de effecten van de hart-long machine

Een hart-long machine (cardiopulmonaire bypass, CPB) neemt de pompfunctie van het hart en gasuitwisseling van de longen over tijdens open hartchirurgie. Grote nadelen van CPB zijn een systemische ontstekingsreactie, acute nierschade en hersenberoertes. Minimaal-invasieve extracorporale circulatie (MiECC) vermindert de systemische ontstekingsreactie door het bloed-lucht contact te verminderen, het circulerend volume te verkleinen en cel-interacties tussen bloedcellen en contactoppervlakken te voorkomen.

In **Hoofdstuk 2** zijn de effecten van CPB verminderd door gebruik te maken van MiECC voor geïsoleerde aortaklep vervangingen. In een gerandomiseerde studie zijn 125 patiënten geloot in de MiECC groep of een geavanceerde conventionele extracorporale circulatie (AdECC). Patiënten in de MiECC groep hadden significant minder bloedverlies dan de AdECC groep (230 vs 288 mL), maar dit heeft geen klinische impact. Er was geen verschil in het aantal bloedtransfusies of andere klinische uitkomsten.

Sommige hartcentra geven de voorkeur aan een conventioneel systeem door vermeende veiligheidsrisico's bij het gebruik van MiECC en de lange trainingsduur van OK-personeel. Een AdECC systeem met inerte contactoppervlakken, een centrifugaal pomp en arteriële filters kan dus een goed alternatief zijn voor deze ziekenhuizen.

Verbeteren van intra-operatieve metingen tijdens coronaire bypass chirurgie

De kransslagaderen voorzien het hart van zuurstof en voedingsstoffen. Vernauwingen (stenosen) kunnen leiden tot pijn op de borst of zelfs een hart infarct. Om symptomen, kwaliteit van leven en overleving te verbeteren kan een dotterbehandeling of omleidingsoperatie (coronaire bypass grafting, CABG) worden uitgevoerd. Helaas is de mate van stenose pre-operatief lastig in te schatten, wat leidt tot suboptimale lange-termijn resultaten van CABG.

Met behulp van Transit Time Flow Metingen (TTFM) kan intra-operatief de bloedstroom door de omleiding worden bepaald. Klinisch-relevante afkapwaarden van TTFM verschillen erg tussen studies en zijn daarom nog niet in behandelrichtlijnen vastgelegd. In **Hoofdstuk 3** worden pre-operatieve inschattingen van coronaire stenosen gecombineerd met intra-operatieve TTFM in 50 CABG patiënten, zonder gebruik te maken van een hart-long machine (off-pump CABG).

Het doel van de studie is om de impact van stenose in de linker voorste dalende kransslagader (LAD) op competitieve flow in de graft (linker borstwand slagader) te bepalen. Competitieve flow is verminderde bloedstroom door de graft door teveel resterende flow in de kransslagader. In deze studie is tevens een nieuwe parameter ontwikkeld: de competitieve flow index (CFI) als verhouding tussen de gemiddelde graft flow (MGF) met de kransslagader (tijdelijk) dicht en open.

Door de LAD tijdelijk dicht te maken steeg de MGF van 20 mL/min naar 30 mL/min. Deze stijging was ook aanwezig toen de mate van stenose in drie groepen werd ingedeeld. Bij 26 patiënten (52%) was de MGF lager dan de klinisch relevante afkapwaarden uit de literatuur. De MGF steeg bij 16 van deze patiënten naar een acceptabele waarde bij het tijdelijk afsluiten van de LAD. Bij patiënten met een ernstige vernauwing (> 70% stenose) was de CFI veel lager dan patiënten met een milde vernauwing (< 50% stenose).

Routinematig gebruik van de CFI kan helpen om competitieve flow in kaart te brengen tijdens de omleidingsoperatie als TTFM geen uitsluitsel biedt. Er is nog meer onderzoek nodig om de rol van CFI en het tijdelijk afsluiten van de kransslagader op uitkomsten na CABG vast te stellen.

De pols slagader: geschikt voor eenmalig gebruik of hergebruik?

Hartkatheterisatie wordt gebruikt om stenosen in de kransslagaders in kaart te brengen. Als toegangsweg wordt voornamelijk de polsslagader (a. radialis) gebruikt. Tegelijkertijd adviseren Europese richtlijnen de a. radialis als CABG graft. Door hartkatheterisatie loopt de a. radialis schade op en kan daardoor niet goed meer open blijven.

Het is onbekend (1) hoe vaak de a. radialis zowel gebruikt wordt voor hartkatheterisatie als CABG, (2) hoe cardiologen in de praktijk omgaan met dit dilemma en (3) of cardiologen op de hoogte zijn van de Europese richtlijnen uit 2018. In **Hoofdstuk 4** wordt dit onderzocht middels een retrospectief data-onderzoek en semigestructureerde interviews onder 50 Nederlandse cardiologen.

Van de 3100 CABG patiënten was minimaal één van de twee aa. radiales tussen 2008 – 2015 in 0.3% van de patiënten reeds gebruikt voor hartkatheterisatie. Dit percentage steeg tot 2.4% tussen 2016-2018. Bij 9 patiënten werd de a. radialis dubbel gebruikt, waarvan één patiënt een her operatie nodig had vanwege graft disfunctie.

Alle 50 cardiologen gaven aan bekend te zijn met de richtlijnen. Maar liefst 56% was niet bekend met het klinische dilemma, waar 18% aangaf dat dit überhaupt geen dilemma is. Interventiecardiologen hadden vaker (64%) een voorkeur voor de linker a. radialis indien de rechter a. radialis onbruikbaar was, dan niet-interventiecardiologen (23%).

Slechts 10% van de cardiologen gaf aan dit dilemma eerder te hebben meegemaakt. Na de interviews zei 36% dat ze de toegangsweg mogelijk gaan aanpassen om de linker

a. radialis te bewaren voor een eventuele CABG. Als beschikbare hulpmiddelen is daarom een stroomdiagram met adviezen gemaakt voor op de hartkatheterisatiekamer.

DEEL II: Technische innovaties in de cardio-thoracale chirurgie

Superkritische CO₂-behandeling van het hartzakje voor toepassingen in de cardio-thoracale chirurgie

In de cardio-thoracale chirurgie worden veel biomaterialen gebruikt met goede korte termijn resultaten. Helaas verkalken deze materialen, er ontstaat littekenweefsel of het biomateriaal wordt afgebroken zoals bij kunsthartkleppen.

Het doel van **Hoofdstuk 5** is om het hartzakje van varkens en runderen te ontdoen van dierlijke cellen met superkritisch CO₂ en de goede eigenschappen te behouden voor toepassingen in de cardio-thoracale chirurgie. Verse en met glutaraaldehyde-behandelde hartzakjes zijn met elkaar vergeleken op mechanische- en structuur eigenschappen.

Hartzakjes behandeld met superkritisch CO₂ behouden hun treksterkte, terwijl de treksterkte van hartzakjes behandeld met glutaraaldehyde juist steeg. Hetzelfde geldt voor de structuur eigenschappen van het hartzakje, waar glutaraaldehyde de extracellulaire matrix beschadigde en deze bij superkritisch CO₂ intact bleef.

De initiële eigenschappen van het hartzakje zijn zeer bruikbaar voor toepassingen in de cardio-thoracale chirurgie. Het behoud van deze eigenschappen na een superkritische CO₂ behandeling is daarom veelbelovend.

Verbeteren van de pomp functie van het hart met slimme materialen

Bij hartfalen is het hart niet meer in staat voldoende bloed rond te pompen. Dit leidt tot klachten van benauwdheid bij inspanning. Helaas is er geen genezing van hartfalen mogelijk. De 5-jaarssterfte ligt op 50% en is daarmee hoger dan vele soorten kanker.

Recent zijn in het lab smart memory alloys (SMA) in de context van hartfalen onderzocht.

In **Hoofdstuk 6** wordt onderzocht of de pompfunctie van het hart met 5% kan worden verbeterd in een ventilatieballonmodel door diverse SMA configuraties en met pulsbreedtemodulatie. De SMA-windingen zijn zowel als spiraal, band, kruislings en schuin aangebracht. Een 380 µm SMA draad in een spiraalvorm met een duty cycle van 80% en een frequentie van 50/min gaf de hoogste volume verplaatsing van 6.2 mL. Hiermee werd een pompfunctie van 3.5% behaald.

Het huidige ontwerp geeft nog geen klinisch relevante verbetering van benauwdheidssymptomen. Toekomstig onderzoek moet de spiraalvormige ontwerpen om het hart gaan testen in dynamische modellen of op een ex vivo varkens hart.

DEEL III: Multidisciplinaire aanpak ter verbetering van hartchirurgie

Bewegen is herstellen!

Hoofdstuk 7 beschrijft een prospectieve studie waarbij ziekenhuismobilisatie na hartchirurgie wordt verbeterd met een mobilisatieposter. Patiënten krijgen hierdoor meer regie over hun eigen herstel en zijn gevraagd om feedback op de poster te geven.

Activiteiten zoals in bed liggen, zitten, lopen naar de eigen badkamer, lopen op de gang, fietsen op een home trainer en traplopen zijn onderzocht in een samengestelde maat van de American College of Sports Medicine (ACSM) en een zelf ontworpen Thoraxcentrum Twente (TCT) score.

De ACSM functionele score toonde dagelijkse ontwikkeling van mobilisatie op de verpleegafdeling na hartchirurgie. De interventieposter gaf hier geen verbetering op. De TCT scores zitten, lopen naar de badkamer, lopen op de gang en fietsen verbeterden wel met de interventieposter. Er was geen verschil in ziekenhuisduur of overleving. Verrassend genoeg hadden mannen hogere ACSM-scores dan vrouwen. Patiënten gaven aan de poster helder, motiverend en niet opdringerig te vinden. Familieleden waren met de poster meer betrokken bij het herstel van patiënten.

Bovenstaande activiteiten kunnen nog sneller ontwikkelen als er patiënt- en dag specifieke oefeningen worden aangeboden middels persuasieve strategieën. Het verschil tussen mannen en vrouwen moet worden onderzocht met objectieve meetmethoden zoals met draagbare technologie.

Heel kundig handelen vóór patiëntenzorg

Dit proefschrift eindigt daar waar (technische) geneeskunde studenten hun klinische carrière starten.

In **Hoofdstuk 8** wordt een chirurgisch vaardigheidscurriculum voor masterstudenten Technische Geneeskunde ontworpen en geëvalueerd op basis van bekwaamheid in een gesimuleerde beroepspraktijk. Leeruitkomsten als kennis en vaardigheid zijn onderzocht alsook reacties van studenten tijdens de klinische stages.

In het chirurgisch vaardigheidsonderwijs staat de patiëntroute tijdens een chirurgische opname nu centraal. Het vak richt zich op anatomische en fysiologische kennis, technische vaardigheden en professionele vaardigheden zoals besluitvoering en leiderschap. De beoordelaars van het praktijkexamen werden getraind om subjectieve beoordelingen te voorkomen.

Tijdens de klinische stages hanteerden studenten steriel instrumentarium, gebruikten ze steriele technieken op- en rond de operatiekamer en voerden ze hechttechnieken uit. De meerderheid van studenten voelde zich zelfverzekerd tijdens (het bijwonen van) operaties en gaven aan een professionele houding aan te kunnen nemen.

Op basis van dit onderzoek bevelen we aan dat een chirurgisch vaardigheidscurriculum op basis van bekwaamheid in een gesimuleerde beroepspraktijk standaard zou moeten zijn voordat studenten de patiëntenzorg in gaan.

Algemene conclusie en aanbevelingen

Minimaal invasieve hartchirurgie kan voor grote patiëntengroepen leiden tot betere uitkomsten door het verminderen van de effecten van een hart-long machine. Het combineren van patiëntkarakteristieken en operatietechnieken moet de besluitvorming voor een (minimaal invasieve) hartoperatie, katheter behandeling, of afzien van behandeling nog verder gaan ondersteunen. Technische ontwikkelingen zoals

verbeterde biomaterialen voor reconstructieve hartchirurgie en slimme materialen gaan de resultaten van hartchirurgie voor patiënten verder verbeteren.

Veel potentiële nadelen aan off-pump CABG zijn gerelateerd aan het aanleren hiervan. Vaak is off-pump CABG training niet aanwezig voor arts-assistenten of hartchirurgen, richt het zich puur op de handeling zelf of wordt het überhaupt niet gebruikt. Daarom moet een chirurgisch vaardigheidscurriculum op basis van bekwaamheid in een gesimuleerde beroepspraktijk een vereiste zijn voordat technieken in de patiëntenzorg worden toegepast.

Ten laatste zal alleen een multidisciplinaire aanpak met gezamenlijke besluitvoering tussen patiënten (technisch) medisch specialisten, verpleegkundigen, fysiotherapeuten en andere aanverwante beroepen leiden tot betere uitkomsten van hartchirurgie.

CHAPTER 1

GENERAL INTRODUCTION

Introduction and scope

As late as in 1880 surgical treatment of heart disease was generally disapproved. The Austrian influential surgeon prof. Theodor Billroth stated that “No surgeon who wished to preserve the respect of his colleagues would ever attempt to suture a wound of the heart” [1]. His English colleague Stephen Paget wrote in his 1896 book *The Surgery of the Chest*: “Surgery of the heart has probably reached the limits set by Nature to all surgery: no new method, and no new discovery, can overcome the natural difficulties that attend a wound of the heart” [2].

After World War II cardiac surgery truly developed with commissurotomy/valvuloplasty of the mitral valve in 1948 [3, 4] with initial high mortality rates. In the early 1950s, hypothermia and the development of cardiopulmonary bypass resulted in open heart procedures. Coronary artery bypass grafting (CABG) was developed in the 1960s to treat ischaemic cardiac disease.

Now, cardio-thoracic surgery envelops surgery of the heart, lungs, mediastinum, large intrathoracic vessels, diaphragm and the thoracic wall. Many operative techniques from 1950 to 1980 are still used today in cardio-thoracic surgery.

Trends in treatment of cardiovascular diseases:

Coronary artery disease

Next to developments in Optimal Medical Therapy, such as “Golden 5” medication for Acute Coronary Syndrome patients, minimal invasive and percutaneous techniques were developed. Myocardial revascularisation by percutaneous coronary intervention (PCI) or CABG improves quality of life of patients and increases exercise capacity [5]. Also, drug intake, death and myocardial infarction are reduced.

A major disadvantage of cardiopulmonary bypass is the Systemic Inflammatory Response Syndrome, where complement and coagulation cascades are activated and oxidative radicals are produced [6]. Minimal invasive extracorporeal circulation (MiECC) was introduced in the 1990s to reduce these effects. The main goal of these developments is to reduce air-blood contact and therefore reduce coagulopathies and an inflammatory response. Despite many theoretical advantages, clinical benefit of this innovation is limited to reduced inflammatory markers or shorter intensive care unit stay or is determined in retrospective studies [7, 8].

For CABG, cardiopulmonary bypass can be abandoned by performing off-pump coronary artery bypass grafting (OPCAB) where the heart keeps beating during surgery. Here, initial results were promising with respect to lower cerebral vascular accidents and improved renal function, yet long term outcome is regarded as non-superior to CABG in many studies due to incomplete revascularisation or conversions to on-pump surgery. Furthermore, a steep learning curve reduces beneficial effects of OPCAB for the first 150 patients [9], making surgeons not eager to learn this technique.

Continuous use of aortic side-clamps for proximal anastomoses fail to match no-touch aorta techniques with respect to cerebral vascular accidents, although specified operative techniques are often lacking from large randomised studies. Furthermore, residents might perform OPCAB as primary surgeon [10] and the use of saphenous vein

grafts with low patency rates increase revascularisation rates [11]. Contrary, using no-touch aorta OPCAB techniques without manipulating the ascending aorta give similar good results as PCI with respect to neurological outcome [12].

Choosing optimal conduits as graft material is still subject of many studies. Where autologous veins are easy to harvest and to use as bypass graft, in-situ mammary arteries are superior in long-term graft patency and freedom from myocardial infarction, death or reintervention. With proper handling, complete arterial revascularisation with internal mammary, radial or gastroepiploic arteries proves to be superior to saphenous vein grafts [13-15] and is depicted in Figure 1.

Figure 1 In-situ arterial conduits used for arterial revascularisation of the heart. RIMA/LIMA = Right/Left internal mammary artery; LAD = Left anterior descending artery. Adapted from [16].

With 115 randomised trials, many expert opinions and strategies for conduit use, optimal revascularisation for patients remains under debate [17].

Technological advancements came not only with benefits. Balloon angioplasty, first- and second generations of drug eluting stents came with high rates of major adverse cardiac and cerebrovascular events (MACCE). Newer bioresorbable vascular scaffolds turned out to have higher rates of stent thrombosis [18, 19]. Unfortunately, long-term follow-up after percutaneous procedures is still scarce and follow-up ends after 5 years [20]. Direct comparison in long-term follow-up after percutaneous or surgical revascularisation is thus unavailable for large groups of patients.

Trends in treatment of cardiovascular diseases: Aortic valve disease and heart failure

Surgical aortic valve replacement (SAVR) remains largely unchanged since the introduction of mechanical and porcine heart valves in the 1960s and bovine pericardial valves in the 1970s. Prosthetic aortic valves developed into lifelong enduring mechanical prostheses with anticoagulation use for patients, or biological prosthesis with a limited lifespan due to structural valve degradation and no need for anticoagulation. Cardiopulmonary bypass-related complications persist.

Transcatheter aortic valve implantation (TAVI) was developed as an alternative to SAVR for inoperable or octogenarian patients. However, in TAVI a two-fold increase of permanent pacemaker implantations (22% vs 12%) and a three-fold increase in vascular complications (6% vs 2%) are observed in a direct comparison to SAVR [21].

Patients with previous cardiac interventions are getting older due to successful treatment, yet experience more chronic cardiac diseases such as heart failure. Heart failure already affects over 6.5 million Americans and is expected to increase by 30% in 2030 [22]. Unfortunately, heart failure is incurable and 5-year mortality is as high as 50%, exceeding many types of cancer [23].

A healthy lifestyle and use of beta blockers and ACE-inhibitors decrease mortality of heart failure and increase quality of life temporarily. To prevent sudden cardiac death, an internal cardioverter defibrillator can be implanted. For a small patient group, cardiac resynchronisation therapy is indicated, with over 30% of these patients still being non-responders [24]. While treatment options become limited (Figure 2), very few patients receive left ventricular assist devices or heart transplantation, and death awaits.

New technologies are required to move forward. A non-development or even stasis of developments in cardio-thoracic surgery is a potential threat to future patient care.

Figure 2 Typical heart failure progression and treatment options. Inspired from [25].
CRT = Cardiac resynchronisation therapy; LVAD = Left ventricular assist device

Together everyone achieves more

Team efforts with patients, (technical) medical specialists, nurses, physiotherapists and other professionals can bring treatments in cardio-thoracic surgery further. This starts with educational training for students.

Training in healthcare education ultimately gives better outcomes in direct patient care. Often only a reaction on educational content and increase in skills or knowledge is observed with limited use in daily practice. Unfortunately, many students learn their clinical or technical skills on patients with damage to patients and a negative patients perspective on young healthcare professionals. In the United Kingdom, mortality rates are 6% higher on the first day of junior medical doctors [26].

Simulation in healthcare aims to decrease these effects during mastering of these clinical and technical skills. A well-defined clinical situation is demonstrated in a safe environment where mistakes do not lead to disastrous effects (Figure 3).

Figure 3 Surgical Skills simulation at University of Twente (Photo by Arthur Veugelers)

Often, only limited simulation time is still present in (post-)graduate and continuous professional medical education. Furthermore patients (should) have a more prominent role in decision making and control of their own recovery. A well informed patient experiences less complications after surgery. Also pre-operative optimisation on diet, smoking cessation, increase of exercise tolerance improve surgical outcome [27]. Even after surgery, patients are able to improve their recovery with active mobilisation strategies. Contrarily patients in daily practice are afraid to be active after major surgery, being afraid to damage muscles and wounds or do not know why active recovery is so

important to them. Shared decision making and what really matters to patients remain undiscussed.

Finally, joint efforts of surgeons, cardiologists, technical physicians and other professionals should determine optimal treatment and diagnostic procedures for individual patients. Geriatricians determine operability of elderly patients, medical microbiologists advice optimal antibiotic treatment and anaesthesiologists suitability for narcosis.

Where heart team discussions already proved to increase patient outcome [5], additional experts for specific cases are increasingly becoming more important for more complex patients.

Aim and structure of this thesis

Cardiac surgery is unmatched on long-term clinical outcome by cardiological interventions. However, a perceived drawback is its invasiveness. As a result, numbers are dropping and developments are mainly funded for interventional cardiology at the expense of cardiac surgery.

To prevent cardiac surgery becoming a secondary treatment, several themes can be defined to make cardiac surgery future sustainable. The hypothesis is that cardiac surgery remains a first time right strategy for patients when these themes are adopted in clinical practice. This results in this thesis: “Innovations in cardio-thoracic surgery: Predicting and optimising outcome with state of the heart technology”

This thesis is divided into three parts, preceded by this introductory **Chapter 1** and followed by a conclusion and discussion.

PART I: Minimally invasive cardiac surgery

By reducing the impact of cardiopulmonary bypass, outcomes for large groups of patients might improve whereas other patient groups might even be unsuitable for cardiac surgery with cardiopulmonary bypass.

In **Chapter 2** systemic effects of cardiopulmonary bypass are reduced by using a minimal invasive extracorporeal circulation approach for aortic valve replacement. In a randomised controlled trial effects of this approach on blood loss are described.

Coronary artery bypass grafting (CABG) of the left internal mammary artery to the left anterior descending artery is superior to percutaneous interventions with respect to graft patency. Furthermore, off-pump CABG (OPCAB) proves to offer peri-operative evaluation of technical quality of the anastomosis.

Chapter 3 describes a prospective study of these peri-operative measurements using transit time flow measurements to reduce early graft failure with respect to competitive flow of the native coronary arteries.

Large randomised trials comparing OPCAB to CABG fail to show superior results. Reasons are a steep learning curve, side clamping of the aorta and use of venous grafts instead of complete arterial revascularisation. As a second or third arterial graft the radial artery is

recommended. However, previous vascular access during coronary angiography damages the radial artery and limits its use as graft for CABG.

In a semi-structured interview and retrospective study, **Chapter 4** gives an overview how Dutch cardiologists cope with this clinical dilemma and determines the scope of the clinical problem in a high volume transradial access and radial artery graft centre.

PART II: Technological innovations in cardio-thoracic surgery

Technological innovations in cardio-thoracic surgery are necessary to further improve surgical outcome. A major drawback of biological prosthesis is structural valve degradation and calcification. Unfortunately, reoperation is associated with higher risks for patients.

Chapter 5 describes a biomechanical analysis of supercritical carbon dioxide treatment for pericardium for potential use as bioprosthetic heart valve or for other applications.

As heart failure will increase in the general population and limited treatments options exist for patients with advanced heart failure, new treatments should be developed.

Chapter 6 describes the first efforts to develop such a device. Here *in vitro* experiments demonstrated the possibility of increasing the ejection fraction and potentially increase quality of life of patients and mortality.

PART III: Multidisciplinary approaches to improve outcome of heart surgery

Using a multidisciplinary approach with efforts from patients, (technical) medical specialists, nurses, physiotherapists and other professionals can bring treatments in cardio-thoracic surgery further.

Chapter 7 describes a prospective study to improve early mobilisation after heart surgery and increase patient self-control of their rehabilitation. Patients were asked to reflect on this approach.

A multidisciplinary approach also includes advanced simulation specialists and deliberate practice in a simulated environment before practicing on patients.

Chapter 8 discusses the design of a new course on graduate surgical skill simulation, including assessment development and validation of practical skills and theoretical knowledge. Here, we asked students during their clinical rotations how they value this new course.

Chapter 9 is a general discussion and conclusion on the findings of this thesis, followed by an outlook on future directions of cardio-thoracic surgery.

This thesis concludes with a list of publications and activities.

References

1. Weisse AB. *Medical odysseys : the different and sometimes unexpected pathways to twentieth-century medical discoveries*. New Brunswick, N.J.: Rutgers University Press; 1991.
2. Paget S. *The Surgery of the Chest* 1896.
3. Harken DE, Ellis LB, et al. The surgical treatment of mitral stenosis; valvuloplasty. *The New England journal of medicine*. 1948;239:801-809.
4. Baker C, Brock RC, Campbell M. Valvulotomy for mitral stenosis; report of six successful cases. *Br Med J*. 1950;1:1283-1293.
5. Neumann FJ, Sousa-Uva M, Ahlsson A, et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. *Eur Heart J*. 2019;40:87-165.
6. Butler J, Rocker GM, Westaby S. Inflammatory response to cardiopulmonary bypass. *Ann Thorac Surg*. 1993;55:552-559.
7. Baumbach H, Rustenbach CJ, Ahad S, et al. Minimally Invasive Extracorporeal Bypass in Minimally Invasive Heart Valve Operations: A Prospective Randomized Trial. *Ann Thorac Surg*. 2016;102:93-100.
8. Wang C, Hua K, Yin L, Wang Y, Li W. A Meta-Analysis of Miniaturized Versus Conventional Extracorporeal Circulation in Valve Surgery. *Ann Thorac Surg*. 2016;102:2099-2108.
9. Bougioukakis P, Kluegl SJ, Babin-Ebell J, et al. Presentation of a quality management program in off-pump coronary bypass surgery. *Innovations (Phila)*. 2014;9:317-321.
10. Lamy A, Devereaux PJ, Prabhakaran D, et al. Off-pump or on-pump coronary-artery bypass grafting at 30 days. *The New England journal of medicine*. 2012;366:1489-1497.
11. Shroyer AL, Grover FL, Hattler B, et al. On-Pump versus Off-Pump Coronary-Artery Bypass Surgery. *New England Journal of Medicine*. 2009;361:1827-1837.
12. Arrigoni SC, Mecozzi G, Grandjean JG, Hillege JL, Kappetein AP, Mariani MA. Off-pump no-touch technique: 3-year results compared with the SYNTAX trial. *Interactive cardiovascular and thoracic surgery*. 2015;20:601-604.
13. Halbersma WB, Arrigoni SC, Mecozzi G, et al. Four-year outcome of OPCAB no-touch with total arterial Y-graft: making the best treatment a daily practice. *Ann Thorac Surg*. 2009;88:796-801.
14. Gaudino M, Benedetto U, Fremes S, et al. Radial-Artery or Saphenous-Vein Grafts in Coronary-Artery Bypass Surgery. *The New England journal of medicine*. 2018;378:2069-2077.
15. Gaudino M, Benedetto U, Fremes SE, et al. Angiographic Outcome of Coronary Artery Bypass Grafts: The Radial Artery Database International Alliance. *Ann Thorac Surg*. 2020;109:688-694.
16. Taggart DP. How I deploy arterial grafts. *Ann Cardiothorac Surg*. 2018;7:690-697.
17. Gaudino M, Angelini GD, Antoniadis C, et al. Off-Pump Coronary Artery Bypass Grafting: 30 Years of Debate. *J Am Heart Assoc*. 2018;7:e009934.
18. Tarantini G, Masiero G, Barioli A, et al. Absorb bioresorbable vascular scaffold vs. everolimus-eluting metallic stent in small vessel disease: A propensity matched analysis of COMPARE II, RAI, and MAASSTAD-ABSORB studies. *Catheterization and cardiovascular interventions : official journal of the Society for Cardiac Angiography & Interventions*. 2018;92:E115-E124.
19. Raber L, Yamaji K, Kelbaek H, et al. Five-year clinical outcomes and intracoronary imaging findings of the COMFORTABLE AMI trial: randomized comparison of biodegradable polymer-based biolimus-eluting stents with bare-metal stents in patients with acute ST-segment elevation myocardial infarction. *Eur Heart J*. 2019;40:1909-1919.
20. Zocca P, Kok MM, Tandjung K, et al. 5-Year Outcome Following Randomized Treatment of All-Comers With Zotarolimus-Eluting Resolute Integrity and Everolimus-Eluting PROMUS Element

Coronary Stents: Final Report of the DUTCH PEERS (TWENTE II) Trial. *JACC Cardiovasc Interv.* 2018;11:462-469.

21. Gleason TG, Reardon MJ, Popma JJ, et al. 5-Year Outcomes of Self-Expanding Transcatheter Versus Surgical Aortic Valve Replacement in High-Risk Patients. *Journal of the American College of Cardiology.* 2018;72:2687-2696.
22. Benjamin EJ, Virani SS, Callaway CW, et al. Heart Disease and Stroke Statistics-2018 Update: A Report From the American Heart Association. *Circulation.* 2018;137:e67-e492.
23. Gerber Y, Weston SA, Redfield MM, et al. A contemporary appraisal of the heart failure epidemic in Olmsted County, Minnesota, 2000 to 2010. *JAMA internal medicine.* 2015;175:996-1004.
24. Auricchio A, Prinzen FW. Non-responders to cardiac resynchronization therapy: the magnitude of the problem and the issues. *Circulation journal : official journal of the Japanese Circulation Society.* 2011;75:521-527.
25. Murray SA, Kendall M, Grant E, Boyd K, Barclay S, Sheikh A. Patterns of social, psychological, and spiritual decline toward the end of life in lung cancer and heart failure. *J Pain Symptom Manage.* 2007;34:393-402.
26. Jen MH, Bottle A, Majeed A, Bell D, Aylin P. Early in-hospital mortality following trainee doctors' first day at work. *PloS one.* 2009;4:e7103.
27. Lassen K, Soop M, Nygren J, et al. Consensus review of optimal perioperative care in colorectal surgery: Enhanced Recovery After Surgery (ERAS) Group recommendations. *Arch Surg.* 2009;144:961-969.

PART I

MINIMALLY INVASIVE CARDIAC SURGERY

CHAPTER 2

RANDOMIZED TRIAL OF MINIMAL INVASIVE EXTRA-CORPOREAL CIRCULATION VERSUS STANDARD EXTRA-CORPOREAL CIRCULATION IN AORTIC VALVE SURGERY

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Randomized trial of miniaturized versus standard extracorporeal circulation in aortic valve surgery

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Abbreviations and acronyms

AdECC	Advanced extracorporeal circulation
AVR	Aortic valve replacement
CK	Creatine kinase
ECC	Extracorporeal circulation
Hb	Haemoglobin
ICU	Intensive care unit
MiECC	Minimal invasive extracorporeal circulation
MiECTiS	Minimal invasive Extra-Corporeal Technologies international Society

Abstract

Background

Complications related to extracorporeal circulation remain serious. Although a minimal invasive extra corporeal circulation (MiECC) system was developed to cope with these complications, its effectivity on patient-related outcomes such as blood loss remain uncertain. Therefore, the aim of this study is to compare MiECC to an advanced standard system with respect to blood loss.

Methods

A total of 128 adult patients undergoing elective isolated aortic valve replacement were enrolled in a randomised clinical trial. Patients who had undergone previous heart operations and with pre-existing kidney failure were excluded.

The primary end point was postoperative blood loss after 12 hours and at drain removal. Secondary end points included intensive care and total length of stay and intubation time. After 1 hour and 12 hours after surgery, clinical laboratory data were determined. Early clinical outcomes and long-term survival were determined.

Results

MiECC patients (n = 63) had a significant lower blood loss (230 mL, 95% confidence interval: [203 to 261 mL]) than regular patients (n = 62) after 12 hours (288 mL, 95% Confidence Interval : [241 to 344 mL], $p = 0.04$). A preservation of haemoglobin levels 1 hour and 12 hours after surgery in the MiECC group were observed ($p < 0.001$). No difference was found in early clinical outcomes and long-term survival.

Conclusions

This randomised controlled trial compares MiECC and an advanced system for aortic valve replacement with blood loss as primary endpoint. We conclude that using MiECC is clinically equal for short- and long term follow-up regarding blood loss.

Clinical trial registration: NTR3378.

Introduction

Since the introduction of cardiopulmonary bypass or extracorporeal circulation (ECC) in the 1950s, mortality from cardiac surgery dropped to low levels. In the 1990s however, complications related to ECC remained serious such as the systemic inflammatory response syndrome [1].

To reduce systemic effects of ECC, a primitive minimal invasive ECC (MiECC) was developed. The main goal of these developments is to reduce air-blood contact and therefore to reduce coagulopathies and an inflammatory response. In the early days of MiECC major concerns existed for possible air embolisation, yet adequate team management, continuous carbon dioxide field flooding and a venous air bubble trap resolved most of the safety concerns [2-4].

The Minimal invasive Extra-Corporeal Technologies international Society (MiECTiS) set standards to describe a MiECC and categorizes MiECC systems in four categories [5]. Main components of these systems are listed in Table 1.

Table 1 Characteristics of minimal invasive extracorporeal circulation as defined by the Minimal invasive Extra-Corporeal Technologies international Society [5]

Characteristic	
Closed cardiopulmonary bypass circuit	Heat exchanger
Biologically inert blood contact surfaces	Cardioplegia system
Reduced priming volume	Venous bubble trap
Centrifugal pump	Shed blood management system
Membrane oxygenator	

Many theoretical advantages exist about the use of MiECC for isolated aortic valve replacements (AVRs). Still, in 2013 MiECC was used in only 20% of all isolated AVRs in Germany [6].

A meta-analysis on short-term outcome of MiECC found a significant ($p = 0.04$) reduction of blood loss of 114 mL and was pooled from four small early MiECC studies [7], yet these studies had blood loss as secondary endpoint. Thus far, only small cohort studies and poorly constructed small randomised controlled trials were conducted for MiECC use in isolated AVR patients [2, 3, 8]. Moreover, these studies used roller pumps that are an important factor in haemolysis and platelet activation [9]. Furthermore, these studies demonstrated equipoise on safety end points such as clinical laboratory data and in-hospital mortality and morbidity, yet they did not include blood loss as a primary end point. Finally, since the introduction of MiECC, some conventional systems advanced into less-invasive systems by decreasing blood-air contact.

Therefore, the aim of this study is to compare MiECC with an advanced ECC (AdECC) with respect to blood loss in patients undergoing isolated AVR.

Patients and methods

Trial design and study population

This was a single centre, 1 : 1 intention-to-treat parallel-group study conducted at Thorax Centrum Twente (Medisch Spectrum Twente Hospital, Enschede, The Netherlands), a tertiary non-academic teaching hospital. Patients were included from April 2012 to January 2016. During the trial, the original protocol was amended to extend the study period from January 2014 to January 2016 after a delay in recruiting because of unavailability of the MiECC system.

This study is reported as per the consolidated standards of reporting trials guidelines [10] and standards for publishing randomised controlled trials in the Annals of Thoracic Surgery [11]. Eligible participants were all adults aged 18 or older undergoing elective isolated AVR for moderate-severe aortic valve stenosis or aortic regurgitation and eligible for MiECC perfusion (Body mass index [BMI] 20 – 50). Exclusion criteria were previous heart surgery and pre-existing kidney failure. Patients were recruited at the day of admission to the hospital.

Four cardiothoracic surgeons participated in the study. All team members were previously trained for MiECC for at least 1 year and 50 patients. Ethical approval was acquired from a local Medical Ethical Committee (NL39386.044.12) and institutional review board. Written consent was obtained according to the Declaration of Helsinki.

Anaesthesia management and surgical approach

All eligible patients received standard preoperative care as determined by the attending physician. Anaesthesia was standardized when possible and was induced by sufentanil (0.5 to 1 µg/kg), combined with etomidate (0.2 – 0.3 mg/kg), rocuronium (0.6 mg/kg) and dexamethasone (1 mg/kg). Anaesthetic management was maintained with propofol infusion (2 mg/kg/h), sufentanil perfusion (0.5 µg/kg/hr) and sevoflurane, according to the patient's needs and bispectral index (target values: 40 to 50).

Surgical access was achieved through a full median sternotomy and central cannulation was established after heparinisation (400 IU/kg). In all patients a target activated clotting time of 440 seconds was achieved and normothermia (35 to 37°C) was applied. Intermittent blood cardioplegia was given after cross clamping the aorta and repeated every 15 min after total cardiac arrest.

Heparinisation was reversed with protamine sulphate (1 mg per 100 UI of heparin) to reach an activated clotting time within 10% of baseline level in both groups. A cell saver device (Sorin Electa, Sorin Group, Mirandola, Italy) was used in all patients to reinfuse pericardial shed blood and to remove activated platelets and coagulation factors.

All patients were admitted to the intensive care unit (ICU) after surgical procedures. Postoperative care and rethoracotomy policy were at the discretion of the attending physician. Patients received a packed cell transfusion with haematocrit levels less than 25%, and according to the 6 – 5 – 4 transfusion policy [12].

AdECC (Control)

We used an advanced conventional extracorporeal system characterized as a MiECTiS type IV-like circuit [5] with a Bioline-coated circuit (Maquet Cardiopulmonary, Rastatt, Germany), diffusion membrane oxygenator (Quadrox-iD, Maquet) with integrated arterial filter and heat exchanger, a centrifugal pump (Rotaflow, Maquet), a soft-shell reservoir for systemic blood and a cardiotomy reservoir for shed mediastinal blood suction, aortic root, and left heart venting. A suction vent was positioned in the aortic root and right superior pulmonary vein. We name this our gold standard group and refer to it as the AdECC group.

The circuit was primed with 1500 mL of Ringer's lactate, 200 mL of mannitol 15%, 200 mL of albumin, 30 mL of sodium carbonate 8.4%, and 75 mg of porcine heparin (7500 IU); 850 mL retro priming was applied to reduce priming volume.

MiECC

The MiECC system (MECC, Maquet) was a MiECTiS type II closed miniaturized circuit with no blood–air contact and no open venous reservoir. The system components included a centrifugal Rotaflow pump (Maquet), a diffusion membrane oxygenator (Quadrox-i, Maquet) with integrated heat exchanger and a venous bubble trap (VBT160, Maquet) located between the venous line and the centrifugal pump. A suction vent was positioned in the aortic root and pulmonary artery. All components were Bioline coated (Maquet). The MiECC circuit was primed with 800 mL physiological saline solution and retro priming was used.

Study design and variable definition

The primary end point was postoperative blood loss measured after 12 hours or at drain removal if earlier than 12 hours. Secondary endpoints included ICU length of stay, length of total hospital stay and intubation time. Plasma loss was measured as plasma separated from pericardial blood after cell saver centrifugation. After 1 hour and 12 hours after surgery, haemoglobin, haematocrit and thrombocytes levels were determined. After 12 hours after surgery, leukocytes, C-reactive protein, urea, creatine kinase (CK), CK-myocardial band and creatinine were also determined.

Further clinical relevant secondary end points were determined as follows. Periprocedural myocardial infarction was based on CK-myocardial band values 10 times CK and new alterations in electrocardiography or transthoracic echocardiography, and postoperative acute kidney injury was based on estimated glomerular filtration rate reduction greater than 50% within 48 hours after surgery and was calculated by using the modification of diet in renal disease formula.

We recorded rethoracotomy during hospital admission, postoperative atrial fibrillation and calculated major adverse cardiac and cerebrovascular events as composite endpoint of Periprocedural Myocardial Infarction, stroke and 30-day mortality. Thirty-, 120-, and 365-day and overall mortality were determined as survival proportions.

Patients were allocated by using sealed envelopes in block randomisation for intervention and were equally distributed among surgeons. Random allocation sequence was done by an independent researcher with a 1 : 1 allocation using a block size of 5.

Envelopes were opened after surgeons acquired informed consent from patients the day before surgery. Because of the nature of intervention, patients, surgeons and researchers were aware of the allocated arm of treatment.

Statistical analysis

To detect a reduction in blood loss with the use of MiECC, we used 66 MiECC/AdECC AVR from our own centre. With a one-sided 5% significance level and power of 80%, a sample size of 55 patients per group was necessary. Statistical analysis was performed with SPSS version 23.0 (SPSS Inc, Chicago, IL). A p-value of less than 0.05 was set as statistical significance.

All continuous variables were tested for normality with the Kolmogorov–Smirnov and Shapiro-Wilk test and visual inspection of histograms. Non-normal data were log-transformed. Variables were analysed with t-tests for independent samples or with the analysis of variance (ANOVA) for repeated measures. For unsuccessful log-transformation the Mann-Whitney U test was applied and with overdispersion we used a negative binomial regression.

Categorical variables were compared with the χ^2 test. A Kaplan-Meier analysis estimated survival over time. Imbalances in baseline characteristics were assessed using univariate analysis for influence on blood loss, including variables with p less than 0.10. Results are reported as mean $\pm$ SD when normally distributed and median with interquartile range in non-normal distributions.

Results

One hundred twenty-eight patients were included in this study, with MiECC and AdECC evenly distributed between the groups. Three patients were excluded after being randomly assigned because of BMI less than 20 ($n = 2$) and concomitant elective planning for coronary artery bypass graft surgery ($n = 1$). Therefore, 125 patients were included in this analysis: 63 in the MiECC-group and 62 in the AdECC group. Eligible patients were included from April 2012 to January 1st 2016. Follow-up on mortality was 100% for this analysis and ended February 12th 2018.

Baseline characteristics

Baseline demographic and clinical characteristics of this study are shown in Table 2. No significant differences were found between the study groups, except for BMI (MiECC: 29 ± 4.1 kg/m²; AdECC: 27 ± 3.6 kg/m², $p = 0.008$). Both BMI and ECC type were used in an univariate analysis for influence on blood loss. Tests of between-subjects effects showed no influence of BMI on blood loss (Supplementary Figure 1).

Table 2 Baseline characteristics

Variable	MiECC (n = 63)	AdECC (n = 62)	p value
Sex (male)	48% (30)	53% (33)	0.59
Age, years	71 ± 8.4	72 ± 8.8	0.35
BMI, kg/m ²	29 ± 4.1	27 ± 3.6	0.008
NYHA class	...	...	0.89
I	13	15	...
II	30	28	...
III	20	19	...
IV	0	0	...
CCS class	...	...	0.74
0	26	22	...
1	14	18	...
2	22	20	...
3	1	2	...
4	0	0	...
Aortic valve area, cm ²	0.82 ± 0.18	0.79 ± 0.19	0.35
Aortic valve gradient, mm Hg	79 ± 23	76 ± 20	0.37
EuroSCORE I, log	5.6 ± 3.5	6.2 ± 4.0	0.38
Preoperative Aspirin	41% (26)	45% (28)	0.72
Aspirin stopped preoperative, days	2.8 ± 2.9	2.6 ± 3.0	0.89
Preoperative DAPT	4.8% (3)	4.8% (3)	1.0
DAPT stopped preoperative, days	4.0 ± 3.6	6.5 ± 2.1	0.45
Preoperative anticoagulant agents	21% (13)	16% (10)	0.65
Anticoagulant agents stopped preoperative, days	3.1 ± 2.2	3.3 ± 2.0	0.87
INR	1.0 [1.0 – 1.1]	1.0 [1.0 – 1.1]	0.90
Preoperative creatinine, µmol/L	80 [68 – 92]	81 [68 – 97]	0.83
Preoperative haemoglobin, mmol/L	8.5 ± 0.87	8.5 ± 0.86	0.92
Preoperative haematocrit, L/L	0.41 ± 0.04	0.41 ± 0.04	0.92
Thrombocytes pre-surgery, ×10 ⁹ /L	215 [179 – 249]	217 [190 – 267]	0.12

1 mmol/L haemoglobin = 1.61 g/dL haemoglobin.

AdECC = Advanced extracorporeal circulation; BMI = Body mass index; CCS = Canadian Cardiovascular Society; DAPT = Dual anti platelet therapy; EuroSCORE = European system for cardiac operative risk evaluation; INR = International normalised ratio; MiECC = Minimal invasive extracorporeal circulation; NYHA = New York Health Association

Intraoperative characteristics

No conversions to an open ECC system nor air bubbles in the circuit were encountered, and operative mortality was not observed. No significant differences were found in intraoperative characteristics (Table 3).

Plasma loss during surgery was twice as high in the MiECC group (841 ± 452 mL) than in the AdECC group (409 ± 300 mL, $p < 0.001$) and return of pericardial shed blood using a cell saver device was comparable with the former plasma loss.

Table 3 Intraoperative characteristics

Variable	MiECC (n = 63)	AdECC (n = 62)	p value
Cardiopulmonary bypass time, minutes	74 ± 18	80 ± 26	0.14
Aortic cross-clamp time, minutes	51 ± 17	54 ± 20	0.32
Biological aortic valve prosthesis	83% (52)	81% (50)	0.82
Valve size, mm	...	...	0.45
19	1	0	...
21	14	15	...
23	32	25	...
25	12	17	...
27	4	5	...

In-hospital postoperative characteristics

Table 4 shows postoperative blood management, laboratory results, and clinical end points. Blood loss, our primary end point, was non-normally distributed and successfully log transformed into a normal distribution. We found a significant difference in blood loss between both groups, favouring the MiECC (230 mL, 95% Confidence Interval: [203 to 261 mL]) compared with the AdECC (288 mL, 95% CI: [241 to 344 mL], $p = 0.043$) patients ($n = 62$) after 12 hours (Figure 1).

In 4 of 6 AdECC patients with blood loss more than 750 mL, a rethoracotomy was performed when two minor surgical bleeding sites were discovered. For both MiECC patients with a blood loss more than 750 mL, no rethoracotomies were deemed necessary. However, 1 patient received 1 unit of packed red blood cells.

Figure 1 Blood loss 12 hours after surgery. Blood loss was significantly higher in the advanced extracorporeal circulation (AdECC) group than in the minimal invasive extracorporeal circulation (MiECC) group. * $p = 0.043$. Whiskers show the 25th and 75th percentile $\pm$ 1.5 times interquartile range (Tukey box-and-whiskers plot)

Figure 2 Boxplot of haemoglobin (Hb) levels 1 hour after surgery. Hb was significantly higher in the minimal invasive extracorporeal circulation (MiECC) group than in the advanced extracorporeal circulation (AdECC) group. *** $p < 0.001$. 1 mmol/L = 1.61 g/dL Hb

Simultaneously, haemoglobin (Hb) levels were significantly higher at all time points in the MiECC group (Hb 1 hour after surgery: 6.7 ± 0.97 mmol/L; Hb 12 hours after surgery: 7.3 ± 0.80 mmol/L) compared with the AdECC group (Hb 1 hour: 6.1 ± 0.88 mmol/L; Hb 12 hours: 6.7 ± 0.77 mmol/L, $p < 0.001$). A distribution of haemoglobin levels 1 hour after surgery is displayed in Figure 2.

An ANOVA for repeated measures showed a significant time effect as well as interaction of time and ECC-type (ANOVA, $F(1.98, 243) = 11.9$, $p < 0.001$), see Supplementary Figure 1.

C-Reactive Protein as a marker for inflammation was slightly decreased in the MiECC group (35 ± 20 mg/L) compared with the AdECC (43 ± 23 mg/L, $p = 0.043$). No other markers for organ damage were observed (Table 4).

Because our transfusion data was over-dispersed (many zero transfusions), a negative binomial regression analysis was used. No influence of ECC type on packed red blood cells, fresh frozen plasma or thrombocyte transfusions was found ($p > 0.27$).

Long term follow-up

We had a 30-day survival of 98.4% in both groups (Figure 3). After 120 days survival was still 96.8% in both groups. Median follow-up was 1,571 days in the MiECC group and 1,612 days in the AdECC group with no significant differences at all timepoints (Figure 3).

Table 4 Postoperative results and laboratory data

Variable	MiECC (n = 63)	AdECC (n = 62)	p value
Haematology and blood management			
Blood loss after 12 hours, mL	230 [203 – 261]	288 [241 – 344]	0.04 ^a
Plasma loss, mL	841 ± 452	409 ± 300	< 0.001
Reinfusion of cells, mL	776 ± 519	348 ± 262	< 0.001
Haemoglobin after 1 hour, mmol/L	6.7 ± 0.97	6.1 ± 0.88	< 0.001
Haemoglobin after 12 hours, mmol/L	7.3 ± 0.80	6.7 ± 0.77	< 0.001
Haematocrit after 1 hour, L/L	0.33 ± 0.05	0.30 ± 0.04	< 0.001
Haematocrit after 12 hours, L/L	0.36 ± 0.04	0.33 ± 0.04	< 0.001
Thrombocytes after 1 hour, ×10 ⁹ /L	131 ± 45	139 ± 54	0.42
Thrombocytes after 12 hours, ×10 ⁹ /L	151 ± 48	162 ± 44	0.18
Laboratory data			
Leukocytes after 12 hours, ×10 ⁹ /L	15 ± 3.5	14 ± 4.2	0.29
CRP after 12 hours, mg /L	35 ± 20	43 ± 23	0.04
Urea, mmol/L	7.7 ± 2.7	7.8 ± 2.4	0.87
CK, U/L	303 [226 – 454]	318 [254 – 463]	0.61
CK myocardial band, ng/mL	18 [14 – 25]	21 [14 – 24]	0.50
Troponin T high sensitivity, ng/L	324 ± 171	363 ± 311	0.39
Creatinine after 24 hours, µmol/L	72 [61 – 92]	75 [61 – 89]	0.72
eGFR reduction > 50% within 48 hours	1.6% (1)	4.8% (3)	0.37
Clinical end points			
MACCE	7.9% (5)	8.1% (5)	1.00
Periprocedural Myocardial Infarction	6.3% (4)	6.5% (4)	1.00
Stroke	0% (0)	0% (0)	1.00
Packed red blood cells transfusion	19% (12)	27% (17)	0.30 ^b
Fresh frozen plasma transfusion	8% (5)	15% (9)	0.27 ^b
Thrombocytes transfusion	8% (5)	9.7% (6)	0.76 ^b
Post-operative atrial fibrillation	40% (25)	37% (23)	0.86
Rethoracotomy	1.6% (1)	6.5% (4)	0.21
Intensive Care Unit stay, days	1 [1 – 1]	1 [1 – 2]	0.55
Length of stay, days	6 [5 – 7]	6 [5 – 7]	0.20
Ventilation time, hours	7 [6 – 11]	8 [5 – 12.5]	0.44 ^b

^a p value of log-transformed data; ^b p value of negative binomial regression analysis

Values are expressed as n (%), mean ± SD, or median [interquartile range]

AdECC = Advanced extracorporeal circulation; CK = Creatine kinase; CRP = C-Reactive Protein; eGFR = Estimated glomerular filtration ratio; MACCE = Major adverse cardiovascular and cerebrovascular event; MiECC = Minimal invasive extracorporeal circulation

Years post procedure / Patients at risk						
Year	0	1	2	3	4	5
MiECC	63	62	61	53	42	13
AdECC	62	59	56	47	42	12

Figure 3 Survival proportions of both groups showing no significant difference in survival at all time points. AdECC = Advanced extracorporeal circulation; MiECC = Minimal invasive extracorporeal circulation; NS = not significant

Comment

We compared a MiECC to AdECC on blood loss after aortic valve surgery in a randomised controlled trial. We found a significant reduction in our primary end point of blood loss after 12 hours in the MiECC group (230 mL) compared with the AdECC group (288 mL, $p = 0.04$). A preservation of haemoglobin levels 1 hour and 12 hours after surgery in the MiECC group was observed ($p < 0.001$).

This study is the largest randomised controlled trial to compare MiECC with AdECC for isolated aortic valve surgery with blood loss as primary end point. A pooled analysis from three trials on AVR surgery with considerable heterogeneity ($I^2 = 81\%$) showed a significant reduction of postoperative blood loss of 115 mL in MiECC procedures, ranging from 36 mL to 208 mL [13]. Our blood loss difference of 58 mL is within the range of these studies. A meta-analysis of previous studies in AVR surgery was published by Wang and colleagues in 2016 and showed a minor reduction in ICU stay for 6 hours and total hospital stay for 18 hours, favouring MiECC greater than conventional ECC [14], which we were not able to demonstrate.

Clinical and research implications of this study

Although we find a significant difference in blood loss between AdECC and MiECC of 58 mL (288 vs 230 mL), this difference has no major clinical impact for a general population. There was no difference in blood product use or other clinical endpoints. A

reason for this finding could be that blood loss difference was smaller than the transfusion trigger [12]. Plasma loss was significantly higher in the MiECC group, where more pericardial blood drained into the cell saver and separated plasma was discarded. Our data suggests that this has no specific impact on patient outcome.

Unfortunately, literature about long term follow up is scarce and other studies or systematic reviews frequently mention only in-hospital or 30-day mortality [7, 13], while early mortality of cardio-thoracic surgery continues up to 120-days [15]. Our 30-day mortality is low (1.6% in both groups), as well as our in-hospital mortality (1.6% in both groups) compared with other trials (Table 5) or The Society of Thoracic Surgeons unadjusted operative mortality for AVR (2.4%) [16].

Although our study was not powered for this safety endpoint, our long term follow up with median follow up of more than 4 years (1600 days) indicate no difference in long-term survival between both groups.

Limitations

We obtained a significantly higher BMI in the MiECC group than in the AdECC group (29 vs 27 kg/m², $p = 0.008$) despite our random assignment of patients. A high BMI might influence haematology because of increased circulation volume; therefore, we included BMI and ECC-type in an univariate analysis on blood loss. Here, we found no influence of BMI on blood loss (Supplement 1).

Nolan and colleagues found a decreased postoperative blood loss in overweight and obese BMI in patients with coronary artery bypass grafting [17]. With the use of their categorisation, still no effect on (log transferred) blood loss was observed in our AVR study.

Furthermore, analysis of the coagulation cascade might have given insights of in vivo haemostasis. No differences in pre-operative aspirin or dual anti platelet therapy were observed between both groups (Table 2). For future studies, thromboelastography and thromboelastometry can be beneficial.

Comparison between both systems

In our study we used a MiECTiS type II MiECC as the intervention group (MiECC) and a modified conventional ECC with MiECC characteristics (AdECC, MiECTiS type IV-like). We define this as “MiECTiS type IV-like” because we used a fully coated circuit, a centrifugal pump, arterial filter and soft-shell reservoir with a miniaturized circuit volume because of retro priming. Therefore, this was not fully complying to MiECTiS type IV classification (reduced priming volume) yet also not defined as conventional ECC in most studies.

Most studies compared conventional ECC with roller pumps and uncoated circuits to MiECC in small retrospective or poorly designed randomizes studies. Here, we show that there is a small advantage in blood loss reduction even between two advanced ECC systems.

Table 5 In-hospital and 30-day mortality of randomised controlled trials comparing MiECC with conventional ECC in AVR surgery

First author, year [Reference]	Patients	No. of patients		MiECTIS type	Conventional ECC type	Mortality MiECC	Mortality CECC	p value
		MiECC	CECC					
Remadi, 2004 [2]	AVR	50	50	I, SC	NPV, RP, NC, OS	2% ^a	4% ^a	0.2
Castiglioni, 2009 [3]	AVR	60	60	I	NPV, RP, HC, OS	0% ^b	0% ^b	1.0
Rimpiläinen, 2011 [18]	AVR, CABG+AVR	20	20	III	NPV, RP, PC, SC	0% ^b	0% ^b	1.0
Baumbach, 2016 [19]	AVR, MVR	101	99	III	NPV, RP, HC, SC	1% ^b	3% ^b	0.34
This study, 2019	AVR	63	62	II	RPV, CP, HC, SC ^c	1.6% ^{a,b}	1.6% ^{a,b}	1.0

^a 30-day mortality, ^b In-hospital mortality, ^c Type IV MiECC

AVR = Aortic valve replacement; CABG = Coronary artery bypass grafting; CECC = Conventional extracorporeal circulation; CP = Centrifugal pump; ECC = Extracorporeal circulation; HC = Heparin coated; MiECC = Minimal invasive extracorporeal circulation; MVR = Mitral Valve replacement; NC = Not coated; NPV = Normal priming volume; OS = Open system; PC = Phosphoryl choline coated; RP = Roller pump; RPV = Reduced (retro)priming volume, SC = Semi-closed system

To conclude, some centres prefer a conventional ECC system due to perceived safety concerns and training of dedicated teams. In our centre, only specifically trained perfusionists and surgeons run MiECC after a training of at least 50 patients. Using an AdECC system might be an alternative to these centres, with added benefits from fully coated lines, a centrifugal pump and arterial filters.

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Disclosures

All authors had freedom of investigation and full control of the design of the study, methods used, outcome parameters and results, analysis of data and production of the written report.

References

1. Butler J, Rocker GM, Westaby S. Inflammatory response to cardiopulmonary bypass. *Ann Thorac Surg.* 1993;55:552-559.
2. Remadi JP, Rakotoarivello Z, Marticho P, et al. Aortic valve replacement with the minimal extracorporeal circulation (Jostra MECC System) versus standard cardiopulmonary bypass: a randomized prospective trial. *The Journal of thoracic and cardiovascular surgery.* 2004;128:436-441.
3. Castiglioni A, Verzini A, Colangelo N, Nascimbene S, Laino G, Alfieri O. Comparison of minimally invasive closed circuit versus standard extracorporeal circulation for aortic valve replacement: a randomized study. *Interactive cardiovascular and thoracic surgery.* 2009;9:37-41; discussion 41.
4. Yilmaz A, Sjatskig J, van Boven WJ, et al. Combined coronary artery bypass grafting and aortic valve replacement with minimal extracorporeal closed circuit circulation versus standard cardiopulmonary bypass. *Interactive cardiovascular and thoracic surgery.* 2010;11:754-757.
5. Anastasiadis K, Murkin J, Antonitsis P, et al. Use of minimal invasive extracorporeal circulation in cardiac surgery: principles, definitions and potential benefits. A position paper from the Minimal invasive Extra-Corporeal Technologies international Society (MiECTiS). *Interactive cardiovascular and thoracic surgery.* 2016;22:647-662.
6. Funkat A, Beckmann A, Lewandowski J, et al. Cardiac surgery in Germany during 2013: a report on behalf of the German Society for Thoracic and Cardiovascular Surgery. *The Thoracic and cardiovascular surgeon.* 2014;62:380-392.
7. Anastasiadis K, Antonitsis P Fau - Haidich A-B, Haidich Ab Fau - Argiriadou H, Argiriadou H Fau - Deliopoulos A, Deliopoulos A Fau - Papakonstantinou C, Papakonstantinou C. Use of minimal extracorporeal circulation improves outcome after heart surgery; a systematic review and meta-analysis of randomized controlled trials. 2013.
8. Kutschka I, Skorpil J, El Essawi A, Hajek T, Harringer W. Beneficial effects of modern perfusion concepts in aortic valve and aortic root surgery. *Perfusion.* 2009;24:37-44.
9. Morgan IS, Codispoti M, Sanger K, Mankad PS. Superiority of centrifugal pump over roller pump in paediatric cardiac surgery: prospective randomised trial. *European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery.* 1998;13:526-532.
10. Schulz KF, Altman DG, Moher D, Group C. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *BMJ.* 2010;340:c332.
11. Colditz GA, Stoll CR. Reporting Standards for Randomized Trials Published in The Annals of Thoracic Surgery. *Ann Thorac Surg.* 2016;101:1639-1640.
12. (CBO); DIFHI. Dutch Blood Transfusion Guideline: International Society of Blood Transfusion; 2011:172-173.
13. Anastasiadis K, Dimatis I, H A. *Principles of Miniaturized ExtraCorporeal Circulation: From Science and Technology to Clinical Practice.* 1 ed: Springer-Verlag Berlin Heidelberg; 2013.
14. Wang C, Hua K, Yin L, Wang Y, Li W. A Meta-Analysis of Miniaturized Versus Conventional Extracorporeal Circulation in Valve Surgery. *Ann Thorac Surg.* 2016;102:2099-2108.
15. Siregar S, Groenwold RH, de Mol BA, et al. Evaluation of cardiac surgery mortality rates: 30-day mortality or longer follow-up? *European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery.* 2013;44:875-883.
16. STS Adult Cardiac Surgery Database (ACSD). Unadjusted Operative Mortality for Aortic Valve Replacement (2012-2015). Vol 2017. 2017h2 ed2017.

17. Nolan HR, Davenport DL, Ramaiah C. BMI Is an Independent Preoperative Predictor of Intraoperative Transfusion and Postoperative Chest-Tube Output. *Int J Angiol.* 2013;22:31-36.
18. Rimpilainen R, Hautala N, Koskenkari JK, et al. Comparison of the use of minimized cardiopulmonary bypass with conventional techniques on the incidence of retinal microemboli during aortic valve replacement surgery. *Perfusion-Uk.* 2011;26:479-486.
19. Baumbach H, Rustenbach CJ, Ahad S, et al. Minimally Invasive Extracorporeal Bypass in Minimally Invasive Heart Valve Operations: A Prospective Randomized Trial. *Ann Thorac Surg.* 2016;102:93-100.

Supplements

Supplementary Figure 1

Supplementary Figure 1 Haemoglobin levels (Hb, mmol/L) before and after surgery. Hb levels were higher in the MiECC group at all timepoints after surgery, compared with the AdECC group (ANOVA, $F(1.98, 243) = 11.9$, $p < 0.001$). AdECC = Advanced extracorporeal circulation; MiECC = Minimal invasive extracorporeal circulation

CHAPTER 3

INTRAOPERATIVE TRANSIT TIME FLOW MEASUREMENTS: THE IMPACT OF CORONARY STENOSIS ON COMPETITIVE FLOW

Submitted

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Abbreviations and acronyms

ACI	Acoustic coupling index
BF	Backflow
CABG	Coronary artery bypass grafting
CFI	Competitive flow index
DF	Diastolic flow
EACTS	European Association for Cardio-Thoracic Surgery
ESC	European Society of Cardiology
EuroSCORE	European system for cardiac operative risk evaluation
FFR	Fractional flow reserve
LAD	Left anterior descending coronary artery
D	Diagonal branch
LIMA	Left internal mammary artery
LM	Left main coronary artery
MGF	Mean graft flow
NYHA	New York Health Association
OPCAB	Off-pump coronary artery bypass grafting
PI	Pulsatility index
QCA	Quantitative coronary analysis
TTFM	Transit time flow measurements

Abstract

Background

Combining preoperative angiography findings with intraoperative transit time flow measurements (TTFM) may improve patency of coronary artery bypass grafts. Nevertheless, graft flow might be impaired by native coronary flow based on the severity of proximal stenoses, with consequences on long-term outcomes. This study investigates the impact of left anterior descending artery (LAD) stenosis on competitive flow measured in left internal mammary artery (LIMA) grafts.

Methods

Fifty patients were included in this prospective single-centre cohort study. LAD stenosis was assessed with quantitative coronary analysis (QCA) and stratified into three groups based on its severity. TTFM of LIMA grafts were performed with LAD open and temporarily occluded. A change in mean graft flow after LAD snaring was the primary endpoint. Secondary endpoints included further TTFM parameters, clinical outcomes and competitive flow index (CFI), defined as the ratio of mean graft flow with open or closed LAD.

Results

Mean LAD stenosis objectified with QCA was $58 \pm 15\%$. Mean LIMA graft flow increased from 20 mL/min with open LAD to 30 mL/min with snared LAD ($p < 0.001$) and no differences among groups were observed. TTFM cut-off values for graft patency improved in 26% to 42% of patients after LAD occlusion. Median CFI was 0.66 (IQR: 0.56 – 0.82). Postoperative myocardial infarction occurred in 2.0% of patients, 120 day mortality was 0% and 2 year mortality was 6.0%.

Conclusions

Routine snaring of the LAD with CFI calculation during coronary artery bypass grafting is useful to detect significant competitive flow in LIMA grafts, potentially preventing unnecessary intraoperative graft revisions.

Introduction

Myocardial revascularisation by percutaneous coronary intervention or coronary artery bypass graft (CABG) is an effective strategy to improve symptoms, quality of life and survival in patients suffering from severe coronary stenosis [1]. Indication for revascularisation is mainly based on visual quantification of the stenosis performed by an interventional cardiologist. Notwithstanding, this method is affected by a high intra and inter-observer variability with low concordance on clinical relevant cut-off points [2, 3].

Quantitative coronary analysis (QCA) using cardiac angiography has been applied for anatomical evaluation of coronary stenoses but its predictive value in terms of graft patency is yet not comparable to functional assessment methods such as the more invasive fractional flow reserve (FFR) measurement [4]. Consequently, the degree of a coronary stenosis can be misjudged impacting short and long-term outcomes of coronary artery bypass grafts. This is particularly true for arterial grafts. On one side, arterial grafts demonstrated excellent long-term disease-free survival, low myocardial revascularisation rates and high graft patency [5, 6]. On the other side, they require proper handling to avoid early technical failure and their patency can be significantly affected by the presence of competitive flow from native coronaries [7]. Therefore, early detection of competitive flow on arterial grafts might be relevant to predict their long-term patency.

Competitive flow is defined as bypass graft flow impaired by native coronary flow, or as bypass graft flow that progressively lessens as proximal coronary artery stenosis decreases [8]. In detail, competitive flow occurs when resistance of the graft matches or exceeds native coronary artery resistance and is related to the degree of a proximal stenosis [9]. Thus far, the impact of stenosis and competitive flow on arterial grafts was observed only in animal studies. Small canine and porcine studies showed a decrease in left internal mammary artery (LIMA) flow in patent coronary arteries [10-12]. Furthermore, a human study investigating the use of LIMA grafting in moderately stenotic coronary arteries [13] and one case report [14] showed similar results.

Intraoperative flow measurements

Intraoperative evaluation of competitive flow can be performed through transit time flow measurements (TTFM). Studies showed that TTFM detects intraoperative graft occlusion in up to 5 to 11% of cases [15, 16] and improves short-to-middle term outcomes in both on-pump and off-pump CABG (OPCAB) [16, 17]. Moreover, European Society of Cardiology (ESC)/European Association for Cardio-Thoracic Surgery (EACTS) guidelines on myocardial revascularisation recommend the routine use of intraoperative graft flow assessment through TTFM[1]. Nevertheless, clinical relevant TTFM cut-off values for graft failure vary between studies and are still debated [18].

Combining preoperative angiography findings with intraoperative TTFM may significantly impact graft patency. This becomes particularly important for grafts such as the LIMA to left anterior descending coronary (LAD) which has the highest influence on clinical outcomes [1, 19]. This study investigates the impact of coronary stenosis on competitive flow in off-pump LIMA to LAD bypass grafts with the hypothesis that competitive flow increases with a lower degree of LAD stenosis.

Methods

Study design and setting

This is a prospective single-centre cohort study, reported as per the STROBE recommendations for observational research [20]. Adult patients undergoing OPCAB with LIMA to LAD anastomosis between September 2016 and August 2017 were recruited at Medisch Spectrum Twente (Enschede, the Netherlands).

Patients with previous CABG, chronic total occlusion of the LAD and patients requiring emergency surgery were excluded. The number of OPCAB surgeries during the study period determined study size. Follow-up data were retrieved from the Netherlands Heart Registry [21]. Follow-up regarding revascularisation and myocardial infarction ended on October 29th 2019. Follow-up on mortality ended on May 1st 2020 as part of routine follow-up [21] to prevent information bias. Patient records from referring hospitals were retrieved to complete routine follow-up. This study was exempted from the Medical Research Involving Human Subjects Act by the Medical Ethics Committee Twente (METC Twente: K16 – 63) and approved on August 11th 2016 by the local institutional review board.

Preoperative evaluation and surgical procedure

LAD stenosis was quantified with QCA using QAngio XA (Medis, Leiden, the Netherlands) software (Figure 1). A significant left main (LM) stenosis was defined as LAD/circumflex equivalent. Choice of best angiographic recording was based on image-plane, background contrast and LAD runoff. LAD stenosis as determined by QCA was stratified into three groups: <50%, 50 to 70% and >70% [22, 23]. Indication to surgical myocardial revascularisation was based on heart team consensus after evaluation of clinical data, visual quantification of coronary stenosis and FFR.

All surgical procedures were performed by three experienced OPCAB surgeons. LIMA was harvested as pedicle. For flow measurements, 1 – 2 cm of distal LIMA was skeletonized. After harvesting, LIMA was injected with 1 mg/mL papaverine diluted in 50 mL saline solution to prevent spasm. Graft composition, i.e. single, sequential and/or composite graft, was at surgeon's discretion. A dedicated OPCAB stabilizer (ACROBAT SUV Vacuum, Maquet, Rastatt, Germany) was used for constructing the anastomosis.

After completion of the LIMA to LAD graft, TTFM were performed with a VeriQ C (MediStim, Oslo, Norway) system. The LAD was temporarily closed by placing a metal bulldog proximally to the anastomosis and remained closed until stable mean graft flow (MGF) in the LIMA graft was achieved. TTFM of LIMA flow with closed LAD were recorded and the bulldog clamp was removed. After stabilisation of the flow, a new measurement was performed with proximal LAD open. For Y-graft configurations with a radial artery, the proximal radial Y-branch was temporarily occluded before flow measurements. Revision of the anastomosis was based on abnormal TTFM findings regarding flow profile. Only measurements with an acoustic coupling index (ACI) over 50% were included. If despite efforts contact could not be improved by skeletonizing the LIMA or increasing amount of ultrasound gel, a suboptimal contact (ACI 30 – 50%) was accepted. TTFM were matched with electrocardiography to distinguish systolic from diastolic flow.

Primary and secondary endpoints

Primary endpoint of this study was the change in mean LIMA graft flow (mL/min) measured with open and closed LAD. Secondary TTFM endpoints were pulsatility index (PI), backflow (BF), diastolic filling (DF), peak systolic flow and peak diastolic flow. A full description of these TTFM parameters can be found in previous publications [16]. Secondary clinical endpoints included postoperative cardiac enzymes, mortality at 120 days and 2 years, myocardial infarction and need for revascularisation according to Netherlands Heart Registry definitions [24].

A new parameter named competitive flow index (CFI) was developed to quantify competitive flow and it was defined as follows:

$$\text{Competitive Flow Index} = 1 - \frac{MGF_{LIMA}^{LAD\ Open}}{MGF_{LIMA}^{LAD\ Closed}}$$

where $MGF_{LIMA}^{LAD\ Open}$ is mean LIMA graft flow with LAD open (mL/min) and $MGF_{LIMA}^{LAD\ Closed}$ is mean LIMA graft flow with LAD snared. A CFI of 1 indicates high competitive flow and a CFI of 0 indicates absence of competitive flow.

Statistical analysis

Continuous variables were tested for normality with visual inspection of histograms and skewness/kurtosis measures. A p value of less than 0.05 was set as statistically significant.

Patients were analysed by intention-to-treat. Primary and secondary endpoints were converted into clinically relevant dichotomous values and analysed with a χ^2 -test or Fischer Exact test when less than 5 events occurred.

Dichotomous cut-off values for graft patency were determined as $MGF > 20$ mL/min [25, 26], $PI < 3$ [25, 27], $BF > 3\%$ [25] and $DF > 50\%$ [15]. A strict composite endpoint cut-off for graft patency of $MGF > 15$ mL/min and $PI < 3$ as proposed by previous studies was also applied [27, 28].

Variables were analysed with a paired t-test or Wilcoxon signed-rank test for comparison within individual patients. A Kruskal-Wallis test was used for group analysis based on QCA. A post-hoc analysis with Holm-Bonferroni correction was performed. A linear mixed model was used to determine differences in TTFM parameters between open and closed LAD and between QCA groups. Survival was examined by a Kaplan-Meier curve. Follow-up was protocolized as standard care [24] and missing data or loss to follow-up were thus not expected.

Indication for revascularisation was sometimes based on a significant LM stenosis in the absence of a significant LAD stenosis. A sensitivity analysis with and without LM stenosis was therefore performed. Moreover, a sensitivity analysis excluding LIMA sequential grafts was performed to evaluate the impact of coronary territories extension on grafts runoff and competitive flow.

Results are reported as mean $\pm$ SD or median with interquartile range [IQR]. Frequencies are reported as n (%). Whiskers show the 25th and 75th percentile $\pm$ 1.5 times IQR in the Tukey box-and-whiskers plot.

Figure 1 Coronary angiography with left lateral view and quantitative coronary analysis. Red: reference diameter of LAD; Yellow: Actual diameter of LAD. Here, a stenosis of 58% was present in the proximal LAD. LAD = Left anterior descending coronary artery

Baseline characteristics and quantitative coronary analysis

A total of 50 patients were included in this study and received a LIMA to LAD graft. All patients completed the 2-year follow-up analysis on mortality. Baseline characteristics of this study are given in Table 1. Mean age was 68 ± 9.1 years, 96% of patients were men and mean BMI was 28 ± 4.6 kg/m² with 98% of cases diagnosed with multivessel disease.

Mean LAD stenosis objectified with QCA was $58 \pm 15\%$. Detailed lesion characteristics are shown in supplemental Table 1. LAD stenosis was stratified into three groups as follows: <50% stenosis (n = 14, 28%), 50-70% stenosis (n = 22, 44%), >70% stenosis (n = 14, 28%). The majority of patients with <50% LAD stenosis had a significant LM stenosis (9/14, 64%). Thirteen patients (26%) received a sequential graft on the diagonal branch (LIMA-D-LAD) with a mean LAD-D stenosis of $55 \pm 16\%$. One patient received a sequential graft on the anterolateral artery.

A LM stenosis was present in 15 patients (30%), with a mean value of $56 \pm 17\%$. In 12 of these patients, revascularisation was indicated based on LM stenosis only with corresponding mild LAD stenosis based on visual quantification. Seventeen patients (34%) underwent preoperative FFR measurements and all of them showed values under 0.80. In all these cases, indication to revascularisation was given based on FFR data and according to international guidelines for revascularisation [1].

All these patients had a visual estimation of stenosis degree under 90% and QCA of the LAD under 80% (Scatterplots of FFR, eyeballing and QCA, showed in Supplemental Figure 1).

Table 1 Baseline and peri-procedural characteristics (n = 50)

Variable	Patients
Age, years	68 ± 9.1
Gender, male	48 (96)
BMI, kg/m ²	28 ± 4.6
Diabetes, n (%)	14 (28)
Multivessel disease, n (%)	48 (98)
Recent myocardial infarction within 90 days, n (%)	11 (22)
Left main stenosis, n (%)	15 (30)
LVEF, n (%)	
Poor, < 30%	3 (6.0)
Moderate, 30 – 50%	8 (16)
Good, > 50%	39 (78)
Previous PCI, n (%)	7 (14)
NYHA class, n (%)	
I	44 (88)
II	5 (10)
III	1 (2)
IV	0 (0)
Urgency, n (%)	
Elective	23 (46)
Urgent	27 (54)
Emergency/Salvage	0 (0)
EuroSCORE I, log,	2.3 [1.3 – 3.7]
EuroSCORE II, log	1.06 [0.91 – 1.48]
Periprocedural characteristics, n (%)	
Isolated LIMA to LAD graft	7 (14)
Composite graft with radial artery	29 (58)
Sequential graft	14 (28)
LIMA-D-LAD	13 (26)
LIMA-AL-LAD	1 (2.0)

Values are expressed as n (%), mean ± SD, or median [interquartile range]

AL = Anterolateral or intermediate artery; BMI = Body mass index; EuroSCORE = European system for cardiac operative risk evaluation; LVEF = Left ventricular ejection fraction; LIMA = Left internal mammary artery; NYHA = New York Health Association

Intraoperative measurements

Intraoperative MGF and other TTFM parameters of LIMA to LAD graft with native LAD open or temporarily snared are displayed in Figure 2 and Table 2.

No significant variations in mean arterial pressure and heart rate were recorded during TTFM. All flow profiles had a diastolic flow waveform. Overall, MGF increased significantly from 20 [14 – 30] mL/min with open LAD to 30 [22 – 41] mL/min with snared LAD (Figure 3a and 3b, $p < 0.001$). In 26 patients (52%) MGF was under 20 mL/min with LAD open and increased in 16 patients over 20 mL/min after snaring the LAD. Normal flow profiles in the other patients were observed and no revisions were performed.

Table 2 Perioperative measurements of graft flow in closed vs snared LAD (n = 50)

	LAD, open	LAD, snared	P value
Heart rate, beats per minute	63 [56 – 78]	63 [56 – 72]	0.19
Systolic blood pressure, mmHg	101 [90 – 107]	101 [93 – 108]	0.26
Diastolic blood pressure, mmHg	51 ± 7.6	51 ± 7.9	0.75
Mean arterial pressure, mmHg	66 ± 8.5	66 ± 8.6	0.78
Acoustic coupling index, %	55 ± 16	54 ± 16	0.69
TTFM parameters and clinical cut-off values			
Mean graft flow, mL/min	20 [14 – 30]	30 [22 – 41]	< 0.001
Mean graft flow ≤ 20 mL/min	26 (52)	10 (20)	< 0.001
Mean graft flow ≤ 15 mL/min	17 (34)	4 (8)	0.01
Pulsatile index	3 [2.2 – 4.0]	2.1 [1.7 – 2.5]	< 0.001
Pulsatile index ≥ 3, n (%)	26 (52)	5 (10)	1.00
Diastolic filling, %	73 ± 6.5	73 ± 6.0	0.931
Diastolic filling < 50%	0 (0)	0 (0)	1.000
Backflow, %	3.6 [0.9 – 7.8]	0.40 [0 – 1.2]	< 0.001
Backflow > 3%	26 (53)	7 (14)	0.01
Peak systolic flow, mL/min (n = 32)	27 [14 – 42]	32 [23 – 45]	0.005
Peak diastolic flow, mL/min	40 [28 – 59]	54 [38 – 77]	< 0.001
Mean graft flow ≤ 15 mL/min and PI ≥ 3, n (%)	13 (26)	1 (2)	0.26

Values are expressed as n (%), mean ± SD, or median [interquartile range]

LAD = Left anterior descending coronary; TTFM = Transit time flow measurements

All other parameters, except for DF, showed a significant change in absolute values ($p < 0.001$, peak systolic flow $p = 0.005$) with LAD snared. After LAD occlusion, improved clinical cut-off values for MGF ≤ 15 and PI ≥ 3 were observed in 26% and 42% of patients. Three patients with LAD open and a PI over 5 shifted to a PI under 5 with LAD snared.

Stratification of TTFM parameters on severity of LAD stenosis

All LAD stenosis groups showed significant higher values of LIMA MGF measured with snared LAD (Figure 3). No differences in LIMA MGF were noticed among QCA groups in the overall population (Figure 3a, $p = 0.18$) nor in the analysis performed after exclusion of patients diagnosed with an LM stenosis (Figure 3b, $p = 0.52$). Similar results were found for other TTFM parameters except for PI, where a significant difference between QCA groups was noticed ($p = 0.04$). A post-hoc analysis demonstrated only a significant pairwise comparison for PI between the 50 to 70% stenosis group and > 70% stenosis ($p = 0.01$).

Results from linear mixed model analysis for all measurements and without LM stenosis are depicted in Supplemental Table 2 and were consistent with sensitivity analyses without sequential grafts (Supplemental Tables 3.1 to 3.3). Only peak systolic flow in non-sequential grafts showed no difference between LAD open and closed ($p = 0.16$).

Figure 2 Transit time flowmetry of LIMA to LAD graft with **A** LAD open and **B** LAD snared. An increase in mean LIMA graft flow and decrease of PI is observed when snaring the LAD. ACI = Acoustic coupling index; DF = Diastolic flow; HR = Heart rate; LAD = Left anterior descending coronary artery; LIMA = Left internal mammary artery; PI = Pulsatility index.

Figure 3 Mean LIMA graft flow (mL/min) increased with LAD snared compared to open LAD stratified to degree of stenosis. **A** Overall group; **B** Subgroup analysis without significant left main (LM) stenosis. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

LAD = Left anterior descending coronary artery; LIMA = Left internal mammary artery

Competitive flow index and absolute difference in mean graft flow

Median CFI as ratio of LIMA MGF with LAD open and snared was 0.66 [0.56 – 0.82]. Although theoretically not possible, 5 patients had a CFI below 0. These patients had a MGF over 20 mL/min and a slightly higher MGF in the open LAD compared to closed LAD (mean difference 2.6 mL/min). A significant difference of CFI was observed among QCA groups ($p = 0.03$) and patients without LM stenosis (Figure 4a, $p = 0.03$). Post-hoc analysis showed a significant difference in CFI between < 50% and > 70% stenosis (overall: $p = 0.04$; without LM stenosis $p = 0.03$).

Absolute change in LIMA MGF between open and snared LAD was 11 [4.8 – 14] mL/min in the < 50% stenosis group, 11 [8.8 – 16] mL/min in the 50 to 70% group and 4.5 [2 – 15] mL/min in the > 70% group. There was no difference between stenosis groups (Figure 4b, $p = 0.19$) in the analysis including the overall population, but only in the subgroup analysis after exclusion of patients with LM stenosis ($p = 0.03$). Here, post-hoc analysis showed a significant difference between 50 to 70% versus > 70% stenosis groups ($p = 0.04$).

Clinical outcomes

Median follow-up on mortality was 1,212 days and 841 days for myocardial infarction and revascularisation. Incidence of postoperative myocardial infarction during follow-up was 2%, 120 days mortality was 0% and 2 year mortality was 6.0% (Table 3 and Kaplan-Meier survival curve in Supplemental Figure 2).

Figure 4 Competitive flow index (CFI) of LIMA MGF with LAD open and snared and absolute difference in MGF, stratified by LAD stenosis. **A** Patients with an < 50% stenosis had a lower CFI compared to an > 70% stenosis in the overall group ($p = 0.04$), and without left main stenosis (No LM#, $p = 0.03$). **B** Patients with a 50 to 70% stenosis had an higher MGF difference compared to > 70% stenosis in the subgroup without LM stenosis ($p = 0.04$). LAD = Left anterior descending coronary artery; LIMA = Left internal mammary artery; MGF = Mean graft flow

Five patients died during follow-up. Two patients died of cerebrovascular embolism related to atrial fibrillation, one died of progression of multiple myeloma and two died of progressive heart failure. One patient received drug eluting stent implantation in the LM to circumflex artery due to incomplete revascularisation of the marginal obtuse artery two years after OPCAB with an open LIMA to LAD graft.

One postoperative myocardial infarction occurred 36 days after OPCAB in a 83 year old patient with recent myocardial infarction and previous percutaneous coronary intervention. Patient was accepted for OPCAB with three vessel disease with a LAD stenosis of 34% (QCA) and moderate left main stenosis (visual evaluation 40%). LIMA MGF with open LAD was 9 mL/min and 20 mL/min with snared LAD.

Table 3 Follow-up after off-pump coronary artery bypass grafting (OPCAB) (n = 50)

Variable	Patients
Troponin T high sensitivity after 12 hours, ng/L	142 [95 – 330]
Creatine kinase myocardial band after 12 hours, ng/mL	7.8 [5.7 – 15]
120 days mortality, n (%)	0 (0)
1 year mortality, n (%)	2 (4.0)
2 year mortality, n (%)	3 (6.0)
Revascularisation, n (%)	1 (2.0)
Myocardial infarction, n (%)	1 (2.0)

Values are expressed as n (%) or median [interquartile range]

Intraoperative competitive flow was accepted based on other acceptable TTFM values with LAD snared and mild coronary stenosis (Supplemental Table 4 and Supplemental Figure 3).

Discussion

This is the first study to investigate the impact of LAD stenosis on competitive flow measured in LIMA grafts. Mean LIMA graft flow increased by 11 mL/min after LAD snaring, in case of a proximal stenosis quantified as < 50% or 50 to 70%. In patients with a > 70% proximal stenosis, mean LIMA graft flow increased by 4.5 mL/min after LAD occlusion. A lower mean LIMA flow in sequential grafts was observed compared to single grafts because of LAD-D runoff. This phenomenon was present for both LAD open and snared and did not affect TTFM interpretations.

TTFM clinical cut-off values to predict graft patency are extensively reported [15, 25-28], yet not included in guidelines on myocardial revascularisation [1, 19]. In this study 26 to 42% of the patients shifted from a TTFM-driven unacceptable graft to an acceptable graft after LAD snaring (Table 2). This shift can indicate an open and functional anastomosis affected by a certain degree of competitive flow from the native coronary artery. In such events, a surgical revision of the graft would not be able to improve baseline TTFM values or graft patency, resulting in a useless or even harmful procedure. To quantify and normalize the amount of this competitive flow, the competitive flow index calculated as

$$1 - \frac{MGF_{LIMA}^{LAD\ Open}}{MGF_{LIMA}^{LAD\ Closed}} \text{ was developed.}$$

In case of intraoperative borderline TTFM values, the calculation of CFI as described in this study might unmask significant competitive flow and prevent unnecessary graft revision. However, while CFI is a tool to evaluate the graft quality, patency and flow, it cannot be used as predictor of clinical outcome as this ratio is independent of absolute flow needed to perfuse the heart.

The intraoperative TTFM strategy applied in this study showed good outcomes in terms of myocardial infarction and mortality in the long-term follow-up. Only one patient (2%) diagnosed with intraoperative competitive flow experienced a postoperative myocardial infarction and none of our patients had myocardial revascularisation related to competitive flow during follow-up, based on coronary angiography. These data are in line or even lower compared to those reported in the Netherlands Heart Registry [21] or in other TTFM studies presenting a one-year myocardial infarction rate of 5.1% [29].

Limitations

Patients with LM stenosis were regarded as LAD/Circumflex equivalent, but might not have a significant LAD stenosis based on QCA. Indeed, 9/14 patients with a non-significant LAD stenosis (< 50%) had a significant LM stenosis. Stratification of patients for LAD stenosis is thus biased and an unplanned subgroup analysis of patients with no LM stenosis was performed where intraoperative TTFM parameters were comparable (Figure 3 and 4). On the contrary, patients with both a significant LM and LAD stenosis have a tandem or long lesion and thus an overestimated impact of coronary stenosis.

For this study 50 patients were included to characterize the relationship of competitive flow from LAD with LIMA MGF. Although this is sufficient to determine this relationship, clinical relevant cut-off values on acceptable MGF or other parameters are underpowered.

Last, women (n = 2, 4%) were underrepresented in this study compared to the reported Dutch data for isolated CABG (women: 20%) [21].

Conclusions

To conclude, routine snaring of the LAD during OPCAB demonstrated an increase in MGF among all coronary stenosis groups. With LAD snared, 26 to 42% of clinical cut-off TTFM values for graft failure shifted to acceptable values. Therefore, routine application of the competitive flow index according to the method described in this study can be useful to identify competitive flow in case of intraoperative borderline TTFM parameters. Further studies are needed to establish definitive evidence regarding the role of CFI and routine snaring of the LAD during off-pump CABG, with special focus on prevention of unnecessary intraoperative graft revisions and postoperative myocardial infarction.

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Disclosure

The authors have nothing to disclose.

References

1. Neumann FJ, Sousa-Uva M, Ahlsson A, et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. *Eur Heart J*. 2019;40:87-165.
2. Leape LL, Park RE, Bashore TM, Harrison JK, Davidson CJ, Brook RH. Effect of variability in the interpretation of coronary angiograms on the appropriateness of use of coronary revascularization procedures. *American heart journal*. 2000;139:106-113.
3. Sen T, Kilit C, Astarcioglu MA, et al. Comparison of quantitative and qualitative coronary angiography: computer versus the eye. *Cardiovasc J Afr*. 2018;29:278-282.
4. Glineur D, Grau JB, Etienne PY, et al. Impact of preoperative fractional flow reserve on arterial bypass graft anastomotic function: the IMPAG trial. *Eur Heart J*. 2019;40:2421-2428.
5. Gaudino M, Benedetto U, Fremes S, et al. Radial-Artery or Saphenous-Vein Grafts in Coronary-Artery Bypass Surgery. *The New England journal of medicine*. 2018;378:2069-2077.
6. Gaudino M, Benedetto U, Fremes S, et al. Radial artery versus saphenous vein for coronary artery bypass surgery at long-term follow-up. *American College of Cardiology (ACC) 2020*2020.
7. Schwann TA, Tatoulis J, Puskas J, et al. Worldwide Trends in Multi-arterial Coronary Artery Bypass Grafting Surgery 2004-2014: A Tale of 2 Continents. *Seminars in thoracic and cardiovascular surgery*. 2017;29:273-280.
8. Sabik JF. Should Coronary Artery Bypass Grafting Be Performed in Patients With Moderate Stenosis of the Left Anterior Descending Coronary Artery? *Circulation*. 2016;133:111-113.
9. Glineur D, Hanet C. Competitive flow and arterial graft a word of caution. *European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery*. 2012;41:768-769.
10. Spence PA, Lust RM, Zeri RS, et al. Competitive flow from a fully patent coronary artery does not limit acute mammary graft flow. *Ann Thorac Surg*. 1992;54:21-25; discussion 25-26.
11. Nordgaard H, Nordhaug D, Kirkeby-Garstad I, Lovstakken L, Vitale N, Haaverstad R. Different graft flow patterns due to competitive flow or stenosis in the coronary anastomosis assessed by transit-time flowmetry in a porcine model. *European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery*. 2009;36:137-142; discussion 142.
12. Karapanos NT, Suddendorf SH, Li Z, Huebner M, Joyce LD, Park SJ. The impact of competitive flow on distal coronary flow and on graft flow during coronary artery bypass surgery. *Interactive cardiovascular and thoracic surgery*. 2011;12:993-997.
13. Kawasuji M, Sakakibara N, Takemura H, Tedoriya T, Ushijima T, Watanabe Y. Is internal thoracic artery grafting suitable for a moderately stenotic coronary artery? *J Thorac Cardiovasc Sur*. 1996;112:253-259.
14. Bolotin G, Kypson AP, Nifong LW, Chitwood WR, Jr. A technique for evaluating competitive flow for intraoperative decision making in coronary artery surgery. *Ann Thorac Surg*. 2003;76:2118-2120.
15. Balacumaraswami L, Taggart DP. Intraoperative imaging techniques to assess coronary artery bypass graft patency. *Ann Thorac Surg*. 2007;83:2251-2257.
16. Amin S, Pinho-Gomes AC, Taggart DP. Relationship of Intraoperative Transit Time Flowmetry Findings to Angiographic Graft Patency at Follow-Up. *Ann Thorac Surg*. 2016;101:1996-2006.
17. Becit N, Erkut B, Ceviz M, Unlu Y, Colak A, Kocak H. The impact of intraoperative transit time flow measurement on the results of on-pump coronary surgery. *European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery*. 2007;32:313-318.

18. Niclauss L. Techniques and standards in intraoperative graft verification by transit time flow measurement after coronary artery bypass graft surgery: a critical review. *European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery*. 2017;51:26-33.
19. Aldea GS, Bakaeen FG, Pal J, et al. The Society of Thoracic Surgeons Clinical Practice Guidelines on Arterial Conduits for Coronary Artery Bypass Grafting. *Ann Thorac Surg*. 2016;101:801-809.
20. Vandembroucke JP, von Elm E, Altman DG, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. *PLoS Med*. 2007;4:e297.
21. Netherlands Heart Registry (NHR). Netherlands Heart Registry (NHR) Annual Report 2019/2020.
22. Chen ML, Mo YH, Wang YC, et al. 64-slice CT angiography for the detection of functionally significant coronary stenoses: comparison with stress myocardial perfusion imaging. *The British journal of radiology*. 2012;85:368-376.
23. Nallamothu BK, Spertus JA, Lansky AJ, et al. Comparison of clinical interpretation with visual assessment and quantitative coronary angiography in patients undergoing percutaneous coronary intervention in contemporary practice: the Assessing Angiography (A2) project. *Circulation*. 2013;127:1793-1800.
24. Netherlands Heart Registry (NHR). Handbook v2018.0.4. Utrecht, the Netherlands 2018.
25. Honda K, Okamura Y, Nishimura Y, et al. Graft flow assessment using a transit time flow meter in fractional flow reserve-guided coronary artery bypass surgery. *The Journal of thoracic and cardiovascular surgery*. 2015;149:1622-1628.
26. Amin S, Madsen PL, Werner RS, Krasopoulos G, Taggart DP. Intraoperative flow profiles of arterial and venous bypass grafts to the left coronary territory. *European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery*. 2019;56:64-71.
27. Jokinen JJ, Werkkala K, Vainikka T, Perakyla T, Simpanen J, Ihlberg L. Clinical value of intraoperative transit-time flow measurement for coronary artery bypass grafting: a prospective angiography-controlled study. *European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery*. 2011;39:918-923.
28. Di Giammarco G, Canosa C, Foschi M, et al. Intraoperative graft verification in coronary surgery: increased diagnostic accuracy adding high-resolution epicardial ultrasonography to transit-time flow measurement. *European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery*. 2014;45:e41-45.
29. Singh SK, Desai ND, Chikazawa G, et al. The Graft Imaging to Improve Patency (GRIIP) clinical trial results. *The Journal of thoracic and cardiovascular surgery*. 2010;139:294-301, 301 e291.

Supplements

Supplementary tables

Supplemental Table 1 Coronary artery lesion characteristics based on quantitative coronary assessment

Variable	Overall (n = 50)	Without left main stenosis (n = 35)*
LAD reference diameter, mm	3.0 ± 0.66	3.1 ± 0.68
LAD stenosis diameter, mm	1.3 ± 0.52	1.2 ± 0.49
LAD stenosis, length, mm	13 ± 5.8	13 ± 5.9
LAD stenosis, %	58 ± 15	62 ± 12
Left Main stenosis, %	56 ± 17	-
Fractional Flow Reserve (n = 17)	0.68 ± 0.08	0.69 ± 0.10

* As determined by heart team discussion. Values are expressed as mean ± SD

LAD = Left anterior descending coronary artery

Supplemental Table 2 TTFM parameters and linear mixed model results for stratification based on QCA stenosis

Variable	Overall n = 50		Without left main stenosis n = 35	
	LAD open vs LAD snared	LAD open vs LAD snared, stratified to QCA groups*	LAD open vs LAD snared	LAD open vs LAD snared, stratified to QCA groups*
Mean LIMA graft flow, mL/min	-10 (-12 to -8), p < 0.001	p = 0.18	-9.1 (-11 to -6.8), p < 0.001	p = 0.53
Pulsatile index	1.1 (0.78 to 1.3), p < 0.001	0.70 (0.15 to 1.25), p = 0.04†	1.2 (0.85 to 1.6), p < 0.001	p = 0.05
Diastolic filling, %	p = 0.93	p = 0.09	p = 0.74	p = 0.18
Backflow, %	3.6 (2.6 to 4.7), p < 0.001	p = 0.18	4.4 (3.0 to 5.9), p < 0.001	p = 0.26
Peak systolic flow, mL/min	-6.9 (-12 to -2.1), p = 0.006	p = 0.34	-7.4 (-11 to -3.5), p = 0.001	p = 0.74
Peak diastolic flow, mL/min	-11 (-17 to -6), p < 0.001	p = 0.12	-9.2 (-15 to -3.4), p = 0.003	p = 0.26

* QCA groups < 50% LAD stenosis, 50 to 70% and > 70%

† Post-hoc analysis revealed a significant difference between 50 to 70% stenosis and >70% stenosis, p = 0.01

P values are estimates of fixed effects in a linear mixed model with maximum likelihood. Values are expressed as estimate of fixed effects (95% confidence interval).

QCA = Quantitative coronary analysis; LAD = Left anterior descending coronary artery;

LIMA = Left internal mammary artery; TTFM = Transit time flow measurements

Supplemental Table 3.1 Left coronary artery lesion characteristics objectified with QCA

Variable	Overall (n = 36)	Without LM stenosis (n = 23)*
LAD reference diameter, mm	3.1 ± 0.62	3.2 ± 0.62
LAD stenosis diameter, mm	1.4 ± 0.50	1.28 ± 0.49
LAD stenosis, length, mm	13 ± 4.9	13 ± 4.9
LAD stenosis (%)	56 ± 15	60 ± 12
LM stenosis (%)	52 ± 16	-
Fractional flow reserve (n = 14)	0.68 ± 0.08	0.67 ± 0.09

* As determined by heart team discussion

QCA = Quantitative coronary analysis; LAD = Left anterior descending coronary artery;

LM = Left main coronary artery

Supplemental Table 3.2 Perioperative measurements of graft flow in closed vs snared LAD (n = 36)

Variable	LAD, open	LAD, snared	P value
Heartrate, per minute	63 [56 – 73]	63 [55 – 632]	0.19
Systolic blood pressure, mm Hg	101 [91 – 109]	101 [93 – 111]	0.84
Diastolic blood pressure, mm Hg	51 ± 8.6	50 ± 8.6	0.43
Mean Arterial Pressure, mm Hg	67 ± 9.6	66 ± 9.7	0.71
Acoustic Coupling Index, %	58 ± 15	54 ± 15	0.21
TTFM parameters and clinical cut-off values			
Mean graft flow, mL/min	22 [15 – 34]	33 [24 – 44]	< 0.001
Mean graft flow ≤ 20 mL/min	17 (47)	7 (19)	0.002
Mean graft flow ≤ 15 mL/min	10 (28)	3 (8)	0.02
Pulsatile index	3 [2.2 – 4.1]	2.1 [1.7 – 2.6]	< 0.001
Pulsatile index ≥ 3	19 (53)	5 (14)	1.00
Diastolic filling, %	73 ± 6.8	73 ± 6.4	0.73
Diastolic filling < 50%	0 (0)	0 (0)	1.000
Backflow, %	4.5 [1.9 – 8.9]	0.55 [0.0 – 2.3]	< 0.001
Backflow > 3%	21 (60)	7 (20)	0.03
Peak systolic flow, mL/min (n = 19)	31 [19 – 51]	39 [27 – 54]	0.16
Peak diastolic flow, mL/min	45 [32 – 70]	59 [39 – 81]	0.02
Mean graft flow ≤ 15 mL/min and PI ≥ 3	7 (19)	1 (3)	0.19

LAD = Left anterior descending coronary artery; TTFM = Transit time flow measurements

Supplemental Table 3.3 TTFM parameters and linear mixed model results for stratification based on QCA stenosis (n = 36)

Variable	LAD open vs LAD snared	LAD open vs LAD snared, stratified to QCA groups*
Mean LIMA graft flow, mL/min	-9.9 (-13 to -7.2), p < 0.001	p = 0.27
Pulsatile Index	1.1 (0.74 to 1.4), p < 0.001	p = 0.08
Diastolic Filling, %	p = 0.72	p = 0.04†
Backflow, %	3.0 (2.7 to 5.3), p < 0.001	p = 0.15
Peak systolic flow, mL/min	p = 0.11	p = 0.41
Peak diastolic flow, mL/min	-9.8 (-17 to -2.6), p = 0.009	p = 0.22

* QCA groups < 50% LAD stenosis, 50 to 70% and > 70%

† Post-hoc analysis revealed a significant difference between < 50% stenosis and > 70% stenosis, p = 0.01

P values are estimates of fixed effects in a linear mixed model with maximum likelihood. Values are expressed as estimate of fixed effects (95% confidence interval)

Supplemental Table 4 TTFM parameters of a patient with myocardial infarction 30 days after off-pump coronary artery bypass grafting

Lesion characteristics as determined with QCA		
LAD reference diameter, mm		3.6
LAD stenosis diameter, mm		2.4
LAD stenosis, length, mm		14
LAD stenosis, %		34%
TTFM parameters	LAD, open	LAD, snared
Mean LIMA graft flow, mL/min	9	20
Pulsatile index	4.6	2.2
Diastolic filling, %	74	69
Backflow, %	11	1.2
Peak systolic flow, mL/min	N/A	N/A
Peak diastolic flow, mL/min	24	38

QCA = Quantitative coronary analysis; LAD = Left anterior descending coronary artery; LIMA = Left internal mammary artery; TTFM = Transit time flow measurements

Supplementary figures

Supplemental Figure 1 Scatterplots of preoperative coronary stenosis assessment with **A** Visual evaluation vs QCA; **B** FFR vs QCA; **C** Visual evaluation vs FFR. QCA = Quantitative coronary analysis; FFR = Fractional flow reserve; LAD = Left anterior descending coronary artery

Supplemental figure 2 Kaplan-Meier survival curve after off-pump coronary artery bypass grafting

Supplemental figure 3 Intraoperative transit time flow measurements of a 83 year old patient with postoperative myocardial infarction

CHAPTER 4

USE OF THE RADIAL ARTERY AS ACCESS FOR CORONARY ANGIOGRAPHY AND AS A BYPASS CONDUIT: A CLINICAL DILEMMA

Submitted

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Abbreviations and acronyms

CABG	Coronary artery bypass grafting
EACTS	European Association for Cardio-Thoracic Surgery
ESC	European Society of Cardiology
LAD	Left anterior descending coronary artery
LIMA	Left internal mammary artery
PCI	Percutaneous Coronary Intervention

Abstract

Purpose

Recent European guidelines recommend both transradial access for coronary angiography and intervention as well as use of the radial artery as a conduit for coronary artery bypass grafting (CABG). These recommendations may pose a clinical dilemma, as transradial access exposes these arteries to vascular trauma which makes them potentially unsuitable as future grafts. In this study, we investigated the awareness and views of cardiologists on these guideline recommendations.

Methods

We performed semi-structured interviews with 50 Dutch cardiologists from 19 centres, who regularly perform coronary angiographies, and outlined clinical scenarios to evaluate their preference of vascular access. In addition, we assessed whether preference was related to sub-specialisation.

Results

The interviewed cardiologists had a work experience of 16 ± 9.3 years. There were 23 (46%) cardiologists from 7 centres without percutaneous coronary intervention facilities, and 27 (56%) from 12 interventional centres. All 50 (100%) cardiologists indicated familiarity with the guidelines, yet 28 (56%) said not to be familiar with the aforementioned dilemma, and 9 (18%) stated there was no dilemma at all. Responses did not differ significantly between interventional ($n = 28$) and non-interventional ($n = 22$) cardiologists; however, if the right radial artery was unavailable (e.g., occluded), interventional cardiologists more often than non-interventional cardiologists said to prefer access via the left radial artery (18 [64%] vs 5 [23%], $p = 0.001$).

Conclusion

More than half of the cardiologists said not to realise that left transradial access preceding CABG may preclude later use of this artery as a conduit. Notably, in case of unavailability of the right radial artery, interventional cardiologists preferred left transradial access more often than non-interventional cardiologists.

Introduction

The 2018 European guidelines for myocardial revascularisation recommend radial vascular access as a standard approach for coronary angiography and percutaneous coronary intervention (PCI) [1, 2]. Studies have shown clear benefits of radial over femoral access, including a lower risk of mortality and major bleeding [3-5]. The *right* radial artery is most commonly used for vascular access, as operators generally stand on the right-hand side of their patient. But *left* radial artery access may be required in case of challenging *right* radial artery anatomies, spasm or occlusion, or for left internal mammary artery (LIMA) graft visualisation.

However, the radial artery is also recommended for use as a conduit for coronary artery bypass grafting (CABG) for cardiothoracic surgeons (Figure 1). In terms of surgical revascularisation, European guidelines recommend the use of an internal mammary artery to the left anterior descending artery (LAD), followed by the use of a second arterial graft that may either be a radial artery or the contralateral internal mammary artery [1]. As in some patients the use of bilateral internal mammary artery grafting has been associated with an increased risk of post-procedural complications [6, 7], use of the radial artery – most often the *left* radial artery – is a suitable option. There is substantial variation between countries in radial artery use as a conduit for CABG, for example, between 2004 to 2014 it was 5% in the United States of America and 45% in Australia [8]. However, with recently published results of a large randomised trial showing excellent long-term outcomes after use of radial artery bypass grafts [9, 10], its use is likely to become increasingly common in the near future.

Notably, current guidelines discourage the use of a radial artery as bypass conduit after recent coronary angiography through that vessel [1], as the two options of using the radial artery interfere with each other. Transradial coronary procedures expose the artery to some degree of vascular trauma, which may still be present after months [11-13] and may reduce bypass graft patency [14, 15]. Consequently, a radial artery is less suitable (or even unsuitable) as a bypass conduit following a recent transradial procedure. Thus, in a scenario in which both radial arteries have been used for vascular access and CABG is required at a later stage, a patient may lose the option of receiving a radial artery bypass graft.

Yet, it is unknown (1) how often a percutaneous intervention via the *left* radial approach precedes CABG, (2) how cardiologists deal with the problem of having multiple options for use of the radial artery that mutually exclude each other, and (3) to what extent cardiologists are aware of the new 2018 European guidelines for myocardial revascularisation. Therefore, we assessed in a database of our tertiary centre for cardiac intervention the frequency of coronary angiography or PCI via *left* transradial approach followed by CABG. In addition, we performed semi-structured interviews with a total of 50 Dutch cardiologists to investigate their awareness of the outlined potential 'dilemma' and to evaluate their preference of vascular access in outlined scenarios.

2018 ESC/EACTS recommendations	Class of recommendation	Level of evidence
Recommendation on access site		
Radial access is recommended as the standard approach, unless there are overriding procedural considerations.	I	A
Recommendations on conduit selection		
Arterial grafting with internal mammary artery to the LAD system is recommended.	I	B
An additional arterial graft should be considered* in appropriate patients.	IIa	B
The use of the radial artery is recommended over the saphenous vein in patients with high-grade coronary artery stenosis.	I	B
* The radial artery should not be used if previously catheterised, if the Allen test is positive or if calcific degeneration is present.		

Figure 1 Recommendations on access site and conduit selection extracted from the 2018 ESC/EACTS guidelines on myocardial revascularisation (modified from [1]).

EACTS = European Association for Cardio-Thoracic Surgery;

ESC = European Society of Cardiology

Methods

A retrospective analysis was conducted on transradial vascular access for coronary angiography or PCI, and use of radial artery grafts for CABG, performed from 2008 to 2018 at a tertiary centre for cardiac interventions (Thoraxcentrum Twente, Enschede, the Netherlands). First, all percutaneous coronary procedures (coronary angiography or PCI) with corresponding vascular access route, as well as all isolated CABG procedures, were extracted from clinical patient files. Second, a case-by-case review was conducted for all patients who received CABG after catheter-based *left* transradial procedures. In addition, we searched in clinical files for information about potential graft dysfunction during a follow-up period from January 1st 2008 to January 1st 2019.

Furthermore, a prospective semi-structured interview study was performed. Dutch cardiologists were approached by e-mail, telephone and during personal contact by two cardiologists of Thoraxcentrum Twente, Enschede, the Netherlands. Cardiologists were eligible if they regularly performed coronary angiographies. Semi-structured interviews were performed with the participants between April and June 2019. Three clinical cases were outlined, investigating the cardiologist's preference of vascular access. Cases were designed to stimulate the cardiologist with increasing persuasiveness to consider preserving the *left* radial artery as a conduit for future CABG.

Statistical methods

For statistical analysis, participants were grouped by subspecialisation (i.e. interventional cardiologist versus non-interventional cardiologist). Statistical analysis was performed with SPSS 25.0 (SPSS Inc, Chicago, IL). Results were considered statistically significant at a p-value of 0.05. Continuous variables were presented as mean with standard deviation or median with interquartile range, depending on the distribution. All continuous variables were tested for normality with visual inspection of histograms and skewness and kurtosis measures. A Mann-Whitney U test was done for comparisons between groups. Categorical variables were presented as numbers with corresponding frequencies. Categorical variables were compared using Chi-square or Fischer's Exact Test, as

appropriate. In case of multiple testing, a post hoc Holm-Bonferroni correction was performed.

Results

Retrospective analysis

From January 2016 on, there was an explicit change in the preferential route of vascular access. While from January 2008 to December 2015 diagnostic and therapeutic coronary interventions were performed via transradial access in no more than 22% of all procedures, the transradial access rate was 78% from January 2016 to December 2018 ($p < 0.001$). Table 1 presents data on procedures at Thoraxcentrum Twente that involved the radial artery for vascular access or as conduit for CABG, separately showing frequencies for procedures that were performed during the entire study period as well as from 2008 – 2015 and from 2016 – 2018.

Left transradial access prior to CABG increased from 0.3% in 2008 – 2015 to 2.4% in 2016 – 2018. Similarly, the frequency of bilateral transradial access prior to CABG increased from 0.2% in 2008 – 2015 to 1.4% in 2016 – 2018. Nine patients, who received a radial artery conduit during CABG surgery, had prior transradial procedures through this vessel. One (11%) of these patients experienced radial graft dysfunction resulting in repeated CABG.

Table 1 Procedures involving the radial artery for vascular access or as conduit for CABG at our centre

	2008 – 2018	2008 – 2015	2016 – 2018	p value
All percutaneous coronary procedures (angiography and PCI)	36,631	26,419	10,212	
via transradial access	13,782 (37)	5,773 (22)	8,009 (78)	< 0.001
via <i>left</i> transradial access	1,309 (3.5)	783 (3.0)	526 (5.2)	< 0.001
All isolated CABG	5,800	4,320	1,480	
Isolated CABG using a radial artery as conduit	2,520 (43)	1,817 (42)	703 (48)	< 0.001
Isolated CABG after coronary angiography with known access route*	3,161	2,286	875	
<i>Left</i> transradial access prior to CABG (including bilateral access)	31 (1.0)	10 (0.3)	21 (2.4)	< 0.001
<i>Bilateral</i> transradial access preceding CABG	18 (0.6)	6 (0.2)	12 (1.4)	< 0.001
Use of radial artery as conduit after transradial access of this artery†	9 (0.3)	1 (0.04)	8 (0.9)	< 0.001

Numbers are n (%)

* Access route was unknown for patients who were referred for isolated CABG from a different hospital

† From 2008 – 2015 1 *left* radial artery with prior transradial access was used as a conduit, from 2016 – 2018 7 *left* radial arteries and 1 *right* radial artery with prior transradial access were used as a conduit

CABG = Coronary artery bypass grafting; PCI = Percutaneous coronary intervention

Interviews

A total of 72 Dutch cardiologists were approached, of whom 51 agreed to participate (response rate: 71%). One cardiologist did not perform coronary angiography and was therefore excluded. Thus, semi-structured interviews were performed with 50 cardiologists from 19 centres. Hospitals ranged from secondary centres without PCI facilities to academic centres. An overview of the centres’ geographic locations and settings is depicted in Figure 2. Key characteristics of the interviewed cardiologists are presented in Table 2.

Table 2 Characteristics of interviewed cardiologists (n = 50)	
Age, years	51 [41 – 58]
Experience as cardiologist, years	16 ± 9.3
Interventional cardiologist	28 (56)
Number of annual coronary procedures	300 [144 – 505]
Hospital type	
Academic	9 (18)
Tertiary with cardiac surgery	11 (22)
Secondary with PCI	7 (14)
Secondary with coronary angiography	23 (46)
Personal preference for radial access, %	90% [90 – 95]
Observed increase in radial access in past 5 – 10 years in own centre	
Yes	39 (78)
No	4 (8)
Employed in current centre for < 5 years	7 (14)
Personal preference for catheter size	
4 French	3 (6)
5 French	14 (28)
6 French	29 (58)
Other*	4 (8)

Numbers are n (%), mean ± standard deviation or median [inter quartile range]
* Other includes “both”, “depending on patient characteristics” and “don’t know”
PCI = Percutaneous coronary intervention

Case 1: Preferred vascular access route for PCI in a 60-year-old patient

A clinical case was introduced of a relatively young patient who required PCI. Cardiologists were asked about their preference for vascular access. All cardiologists preferred using the *right* radial artery (100%). The main reasons for this choice were convenience of vascular access (82%) followed by a reduction in bleeding risk (Supplementary Table 1). None of the interviewed cardiologists mentioned quality of the *left* radial artery as a possible conduit for future CABG.

Case 2: Preferred vascular access for PCI in a 60-year-old patient with non-availability of the *right* radial artery

The second case narrowed options for vascular access, as the *right* radial artery was (temporarily) unavailable in the same 60-year-old patient. Most cardiologists preferred the *left* radial artery (46%) over the femoral artery (36%). The most common motivation for preferring *left* transradial access was reduced bleeding risk, while the most common motivation for transfemoral access was technical setup of the catheterisation laboratory.

Figure 2 Geographical distribution of hospitals of the interviewed cardiologists ($n = 50$)

In 18% of all cardiologists, the patient's preference or situational context determined their choice of vascular access (Table 3). Interventional cardiologists preferred *left* transradial access significantly more often than non-interventional cardiologists ($p = 0.001$).

Case 3: Preferred access route in a 60-year-old patient with 3-vessel disease and previous CABG

The third case further closed in on considering to preserve the *left* radial artery for CABG. A 60-year-old patient with 3-vessel disease and a previous CABG with a *left* internal mammary artery (LIMA) graft on the LAD and a saphenous vein graft was presented. The *right* radial artery was not accessible, and non-invasive myocardial perfusion imaging showed multiple reversible perfusion defects indicating a reasonable likelihood of a potential need for repeating CABG.

The majority of participants (58%) still chose the *left* radial access for coronary angiography due to its convenience for visualising the LIMA graft. A smaller proportion of the participants chose a femoral artery for vascular access because of convenient visualisation of the grafts (36%). Only four cardiologists (8%) mentioned preserving the radial artery as a possible conduit for CABG in favour of using the transfemoral approach. In 6% of the participants, patient preference or situational context determined the preferred vascular access route (Table 3).

Table 3 Responses of interviewed cardiologists on preference for vascular access site and familiarity with ESC guidelines on myocardial revascularisation

	Total group n = 50	Interventional cardiologists n = 28	Non- interventional cardiologists n = 22	p value
Case 1: Preferred access route for PCI in a 60-year-old patient				
<i>Right</i> radial artery	50 (100)	28 (100)	22 (100)	
Case 2: Preferred access route for PCI in a 60-year-old patient except <i>right</i> radial artery				
Vascular access route				< 0.001
<i>Left</i> radial artery	23 (46)	18 (64)	5 (23)	
Femoral artery	18 (36)	4 (14)	14 (64)	
Depends on patient preference or situational context	9 (18)	6 (21)	3 (14)	
Case 3: Preferred access route in a 60-year-old patient with three vessel disease and previous CABG				
Vascular access route				0.09
<i>Left</i> radial artery	29 (58)	18 (64)	11 (50)	
Femoral artery	18 (36)	7 (25)	11 (50)	
Depends on patient preference or situational context	3 (6)	3 (11)	0	
Familiarity with 2018 ESC/EACTS guidelines on myocardial revascularisation				
Yes, familiar with guidelines	50 (100)	28 (100)	22 (100)	1.00
Yes, familiar with details on radial access and graft preference	22 (44)	13 (46)	9 (41)	0.70
Familiar with clinical dilemma in guidelines				0.89
Yes	13 (26)	8 (29)	5 (23)	
This is no dilemma	9 (18)	5 (18)	4 (18)	
Not familiar with this dilemma	28 (56)	15 (54)	13 (59)	
Estimated percentage of dilemma in own hospital (n = 32)	3% [0.5 – 5%]	3% [0 – 5%]	3% [0.5 – 5%]	0.48
Personal experience with problem	5 (10)	3 (11)	2 (9)	0.85
Change of vascular access after this interview				0.18
Yes	18 (36)	12 (43)	6 (27)	
No	27 (54)	12 (43)	15 (68)	
Unclear	5 (10)	4 (14)	1 (5)	

Numbers are n (%)

CABG = Coronary artery bypass grafting; ESC = European Society of Cardiology;

EACTS = European Association of Cardio-Thoracic Surgery;

PCI = Percutaneous coronary intervention

There was no significant difference between interventional cardiologists and non-interventional cardiologists in choosing a different access route (64% vs 50%, $p = 0.09$). Participants who indicated at the very start of the interview to have a particularly strong preference ($> 90\%$) for the transradial approach were in this case more likely to choose *left* radial access as compared to all other participants (79% vs 39%, $p < 0.001$).

Familiarity with 2018 ESC/EACTS guidelines on myocardial revascularisation

The last part of the interview reflected on familiarity with the 2018 ESC/EACTS guidelines on myocardial revascularisation [1]. All cardiologists indicated to be familiar with these guidelines but less (44%) were familiar with all details about the recommended vascular access route and use of arterial grafts. A minority of cardiologists was familiar with the clinical dilemma of having multiple options for using the radial artery that mutually exclude each other (26%), while 18% felt that there was no dilemma at all. There was no difference between interventional or non-interventional cardiologists (Table 3, $p = 0.89$).

While only 10% of all participants indicated that they had personal experience with the aforementioned dilemma, 36% said that they would change vascular access after this interview in order to preserve the (*left*) radial artery for CABG in selected patients.

Figure 3 provides a flowchart which illustrates how to consider preserving the radial artery as a bypass conduit when deciding on a vascular access route for percutaneous coronary procedures.

Figure 3 Cath lab flowchart on transradial artery access for daily use.
*e.g. when LIMA needs to be visualised
† Carefully considering bleeding risk, peripheral vascular disease, accessibility of femoral artery and operator's experience. CABG = coronary artery bypass grafting;
LIMA = left internal mammary artery; PCI = percutaneous coronary intervention; RA = radial artery

Discussion

During the entire period from 2008 to 2018, transradial coronary procedures preceded use of the radial artery as a bypass conduit in no more than 9 (0.3%) of all 3,161 patients, who underwent CABG at our centre. With the recent recommendation of transradial vascular access for percutaneous coronary procedures, this issue is likely to be increasingly common. Indeed, 8 of these 9 patients were treated during the last 3 years of the entire 10-year period. One (11%) of these patients experienced radial graft dysfunction that required repeating CABG. Thus far, no data has been published on inter-centre variability in the Netherlands of transradial access preceding radial artery use as a bypass conduit for CABG.

All 50 interviewed cardiologists indicated that *right* transradial access was their first choice for percutaneous coronary angiography and PCI. This choice was mainly based on a reduction in bleeding risk and an increase in convenience. If the *right* radial artery was not available for vascular access, most cardiologist preferred using *left* transradial access. In absence of an accessible *right* radial artery, interventional-cardiologists showed a particular preference for using the *left* radial artery, whereas non-interventional cardiologists more frequently chose transfemoral access. If the interviewed cardiologists had to perform a coronary angiography on a patient with previous CABG including LIMA and vein grafts and a high likelihood of requiring a repeated CABG, the majority still preferred using the *left* radial artery for vascular access.

When asked about familiarity with the guidelines, 44% of the cardiologists indicated to be familiar with all details of the recommended vascular access route and arterial grafts. One in four cardiologists had realised the conflicting guideline recommendations on radial artery use before the interview. Moreover, after the interview, one in three cardiologists indicated (in specific cases) to be willing to use a vascular access site different from the *left* radial artery to preserve this vessel for potential use as a bypass conduit.

Previous research

Previous studies that investigated radial arteries following transradial coronary procedures observed severe functional and morphological vascular damage [16] that sometimes even deteriorated over time [17, 18]. Catheter-induced morphological alterations such as intimal tears and medial dissections may cause intimal hyperplasia and adventitia inflammation that can lead to a reduction in radial artery lumen [15]. Two observational studies showed that such histological findings also translated into inferior clinical outcomes, as they found radial artery graft patency was reduced following transradial catheterisation (of that artery) [19, 20].

A systematic review suggested that smaller catheter size, use of high dose heparin, and shorter duration of post-procedural compression of the radial artery can decrease the risk of radial artery occlusion after cardiac catheterisation. However, it is unclear whether these factors also have an impact on later radial artery graft patency [21].

The available evidence suggests that the use of transradial vascular access for percutaneous coronary procedures may preclude future use of that vessel as a bypass graft. A recent expert opinion paper recommended cardiologists to consider using the

femoral artery instead of the radial artery for coronary angiography in patients who might be eligible for future CABG in centres that routinely use radial artery bypass grafts [22], while others suggested to reduce catheter size [23]. This was also addressed in a 2016 scientific manuscript [16], which advised cardiologists to weigh the benefits of the transradial approach against the risk of damaging the radial artery when choosing the access site for percutaneous coronary procedures.

Yet, among the cardiologists in our study, awareness of this issue still appears to be limited. The common use of transradial percutaneous coronary procedures and the current rise in using radial artery grafts for CABG [24] may more frequently result in a conflicting use of the radial artery. This, in turn, may reduce the patency of radial artery bypass grafts, which can lead to serious complications and inferior clinical outcomes.

Limitations

As a result of the study design, convenience sampling cannot be excluded. Nevertheless, while some interviewed cardiologists from general hospitals refer patients to our centre, other independent tertiary centres for cardiac interventions including academic hospitals are well-represented in this sample. Therefore, the potential bias for the total group may be limited.

Although the clinical cases reflect clinical practice, we cannot exclude that other cases might have given other results. These three cases are meant to create three levels of awareness for preserving the (*left*) radial artery and were framed to receive authentic answers for each case. Interviewing cardiothoracic surgeons might broaden the view on this issue and could be addressed by future studies.

Conclusion

More than half of the interviewed cardiologists said not to realise that *left* transradial access preceding CABG may preclude later use of this artery as a conduit. Notably, in case of unavailability of the *right* radial artery, interventional cardiologists preferred *left* transradial access more often than non-interventional cardiologists.

Conflict of interest

There was no conflict of interest related to the present study. Outside this research, Thoraxcentrum Twente has received institutional research grants from Abbott Vascular, Biotronik, Boston Scientific and Medtronic.

References

1. Neumann FJ, Sousa-Uva M, Ahlsson A, et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. *Eur Heart J*. 2019;40:87-165.
2. Rao SV, Cohen MG, Kandzari DE, Bertrand OF, Gilchrist IC. The transradial approach to percutaneous coronary intervention: historical perspective, current concepts, and future directions. *Journal of the American College of Cardiology*. 2010;55:2187-2195.
3. Valgimigli M, Gagnor A, Calabro P, et al. Radial versus femoral access in patients with acute coronary syndromes undergoing invasive management: a randomised multicentre trial. *Lancet*. 2015;385:2465-2476.
4. Joyal D, Bertrand OF, Rinfret S, Shimony A, Eisenberg MJ. Meta-analysis of ten trials on the effectiveness of the radial versus the femoral approach in primary percutaneous coronary intervention. *The American journal of cardiology*. 2012;109:813-818.
5. Romagnoli E, Biondi-Zoccai G, Sciahbasi A, et al. Radial versus femoral randomized investigation in ST-segment elevation acute coronary syndrome: the RIFLE-STEACS (Radial Versus Femoral Randomized Investigation in ST-Elevation Acute Coronary Syndrome) study. *Journal of the American College of Cardiology*. 2012;60:2481-2489.
6. Dai C, Lu Z, Zhu H, Xue S, Lian F. Bilateral internal mammary artery grafting and risk of sternal wound infection: evidence from observational studies. *Ann Thorac Surg*. 2013;95:1938-1945.
7. Taggart DP, Benedetto U, Gerry S, et al. Bilateral versus Single Internal-Thoracic-Artery Grafts at 10 Years. *The New England journal of medicine*. 2019;380:437-446.
8. Schwann TA, Tatoulis J, Puskas J, et al. Worldwide Trends in Multi-arterial Coronary Artery Bypass Grafting Surgery 2004-2014: A Tale of 2 Continents. *Seminars in thoracic and cardiovascular surgery*. 2017;29:273-280.
9. Gaudino M, Benedetto U, Fremes S, et al. Radial artery versus saphenous vein for coronary artery bypass surgery at long-term follow-up. *American College of Cardiology (ACC) 2020*2020.
10. Gaudino M, Benedetto U, Fremes S, et al. Radial-Artery or Saphenous-Vein Grafts in Coronary-Artery Bypass Surgery. *The New England journal of medicine*. 2018;378:2069-2077.
11. Gaudino M, Leone A, Lupascu A, et al. Morphological and functional consequences of transradial coronary angiography on the radial artery: implications for its use as a bypass conduit. *European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery*. 2015;48:370-374.
12. Batchelor W, Dahya V, Tehrani B, et al. Radial artery remodeling following transradial percutaneous coronary intervention in men and women: insights from serial ultrahigh frequency ultrasonography. *Cardiovasc Revasc Med*. 2019.
13. Lim LM, Galvin SD, Javid M, Matalanis G. Should the radial artery be used as a bypass graft following radial access coronary angiography. *Interactive cardiovascular and thoracic surgery*. 2014;18:219-224.
14. Tatoulis J, Schwann TA. Long term outcomes of radial artery grafting in patients undergoing coronary artery bypass surgery. *Ann Cardiothorac Surg*. 2018;7:636-643.
15. Dragasis S, Liakos CI, Kafkas N. Radial artery as a graft for coronary artery bypass surgery in the era of transradial catheterization. *Hellenic J Cardiol*. 2018;59:150-154.
16. Mounsey CA, Mawhinney JA, Werner RS, Taggart DP. Does Previous Transradial Catheterization Preclude Use of the Radial Artery as a Conduit in Coronary Artery Bypass Surgery? *Circulation*. 2016;134:681-688.
17. Yan Z, Zhou Y, Zhao Y, Zhou Z, Yang S, Wang Z. Impact of transradial coronary procedures on radial artery function. *Angiology*. 2014;65:104-107.

18. Burstein JM, Gidrewicz D, Hutchison SJ, Holmes K, Jolly S, Cantor WJ. Impact of radial artery cannulation for coronary angiography and angioplasty on radial artery function. *The American journal of cardiology*. 2007;99:457-459.
19. Kamiya H, Ushijima T, Kanamori T, et al. Use of the radial artery graft after transradial catheterization: Is it suitable as a bypass conduit? *Ann Thorac Surg*. 2003;76:1505-1509.
20. Ruzieh M, Moza A, Siddegowda Bangalore B, Schwann T, Tinkel JL. Effect of Transradial Catheterisation on Patency Rates of Radial Arteries Used as a Conduit for Coronary Bypass. *Heart Lung Circ*. 2017;26:296-300.
21. Rashid M, Kwok CS, Pancholy S, et al. Radial Artery Occlusion After Transradial Interventions: A Systematic Review and Meta-Analysis. *J Am Heart Assoc*. 2016;5.
22. An KR, Tam DY, Gaudino MFL, Fremes SE. Radial arteries for coronary angiography and coronary artery bypass surgery: Are two arteries enough? *The Journal of thoracic and cardiovascular surgery*. 2019;157:573-575.
23. Bernat I, Aminian A, Pancholy S, et al. Best Practices for the Prevention of Radial Artery Occlusion After Transradial Diagnostic Angiography and Intervention: An International Consensus Paper. *JACC Cardiovasc Interv*. 2019;12:2235-2246.
24. Gaudino M, Taggart D, Suma H, Puskas JD, Crea F, Massetti M. The Choice of Conduits in Coronary Artery Bypass Surgery. *Journal of the American College of Cardiology*. 2015;66:1729-1737.

Supplements

Supplementary Table 1

Supplementary Table 1 Preferred access route for PCI in a 60-year old patient	
Case 1: Vascular access route for PCI in a 60-year-old patient	
Right radial artery	50 (100%)
Reason to choose for <i>right</i> radial artery (multiple options)	
Easy access	41 (82%)
To reduce bleeding risk	22 (44%)
To increase patient comfort	12 (24%)
Because of training	10 (20%)
To increase early mobilisation	8 (16%)
Age of patient	1 (2%)
Possible challenges for <i>right</i> radial artery access (multiple options)	
Complicated vascular access	16 (32%)
Size of radial artery	11 (22%)
Spasm of radial artery	17 (34%)
Age of patient	7 (12%)
Gender of patient	10 (20%)
Profession of patient	7 (14%)
Favouring <i>right</i> over <i>left</i> radial artery	
Favours <i>right</i> over <i>left</i> radial artery	40 (80%)
Favours because of cathlab setup	36 (90%)

PART II

TECHNOLOGICAL INNOVATIONS
IN CARDIO-THORACIC SURGERY

CHAPTER 5

SUPERCRITICAL CARBON DIOXIDE DECELLULARISED PERICARDIUM: MECHANICAL AND STRUCTURAL CHARACTERISATION FOR APPLICATIONS IN CARDIO-THORACIC SURGERY

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Abbreviations and acronyms

BP	Bovine pericardium
CD	Cross direction
DEE	Detergent and enzyme extraction
ECM	Extracellular matrix
E _{mod}	Elastic modulus
Fr-PP	Fresh porcine pericardium
Glut-BP	Glutaraldehyde treated bovine pericardium
MD	Machine direction
PP	Porcine pericardium
scCO ₂	Supercritical carbon dioxide
SEM	Scanning electron microscopy
SIS-ECM	Small intestine-submucosa extracellular matrix
TS	Trypsin
TSD	Sodium-deoxycholate
UTS	Ultimate Tensile Strength

Abstract

Introduction

Many biomaterials are used in cardio-thoracic surgery with good short-term results. However, calcification, dehiscence, and formation of scar tissue are reported. The aim of this research is to characterize decellularised pericardium after supercritical carbon dioxide (scCO₂) processing as an alternative biological material for uses in cardio-thoracic surgery.

Methods

Porcine and bovine pericardium were decellularised using scCO₂. Mechanical properties such as tensile strength, elastic modulus, fracture toughness and suture retention strength were determined. Ultrastructure was visualised using scanning electron microscopy. Water uptake and swelling was experimentally determined. Commercially available glutaraldehyde treated bovine pericardium was used as gold standard for comparison.

Results

scCO₂ decellularised porcine and bovine pericardium maintained their tensile strength compared to untreated native pericardium (13.3 ± 2.4 MPa vs 14.0 ± 4.1 MPa, $p = 0.73$). Tensile strength of glutaraldehyde treated pericardium was significantly higher compared to untreated pericardium (19.4 ± 7.3 MPa vs 10.2 ± 2.2 MPa, $p = 0.02$). Suture retention strength of scCO₂ treated pericardium was significantly higher than glutaraldehyde treated pericardium ($p = 0.01$).

We found no anisotropy of scCO₂ or glutaraldehyde treated pericardium based on a trouser tear test. Ultrastructure was uncompromised in scCO₂ treated pericardium, while glutaraldehyde treated pericardium showed deterioration of extracellular matrix.

Conclusion

scCO₂ processing preserves initial mechanical and structural properties of porcine and bovine pericardium, while glutaraldehyde processing damages the extracellular matrix of bovine pericardium. Decellularisation of tissue using scCO₂ might give long-term solutions for cardio-thoracic surgery without compromising initial good mechanical properties.

Introduction

Many decellularised tissues, such as pericardium or small intestine submucosa, are used in cardio-thoracic surgery as a temporary graft for heart tissue recovery, reconstruction of heart valves and aortic wall, closure of pericardium, and reconstruction of blood vessels (arterioplasty) with good short-term results [1]. These biomaterials provide an interim template to enable patient's own cells to repopulate the repaired tissue and remodel to host tissue.

Specific to cardiac structures, a biomaterial should be pliable, soft, resistant to tearing, calcification and shrinkage, not induce scar tissue, haemostatic, not interfere with patient's growth and not induce a pro-inflammatory response [2]. A specific use of biomaterials is to construct bioprosthetic aortic or mitral valves. These heart valves are made of treated pericardium which consists of a serous membrane (epicardium, or visceral layer), and a fibrous sac (parietal layer) that envelopes the heart [3]. The fibrous parietal layer of pericardium possesses great uniformity in its different regions with multidirectional orientation of collagen fibres [4].

Calcification of current valve prostheses

Last decade, more than half of all aortic valve replacements were biological prostheses made of pericardium, worldwide accounting for 150,000 implantations per year with a shift from mechanical, carbon-based prostheses towards biological heart valves [5]. However, despite its good short term outcome, valve failure based on tissue deterioration and calcification limits the lifetime of the biological prosthesis to 10 – 15 years which necessitate reoperation or results in death in 50 – 60% of the patients [6, 7], resulting in high societal costs. This biomaterial mineralisation is related to age and host metabolism, implant structure and mechanical factors [5].

A better biomimicry is likely to reduce calcification and valve failure. Major causes of calcification are remnant nonviable cells in biomaterials and cytotoxic residues from glutaraldehyde treatment, used to prevent a pro-inflammatory immune response and to restore mechanical properties after chemical decellularisation.

Chemical treatment of pericardium

Decellularisation of tissue reduces immunogenic properties and a wide range of treatments are used to maintain structural and biomechanical integrity of tissues [8]. Detergent and enzyme extraction (DEE), trypsin (TS) and Triton X-100 and sodium-deoxycholate (TSD) methods are commonly used to remove the surface cells. However, mechanical, structural or biological properties are altered in these acidic, detergent and enzymatic decellularisation processes [9, 10].

Low concentration aldehydes, such as glutaraldehyde stabilises pericardium by preventing secondary shrinkage [11]. Major drawbacks however are limited long-term durability due to fixative remnants, free aldehyde groups and phospholipids and lacking removal of animal-specific antigens, causing a chronic inflammation and calcification of pericardium [12-14].

Critical factors for improvement: Decellularisation of tissues

Successful clinical use of decellularised pericardium for cardiovascular applications depends upon preservation of mechanical properties such as ultimate tensile strength (UTS), Elastic modulus (E_{mod}), suture retention strength and fracture toughness. A hypothesised method of gentle decellularisation is supercritical carbon dioxide decellularisation (scCO_2). scCO_2 is an alternative to cytotoxic and calcifying treatments where CO_2 is conditioned above 31.1 °C (304 K) and 73.4 bar (7.3 MPa) to achieve a supercritical phase (Figure 1). scCO_2 is then able to penetrate the tissue, dissolve cells [15] and remove them from tissues. Effective cell removal was observed in porcine aorta [16], but data is lacking about mechanical properties of scCO_2 decellularised porcine and bovine pericardium.

Figure 1 Phase diagram of CO_2 . Focus on supercritical state above 31.1 °C and 73.4 bar. Figure created with data from ChemicalLogic Corporation [17] and optimised for this paper

Many processing purposes are described for scCO_2 including use as (anti)solvent, solute, reagent, supercritical drying of tissues, extraction, cleaning and sterilisation [18]. Where high temperature methods such as steam and autoclave sterilisation are unsuitable for most biomaterials, both gamma irradiation and ethylene oxidation are frequently used [19]. Unfortunately, they also have major drawbacks such as enhanced degradation of biomaterials, cross-linking and cytotoxic residual chemicals [20].

scCO_2 is used in treatment of biomaterials to sterilise in experimental setting at low temperature often in combination with acidic and oxidative reagents [21, 22]. For tendons sterilised with scCO_2 without other processing there was no difference in failure stress between untreated and scCO_2 treated tendons [23], but there is only limited clinical use of scCO_2 treated porcine pericardium [24]. For the purpose of decellularisation (cell removal), biomechanical properties of biomaterials such as pericardium remain uncertain.

Thus, the objective of this study is to characterise ultrastructure and mechanical properties of scCO₂ decellularised porcine and bovine pericardium, in comparison with a commercially available glutaraldehyde treated pericardium for applications in cardio-thoracic surgery. It is expected that better biomimicry reduces the chance of calcification and failure. Therefore, this study also investigates whether scCO₂ pericardium is more similar to native pericardium than currently used chemically treated pericardium.

Materials and methods

Tissue source

Multiple types of pericardium were used in this study: fresh porcine pericardium (Fr-PP), scCO₂ decellularised porcine pericardium (PP), fresh bovine pericardium (Fr-BP), scCO₂ decellularised bovine pericardium (BP), and Peri-Guard® (10 x 16 cm, Synovis Surgical) which is bovine pericardium cross-linked with glutaraldehyde (Glut-BP) and used in many cardio-thoracic procedures. Glut-BP was chemically sterilised by the manufacturer using ethanol and propylene oxide, treated with sodium hydroxide and stored in a storage solution according to manufacturer's instructions [25].

Before testing, Glut-BP was rinsed for a minimum of 10 minutes in physiological saline solution and kept moist at all times. All samples were selected from the anterior pericardium and cut parallel to superficial collagen fibres following visual inspection of the samples. A complete overview on tissues used in each experiment is depicted in Supplementary table 1.

Processing and decellularisation

Fresh porcine pericardia were obtained from the local slaughterhouse, stored in physiological saline solution and manually cleaned of fat and adventitial tissue. Bovine pericardia were purchased from Southern Lights Biomaterials (New Zealand). Both porcine and bovine pericardia in the scCO₂ group were processed with 25 weight% hydrogen peroxide, 1.25 M sodium hydroxide and 0.1 M phosphoric acid and decellularised with scCO₂ at 35 °C (308 K) and 100 bar (10 MPa) for one hour in a Nova 2200 (Novasterilis, U.S.A.) device.

Samples were freeze-dried at manufacturer (European Medical Contract Manufacturing, The Netherlands) in a sublimator (Zirbus, The Netherlands) at -40 °C for 240 minutes, with primary drying at -5°C for 240 minutes and secondary drying at 25 °C for 840 minutes at 0.650 mbar. When applicable, samples were sterilised with a 25 kGy Cobalt-60 source in concordance with ISO protocol 11737.

Scanning electron microscopy (SEM)

PP and BP were freeze-dried using above protocol. Glut-BP was subjected over night to lyophilisation. Scaffolds were sputtered with gold (Cressington, UK) for 40 seconds at 30 mA prior to SEM analysis. Ultrastructure and architecture were characterised by environmental SEM (XL-30 ESEM-FEG, Philips, The Netherlands).

Mechanical testing

Uniaxial tensile testing was performed on Fr-PP, Fr-BP, PP, BP and Glut-BP on a tensile tester (Zwick Z2020, Germany) with a load cell of 0.5 kN, preload of 0.1 N, test speed of 3 mm/min and increased tension until sample failure. Ultimate tensile stress (UTS), strain and elastic modulus (Young's modulus, E_{mod}) were determined. E_{mod} was determined using the slope of the linear region of the tensile stress-strain curve. Here, a high E_{mod} is a measure for a stiff material. Sample dimensions of pericardium were 40 x 20 mm and thickness of pericardium was measured with a digimatic indicator (Mitutoyo, Japan) for each sample in triplicate along the oblique axis and averaged.

Fracture toughness was defined as 'a material's resistance to crack propagation' [26] and was tested in a 'trouser tear test' to determine (an)isotropy of pericardium and calculated by the area under the tensile curve [27, 28]. The tear was propagated parallel to the orientation of collagen fibres (machine direction, MD), perpendicular (cross direction, CD) or at a 45° angle (45).

When applicable, samples were rehydrated for at least 10 minutes in physiological saline solution. For determining suture retention strength, both one and three simple interrupted Prolene 4-0 and 5-0 sutures (Ethicon, U.S.A.) were placed in the pericardium with a suture bite of 5 mm. A test speed of 80 mm/min was used.

Water uptake and swelling

Circular BP with a diameter of 25 mm and PP of 15 mm (20 x 30mm sample) were weighted and diameter was recorded at dry state. Samples were hydrated in physiological saline with measurement of diameter and weight increment over time after gentle blotting of swollen samples on filter paper. Both weight ratio and diameter ratio as measures of swelling were calculated and compared over different time points.

Statistical analysis

The statistical analysis was performed with SPSS 23.0 (SPSS Inc, Chicago, IL). Results were considered statistically significant at the 5% level. Variables were analysed with t-tests for independent samples. Literature results were grouped with a standard deviation (SD) calculated by individual studies and the number of samples tested. For trouser tear, multiple groups were compared using a one-way analysis of variance (ANOVA) and comparison between tissue sources was performed using a two-way ANOVA. An ANOVA for repeated measures was conducted for water uptake. Results are reported as mean $\pm$ SD.

Results

Ultrastructure

SEM analysis of PP (n = 6 from two samples) and BP (n = 4 from 1 sample) identified the parietal serous pericardium as a smooth surface with remnant polygonal mesothelial cell borders still visible without the presence of cells (Figure 2A). Minor disruptive areas of on average 5 μm^2 are present. Fibrous pericardium shows the presence of intact elastin and collagen fibres (Figure 2B). Glut-BP (n = 5 from 1 sample) looked similar to PP and BP, with larger disruptive areas of on average 10 μm^2 (Figure 2C, 2D).

Figure 2 Representative scanning electron microscopy images of BP and Glut-BP. **A, B** Bovine pericardium decellularised with scCO₂. **C, D** Bovine pericardium treated with glutaraldehyde (Peri-Guard®).

Mechanical properties

Fresh and glutaraldehyde treated pericardium

Our stress/strain curve for tensile testing on fresh pericardium is presented in Figure 3A. Fr-PP (n = 6) had a tensile strength of 13.3 (± 2.4 MPa and average thickness of 103 ± 29 µm. No transition at 2% strain was observed. UTS of Fr-BP (n = 5) was 10.2 ± 2.2 MPa with average thickness of 477 ± 128 µm.

Glut-BP (n = 6) had a tensile strength of 19.4 ± 7.3 MPa, average thickness of 439 ± 143 µm and showed no transition at 2% strain (data not shown). UTS was significantly higher compared to native untreated bovine pericardium (Figure 4, p = 0.02).

Figure 3 Stress-strain curves from **A** fresh porcine and bovine pericardium **B** scCO_2 treated porcine and bovine pericardium **C** Glutaraldehyde treated bovine pericardium. UTS = Ultimate tensile strength

Figure 4 Overview of ultimate tensile strength (UTS) for fresh (native) and scCO₂ decellularised porcine and bovine pericardium as well as glutaraldehyde treated pericardium (gold standard). ns: $p > 0.05$, * $p = 0.02$

scCO₂ decellularised pericardium

Tensile strength for BP ($n = 6$) and PP ($n = 5$) samples was 11.0 ± 2.1 MPa and 14.0 ± 4.1 MPa, respectively (Figure 3B). Thickness of BP was 577 ± 71 μm , compared to 200 ± 56 μm in PP. At 2 – 5% strain all dehydrated samples showed a temporary flattening at the toe of the stress/strain curve (See supplementary Figure 1).

In hydrated BP ($n = 4$), strain almost doubled at maximum force (70% vs 40%) with comparable tensile strength of 13.4 ± 3.0 MPa, and a thickness of 482 ± 12 μm . No transition at 2% strain was observed. There was no significant difference in UTS between PP ($p = 0.73$) and BP (dehydrated $p = 0.54$, rehydrated $p = 0.10$), compared to fresh pericardium.

Fracture toughness

BP and Glut-BP were subjected to propagation of a tear in a trouser tear test. For BP (dehydrated), a 25 mm “trouser” dissected after 40% elongation when propagated parallel to collagen fibres (MD, $n = 3$). In CD ($n = 3$), this varied from 30 – 90% and in the 45° group ($n = 3$) this occurred directly from the beginning or from 15%. A high variation in stress-strain curves between each sample was observed. Average fracture toughness in MD was 15.3 ± 6.10 $\text{J} \cdot \text{m}^{-3}$ (MPa $\times$ % strain), CD 13.6 ± 9.09 $\text{J} \cdot \text{m}^{-3}$ and 45° 28.5 ± 18.5 $\text{J} \cdot \text{m}^{-3}$ (Figure 5). There was no statistically significant difference between orientation means as determined by one-way ANOVA ($F(2,6) = 1.308$, $p = 0.34$).

In Glut-BP a dissection of tissue was only observed in two samples after 40% (CD) and 120% (45°) elongation. Average fracture toughness in MD was 64.9 ± 40.4 $\text{J} \cdot \text{m}^{-3}$ ($n = 2$), CD was 82.6 ± 5.4 $\text{J} \cdot \text{m}^{-3}$ ($n = 2$) and 45° 98.5 ± 32.2 $\text{J} \cdot \text{m}^{-3}$ ($n = 3$). There was also no statistically significant difference between orientation means (ANOVA ($F(2,4) = 0.7344$, $p = 0.54$)).

Figure 5 Fracture toughness of BP (dehydrated) and Glut-BP (hydrated) in a trouser tear test. There were no significant differences between orientation on fracture toughness. Group means of BP and Glut-BP were significantly different ($p = 0.0002$). *** $p < 0.001$ BP = Bovine pericardium; CD = Cross direction; Glut-BP = Glutaraldehyde treated bovine pericardium; MD = Machine direction; 45° = 45° on MD.

A two-way ANOVA examined the role of tissue source and orientation on fracture toughness. There was a statistically significant effect of tissue source on fracture toughness, $F(1,10) = 32.74$, $p < 0.001$.

Suture retention strength

To determine the force needed to pull out a simple suture (suture retention strength), BP (dry), BP (hydrated) and Glut-BP (each condition $n = 4$) were measured. Each sample had three simple interrupted sutures (Figure 6), making a total of 12 individual sutures. Three phenomena were observed: suture knot failure ($n = 3$), the suture working as a knife ($n = 5$), the suture tearing the tissue apart ($n = 4$), starting at a force of 25 N.

Maximum force at break was 33 ± 4 N in sutured rehydrated BP and significantly higher than 20 ± 6 N of Glut-BP ($p = 0.01$), see Table 1.

Figure 6 Representative suture retention strength of hydrated BP **A** surgical knot failure and tearing **B** cutting of suture through pericardium **C** tearing of pericardium

Table 1 Suture retention strength

Source	Treatment	Suture retention strength (N)	UTS (MPa)
Triple interrupted sutures (Prolene 5-0)			
Bovine	Glutaraldehyde (Peri-Guard)	20 ± 6.3	2.2 ± 0.66
Bovine	scCO ₂ (dehydrated)	22 ± 6.7	3.5 ± 0.47
Bovine	scCO ₂ (rehydrated)	33 ± 3.8	3.3 ± 0.16
Simple interrupted suture (Prolene 4-0)			
Porcine	scCO ₂ (rehydrated)	5.1 ± 1.3	1.9 ± 0.97
Bovine	scCO ₂ (rehydrated)	7.2 ± 0.67	0.96 ± 0.15

We also investigated use of simple interrupted sutures in rehydrated PP (n = 5) and BP (n = 2). We observed a reduction in suture retention strength compared to triple interrupted sutures (Table 1), with no significant difference between PP and BP (p = 0.11).

Water uptake

Water uptake in dehydrated PP and BP was measured as a function of time to get an impression of the speed of saturation (n = 2 for each condition). Final ratio on weight (w_i) was $393 \pm 2.1\%$ for BP and $356 \pm 18\%$ for PP, both stabilising after one minute of rehydration. There was no different increase in weight ratio for both measurements at the different time points after one minute (ANOVA, $F(1,1) = 2.10$, $p = 0.39$ for BP, ANOVA, $F(1,1) = 0.93$, $p = 0.51$ for PP). Final ratio on diameter (d_i) was $10 \pm 2.8\%$ for BP and $6 \pm 0.95\%$ for PP. An equilibrium was reached after 2 minutes (Figure 7).

There was no different increase in diameter ratio for both measurements at the different time points after one minute (ANOVA, $F(1,1) = 2.00$, $p = 0.39$ for BP, ANOVA ($F(1,1) = 0.89$, $p = 0.52$ for PP).

Figure 7 Water uptake of PP and BP. On lower Y-axis, diameter ratio (d_i) is shown, on upper Y-axis weight ratio (w_i). Both ratios of PP and BP are not significantly different in time after one minute

Discussion

Currently, several biomaterials are used in clinical setting for reconstruction of cardiac tissue, repair of large intra-thoracic vessels and repair of pericardium, such as small intestine submucosa ECM (SIS-ECM) or glutaraldehyde fixed pericardium. However, these tissues tend to calcify as a result of chronic inflammation. This study characterised decellularised porcine and bovine pericardium after supercritical carbon dioxide processing for uses in cardio-thoracic surgery.

This study has a wide scope of characterisation of scCO₂ decellularised pericardium. Indeed, this study investigates mechanical aspects, such as tensile strength, water uptake and swelling. Next, the ultrastructure was imaged with SEM, visualising both rough, fibrous pericardium as well as smooth, serous pericardium.

Ultrastructure

SEM analysis (Figure 2) indicated preservation of ultrastructure of porcine and bovine pericardium when decellularised with scCO₂ with minor disruptive areas. Glutaraldehyde treated bovine pericardium showed more and larger disruptive areas, yet this could not statistically be objectified.

We used freeze-dried BP from the manufacturer and freeze-dried Glut-BP to conduct SEM-analysis, which may have impact on superficial structure of pericardium [29]. Previous research on scCO₂ decellularised porcine aorta suggested a possible disruption of ECM due to the pressure used in scCO₂ processing [9, 16]. Contrarily, our study shows a preservation of ultrastructure. Others have used higher operating pressures up to 35 MPa that could explain the different findings and also reported residual phospholipids at lower pressures [16], suggesting incomplete processing in previous studies. Our scCO₂ processing use much lower pressures of 7 MPa and minimising disruption of ECM due to these lower pressures.

Mechanical properties

Ultimate tensile strength

First, tensile strengths of PP and BP are uncompromised after scCO₂ treatment compared to Fr-PP, a new finding compared to other treatments found in literature (Table 2). For chemically decellularised pericardium using SDS, Min et al. found an UTS of 7.3 ± 1.6 MPa ($n = 5$) [30]. Comparing both groups, a significant lower UTS in the chemically decellularised porcine pericardium group is observed compared to our native porcine pericardium group ($p < 0.001$, Figure B). For bovine pericardium, Hülsmann et al. also showed an UTS of 7.1 ± 1.7 MPa in the SDS-group which was significantly lower ($p = 0.012$) than our results [31].

We observed a high standard deviation on UTS in the Glut-BP group that can be explained by 2/6 samples having an UTS of 28 MPa and 4/6 ranging from 10 – 18 MPa. We measured all samples in one session, therefore eliminating operator and system influences. Increasing sample size might reduce the influence of biological variability. However, a study from Polak et al. measuring 50 bovine pericardia showed a similar standard deviation of UTS [29].

Table 2 Mechanical properties of pericardia

Source	Treatment	Tensile strength (MPa)	Elastic modulus (MPa)	Reference
Porcine	Untreated	14.4	76 ± 10	Dong, 2013 [32]
Porcine	Untreated	13.3 ± 2.4	50 ± 16	This study
Porcine	Triton X-100	8.0 ± 1.8	51 ± 7	Dong, 2013 [32]
Porcine	SDS	8.4 ± 1.4	37 ± 5	Dong, 2013 [32]
Porcine	SDS +Glutaraldehyde	7.3 ± 1.6	-	Min, 2012 [30]
Porcine	scCO₂ (dry)	14.0 ± 4.1	131 ± 21	This study
Human	Glutaraldehyde	10 ± 3	51 ± 15	Yamashita, 2012 [33]
Bovine	Untreated	9 ± 3	26 ± 5	Hülsmann, 2012 [31]
Bovine	Untreated	14.9 ± 4.6	33 ± 12	Guhathakurta, 2008 [34]
Bovine	Untreated	17.1 ± 2.9	-	Nam, 2012 [35]
Bovine	Untreated	10.2 ± 2.2	-	This study
Bovine	Triton X-100	10.2 ± 2.2	40 ± 12	Kayed, 2015 [36]
Bovine	scCO₂ (dry)	11.0 ± 2	83 ± 14	This study
Bovine	scCO₂ (hydrated)	13.4 ± 3	48 ± 12	This study
Bovine	Glutaraldehyde	10 ± 3	-	Van den Heever, 2013 [14]
Bovine	Glutaraldehyde	12.8 ± 1.1	50 ± 6	Kayed, 2015 [36]
Bovine	Glutaraldehyde (Peri-Guard)	19.4 ± 7.3	91 ± 38	This study
Bovine	Glycerol (dry)	18.9 ± 9.6	197 ± 84	Polak, 2011 [29]
Bovine	SDS + Glutaraldehyde	4.2 ± 1	5 ± 2	Hülsmann, 2012 [31]
Bovine	SDS + Triton X-100 + Glutaraldehyde	15.3 ± 3.0	-	Nam, 2012 [35]

In our study, a temporary flattening of the stress/strain curve was observed at 2 – 5% strain in all dehydrated samples (see Supplementary Figure 1). We hypothesise that dehydrated samples are not capable in transferring applied force into the tissue, due to a lack of uncrimping of collagen in the absence of water. Hydrated samples do show uncrimping of collagen and no temporary flattening was observed. For future clinical use, this phenomenon thus advocates using (re-)hydrated pericardium instead of dehydrated pericardium.

Elastic modulus

Next, E_{mod} of BP increased only slightly after scCO₂ treatment compared to untreated bovine pericardium. In our study, we determined the E_{mod} as the slope of the stress/strain curve in a linear part (Young's modulus). Differences in E_{mod} may arise due to tissue preparation or test method. Indeed, biomechanical properties of pericardium are mainly determined by the distribution and orientation of collagen bundles. A low E_{mod} is desired as tissues in the human body should be able to withstand elastic deformity.

A decreased tensile strength is associated with a lower water content, in which the reorganisation of collagen fibres at increased tensile forces is reduced [14]. Indeed, we observed that dehydrated pericardium had a higher E_{mod} than rehydrated pericardium. Most studies used glutaraldehyde fixed pericardium [31-33] and demonstrated a decrease in E_{mod} . However, others have shown that cross-linking increases the E_{mod} of

collagen [37], which is in line with the hypothesis that cross-linking increase the stiffness of a material.

(An)isotropy of pericardium

A tear (crack) propagation parallel to the orientation of collagen fibres is the most important indicator for collagen-matrix interaction and is clinically relevant as propagation across the collagen fibres is more difficult [28]. However, our data on tear propagation did not confirm this statement, where there was no significant difference between different orientations. Early research on human and canine pericardium showed that strip orientation did not significantly affect UTS in uniaxial and biaxial testing [38, 39]. Others found a significant lower UTS of bovine pericardium in perpendicular tensile testing, compared to axial tensile testing, yet no difference was found in porcine pericardium [40].

The isotropy of pericardium in our study can be explained by a 3D crossed-fibrillar structure [38], with superficial fibres being perpendicular to deep collagen fibres [41]. Multiple fibre directions provide an increased resistance to crack propagation and shear.

Cross-linking of collagen fibres by glutaraldehyde makes propagation of a tear more difficult [42]. Indeed, in our trouser tear test Glut-BP needed more energy than BP ($p = 0.0002$). Next, biological variation and difficulty in assessing fibre orientation might have influenced categorisation of the samples. Future research should address biological variation by measuring more samples and quantify superficial and deep fibre orientation appropriately in scCO₂ treated pericardium.

Impact for future clinical use

Data from untreated bovine, porcine and human pericardium is scarce and studies with untreated pericardia [31, 32, 36, 43] have not been reproduced yet. This study includes untreated pericardia, glutaraldehyde treated pericardia, and scCO₂ decellularised pericardia and subjects all materials to identical test methods, thus enabling a good comparison of the effect of decellularisation on mechanical properties.

Also, based on tensile strength, scCO₂ decellularised pericardium is more similar to native, untreated pericardium compared to glutaraldehyde treated pericardium and therefore has a better biomimicry. In both hydrated and dehydrated conditions, this tensile strength is prolonged with more than a quarter increase in strain before deformation of the material, compared to the dehydrated tissue. This suggests that it can be used in a pulsatile environment with a strain of approximately 30% to the original size before failure. For future clinical use, this is an important feature for replacement of the ascending aorta where high strains are observed.

Before clinical use as a vascular replacement, an uniaxial ring test should be conducted that predicts biomaterial mechanical response in these situations [44]. This research did not include repetitive stress tests, making the true usability in a pulsatile environment to be determined in future studies.

Water uptake

Rehydration of dehydrated samples is essential for tissue function *in vivo*. We observed a stabilisation of water uptake within 2 minutes (Figure 7) in PP and BP (both freeze-dried) which was statistically equal in both measurements. The swelling degree on weight (w_s) of BP and PP (358% – 398%) is in line with swelling kinetics of native freeze-dried bovine pericardium from Polak et al. (250% – 325%), yet a much faster equilibrium is established in BP and PP [29].

In current products for tissue reconstruction based on bovine pericardium, human skin and porcine SIS-ECM, such as Peri-Guard (Synovis Surgical), AlloDerm (Lifecell), Restore (DePuy), CorMatrix (Cook Biotech) and Matristem (Acell) rehydration or rinsing times vary from 3 to 40 minutes according to manufacturer's instructions for use. This step also dilutes toxic preservation solutions in the aforementioned products. Our rehydration times of under 2 minutes are therefore no barrier for direct application in the operating room and corresponding delay of surgery pace.

Limitations

A limitation of this study on the potential of $scCO_2$ decellularised pericardium is the comparison with bovine pericardium treated with glutaraldehyde (Peri-Guard[®]). Peri-Guard[®] is bovine pericardium, cross-linked with glutaraldehyde without decellularisation but with fixation of cells. Cross-linking promotes a body response with fibrous tissue formation, chronic inflammation and inhibition of cellular infiltration and scaffold degradation [45]. Interestingly, degradation products from ECM have anti-microbial properties against *i.e.* *Staphylococcus aureus* [46], one of the most frequent causes of mediastinal infections after sternotomy. No inhibition of bacterial growth was seen in intact ECM [47]. This advocates for an unlinked scaffold where degradation does take place. As not all products available for patient care are cross-linked, non-inferiority of PP or BP is unclear until future work compare PP and BP with CorMatrix or equivalent unlinked SIS-ECM tissues.

Next, configuration of collagen fibres vary with age as they are straight in the foetus, become wavy after birth and straight again in old age [3]. Also, total number of elastic fibres is higher in old age [38]. As more fibres reduce elasticity, pericardium of young adults is more elastic than that of elderly. Pericardia used in our experiments are of young adult animals. Future research should determine the different appearance of bovine young calf and bovine adult pericardium by SEM and Immunohistochemistry (IHC) staining of collagen and elastin. In surgeries where higher strains are observed, *i.e.* thoracic aorta surgery, bovine young calf could be more useful.

Sterilisation methods

The choice of sterilisation method might influence structural properties of biomaterials. Freytes et al. found a reduced maximum force in porcine urinary bladder matrix in gamma irradiated samples, compared to ethylene oxide and unsterilised samples [48]. Contrarily, Daar et al. demonstrate collagen fibre changes in irradiated bovine pericardium, but state that biological variability between samples is more important to UTS than gamma irradiation ranging up to 80 kGy [49]. We therefore expect that

difference in processing treatments (scCO₂ vs glutaraldehyde) are more important to UTS than sterilisation.

Long term durability

A major problem of current biomaterials in heart surgery is long-term durability [7]. A limitation of this study is the lack of information about long-term durability of scCO₂ treated pericardium including tissue degradation and calcification of pericardium. A mineralisation assay can provide some information on this calcification process, together with culturing cells in (salt enriched) simulated body fluid solution to enhance calcification process [50], as well as X-ray spectroscopy [51]. However, laboratory tests are only limited in predictability of calcification and in vivo studies should address induction of scar tissue, induction of a pro-inflammatory reaction or hypothesised full remodelling aspects of scCO₂ decellularised pericardium.

Unfortunately, glutaraldehyde treated pericardium has cytotoxic residues that impact remodelling of surrounding tissue [20]. Since scCO₂ processing is solvent-free processing, only CO₂ and H₂O is released during degradation and no cytotoxicity and genotoxicity is expected. Long-term stability however is also based on adequate DNA and α -Gal epitope removal from xenogeneic tissue [52]. So far, no tissue treatment has been able to completely remove such epitopes without compromising mechanical properties [30], and the effect of scCO₂ on xeno-antigen removal should be subject to further research.

Conclusion

This study characterises porcine and bovine pericardium decellularised by scCO₂ in comparison with native pericardium and glutaraldehyde-fixed pericardium (Glut-BP). Ultimate tensile strength of scCO₂ decellularised pericardium was not significantly different from native pericardium, where Glut-BP was significantly higher ($p = 0.02$). Next, suture retention strength of scCO₂ treated pericardium was significantly higher than Glut-BP ($p = 0.01$). Rehydration of scCO₂ treated pericardium reached an equilibrium after 2 minutes and is therefore no limiting factor in the operating room. Thus, scCO₂ decellularisation preserves the initial good mechanical properties of pericardium. We conclude that pericardium decellularised by scCO₂ meets the requirements for biomaterial use in cardio-thoracic surgery such as resistance to tearing in physiological human conditions, resistance to shrinkage and pliability.

Initial mechanical properties of pericardium are of great interest for surgical use and with preservation of these properties using scCO₂ decellularisation we expect a promising scaffold for applications in cardio-thoracic surgery.

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References

1. Eckhauser AW, Hannon D, Molitor M, Scaife E, Gruber PJ. Repair of Traumatic Aortoinnominate Disruption Using CorMatrix. *The Annals of Thoracic Surgery*. 2013;95:e99-e101.
2. Quarti A, Nardone S, Colaneri M, Santoro G, Pozzi M. Preliminary experience in the use of an extracellular matrix to repair congenital heart diseases. *Interactive cardiovascular and thoracic surgery*. 2011;13:569-572.
3. Holt JP. The normal pericardium. *The American journal of cardiology*. 1970;26:455-465.
4. Braga-Vilela AS, Pimentel ER, Marangoni S, Toyama MH, de Campos Vidal B. Extracellular matrix of porcine pericardium: biochemistry and collagen architecture. *The Journal of membrane biology*. 2008;221:15-25.
5. Schoen FJ, Levy RJ. Calcification of tissue heart valve substitutes: progress toward understanding and prevention. *Ann Thorac Surg*. 2005;79:1072-1080.
6. Hammermeister K, Sethi GK, Henderson WG, Grover FL, Oprian C, Rahimtoola SH. Outcomes 15 years after valve replacement with a mechanical versus a bioprosthetic valve: Final report of the Veterans Affairs randomized trial. *Journal of the American College of Cardiology*. 2000;36:1152-1158.
7. Stassano P, Di Tommaso L, Monaco M, et al. Aortic valve replacement: a prospective randomized evaluation of mechanical versus biological valves in patients ages 55 to 70 years. *Journal of the American College of Cardiology*. 2009;54:1862-1868.
8. Khor E. Methods for the treatment of collagenous tissues for bioprostheses. *Biomaterials*. 1997;18:95-105.
9. Crapo PM, Gilbert TW, Badylak SF. An overview of tissue and whole organ decellularization processes. *Biomaterials*. 2011;32:3233-3243.
10. Cissell DD, Hu JC, Griffiths LG, Athanasiou KA. Antigen removal for the production of biomechanically functional, xenogeneic tissue grafts. *J Biomech*. 2014;47:1987-1996.
11. Gilbert TW, Sellaro TL, Badylak SF. Decellularization of tissues and organs. *Biomaterials*. 2006;27:3675-3683.
12. Konakci KZ, Bohle B, Blumer R, et al. Alpha-Gal on bioprostheses: xenograft immune response in cardiac surgery. *European journal of clinical investigation*. 2005;35:17-23.
13. Guldner NW, Jasmund I, Zimmermann H, et al. Detoxification and Endothelialization of Glutaraldehyde-Fixed Bovine Pericardium With Titanium Coating A New Technology for Cardiovascular Tissue Engineering. *Circulation*. 2009;119:1653-1660.
14. van den Heever JJ, Neethling WML, Smit FE, Litthauer D, Joubert G. The effect of different treatment modalities on the calcification potential and cross-linking stability of bovine pericardium. *Cell Tissue Bank*. 2013;14:53-63.
15. Eckert CA, Knutson BL, DeBenedetti PG. Supercritical fluids as solvents for chemical and materials processing. *Nature*. 1996;383:313-318.
16. Sawada K, Terada D, Yamaoka T, Kitamura S, Fujisato T. Cell removal with supercritical carbon dioxide for acellular artificial tissue. *Journal of Chemical Technology & Biotechnology*. 2008;83:943-949.
17. Corporation. C. Carbon Dioxide Phase Diagram - Sublimation, Saturation and Melting Lines1999.
18. Garcia-Gonzalez CA, Concheiro A, Alvarez-Lorenzo C. Processing of Materials for Regenerative Medicine Using Supercritical Fluid Technology. *Bioconjugate chemistry*. 2015;26:1159-1171.
19. An YH, Alvi FI, Kang Q, et al. Effects of sterilization on implant mechanical property and biocompatibility. *Int J Artif Organs*. 2005;28:1126-1137.

20. Meyer M, Prade I, Leppchen-Fröhlich K, et al. Sterilisation of collagen materials using hydrogen peroxide doted supercritical carbon dioxide and its effects on the materials properties. *The Journal of Supercritical Fluids*. 2015;102:32-39.
21. Bernhardt A, Wehr M, Paul B, et al. Improved Sterilization of Sensitive Biomaterials with Supercritical Carbon Dioxide at Low Temperature. *PloS one*. 2015;10:e0129205.
22. Checinska A, Fruth IA, Green TL, Crawford RL, Paszczynski AJ. Sterilization of biological pathogens using supercritical fluid carbon dioxide containing water and hydrogen peroxide. *J Microbiol Methods*. 2011;87:70-75.
23. Baldini T, Caperton K, Hawkins M, McCarty E. Effect of a novel sterilization method on biomechanical properties of soft tissue allografts. *Knee Surg Sports Traumatol Arthrosc*. 2016;24:3971-3975.
24. Birkenfeld F, Behrens E, Kern M, Gassling V, Wiltfang J. Mechanical properties of collagen membranes: are they sufficient for orbital floor reconstructions? *J Craniomaxillofac Surg*. 2015;43:260-263.
25. Synovis Surgical. Peri-Guard Repair Patch: Instructions for Use 2011.
26. Ratner BD. *Biomaterials science : an introduction to materials in medicine*. 2nd ed. Amsterdam ; Boston: Elsevier Academic Press; 2004.
27. Purslow PP. Positional variations in fracture toughness, stiffness and strength of descending thoracic pig aorta. *J Biomech*. 1983;16:947-953.
28. Kim HL, LaBarbera MC, Patel RV, Cromie WJ, Bales GT. Comparison of the durability of cadaveric and autologous fascia using an in vivo model. *Urology*. 2001;58:800-804.
29. Polak R, Pitombo RN. Care during freeze-drying of bovine pericardium tissue to be used as a biomaterial: a comparative study. *Cryobiology*. 2011;63:61-66.
30. Min BJ, Kim YJ, Choi JW, Choi SY, Kim SH, Lim HG. Histologic Characteristics and Mechanical Properties of Bovine Pericardium Treated with Decellularization and alpha-Galactosidase: A Comparative Study. *The Korean journal of thoracic and cardiovascular surgery*. 2012;45:368-379.
31. Hulsmann J, Grun K, El Amouri S, et al. Transplantation material bovine pericardium: biomechanical and immunogenic characteristics after decellularization vs. glutaraldehyde-fixing. *Xenotransplantation*. 2012;19:286-297.
32. Dong J, Li Y, Mo X. The study of a new detergent (octyl-glucopyranoside) for decellularizing porcine pericardium as tissue engineering scaffold. *The Journal of surgical research*. 2013;183:56-67.
33. Yamashita H, Ozaki S, Iwasaki K, Kawase I, Nozawa Y, Umezu M. Tensile strength of human pericardium treated with glutaraldehyde. *Annals of thoracic and cardiovascular surgery : official journal of the Association of Thoracic and Cardiovascular Surgeons of Asia*. 2012;18:434-437.
34. Guhathakurta S, Balasubramanian V, Ananthakrishnan B, et al. Thrombogenicity studies of three different variants of processed bovine pericardium. *IRBM*. 2008;29:223-230.
35. Nam J, Choi SY, Sung SC, et al. Changes of the Structural and Biomechanical Properties of the Bovine Pericardium after the Removal of alpha-Gal Epitopes by Decellularization and alpha-Galactosidase Treatment. *The Korean journal of thoracic and cardiovascular surgery*. 2012;45:380-389.
36. Kayed HR, Sizeland KH, Kirby N, Hawley A, Mudie ST, Haverkamp RG. Collagen cross linking and fibril alignment in pericardium. *Rsc Adv*. 2015;5:3611-3618.
37. Thompson JI, Czernuszka JT. The effect of two types of cross-linking on some mechanical properties of collagen. *Bio-medical materials and engineering*. 1995;5:37-48.

38. Lee JM, Boughner DR. Mechanical properties of human pericardium. Differences in viscoelastic response when compared with canine pericardium. *Circ Res*. 1985;57:475-481.
39. Lee MC, Fung YC, Shabetai R, LeWinter MM. Biaxial mechanical properties of human pericardium and canine comparisons. *Am J Physiol*. 1987;253:H75-82.
40. Gauvin R, Marinov G, Mehri Y, et al. A comparative study of bovine and porcine pericardium to highlight their potential advantages to manufacture percutaneous cardiovascular implants. *J Biomater Appl*. 2013;28:552-565.
41. Alavi SH, Ruiz V, Krasieva T, Botvinick EL, Kheradvar A. Characterizing the collagen fiber orientation in pericardial leaflets under mechanical loading conditions. *Ann Biomed Eng*. 2013;41:547-561.
42. Olde Damink LHH, Dijkstra PJ, Van Luyn MJA, Van Wachem PB, Nieuwenhuis P, Feijen J. Glutaraldehyde as a crosslinking agent for collagen-based biomaterials. *Journal of Materials Science: Materials in Medicine*. 1995;6:460-472.
43. Cohn D, Younes H, Milgarter E, Uretzky G. Mechanical behaviour of isolated pericardium: species, isotropy, strain rate and collagenase effect on pericardial tissue. *Clinical Materials*. 1987;2:115-124.
44. Shazly T, Rachev A, Lessner S, et al. On the Uniaxial Ring Test of Tissue Engineered Constructs. *Experimental Mechanics*. 2015;55:41-51.
45. Blitterswijk Cv. *Tissue engineering*. Amsterdam ; London: Elsevier / Academic Press; 2008.
46. Sarikaya A, Record R, Wu CC, Tullius B, Badylak S, Ladisch M. Antimicrobial activity associated with extracellular matrices. *Tissue engineering*. 2002;8:63-71.
47. Holtom PD, Shinar Z, Benna J, Patzakis MJ. Porcine small intestine submucosa does not show antimicrobial properties. *Clinical orthopaedics and related research*. 2004:18-21.
48. Freytes DO, Stoner RM, Badylak SF. Uniaxial and biaxial properties of terminally sterilized porcine urinary bladder matrix scaffolds. *J Biomed Mater Res B*. 2008;84B:408-414.
49. Daar E, Kaabar W, Woods E, Lei C, Nisbet A, Bradley DA. Atomic force microscopy and mechanical testing of bovine pericardium irradiated to radiotherapy doses. *Radiat Phys Chem*. 2014;96:176-180.
50. Aimoli CG, Nogueira GM, Nascimento LS, et al. Lyophilized bovine pericardium treated with a phenethylamine-diepoxide as an alternative to preventing calcification of cardiovascular bioprosthesis: preliminary calcification results. *Artificial organs*. 2007;31:278-283.
51. Liu J, Zhong S, Lan H, et al. Mapping the calcification of bovine pericardium in rat model by enhanced micro-computed tomography. *Biomaterials*. 2014.
52. Naso F, Gandaglia A, Iop L, Spina M, Gerosa G. Alpha-Gal detectors in xenotransplantation research: a word of caution. *Xenotransplantation*. 2012;19:215-220.

Supplements

Supplementary Figure 1

Supplementary Figure 1 Zoom in of stress-strain curves from $scCO_2$ treated porcine and bovine pericardium. One can observe a flattening of the stress-strain curve between 2 – 5% strain.

Supplementary Table 1

Supplementary Table 1 Overview of experiments and tissues used for comparison						
Experiment	Tissue Used	Samples (pericardia : total samples)	Processing	Condition [†]	Sterilisation	Remarks
Ultrastructure (SEM)	PP	2 : 6	Freeze-dried	Dehydrated	-	Glut-BP was used as gold standard.
	BP	1 : 4	Freeze-dried	Dehydrated	-	
Uniaxial testing (UTS/Emod)	Glut-BP	1 : 5 [‡]	Lyophilisation	Dehydrated	EtO + gamma	Only dehydrated samples can be used for this test (i.e. Fr-PP, Fr-BP, Glut-BP are unsuitable). This experiment demonstrates rehydration rate after dry storage.
	Fr-PP	3 : 6	Untreated	Hydrated	-	
	PP	3 : 6	Freeze-dried	Rehydrated	-	
	Fr-BP	3 : 5	Untreated	Hydrated	-	
	BP	1 : 5	Freeze-dried	Rehydrated	-	
	Glut-BP	1 : 6	-	Hydrated	EtO + gamma	
	BP	2 : 9	Freeze-dried	Dehydrated	EtO + gamma	
Uniaxial testing (Fracture toughness)	Glut-BP	1 : 7	-	Hydrated	-	Only dehydrated samples can be used for this test (i.e. Fr-PP, Fr-BP, Glut-BP are unsuitable). This experiment demonstrates rehydration rate after dry storage.
	BP	2 : 2	Freeze-dried	Dehydrated	-	
	BP	2 : 2	Freeze-dried	Rehydrated	-	
	Glut-BP	1 : 4 [*]	Lyophilisation	Hydrated	EtO + gamma	
	BP	1 : 2	Freeze-dried	Dehydrated	-	
	PP	1 : 2	Freeze-dried	Dehydrated	-	
	PP	1 : 2	Freeze-dried	Dehydrated	-	

[†] When (re)hydrated, stored in physiological saline solution (0.9% NaCl) for minimal 10 minutes

[‡] In total, 3 Glut-BP of 10 x 15cm were used

Fr-PP = Fresh untreated porcine pericardium; PP = Supercritical CO₂ decellularised porcine pericardium; Fr-BP = Fresh untreated bovine pericardium; BP = Supercritical CO₂ decellularised porcine pericardium; Glut-BP = Bovine pericardium cross-linked with glutaraldehyde (Peri-Guard®); EtO = Ethylene oxide

CHAPTER 6

TECHNICAL FEASIBILITY AND DESIGN OF A SHAPE MEMORY ALLOY SUPPORT DEVICE TO INCREASE EJECTION FRACTION IN PATIENTS WITH HEART FAILURE

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Abbreviations and acronyms

CRT	Cardiac resynchronisation therapy
HF	Heart failure
HFrEF	Heart failure with reduced ejection fraction
LVAD	Left ventricular assist device
SMA	Smart memory alloy

Abstract

Purpose

Heart failure is increasingly prevalent in the elderly. Treatment of patients with heart failure aims at improving their clinical condition, quality of life, prevent hospital (re)admissions and reduce mortality. Unfortunately, only a select group of heart failure patients with reduced ejection fraction are eligible for cardiac resynchronisation therapy where 30 – 40% remain non-responders and need left ventricular support. The aim of this study is to investigate if a shape memory alloy (SMA) is able to increase the ejection fraction of a mono-chamber static heart model by 5%.

Methods

A paediatric ventilation balloon was used as a heart model (mono-chamber). Flexinol®, a SMA, was placed around the heart model in multiple configurations and activated using pulse width modulation techniques to determine influence of diameter and configuration on volume displacement. Furthermore, pressure within the heart model was measured with a custom-made pressure sensor.

Results

SMA with a diameter of 0.38 mm, placed in a spiral shape and activated with a duty cycle of 80% and a frequency of 50/min gave the highest ejection fraction increase of 3.5%.

Conclusions

This study demonstrated the feasibility of volume displacement in a static heart model by activation of SMA wires. Configuration, duty cycle, frequency, pulse intervals and diameter were identified as important factors affecting the activation of SMA wires on volume displacement. Future research should include the use of parallel SMA wires, prototype testing in dynamic or ex vivo bench models.

Introduction

Heart failure (HF) is characterized by the “inability of the heart to pump blood at an adequate volume” [1] and results in marked limitation of physical activity. Over 6.5 million Americans have HF and increases by 46% in 2030 [2]. HF is an incurable, lethal disease, where 1 in 8 deaths are related to HF with a 5-year mortality rate after diagnosis of HF of 50% [3]. Also, HF is the most expensive diagnosis for hospitalisations and 30-day readmissions [4].

Treatment of heart failure focuses on quality of life improvement, prevention of hospital admissions and aim to decrease mortality. For patients with a reduced left ventricular ejection fraction (HFrEF) below 40%, pharmacological treatment with angiotensin-converting enzyme inhibitors, beta-blockers and mineralocorticoid/aldosterone receptor antagonists improve survival rates [5]. To reduce the risk of sudden death, implantation of an implantable cardioverter defibrillator is recommended.

For symptomatic patients, cardiac resynchronisation therapy (CRT) is indicated for a select group of patients, yet over 30% of patients are non-responders and do not benefit from this treatment [6]. For patients with resistant symptoms, surgical implantation of a left ventricular assist device (LVAD) or heart transplantation may be considered [5], despite drawbacks of infection of the external battery driveline occurring up to 35% [7, 8] and an increased risk for thrombogenicity and thrombosis [9].

Technological opportunities

Shape memory alloys (SMAs) are able to recover their shape after unloading from a particular stimulus, such as temperature [10]. At high temperature, these SMAs contract and revert to their original state during the cooling process [11]. Application of SMAs in medical practice, such as coronary stents, has continued to emerge since their discovery in the early 1930s [12]. SMAs have effective strain generation up to 4%, with fatigue between 4 – 8%, high strength to weight ratio, and low operating voltage [13, 14].

Recently, the use of SMAs in the treatment of heart failure in bench models generated considerable attention [15, 16]. A mechano-electric artificial myocardial assist system using SMA wires augmented aortic flow rate by 15% in a goat study. Also, systolic left ventricular pressure was elevated by 7% under the cardiac output condition of 3 L/min in these goats [17].

However, challenges remain with respect to energy supply, relaxation times of SMAs and testing in realistic heart models. In this demonstrator study, we investigate which SMA designs, and which pulse width modification (PWM) techniques are able to increase ejection fraction of a mono-chamber static heart model by at least 5%.

Materials and methods

A paediatric silicone resuscitation balloon (Laerdal Benelux B.V., Amersfoort, The Netherlands) was used as a mono-chamber static model with a volume of 475 mL. Flexinol® actuator wires (Dynalloy Inc., Irvine, California, United States) were used as SMA. Flexinol® wires are composed of nickel-titanium alloy (55 wt%Ni, 45 wt%Ti) with a diameter of 150 µm, 250 µm and 380 µm respectively, displaying transformation

temperatures of 70 °C. The density of Flexinol® is 6.45 g/cm³ with a heat capacity of 0.2 cal/g·K and thermal conductivity of 0.18 W/cm·K [18, 19]. A detailed description of nickel-titanium alloys can be found elsewhere [15].

A power supply and pulse generator were used to measure volume displacement after activation of SMAs (Figure 1).

A skeleton composed of Flexinol® wires, micro-tubes, vascular ties, rings and Velcro straps was used based on the experimental setup of Shirashi et al. [14] and is depicted in Figure 2a. Rings were positioned to distribute force more evenly over the balloon. SMA wires were connected to small power cables by cable shoe connectors and attached to screw terminals for proper fixation (Figure 2b).

Figure 1 Schematic representation of test setup. Pulse generator which activates the SMA around the heart model with three major variables: frequency, duty cycle and pulse intervals

Figure 2 *A* Test setup with ventilation balloon as a heart model; *B* detailed overview of heart model

Design configurations

Different configurations of SMA orientation were evaluated, e.g. spiral, band, cross and oblique shaped orientations (Figure 3) at a frequency of 20/min. Volume displacement was measured in a transparent open top plastic tube (height 400 mm, diameter 8 mm), vertically connected to the resuscitation balloon. Both balloon and part of the vertical plastic tube were filled with water (Figure 2a). First two pulses were used to warm-up the SMA-wire and stabilize the system.

Images were recorded with a compact camera, processed by dedicated software using Kinovea 0.8.15 (France) where volume level was tracked as a function of time for all

Figure 3 Conceptual artwork of configurations with *A* spiral *B* band *C* cross *D* oblique orientation

design configurations. Displaced volumes and corresponding ejection fractions were calculated using Microsoft Excel 2016. Graphs were made with GraphPad Prism 5 (GraphPad Software, Inc., San Diego, CA, U.S.A.).

PWM techniques were used (Figure 1) to alter pulse frequency (50 – 90/min), duty cycle (20 – 80%) and pulse intervals (1 – 5) to elicit maximal volume displacement of a single SMA wire.

Pressure measurements

Pressure development was assessed within the resuscitation balloon according to $\Delta P = \rho \cdot g \cdot h$: where ρ is density of the liquid kg/m^3 , g is gravitational acceleration m/s^2 and h is the height difference of the liquid with respect to the initial situation. Pressure development was measured in the resuscitation balloon during the 5th pulse to minimize slope effects. Pressure was controlled and recorded with an intravenous blood pressure sensor (501669001, Merit OEM, the Netherlands) interlinked to a microcontroller (Arduino Uno, Arduino), see Figure 4.

Raw data were filtered with a high-pass Butterworth filter and a moving average filter (Matlab R2016b, MathWorks, Natick, USA).

Statistical analysis

GraphPad Prism 5 was used to perform statistical analysis. Results were considered statistically significant at the 5% level. A one-way ANOVA and a Tukey post hoc test was used for experiments with different SMA configurations and activation frequencies. A repeated measures ANOVA with a Tukey post hoc test was used for experiments with different pulse intervals. Results are reported as mean $\pm$ SD. Error bars represent 95% confidence interval (CI).

Figure 4 Pressure sensor. (1) Inflated transcatheter aortic valve implantation (TAVI) balloon; (2) external pressure sensor; (3) manual pump with pressure gauge to fill TAVI-balloon with water; (4) connection to pressure sensor and microcontroller

Results

Design configurations

SMA wires were applied onto the resuscitation balloon in spiral, band, cross and oblique configurations. Absolute volume displacement differed significantly for peaks 3 – 7 between configurations, ANOVA ($F(3,16) = 652$, $p < 0.0001$). A Tukey post-hoc test indicated significant comparisons between all designs ($p < 0.0001$) favouring spiral design, except for spiral vs band ($p = 0.08$, 95% CI -0.016 to 0.26), see Figure 5.

The influence of wire diameter on volume displacement was studied for 150 μm , 250 μm and 380 μm SMA wires. Maximum volume displacement increased almost linearly with increasing number of windings around the resuscitation balloon ($r^2 = 0.99$) in these wires (Figure 6a). Volume displacement was significantly higher for the 380 μm wire (3.8 ± 1.6 mL) as compared to the 250 μm SMA wire (1.2 ± 0.6 mL, $p < 0.05$). A similar dependency was observed for the required voltage (Figure 6b).

Maximum absolute volume displacement in spiral configuration was 9.0 ± 0.18 cm H_2O , equivalent to 6.9 ± 0.076 mmHg for pulses 3-5 (Figure 7a). The calculated pressure in the resuscitation balloon using our pressure sensor was 7.1 ± 0.49 mmHg (Figure 7b), not statistically significant from the volume displacement ($p = 0.54$, 95% CI 5.9 to 8.3).

A band shaped configuration with 5 windings resulted in a pressure of 10.3 mmHg at an electric current supply of 2.25 A. A current of 2.85 A in combination with assisting rings to distribute forces across the resuscitation balloon, resulted in maximum volume displacement of 16 mL. This corresponds to a pressure build-up of 24 mmHg.

Figure 5 Design of SMA and effect on volume displacement with mean and 95% CI of absolute volume displacement ($p < 0.0001$ for all comparisons, except for spiral vs. band, $p = 0.08$)

Figure 6 Influence of SMA diameter and windings on **A** volume displacement and **B** power supply. A linear regression line is drawn between data points ($r^2 = 0.99$ in both graphs)

Figure 7 Pressure development with **A** measured volume displacement (mmHg) and **B** external pressure sensor (mmHg).

Pulse width modulation (PWM) techniques

Volume displacement of every third pulse was measured at different frequencies with duty cycle kept constant at 75% and pulse interval at 5 (1/5th of frequency). Maximum displaced volume decreased significantly upon increasing pulse frequency, ANOVA ($F(4,25) = 400$, $p < 0.0001$) (Figure 8a).

Furthermore, volume displacement reached a constant volume after 3 pulses, regardless of the employed pulse frequency. A Tukey post hoc test revealed a significantly higher volume displacement for a frequency of 50/min ($1.6 \text{ mL} \pm 0.04$, $p < 0.05$) as compared to other frequencies. Both higher duty cycles and higher electric currents increased volume displacement and flow (Figure 8b and 8c). A duty cycle of 90 or 100% would impair the cooling process and was not tested.

Volume displacement changed remarkably each cycle when supporting every heartbeat at a frequency of 60/min, as compared to other intervals. The SMA was unable to return to its original state within this short cycle time as depicted in Figure 9.

Figure 8 Pulse width modulation (PWM) techniques and effect on volume displacement with **A** pulse frequency; **B** duty cycle; **C** electric current on flow (mL/s)

A Tukey post hoc correction revealed that absolute volume displacement was statistically significant different for an interval of 1 ($2.0 \text{ mL} \pm 0.4$) and the intervals 3 ($1.4 \text{ mL} \pm 0.2$, $p < 0.01$), 4 ($1.3 \text{ mL} \pm 0.1$, $p < 0.001$) and 5 ($1.2 \text{ mL} \pm 0.2$, $p < 0.001$). There was no significant difference between interval 1 and 2 ($1.8 \text{ mL} \pm 0.4$, $p = 0.35$).

Figure 9 Pulse interval and effect on volume displacement. Volume displacement changes drastically when every cycle (interval of 1) is supported in comparison to other pulse intervals

Discussion

In this study we investigated optimal design characteristics of a demonstrator SMA support device for HFrEF patients. A 380 μm SMA Flexinol® wire configured in a spiral oriented shape around a mono-chamber balloon activated with a duty cycle of 80%, a frequency of 50/min gave the highest volume displacement (stroke volume, 6.2 mL). A maximum ejection fraction (EF) of 3.5% was achieved, requiring a power supply of 25 V and 2.85A for each pulse.

Tozzi et al. used a 100 μm diameter SMA nitinol wire with total stimulation of 180 ms, recovery time of 250 ms and contraction rate of 80/min [16]. They achieved a maximum ejected volume of 330 mL/min, a generated systolic pressure of 75 mmHg, ejection fraction of 12% requiring a power supply of 6 V and 250 mA. This is comparable to our maximum ejected volume of 310 mL/min. In their experiments, a double-chamber setup was used, with a balloon volume of only 50 mL. This is much smaller than patients with HFrEF [20] making extrapolation of these results into a physiological situation difficult.

Diameter and volume displacement

Volume displacement and required voltage displayed a linear incremental relation in our experiment with the employed number of SMA wires (windings) for all tested diameters (150, 250 and 380 μm), see Figure 6. This may suggest that the number of required SMA wires for a specific volume displacement and the corresponding voltage may be predicted. An EF of 10% for this balloon (= 475 mL) would then require 46 windings, although maximum strain of SMAs might limit this linear behaviour.

Thermal management

A lower pressure build up was observed in the first contraction cycles (Figures 7a and 7b). Joule heating started the transformation phase but was not completed yet. After a few cycles temperature increased and the transformation phase was completed [11]. A linear relationship between electric current increase and volume displacement was observed by Velazquez et al. [21]. Indeed, we observed that SMA wires had a higher volume displacement when increasing electric current (Figure 8c). However, increasing electric currents above the plateau phase as observed in Figure 8c, may cause overheating and induce stress fatigue.

To reduce heating of surrounding tissue, a silicone tube proved to be effective in goat experiments [17]. Indeed, Shiraishi et al. found no major drawbacks related to heat production in silicone insulated SMA wires in goats. Kalogerakos et al. found that insulated wires produced a lower volume displacement than non-insulated wires [15]. Furthermore, cooling time is slower than heating time and thus urges for interval use such as once in four heart beats.

Pulse width modulation

Heart support during every heartbeat requires rapid compression and expansion of the SMA. This may not be directly attainable, though HF patients may already benefit from partial heart support. Hence the influence of pulse width modulation on volume displacement was investigated. SMA wires that were left to cool down before the

following activation step produced substantially higher volume displacements (Figure 9). In our experiment, pulse intervals of every 3rd or 5th cycles gave higher volume displacements than pulse intervals of every 1st or every 2nd heartbeat. A second, lower peak (“bounce”) was absent with a pulse interval of 1. Here, next activation occurred faster than cooldown and recovery of the SMA wire.

In this demonstrator study, hourly energy consumption of SMA activation ranged from 5.5 to 11.4 Watt-hour, where an increased energy use resulted in higher ejection fractions. This range is lower than the hourly energy consumption of 23.6 Watt-hour of a HeartMate II assist device [22] and is comparable to SMA-prototypes [15] or HeartMate III at 11 Watt-hour [23]. At body temperature, SMA wires consume less energy than bench temperature due to a reduction in temperature gradient [24]. This is promising for battery size reduction and therefore reduces frequent change of the (external) battery.

Limitations of experimental setup

A silicone paediatric resuscitation balloon was employed as a static model and acted as a mono-chamber model with a large end-diastolic volume (EDV) of 475 mL. EDV in HFrEF patients range from 100 – 300 mL, depending on ventricular dilatation [20]. Thus, this model underestimates effect size for clinical use.

Durability of SMAs for cardiac applications should extend beyond patients life expectancy. In this study, no change in volume displacement was observed after 25 minutes (Supplemental Figure 1). Comparable SMAs were tested in a fatigue lifetime test and assured constant stroke after at least 10⁶ cycles [25]. However, for cardiac applications these experiments should ensure SMA stability over 10⁸ cycles.

Also, afterload is reduced in LVAD therapy where effects of a SMA support device on afterload are still unknown. These effects should be addressed in future experimental setups and should be within physiological systemic aortal pressure.

Finally, energy consumption for achieving an ejection fraction of 3.5% was 3-fold higher than a pacemaker. This might affect future clinical use when battery life is too short for internal battery use. External battery use comes with an increased risk for driveline infections and impair patients mobility [8]. An increase of parallel windings can reduce SMA length and resistance, with a reduction in energy consumption to follow.

Future perspectives

Future research should focus on evaluation of spiral or oblique shaped configurations around the heart in advanced bench models such as dynamic setups or an ex vivo porcine cadaver model. The cardiac fibre orientation as described by the helical ventricular myocardial band model should be acknowledged in these designs [26]. This represents a physiologically more realistic model than the proof of principle in an in vitro mono-chamber bench model presented here. Alternatively, a double-chamber bench model with incorporated right ventricle can then include biventricular support. This should increase the technology readiness level from 3 (characteristic proof-of-concept) to 4 (proof-of-concept in defined models). Furthermore, combining both different afterload scenarios such as hypertension or mitral regurgitation and design configurations in a mathematical model might enhance device development.

Effectivity of SMA wire application may be objectified with (ex vivo) magnetic resonance imaging (MRI) on segmental wall motion abnormalities. Also, a mesh such as the CorCap cardiac support device or other supportive materials may be incorporated around the heart in future designs to guide and support SMA wires and prevent dilatation of the left ventricle. This would also prevent incising heart tissue with SMA wires. The resultant exoskeleton then prevents occurrence of dead space between SMA wires and epicardium, thus giving additional support for effective contraction and improved ejection fraction.

An increased stroke volume of 11.8 mL improve patients New York Heart Association (NYHA) functional class on heart failure symptoms by one class [15]. Our current setup might improve these symptoms by half a class, which is not clinically relevant yet. Future studies should aim to improve NYHA-class at least by one and preferably by two classes.

Conclusions

Optimal design characteristics of a SMA support device for HFrEF patients were determined in this demonstrator study. A LVEF increase of 3.5% was demonstrated in a mono-chamber static heart model by activation of SMA wires. Furthermore, effects of configuration, duty cycle, frequency, pulse intervals and diameter on the activation of SMA wires and corresponding volume displacement was evaluated.

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Conflict of Interest

Authors KA, FH, SS, JG, JP declare that they have no conflict of interest for this work. No human or animal studies were carried out by the authors for this article.

References

1. *The ICD-10 classification of mental and behavioural disorders : clinical descriptions and diagnostic guidelines*. WHO; 1992.
2. Benjamin EJ, Virani SS, Callaway CW, et al. Heart Disease and Stroke Statistics-2018 Update: A Report From the American Heart Association. *Circulation*. 2018;137:e67-e492.
3. Gerber Y, Weston SA, Redfield MM, et al. A contemporary appraisal of the heart failure epidemic in Olmsted County, Minnesota, 2000 to 2010. *JAMA internal medicine*. 2015;175:996-1004.
4. Fida N, Pina IL. Trends in heart failure hospitalizations. *Curr Heart Fail Rep*. 2012;9:346-353.
5. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J*. 2016;37:2129-2200.
6. Auricchio A, Prinzen FW. Non-responders to cardiac resynchronization therapy: the magnitude of the problem and the issues. *Circulation journal : official journal of the Japanese Circulation Society*. 2011;75:521-527.
7. Lehnert AL, Hart A, Brouse SD, Charnigo RJ, Branam S, Guglin ME. Left ventricular assist device-related infections: does the time of onset matter? *Journal of Artificial Organs*. 2018.
8. Nienaber JJ, Kusne S, Riaz T, et al. Clinical manifestations and management of left ventricular assist device-associated infections. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*. 2013;57:1438-1448.
9. Abaunza M, Kabbani LS, Nypaver T, et al. Incidence and prognosis of vascular complications after percutaneous placement of left ventricular assist device. *Journal of vascular surgery*. 2015;62:417-423.
10. Huang WM, Ding Z, Wang CC, Wei J, Zhao Y, Purnawali H. Shape memory materials. *Materials Today*. 2010;13:54-61.
11. Jani JM, Leary M, Subic A, Gibson MA. A review of shape memory alloy research, applications and opportunities. *Materials l& Design*. 2014;56:1078-1113.
12. Ölander A. An electrochemical investigation of solid cadmium-gold alloys. *Journal of the American Chemical Society*. 1932;54:3819-3833.
13. Sawyer P, Page M, Baseliust L, et al. Further study of nitinol wire as contractile artificial muscle for an artificial heart. *Cardiovascular diseases*. 1976;3:65.
14. Ma J, Karaman I. Expanding the repertoire of shape memory alloys. *Science*. 2010;327:1468-1469.
15. Kalogerakos PD, Hassoulas J, Ladopoulos VS. Beyond heart transplantation: Potentials and problems of the shape memory alloy fibers in the treatment of heart failure. *ASAIO journal*. 2014;60:263-268.
16. Tozzi P, Michalis A, Hayoz D, Locca D, von Segesser LK. Artificial muscle for end-stage heart failure. *Asaio Journal*. 2012;58:103-108.
17. Shiraishi Y, Yambe T, Saijo Y, et al. Morphological approach for the functional improvement of an artificial myocardial assist device using shape memory alloy fibres. *Engineering in Medicine and Biology Society, 2007. EMBS 2007. 29th Annual International Conference of the IEEE2007*:3974-3977.
18. Dynalloy I. Technical characteristics of Flexinol actuator wires. *CA: Tustin*. 2011.
19. Chikkamaranahalli S, Vallance RR, Khan A, et al. Precision instrument for characterizing shape memory alloy wires in bias spring actuation. *Review of Scientific Instruments*. 2005;76:065105.

20. Solomon SD, Foster E, Bourgoun M, et al. Effect of cardiac resynchronization therapy on reverse remodeling and relation to outcome: multicenter automatic defibrillator implantation trial: cardiac resynchronization therapy. *Circulation*. 2010;122:985-992.
21. Velazquez R, Pissaloux EE. Modelling and temperature control of shape memory alloys with fast electrical heating. *Int. J. of Mechanics and Control*. 2012;13.
22. Wang JX, Smith JR, Bonde P. Energy transmission and power sources for mechanical circulatory support devices to achieve total implantability. *The Annals of thoracic surgery*. 2014;97:1467-1474.
23. Pirbodaghi T, Cotter C, Bourque K. Power consumption of rotary blood pumps: pulsatile versus constant-speed mode. *Artificial organs*. 2014;38:1024-1028.
24. Hassoulas IA, Ladopoulos VS, Kalogerakos PD. Study of shape memory alloy fibers for the development of artificial myocardium. *Hellenic J Cardiol*. 2010;51:301-309.
25. Fumagalli L, Butera F, Coda A. SmartFlex(A (R)) NiTi Wires for Shape Memory Actuators. *J Mater Eng Perform*. 2009;18:691-695.
26. Kocica MJ, Corno AF, Lackovic V, Kanjuh VI. The helical ventricular myocardial band of Torrent-Guasp. *Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu*. 2007:52-60.

Supplements

Supplementary Figure 1

Supplemental Figure 1 Volume displacement of two 380 μm SMA wires in time. A representative selection of 1st, 13th and 22nd minute is shown where volume displacement is stable in time. Horizontal grey lines represent mean of highest and lowest measurement

The background of the entire page is an abstract pattern of thin, flowing lines in shades of orange and yellow. These lines curve and swirl, creating a sense of movement and depth. The lines are more densely packed in some areas, creating a mesh-like effect, while in others, they are more sparse.

PART III

MULTIDISCIPLINARY APPROACHES TO
IMPROVE OUTCOME OF HEART SURGERY

CHAPTER 7

EARLY IN-HOSPITAL MOBILIZATION AFTER CARDIAC SURGERY: A PROSPECTIVE STUDY TO PROMOTE FUNCTIONAL DEVELOPMENT USING A MOBILIZATION POSTER

Submitted

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Abbreviations and acronyms

ACSM	American College for Sports Medicine
BMI	Body mass index
CABG	Coronary artery bypass surgery
COPD	Chronic obstructive pulmonary disease
ICU	Intensive care unit
NYHA	New York Health Association
TCT	Thoraxcentrum Twente
UCG	Usual care group

Abstract

Purpose

To study the effect of early mobilisation after heart surgery with a mobilisation poster on activity classification guide for inpatient activities functional score from the American College for Sports Medicine (ACSM). Second, to determine sensitivity of this ACSM score to measure day-to-day changes. Third, to develop a more descriptive Thoraxcentrum Twente (TCT) score with actual activities patients perform during early mobilisation.

Methods

This was a single centre, observational sequential-group study at a cardio-thoracic surgery ward. 32 patients were in the usual care group and 209 patients in the intervention group. An A1 size poster was developed to stimulate hospital-based mobilisation after heart surgery. Change in ACSM score was defined as primary endpoint. Secondary endpoints included change in a TCT score on actual activities. A subgroup analysis for coronary artery bypass surgery (CABG) was planned. Clinical endpoints included length of stay and survival.

Results

ACSM score was different over time ($p < 0.001$). The mobilisation poster did not increase ACSM score in the overall group ($p = 0.27$) or CABG subgroup ($p = 0.15$). Men had higher ACSM scores than women ($p < 0.001$). The intervention poster increased TCT scores chair, toilet, corridor (all $p < 0.01$) and home trainer ($p = 0.02$). There was no difference in length of stay or survival.

Conclusions

ACSM functional score measured day-to-day changes of patients at a cardiac surgery ward, yet no difference in effects between mobilisation poster and usual care group was observed. Actual activities as measured with the TCT score did improve.

Introduction

Elective cardio-thoracic surgery consists mainly of coronary artery bypass grafting (CABG) followed by valve surgery [1]. These patients have a hospital stay for 5 – 7 days after surgery [1].

Early mobilisation

For patients the importance of mobilisation is often unclear. Most patients stay in bed during hospital stay because they overestimate intensity of physical activities [2]. Next, the hospital environment discourages patients to be physically active [3], and patients acquire a loss in muscle strength and aerobic capacity [4]. Inactivity results in prolonged hospital stay, increased cardiovascular mortality and morbidity and more readmissions to the intensive care unit (ICU) and to the hospital after discharge [5]. Hospitalized patients spent up to 50% lying in bed during daytime, despite enhanced recovery after surgery protocols [6]. Others found that only a minority of patients had their meal outside of bed or walked during their hospital admission [7].

Guidelines do describe features of “phase I rehabilitation”, “inpatient” or “early mobilisation”, e.g. mobilisation that occurs within hospital stay [8-10], yet focus mainly on outpatient rehabilitation. Almost 20% of patients after cardiac surgery receive no physical therapy or inpatient cardiac rehabilitation and when this is utilised less than 30% of the hospital days are covered [11] often without weekend day services [12]. A detailed review of guidelines for cardiac rehabilitation exercise programs showed no consensus in intensity training or exercise prescription [13].

In-hospital exercises include breathing techniques, transfer between bed and chair and walking along the ward. This leads to less pain and depression, a decreased length of stay and are associated with lower mortality and morbidity and lower costs [14]. These early mobilisation strategies increased 6-minute walking assessment distance from 377 m to 444m [15] and respiratory or cardiac function remained stable [16, 17].

Success of mobilisation can be assessed with e.g. the functional independence measure for neurological rehabilitation [18, 19] or the activity classification guide for inpatient activities from the American College for Sports Medicine (ACSM) [20]. The latter is a 6-point score that describes activity classes of patients from sitting up in bed with assistance (class I) to do self-care activities in the bathroom (class III) to independent frequent ambulation (class VI).

However, sensitivity of the ACSM score to measure day-to-day changes in cardio-thoracic surgery patients is unclear. Since the ACSM score aggregates activities, it is unclear which activities patients perform during early mobilisation.

Thus, the primary aim of this study is to evaluate the stimulating effect of early mobilisation after heart surgery with a mobilisation poster on functional independence measured with the ACSM score. The effects are compared to a usual care group. The secondary aim is to evaluate if the ACSM score is sensitive to measure day-to-day changes in cardio-thoracic surgery patients. A third aim is to develop and evaluate a more descriptive score in which the actual activities patients perform during early mobilisation are measured.

Patients and methods

This study is reported as per the STROBE recommendations on the quality of reporting observational studies [21].

Trial design and study population

ACSM score (table 1) of a usual care group (UCG, T₀) was compared with an intervention group (T₁) supported by a mobilisation poster to stimulate early mobilisation.

This single centre, observational sequential-group study was conducted at Thorax Centrum Twente (Medisch Spectrum Twente Hospital, Enschede, The Netherlands), a tertiary non-academic teaching hospital.

Table 1 Activity classification guide for inpatient activities (ACSM score)

Activity class I <ul style="list-style-type: none">• Sits up in bed with assistance• Does own self-care activities-seated, or may need assistance• Stands at bedside with assistance• Sits up in chair 15 – 30 minutes, 2 – 3 times per day	Activity class II <ul style="list-style-type: none">• Sits up in bed independently• Stands independently• Does self-care activities in bathroom-seated• Walks in room and to bathroom (may need assistance)	Activity class III <ul style="list-style-type: none">• Sits and stands independently• Does own self-care activities in bathroom, seated or standing• Walks in halls with assistance short distance (15 – 30m)[†] as tolerated, up to 3 times per day
Activity class IV <ul style="list-style-type: none">• Does own self-care and bathes• Walks in hall short distances (45 – 60m)[‡] with minimal assistance, 3 – 4 times per day	Activity class V <ul style="list-style-type: none">• Walks in halls independently, moderate distances (75 – 150m)[§], 3 – 4 times per day	Activity class VI <ul style="list-style-type: none">• Independent ambulation on unit, 3 – 6 times per day

Table adapted from ACSM’s Guidelines for exercise testing and prescription, 7th edition [20]
Original text: [†] 50 to 100 ft; [‡] 150 to 200 ft; [§] 250 to 500 ft

All patients were admitted to the intensive care unit (ICU) after surgery. Early mobilisation started after transfer to the surgical ward. An A1 size mobilisation poster for each patient room was developed based on preliminary work from the Hospital in Motion project [22].

The “Moving is Improving!”-study recruited from 3rd to 20th October 2016 for T₀ and from 31st October 2016 to 22nd November 2016 for T₁. After interim analysis, the mobilisation poster (translated from Dutch to English, Figure 1) was implemented as new standard care in the cardio-thoracic surgery ward and patients were also included from 10th September 2017 to 26th March 2018 (T₁).

Adult patients undergoing non-salvage cardiac surgery were included. Patients with a Katz index of independence in activities of daily living functioning score larger than 2 before surgery (i.e. patient is not independent in daily life mobilisation) [23] and patients with an ICU stay longer than 72 hours were excluded from the study.

Moving is improving!

Importance of mobilisation
During a hospital stay people tend to move less. This can lead to a reduction in muscle strength, condition, function loss and in the elderly in a reduced autonomy. Any kind of movement can contribute to recovery. Like exercises in bed, in a chair or walking along the corridors in the hospital itself.

Exercises in bed

Exercises

Exercises

While standing up from a chair

Cycling and walking the stairs

Cycling

Facts
Each day without movement you lose up to 3% of muscle strength
Unlimited mobilisation reduces your endurance and balance
Increases risk of falling
A decreased mobility extends your length of hospital stay

Tips

- Wear proper footwear and comfortable clothing during daytime instead of pajamas
- Not sure what to do? Ask your nurse or physiotherapist for advice or help

Regularly move your shoulders in circles to reduce stiffness of the sternum, neck and shoulders

After surgery using a walking stick is prohibited. Therefore we recommend a rollator

When coughing, please support your chest with your arms crossed and your hands on your shoulders

For further information, please contact your caregivers at Thoraxcentrum.

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Medisch Spectrum Twente

Change in in-hospital ACSM score was defined as primary endpoint. Secondary endpoints included change in the detailed TCT score, ICU length of stay, surgical ward stay and 30-, 120-day and overall survival. Follow-up on mortality ended 1st May 2019. No loss-of follow up was expected. Baseline characteristics were determined based on EuroSCORE II definitions [24].

Seven dedicated physical therapists trained for cardio-thoracic physiotherapy practice participated in the study. They were trained in ACSM and TCT classification and a pocket card was handed out for daily use. A physiotherapist noted down patient-reported ACSM score daily at each patient room.

A 3 week interval of cardio-thoracic surgery determined study size for the control group (T_0). A consecutive 3 week interval determined intervention group (T_1) size and was followed by 6 months use of the poster as new standard care (T_1).

Development of TCT score

Six functional activities were deducted from the ACSM score [20] and functional independence measure dimensions [18]: lying in bed, sitting in a chair, walking to the toilet in the patient's private hospital room, walking along the ward corridor, cycling on a home trainer and walking the stairs. Four frequency descriptors were added: never, sometimes, often and always. A matrix of functional activities and frequency descriptors is provided in Supplement 1. A patient questionnaire for poster experience was sent by mail to patients (Supplement 2).

This study was exempted from the Medical Research Involving Human Subjects Act by the Medical Ethics Committee Twente (METC Twente: K16-85) and was approved by the local institutional review board.

Exercise program and milestones

All patients received physical therapy twice a day until the 3rd postoperative day and then once a day. A standardised program starting at ICU discharge included:

Day 1: Breathing exercises, coughing techniques, control mobilisation upper- and lower extremities, transfer from bed to chair with assistance

Day 2: Exercises as on day 1. Self-transfer from bed to chair with or without assistance, ambulation with assistance for 20 m at surgical ward

Day 3: Exercises as on day 2. Ambulation with increase in distance (± 15 m) and frequency (3 times), cycling for 5 – 10 min with 0-10 Watt depending on hemodynamic stability

Day 4: Exercises as on day 3. Walking stairs (1 floor) with assistance, information on home mobilisation, increase cycling duration (5 – 10 min) and power (10 – 15 Watt)

Each patient specific exercise program was based on evaluation findings, comorbidities and patient goals.

Statistical analysis

Statistical analysis was performed with SPSS 25.0 (SPSS Inc, Chicago, IL). Results were considered statistically significant at the 5% level. Continuous variables were presented

as mean with standard deviation (SD) or median with interquartile range (IQR) depending on the distribution. Continuous variables were tested for normality with visual inspection of histograms and skewness and kurtosis measures. Categorical variables were presented as number with corresponding percentages and compared between groups using χ^2 or a Fisher Exact Test.

A linear mixed model was used to determine differences in ACSM score between groups (T_0 and T_1), differences over time (day-to-day ACSM scores) and interaction between group and time to study differences in the course of ACSM score over time between the two groups. A gender subgroup analysis as encouraged by the Institute of Medicine [25] was performed. Furthermore a subgroup analysis of CABG patients was planned for all endpoints because of different Dutch guidelines for CABG and non-CABG in-hospital mobilisation [26].

A Kaplan Meier curve with log rank test was used to test for differences in survival between groups T_0 and T_1 .

Results

Out of 309 patients selected for eligibility, with 37 patients in the UCG (T_0) and 272 patients in the poster group (T_1), in total 59 patients were excluded based on prolonged ICU stay over 72 hours ($n = 36$), salvage surgery ($n = 11$) and absence of major cardiac surgery ($n = 12$) (flow diagram in Supplement 3). Six patients were in a patient room without a poster and did not receive the intervention. Three patients from T_1 were excluded because of incomplete data collection. Thus, 241 patients were included for analysis with 32 patients in the T_0 cohort and 209 patients in the T_1 cohort.

Baseline characteristics

Patients had a mean age of 67 years, a BMI of 28 kg/m^2 , over 50% had multivessel disease and 16% a recent myocardial infarction. There were no significant differences between groups for baseline or in-hospital characteristics (Table 2 and 3).

Median ICU stay was 1.5 [1 – 2] days in T_0 and 1 [1 – 2] day in T_1 ($p = 0.92$) with a median surgical ward stay of 4 days in both groups (T_0 4 [2.5 – 4] and T_1 4 [3 – 5], $p = 0.51$, Table 4).

Median follow-up on mortality was 932 days in T_0 and 553 days in T_1 . There was no difference in mortality at all timepoints (Table 4). No complications such as wound or sternum dehiscence or ventricular tachycardia related to early mobilisation were reported.

American College of Sports Medicine (ACSM) functional score

Median ACSM score one day after ICU discharge was 1 [1 – 1] in T_0 and 1 [1 – 2] in T_1 and increased two days after ICU discharge to 3 [2 – 3] in T_0 and 3 [2 – 4] in T_1 (For a day-to-day boxplot, see Supplement 4). ACSM score at discharge was 5.5 [4 – 6] in T_0 and 5 [4 – 6] in T_1 , $p = 0.28$.

Table 2 Baseline characteristics

Variable	T ₀ (n = 32)	T ₁ (n = 209)	p value
Age, years	66 ± 12	68 ± 11	0.32
Gender, male	24 (75%)	151 (72%)	0.83
Body mass index, kg / m ²	29 ± 4.5	28 ± 4.1	0.20
Diabetes	9 (28%)	57 (27%)	0.94
Multivessel disease	17 (77%)	121 (68%)	0.37
Recent myocardial infarction	6 (19%)	33 (16%)	0.67
Left ventricular function	...	...	0.13
Poor, < 30%	2 (6.3%)	6 (2.9%)	...
Moderate, 30 – 50%	2 (6.3%)	41 (20%)	...
Good, > 50%	28 (88%)	162 (78%)	...
COPD	2 (6.2%)	24 (12%)	0.55
Extracardiac arteriopathy	1 (3.1%)	27 (13%)	0.14
Neurological dysfunction	0 (0%)	6 (2.9%)	1.00
Previous cardiac surgery	0 (0%)	11 (5.3%)	0.37
NYHA class	...	...	0.13
I	28 (88%)	143 (69%)	...
II	4 (13%)	45 (22%)	...
III	0 (0%)	18 (8.7%)	...
IV	0 (0%)	2 (1.0%)	...
Urgency	...	...	0.53
Elective	19 (59%)	131 (63%)	...
Urgent	13 (41%)	72 (34%)	...
Emergency	0 (0%)	6 (2.9%)	...
Salvage	0 (0%)	0 (0%)	...
EuroSCORE I, log	2.8 [1.7 – 5.8]	3.7 [1.9 – 7.5]	0.18
EuroSCORE II, log	1.1 [0.83 – 1.7]	1.4 [0.93 – 2.3]	0.16

Data are means ± SD or medians [IQR] or numbers (proportions)

COPD = Chronic obstructive pulmonary disease; NYHA = New York Health Association.

First, sensitivity of the ACSM score to measure day-to-day changes after cardiac surgery was established. ACSM score was significantly different over time, ($p < 0.001$) with a plateau phase starting from day 4. Men had an overall significantly higher mean ACSM score of 0.50 ($p < 0.001$, 95% CI 0.25 to 0.76) compared to women. Furthermore, there was a significant difference in the course of the ACSM score over time between men and women ($p < 0.001$).

Table 3 Periprocedural characteristics

Variable	T ₀ (n = 32)	T ₁ (n = 209)	p value
Type of surgery	...	...	0.34
CABG	17 (53%)	117 (56%)	...
Valve surgery	5 (16%)	46 (22%)	...
CABG + valve surgery	2 (6.3%)	19 (9.1%)	...
TAVI	3 (9.4%)	9 (4.3%)	...
Other surgery	5 (16%)	18 (8.5%)	...
Cardiopulmonary bypass	18 (62%)	144 (72%)	0.27
Cardiopulmonary bypass time, min	97 [62 – 137]	102 [80 – 127]	0.56

Data are medians [IQR] or numbers (proportions)

CABG = Coronary artery bypass surgery; TAVI = Transcatheter aortic valve implantation

Table 4 Postoperative characteristics and survival

Variable	T ₀ (n = 32)	T ₁ (n = 209)	p value
Intensive care unit stay, days	1.5 [1 – 2]	1 [1 – 2]	0.92
Surgical ward stay, days	4 [2.5 – 4.5]	4 [3 – 5]	0.51
Discharge to:	...	...	0.36
Home	24 (75%)	130 (62%)	...
Referring hospital	8 (25%)	78 (37%)	...
Other	0 (0%)	1 (0.47%)	...
ACSM score at discharge	5.5 [4 – 6]	5 [4 – 6]	0.28
Survival			
30-day survival	32 (100%)	209 (100%)	1.00
120-day survival	32 (100%)	208 (99.5%)	0.70
365-day survival	31 (97%)	206 (99%)	0.48

Data are medians [IQR] or numbers (proportions)

ACSM score was not significantly affected by the intervention poster ($p = 0.27$). Change in ACSM over time comparing T₀ with T₁ is displayed in Figure 2. There was no difference in ACSM score for gender between T₀ and T₁, ($p = 0.23$), nor was there a difference in the course of the ACSM score over time between the two groups ($p = 0.19$).

ACSM increase in CABG patients

A subgroup analysis for CABG patients included 21 patients in T₀ and 142 patients in T₁. There were no differences in baseline or periprocedural characteristics (see Supplement 5). ACSM was significantly different over time ($p < 0.001$). No significant effect of the intervention poster was observed ($p = 0.15$) in the CABG subgroup (Table 5) nor a difference in the course of the ACSM score over time between groups ($p = 0.53$). ACSM score at discharge was 5 [4 – 6] in both groups, $p = 0.74$.

Figure 2 ACSM scores after ICU discharge for the usual care group (T₀; left bars) and intervention group (T₁; right bars). ACSM score changed significantly over time ($p < 0.001$), no difference between both groups was observed ($p = 0.27$). ACSM = American College for Sports Medicine functional score; ICU = Intensive care unit

Table 5 Effect of intervention poster on ACSM functional activity levels and TCT scores

Variable	Increase of score by poster *	95% Confidence Interval	p value
ACSM score			
Overall (n = 241)	0.19	-0.15 to 0.53	0.27
CABG (n = 163)	0.28	-0.10 to 0.66	0.15
Discharged home (n = 154)	0.35	-0.04 to 0.75	0.08
TCT score			
Bed			
Overall (n = 220)	0.13	-0.04 to 0.27	0.06
CABG (n = 150)	0.18	0.02 to 0.33	0.02
Discharged home (n = 146)	0.19	0.04 to 0.34	0.02
Chair			
Overall (n = 220)	0.34	0.18 to 0.49	< 0.001
CABG (n = 150)	0.33	0.16 to 0.51	< 0.001
Discharged home (n = 146)	0.36	0.19 to 0.52	< 0.001
Toilet			
Overall (n = 220)	0.34	0.13 to 0.55	0.002
CABG (n = 150)	0.34	0.10 to 0.58	0.006
Discharged home (n = 146)	0.39	0.15 to 0.62	0.001
Corridor			
Overall (n = 220)	0.30	0.09 to 0.51	0.005
CABG (n = 150)	0.27	0.04 to 0.51	0.006
Discharged home (n = 146)	0.39	0.16 to 0.63	0.001
Home trainer			
Overall (n = 220)	0.24	0.04 to 0.44	0.02
CABG (n = 150)	0.26	0.03 to 0.48	0.02
Discharged home (n = 146)	0.34	0.09 to 0.59	0.007
Stairs			
Overall (n = 220)	-0.06	-0.16 to 0.04	0.21
CABG (n = 150)	-0.06	-0.17 to 0.05	0.29
Discharged home (n = 146)	-0.03	-0.15 to 0.10	0.66

* Point estimate determined with linear mixed model analysis

ACSM = American College of Sports Medicine (ACSM) functional score; CABG = Coronary artery bypass surgery

Discharge from the hospital

Hospital discharge to home or referring hospitals started from day 3 after ICU transfer (Figure 3). Since patients referred to another hospital had a follow up only until referral instead of discharge to home, a sensitivity analysis was performed. This was not planned since no earlier discharge to a referring hospital in the intervention group was expected.

In patients discharged home, the poster group (T_1) had no significant higher mean ACSM score (mean difference 0.35; 95% CI -0.04 to 0.75) compared to patients in T_0 ($p = 0.08$). In this subgroup, ACSM score between T_0 and T_1 did not change differently over time ($p = 0.18$). ACSM score at discharge to home was 6 [4.25 – 6] in T_0 and 6 [5 – 6] in T_1 , $p = 0.89$.

Figure 3 Patients admitted to the hospital after ICU discharge. From day 3 on, patients were discharged to home or referring hospital. A rapid increase in discharge is observed after day 2 (dotted line). ICU = Intensive care unit

TCT descriptive score with actual activities

Incomplete data collection for one or multiple days resulted in exclusion from analysis for 28 patients. In total 32 T₀-patients and 188 T₁-patients were included in TCT score analysis.

Every individual TCT score, bed, chair, toilet, corridor, home trainer and stairs was significantly different over time ($p < 0.001$). TCT scores for chair, toilet, corridor and home trainer were significantly higher in the poster group with differences ranging from 0.24 to 0.33 (see Figure 4 and Table 5).

In both the CABG and discharged home subgroups TCT scores for bed, chair, toilet, corridor and home trainer were significantly higher in the poster group (Table 5).

Discussion

Measuring ACSM functional score for heart surgery patients

ACSM score was sensitive to measure daily improvement of patient functional activities after heart surgery. A stabilisation pattern was observed 4 to 5 days after ICU discharge. The mobilisation poster did not increase ACSM score in the overall group ($p = 0.27$), CABG subgroup ($p = 0.15$) or discharge to home group ($p = 0.08$).

Higher ACSM scores were observed in men who might have a more competitive attitude to mobilisation or overestimate self-reported activities. Also, women might be more hesitant to mobilize after surgery. This finding is in line with a recent study on postoperative mobilisation after total hip arthroplasty [27]. Further research should quantify this difference using objective data from activity trackers.

Guidelines on cardiac rehabilitation from the American College of Cardiology/American Heart Association or the American Association of Cardiovascular and Pulmonary Rehabilitation focus on mobilisation after discharge only [28, 29].

Figure 4A-F TCT score development during hospital stay. A significant improvement of scores chair, toilet, corridor and home trainer was observed in the poster group

A Dutch physical therapy guideline on in-hospital rehabilitation states: “The patient should start dynamic mobilisation exercises of the large muscle groups as soon as possible; the exercises are gradually extended to include walking and stair climbing, while the physical therapist watches out for signs of excessive strain” [26], yet gives no advice on how to achieve this level. Our study shows that early mobilisation is safe and results in increased activity levels.

TCT descriptive score

The intervention poster had a significant impact on sitting in a chair, walking to the toilet and along the corridor and cycling on a home trainer. With effect sizes around 0.30 on a frequency scale from 1 (never) to 4 (always) a modest effect for patients was achieved.

No difference in TCT score for bed and stairs was found. Patients generally only lay in bed at day 1 after ICU discharge and this did not change between T_0 and T_1 . Walking the stairs is mainly a goal before discharge and thus did not change. These TCT scores might be removed in future studies to reduce administrative load for physical therapists.

Study limitations

This study determined ACSM and TCT scores once a day. The exact moment during the day might have varied from day to day and between patients. We however expect that this will have had minimally influences on ACSM and TCT score as maximum daily activity is measured. Next, a prospective sequential-group study might include bias compared to a randomised controlled trial. In this study, baseline characteristics were balanced between control and intervention group (table 2). Furthermore, a parallel randomised design would allow for informal cross-over as patients might see or discuss the poster at the surgical ward.

This study is a single centre study which makes generalisation to other centres more challenging as in-hospital mobilisation strategies vary per centre. Our early mobilisation protocol is comparable in physical activity to other published protocols, e.g. a protocol from Da Costa Torres et al. [30]. Physical therapists in Australia and New Zealand reported in a national survey that all patients are sitting out of bed at first postoperative day and 20% completed one flight of stairs on day 4 after uncomplicated CABG [12]. In our study, 88 to 96% sits on a chair at first postoperative day, 36 to 48% cycled on a home trainer on day 3 and 45 to 75% walked the stairs on day 4. Less intensive mobilisation programs are likely to increase ACSM score during hospital stay as it increased drastically in this study from day 1 to day 4.

A linear mixed model was used because length of stay differed between patients and repeated ACSM or TCT measures from the same patient are more similar than responses from other patients. This model assumes parametric distributions. Although the ACSM score is a 6-point ordinal scale, it has a parametric distribution on days 2 to 4 after ICU discharge. As a consequence, conclusions drawn from this model might be too liberal. Also, a sample size of 32 patients in the control group might be too small to find a significant effect of an intervention poster for a composite measure such as ACSM score.

Future work

Other patient groups with intermediate to long hospital stay might benefit from early mobilisation. At the cardiology ward early mobilisation for patients with or without a mobilisation poster should be measured using the ACSM score. Further studies should investigate the use of ACSM score in other medical disciplines.

The intervention group used an A1 size poster during ward stay. Patients found this poster to be clear, motivating and not pushy (Supplement 2). Functional activities might increase faster with persuasive technology focusing on the current activity level. Future work should focus on patient-specific information and exercises that match the current functional level of patients recovering from cardiac surgery.

The activity measure for post-acute care “6-clicks” basic mobility (AM-PAC) is validated for the entire hospital population [31]. A low AM-PAC is related to readmissions to the hospital after cardiac surgery. Despite its good inter-rater reliability [32], AM-PAC requires additional exercises for patients while ACSM score is patient-reported. Future research should investigate the relation between AM-PAC and ACSM including day-to-day discrimination and determine increase of work for physiotherapists.

Last, information on activity levels now ends when patients are discharged to home or referring hospital. In this study discharge to a hospital was a substantial part of all discharges (25% in T_0 , 37% in T_1). To ensure continuity of active mobilisation strategies activity levels should be measured during full hospital stay.

Conclusions

Although ACSM functional score showed to be sensitive to measure day-to-day changes of patients at a surgical ward after cardiac surgery, no difference in effects between the mobilisation poster and usual care group were observed. Higher ACSM scores were found for men. An early mobilisation strategy using a mobilisation poster however significantly increased sitting in a chair, walking to the toilet and corridor and cycling on a home trainer as measured with the TCT score.

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Declaration of interest statement

The authors report no conflict of interest.

References

1. D'Agostino RS, Jacobs JP, Badhwar V, et al. The Society of Thoracic Surgeons Adult Cardiac Surgery Database: 2019 Update on Outcomes and Quality. *Ann Thorac Surg*. 2018.
2. De Klein K, Valkenet K, Veenhof C. Perspectives of patients and health-care professionals on physical activity of hospitalized patients. *Physiother Theory Pract*. 2019;1-8.
3. Koenders N, van Oorsouw R, Seeger JPH, Nijhuis-van der Sanden MWG, van de Glind I, Hoozeboom TJ. "I'm not going to walk, just for the sake of walking...": a qualitative, phenomenological study on physical activity during hospital stay. *Disabil Rehabil*. 2020;42:78-85.
4. Kortebein P, Symons TB, Ferrando A, et al. Functional impact of 10 days of bed rest in healthy older adults. *J Gerontol A Biol Sci Med Sci*. 2008;63:1076-1081.
5. Anderson L, Oldridge N, Thompson DR, et al. Exercise-Based Cardiac Rehabilitation for Coronary Heart Disease: Cochrane Systematic Review and Meta-Analysis. *Journal of the American College of Cardiology*. 2016;67:1-12.
6. Koenders N, Weenk M, van de Belt TH, van Goor H, Hoozeboom TJ, Bredie SJH. Exploring barriers to physical activity of patients at the internal medicine and surgical wards: a retrospective analysis of continuously collected data. *Disabil Rehabil*. 2019;1-7.
7. Meesters J, Conijn D, Vermeulen HM, Vliet Vlieland T. Physical activity during hospitalization: Activities and preferences of adults versus older adults. *Physiother Theory Pract*. 2019;35:975-985.
8. Royal Dutch Society for Physical Therapy (KNGF). KNGF Clinical Practice Guideline for physical therapy in patients undergoing cardiac rehabilitation. *Dutch J. of Phys Ther*. 2011;121:Suppl 1-52.
9. Balady GJ, Williams MA, Ades PA, et al. Core components of cardiac rehabilitation/secondary prevention programs: 2007 update: a scientific statement from the American Heart Association Exercise, Cardiac Rehabilitation, and Prevention Committee, the Council on Clinical Cardiology; the Councils on Cardiovascular Nursing, Epidemiology and Prevention, and Nutrition, Physical Activity, and Metabolism; and the American Association of Cardiovascular and Pulmonary Rehabilitation. *Circulation*. 2007;115:2675-2682.
10. Piepoli MF, Corra U, Benzer W, et al. Secondary prevention through cardiac rehabilitation: from knowledge to implementation. A position paper from the Cardiac Rehabilitation Section of the European Association of Cardiovascular Prevention and Rehabilitation. *Eur J Cardiov Prev R*. 2010;17:1-17.
11. Pack QR, Priya A, Lagu T, et al. Cardiac Rehabilitation Utilization During an Acute Cardiac Hospitalization: A NATIONAL SAMPLE. *J Cardiopulm Rehabil Prev*. 2019;39:19-26.
12. Hong S, Milross M, Alison J. Physiotherapy mobility and walking management of uncomplicated coronary artery bypass graft (CABG) surgery patients: a survey of clinicians' perspectives in Australia and New Zealand. *Physiother Theory Pract*. 2020;36:226-240.
13. Price KJ, Gordon BA, Bird SR, Benson AC. A review of guidelines for cardiac rehabilitation exercise programmes: Is there an international consensus? *Eur J Prev Cardiol*. 2016;23:1715-1733.
14. Kalisch BJ, Lee S, Dabney BW. Outcomes of inpatient mobilization: a literature review. *J Clin Nurs*. 2014;23:1486-1501.
15. Hirschhorn AD, Richards D, Mungovan SF, Morris NR, Adams L. Supervised moderate intensity exercise improves distance walked at hospital discharge following coronary artery bypass graft surgery--a randomised controlled trial. *Heart Lung Circ*. 2008;17:129-138.

16. Borghi-Silva A, Mendes RG, Costa Fde S, Di Lorenzo VA, Oliveira CR, Luzzi S. The influences of positive end expiratory pressure (PEEP) associated with physiotherapy intervention in phase I cardiac rehabilitation. *Clinics (Sao Paulo)*. 2005;60:465-472.
17. Mendes RG, Simões RP, Costa FdSM, et al. Is applying the same exercise-based inpatient program to normal and reduced left ventricular function patients the best strategy after coronary surgery? A focus on autonomic cardiac response. *Disability and Rehabilitation*. 2014;36:155-162.
18. Linacre JM, Heinemann AW, Wright BD, Granger CV, Hamilton BB. The structure and stability of the Functional Independence Measure. *Arch Phys Med Rehabil*. 1994;75:127-132.
19. Simpson DB, Breslin M, Cumming T, et al. Go Home, Sit Less: The Impact of Home Versus Hospital Rehabilitation Environment on Activity Levels of Stroke Survivors. *Arch Phys Med Rehabil*. 2018;99:2216-2221 e2211.
20. Whaley MH, Brubaker PH, Otto RM, Armstrong LE. *ACSM's guidelines for exercise testing and prescription*. 7th ed. Philadelphia, Pa.: Lippincott Williams & Wilkins; 2006.
21. Vandenbroucke JP, von Elm E, Altman DG, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. *PLoS Med*. 2007;4:e297.
22. van Delft LMM, Bor P, Valkenet K, Veenhof C. Hospital in Motion, a Multidimensional Implementation Project to Improve Patients' Physical Behavior During Hospitalization: Protocol for a Mixed-Methods Study. *JMIR Res Protoc*. 2019;8:e11341.
23. Katz S, Ford AB, Moskowitz RW, Jackson BA, Jaffe MW. Studies of Illness in the Aged. The Index of Adl: A Standardized Measure of Biological and Psychosocial Function. *JAMA : the journal of the American Medical Association*. 1963;185:914-919.
24. Nashef SA, Roques F, Sharples LD, et al. EuroSCORE II. *European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery*. 2012;41:734-744; discussion 744-735.
25. Institute of Medicine (US) Board on Population Health and Public Health Practice. *Sex-Specific Reporting of Scientific Research: A Workshop Summary*. Washington (DC)2012.
26. Achttien RJ, Staal JB, van der Voort S, et al. Exercise-based cardiac rehabilitation in patients with coronary heart disease: a practice guideline. *Netherlands heart journal : monthly journal of the Netherlands Society of Cardiology and the Netherlands Heart Foundation*. 2013;21:429-438.
27. Doppelbauer M, Schuler M, Sauter D. [Postoperative mobilization after total hip arthroplasty : Measured by Fitbit activity trackers]. *Der Orthopade*. 2019.
28. Hillis LD, Smith PK, Anderson JL, et al. 2011 ACCF/AHA Guideline for Coronary Artery Bypass Graft Surgery. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Developed in collaboration with the American Association for Thoracic Surgery, Society of Cardiovascular Anesthesiologists, and Society of Thoracic Surgeons. *Journal of the American College of Cardiology*. 2011;58:e123-210.
29. Kaminsky LA, Brubaker PH, Guazzi M, et al. Assessing Physical Activity as a Core Component in Cardiac Rehabilitation: A POSITION STATEMENT OF THE AMERICAN ASSOCIATION OF CARDIOVASCULAR AND PULMONARY REHABILITATION. *J Cardiopulm Rehabil Prev*. 2016;36:217-229.
30. da Costa Torres D, Dos Santos PM, Reis HJ, Paisani DM, Chiavegato LD. Effectiveness of an early mobilization program on functional capacity after coronary artery bypass surgery: A randomized controlled trial protocol. *SAGE Open Med*. 2016;4:2050312116682256.
31. Jette DU, Stilphen M, Ranganathan VK, Passek SD, Frost FS, Jette AM. Validity of the AM-PAC "6-Clicks" inpatient daily activity and basic mobility short forms. *Phys Ther*. 2014;94:379-391.

32. Geelen SJG, Valkenet K, Veenhof C. Construct validity and inter-rater reliability of the Dutch activity measure for post-acute care "6-clicks" basic mobility form to assess the mobility of hospitalized patients. *Disabil Rehabil.* 2018:1-7.

Supplements

Supplement 1 – TCT matrix of functional activities and frequency descriptors

Translated Thorax Centrum Twente score form

Date	Always/Mostly	Often	Sometimes / Rarely	Never/N.A.
Bed	Continuously in bed (1)	Except during meals (2)	Only after lunch / at night (3)	N.A
Chair	Mainly in chair (4)	2 – 3 hours / day (3)	Max 30 min / day (2)	Never (1)
Toilet	Frequently independent (4)	Independent 1 – 2 x (3)	Toilet chair / with supervision (2)	Never / N.A. (1)
Corridor	> 5 x per day (4)	> 20 m / max 4x per day (3)	Max 20 m / < 2x per day (2)	Never / N.A. (1)
Home trainer	Independent, > 2 x (4)	Independent, 2x (3)	With supervision, max 1 x (2)	Never / N.A. (1)
Stairs	N.A.	Independent (3)	With supervision (2)	Never / N.A. (1)

Original Dutch Thorax Centrum Twente score form

Datum	Vaak/vooral	Regelmatig	Soms / Zelden	Nooit/n.v.t.
Bed	Bedlegerig (1)	Behalve tijdens eten (2)	Rustuur / 's nachts (3)	n.v.t.
Stoel	Vooraf op de stoel (4)	2 – 3 uur / dag (3)	Max 30 min / dag (2)	Niet (1)
Toilet	Frequent zelfstandig (4)	Zelfstandig tot 2x (3)	Po stoel / met begeleiding (2)	Nooit / Nvt (1)
Gang	> 5 x per dag (4)	> 20 m / max 4 x per dag (3)	Max 20 m / < 2 x per dag (2)	Nooit / Nvt (1)
Fietsen	Zelfstandig, > 2 x (4)	Zelfstandig, 2 x (3)	Met begeleiding max 1x (2)	Nooit / Nvt (1)
Trap	n.v.t.	Zelfstandig (3)	Met begeleiding (2)	Nooit / Nvt (1)

Supplement 2 – Patient Questionnaire (English and original Dutch questionnaire)

A patient questionnaire for poster experience was developed with 13 rubric questions and one grading question. Both English and original Dutch questionnaire are attached.

Out of the 45 questionnaires that were sent by mail to patients from the first T1-group, 32 were returned with a respective response rate of 71%. Patients agreed (53%) or strongly agreed (31%) that the poster was clear (see Figure 5). Similar responses were obtained on clearness of the exercises (66% agreed and 28% strongly agreed). Only 19% of these patients (strongly) agreed that the poster needs additional explanation, while 56% (strongly) disagreed. No patient found the poster pushy.

Supplementary Figure 2 Bar chart representation of patient questionnaire on mobilisation poster experience

One patient did not reply questions on the backside of the questionnaire. By accident, a question bullet was missing for the “clearness of the poster” question and 15 patients did not respond to this question.

Response: 32/45 people from T₁-group (October to November 2016).

Supplemental Table 2.1 Responses from patients on mobilisation poster experience

	Strongly disagree	Disagree	Neutral	Agree	Strongly Disagree	Don't know	Missing
The poster							
is clear	0	3	2	17	10	0	0
is easy to understand	0	2	4	15	11	0	0
helped me	1	4	5	14	6	2	0
needs additional explanation	1	17	4	5	1	3	1 [‡]
is pushy	4	22	4	0	0	1	1 [‡]
matches your recovery process	1	2	5	18	5	1	0
is motivating	0	3	5	18	6	0	0
gave me new information	0	3	7	15	4	2	1 [‡]
is to my opinion, complete	0	0	2	11	2	2	15 [‡]
The exercises							
are clear	0	0	1	21	9	1	0 [‡]
are well practicable	0	0	3	20	8	1	0 [‡]
I would like to							
have seen the poster before surgery	1	2	13	8	5	2	1 [‡]
receive the poster at discharge on A4-paper	1	4	5	12	7	2	1 [‡]

[‡] During data collection, it was noted that for this question, "bullets" were missing, resulting in many missing values

[‡] One patient did not fill in the questions on the backside of the paper

Please give a grade for our intervention poster:

Grade	1	2	3	4	5	6	7	8	9	10
Number of responses	0	1	0	0	0	1	5	21	1	1

For information converting grading systems in the Netherlands into U.S. or UK systems, please see: <https://students.uu.nl/sites/default/files/geo-grading-systems-holland-vs-us-uk.pdf>

Supplemental Table 2.2 Original Dutch responses from patients on mobilisation poster experience

	Volledig oneens	Oneens	Neutraal	Eens	Volledig eens	Weet niet	Missend
De poster:							
is overzichtelijk	0	3	2	17	10	0	0
is begrijpelijk	0	2	4	15	11	0	0
heeft mij geholpen	1	4	5	14	6	2	0
heeft aanvullende uitleg nodig	1	17	4	5	1	3	1 [‡]
is opdringerig	4	22	4	0	0	1	1 [‡]
sluit aan bij uw herstel	1	2	5	18	5	1	0
werkt motiverend	0	3	5	18	6	0	0
heeft mij nieuwe informatie gegeven	0	3	7	15	4	2	1 [‡]
is naar mijn idee volledig	0	0	2	11	2	2	15 [‡]
De oefeningen zijn:							
duidelijk	0	0	1	21	9	1	0 [‡]
goed uitvoerbaar	0	0	3	20	8	1	0 [‡]
Ik zou de poster graag							
voor de operatie zien	1	2	13	8	5	2	1 [‡]
bij ontslag krijgen op A4 formaat	1	4	5	12	7	2	1 [‡]

Geef een rapportcijfer voor de interventieposter:

Rapportcijfer	1	2	3	4	5	6	7	8	9	10
Aantal reacties	0	1	0	0	0	1	5	21	1	1

Supplement 3 – Flow chart

CONSORT 2010 flow diagram – Moving is Improving study

Supplement 4 – ACSM day to day boxplot

Supplementary Figure 4.1 ACSM development in time. No difference between T_0 and T_1 was found ($p = 0.26$). Depicted are boxplots with median scores. Whiskers represent 1.5 interquartile range

Supplementary Figure 4.2 Gender differences in ACSM development. Men had a significantly higher ACSM score compared to women ($p < 0.001$)

Supplement 5 – Baseline and periprocedural characteristics CABG subgroup

Supplementary Table 5.1 Baseline characteristics of patients with myocardial revascularisation

Variable	T ₀ (n = 21)	T ₁ (n =142)	p value
Age, years	68 [56 – 73]	70 [63 – 75]	0.10
Gender, male	18 (86%)	111 (78%)	0.57
Body Mass Index, kg / m ²	29 ± 4.6	28 ± 4.2	0.63
Diabetes	7 (33%)	46 (32%)	0.90
Multivessel disease	17 (90%)	121 (90%)	1.00
Recent myocardial infarction	6 (29%)	33 (23%)	0.59
Left Ventricular Function	...	...	0.30
Poor, < 30%	2 (10%)	6 (4.2%)	...
Moderate, 30-50%	2 (10%)	30 (21%)	...
Good, > 50%	17 (81%)	106 (75%)	...
COPD	2 (10%)	14 (10%)	1.00
Extracardiac arteriopathy	1 (4.8%)	21 (15%)	0.31
Neurological dysfunction	0 (0%)	5 (3.5%)	1.00
Previous cardiac surgery	0 (0%)	2 (1.4%)	1.00
NYHA-class	...	...	0.20
I	21 (100%)	115 (82%)	...
II	0 (0%)	18 (13%)	...
III	0 (0%)	7 (5.0%)	...
IV	0 (0%)	1 (0.7%)	...
Urgency	...	...	0.48
Elective	9 (43%)	72 (51%)	...
Urgent	12 (57%)	65 (46%)	...
Emergency	0 (0%)	5 (3.5%)	...
Salvage	0 (0%)	0 (0%)	...
EuroSCORE I, log	2.28 [1.51 – 4.29]	2.89 [1.68 – 6.36]	0.09
EuroSCORE II, log	1.06 [0.80 – 1.61]	1.33 [0.98 – 2.1]	0.09

Data are means ± SD or Medians [IQR] or numbers (proportions)

CABG = Coronary artery bypass surgery; COPD = Chronic obstructive pulmonary disease;

NYHA = New York Health Association

Supplementary Table 5.2 Periprocedural characteristics

Variable	T ₀ (n = 21)	T ₁ (n =142)	p value
Type of surgery	...	...	0.53
CABG, isolated	17 (81%)	117 (82%)	
CABG + valve surgery	2 (10%)	19 (13%)	
CABG + other surgery	2 (10%)	6 (4.2%)	
Off-pump CABG, no cardiopulmonary bypass	11 (52%)	55 (39%)	0.23
Cardiopulmonary bypass time, min	103 [67 – 137]	104 [84 – 128]	0.94
Aortic crossclamp time, min	60 [47 – 82]	73 [54 – 88]	0.37

Data are means ± SD or medians [IQR] or numbers (proportions)

CABG = Coronary artery bypass surgery

CHAPTER 8

DEVELOPMENT AND EVALUATION OF A PROFICIENCY-BASED AND SIMULATION-BASED SURGICAL SKILLS TRAINING FOR TECHNICAL MEDICINE STUDENTS

Submitted

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Abbreviations and acronyms

ECTS	European credit transfer system
ICC	Intraclass correlation coefficients
NOTS	Non-technical skills for surgeons
OR	Operating theatre, operating room
SBT	Simulation-based training
WMO	Dutch Medical Research Involving Human Subjects Act

Abstract

Objective

To develop and evaluate a proficiency-based, simulation-based course for basic surgical skills at graduate level. Learning outcomes were measured at the level of knowledge and skills and students' reactions to the course.

Design

Prospective cohort study with a survey after the first clinical rotations, curriculum design

Setting

A 10-week, 3 European Credit Transfer and Accumulation System credits graduate surgical skills course within the Technical Medicine master program at the Technical Medical Centre, University of Twente, Enschede, The Netherlands. Simulated and tertiary clinical care.

Participants

155 graduate Technical Medicine students from academic years 2015 – 2016 and 2016 – 2017 entered this study. 120 students gave consent.

Results

The surgical skills course covered topics and skills related to pre-, intra-, and post-operative care, including case-based medical reasoning, patient safety, infection management, operating theatre etiquette, scrubbing and donning, instrument handling, local anaesthesia, excision of tissue and suturing. Students were assessed on knowledge and procedural skills. Four experienced and trained assessors evaluated skill performance using a checklist and procedure-specific rating scales specifically designed for this assessment.

Pass rates of the knowledge test were 78% and 87% for the procedural skill assessment. Students struggled most with applying clinical reasoning in the knowledge test and maintaining a safe work environment in the procedural skill assessment. A post-course questionnaire revealed that students were confident about their professional performance in the operating room and were able to apply the acquired knowledge and skills.

Conclusions

Graduate students were able to reach proficiency level in a simulation-based basic surgical skills course. Students stated to go with confidence to the operating room and felt competent in performing four basic surgical skills. Based on this study, we recommend that proficiency-based training using simulation should be standard in surgical curricula before students are allowed to practice on patients.

Introduction

Surgical training

International reports on surgical safety reveal major deficiencies in worldwide surgical skills training [1, 2] which is reflected by the United Kingdom's higher mortality rates (6%) on the first day of junior doctors [3]. Surgical educators express increased concerns about a lack of confidence and competence among residents [4]. Furthermore, non-technical skills for surgeons (NOTSS) such as situational awareness, decision-making, communication and teamwork and leadership are often not assessed but evaluated implicitly [5]. Surgical educators named performance assessment and curriculum development as most important topics in surgical education followed by simulation [6]. Undergraduate medical education in a preparatory curriculum to achieve well-trained practice-ready graduates is needed, yet is often lacking [7].

Simulation-based training

Surgical training moves towards outcome-based performance assessment and simulation is increasingly used for that goal [8, 9]. Simulation-based training (SBT) allows for standardized teaching and objective evaluation of surgical skills [10, 11]. Ideally, SBT is proficiency-based and trainees have to master a particular skill before they progress to a more complex skill or environment [12]. Embedding SBT in a graduate curriculum has the advantage that students attain proficiency prior to their clinical rotations or residency. Training of (surgical) skills before clinical rotations shape behaviour and compliance to guidelines as they form long-term habits during their rotations [13]. Role models in SBT who encourage good hand hygiene compliance and good habit, might strongly influence students' clinical behaviour. Furthermore, simulation might decrease cognitive overload for students stressfully trying to maintain sterility in the OR [14] and benefits students by providing an environment that encourages making mistakes, learning to correct them and reflecting on what is learned [8]. A lack of qualified and available staff in combination with initial high costs of developing SBT often limit incorporation of SBT.

Assessment of surgical skills

Effects of surgical skills training can be assessed with a pre-post survey of participants [15, 16], in metrics such as time to complete a task [15, 16] or expert assessment [17]. Variability in evaluations could result in biased scores or unsafe patient care and undermine validity and reliability of the students' assessment scores.

At the Technical Medical Centre of the University of Twente a compulsory surgical skill course for graduate students in Technical Medicine is given. However, internal student evaluations revealed a limited relationship between course content and current clinical practice. Also, pass/fail decisions relied on a single observation made by a single assessor which introduces bias to the decisions made. Last, educational themes in the course lacked coherence and patient's perspective. These observations prompted us to revise the basic surgical skills course and take abovementioned strategies for successful SBT into account.

Purpose

This study aims to develop a preclinical curriculum to teach 21st century surgical skills, assess surgical skills in an objective way and evaluate this curriculum with a post-course questionnaire after students' clinical rotations.

Materials and methods

Curriculum design

A needs assessment was performed to identify learning goals [18]. The main learning goal was to develop knowledge, understanding and (non) technical skills in surgery that matches daily practice. Hereafter, activities based on general patient surgical flow were developed and discussed with 4 professors in surgery and resulted in a new surgical skills course (Figure 1).

The 10-week 3 European credit transfer and accumulation system (ECTS; 28 hours per ECTS credit) graduate course for Technical Medicine students is described in more detail in Supplement 1. An international comparison of medical education is described elsewhere [19].

The student to lecturer ratio was 1 : 8 in dry/wet lab sessions. Both knowledge test and skills assessment were weighted each for 50% of the final grade on the Dutch 1 – 10 scale

Figure 1 New surgical skills curriculum with patient surgical flow as backbone

[20]. All students had prior training in non-technical communication and professional behaviour skills with simulated patients and followed a mandatory injections and catheterisation skills course prior to enrolment in the surgical skills course [21, 22].

Assessor training and evaluation

Prior to the procedural assessment, assessors were trained and interrater reliability was established for three out of four assessors as one assessor did not complete the evaluation. Each assessor evaluated four video recordings of the suturing station of a previous cohort using the rating scale developed for the current course. Two-way mixed effects single measures absolute agreement intraclass correlation coefficients (ICC), Cohen's kappa, and proportion agreement were calculated to examine interrater reliability. Overall ICC for interrater reliability of the rating scales scores was low, $r = 0.27$ (95% CI = 0.03 – 0.54). Interrater reliability for the pass/fail scores was higher, with a mean proportion agreement of 0.75 (SE = 0.05). However, Cohen's kappa estimates showed clear disagreements in scores when examining each pair of assessors separately. Hereafter, the rating scales were discussed with all assessors until agreement on interpretation was reached.

Technical surgical skills assessment

A four-station procedural assessment was developed of basic surgical tasks that included scrubbing and donning, local anaesthesia, incision/excision and suturing. In accordance with best practices [23, 24], performance indicators and objectives for the four tasks were determined by an expert panel consisting of four professors in surgery and two technical physicians in surgery. These indicators were based on national surgical residency programs and experts opinion and judged to reflect acceptable practice in the Technical Medicine training program (See Supplement 1).

A rubric was developed for scrubbing and donning and procedure-specific rating scales were developed for local anaesthesia, incision/excision, and suturing (example for suturing in Supplementary Figure 1). Critical errors, i.e. compromising patient or personal safety such as not returning sharp instruments to the instrument table or neglecting feedback of the assessor, were defined for each rating scale. Students who made a critical error immediately failed the assessment. For each station benchmarks were set for passing and students needed to pass each station to pass the entire procedural assessment.

Two students were assessed in parallel by one assessor in blocks of 8 students spread over four stations in a 1 – hour timeframe. Assessors were allowed to act as first assistant to the student without giving corrections unless deemed necessary. More than one assessor could be assigned to the same station on consecutive assessment days. Setup of the suturing station including operating theatre (OR) etiquette and hygiene is depicted in Figure 2.

Theoretical assessment

A knowledge test was administered online (Blackboard versions October 2014 and Q4 2015, Washington, D.C., United States of America) and contained essay, closed-ended and multiple choice questions with input from all assessors and guest lecturers. Item-

Figure 2 Setup of the suturing station in a simulated operating room with two examinees (left) and one examiner (right). Permission was obtained for use of this photograph for publication

difficulty (percentage of students who answered a test question correctly) and item-discrimination (the degree to which students with high overall exam scores also answered a particular question correctly) were calculated to examine reliability of the assessment.

Post-course evaluation

A cohort study was conducted of students who received this mandatory surgical skills training in academic years 2015 – 2016 and 2016 – 2017 and was evaluated after at least one clinical rotation, depending on the start of their clinical rotations program. Students were approached by e-mail 8 months after the course. A reminder was sent three months later.

The principles outlined in the Declaration of Helsinki were followed. Written informed consent was obtained from all students before the study. This research was not submitted for Ethics Board approval because this research was not subject to the Dutch Medical Research Involving Human Subjects Act (WMO). Post-hoc ethical review from the University of Twente stated having no ethical concerns regarding this research.

A one-group post-test-only design was used for post-course assessment. The Kirkpatrick model for training evaluation was applied [25]. Knowledge and skills acquired during the course (level 2) were evaluated with a knowledge test and a procedural assessment. Students' reactions to the course (level 1) and self-reported clinical behaviour (level 3) were measured with an online survey after finishing the course.

The online survey (SurveyMonkey, San Mateo, California, USA) consisted of statements related to confidence in own capabilities, patient safety and application of knowledge and self-reported technical skills in practice (see Supplement 2 for full questionnaire). Students reported the number of technical skills they performed and general questions about the course on two 6-point Likert scales.

Statistical analysis

First, internal consistency of the knowledge test, checklist and rating scale items was evaluated. Second, an item analysis of the knowledge test items was performed. Finally, scores, grades and pass/fail rates for all assessment instruments were described and subgroup comparisons made where appropriate.

Quality of assessment instruments was evaluated using internal consistency for the knowledge test, checklist, and rating scale scores using Cronbach's alpha and hierarchical omega (ω_h) [26, 27]. Both Cronbach's alpha and hierarchical omega were used to compare estimates and possibly reduce bias and misinterpretation.

Scores, grades and pass rates for the knowledge test and skills assessment were calculated. Continuous variables were presented as mean with standard deviation (SD) or median with interquartile range (IQR) depending on the distribution. Continuous variables were tested for normality with visual inspection of histograms and skewness and kurtosis measures.

An univariate general linear model was performed to determine coherence between knowledge test and technical skills assessment. A mixed model was used to identify a potential drift in grading during assessments. Here blocks of students were created based on the 1-hour assessment blocks with 8 students.

A gender subgroup analysis as encouraged by the Institute of Medicine [28] was performed. Items of the online survey are presented as number with corresponding percentages and compared between cohorts and male and female students using a Fischer Exact test because less than 5 events occurred per item. A sensitivity analysis with Mann-Whitney U testing was performed by excluding the "not applicable" answer from the 6-point categorical Likert scale resulting in a 5-point ordinal scale.

Results

Curriculum

The surgical skills course was redesigned based on surgical patient flow (Figure 1). A total of 58/71 (82%) students signed informed consent for this study in 2015 – 2016 and 62/84 (74%) students in 2016-2017. An inclusion flow diagram is shown in Supplementary Figure 2. The pass/fail rate for the students who signed consent was similar to the full cohort of students. Table 1 shows a full overview of student population and pass rates. A detailed overview of each station is shown in Supplementary Table 1. Supplementary Figure 2 shows the flow of students through the study.

Table 1 Student population and pass rates of surgical skills course

	Cohort 2015 – 2016	Cohort 2016 – 2017
Students, informed consent for study	58/71 (82%)	62/84 (74%)
Female, %	39/58 (67%)	39/62 (63%)
Pass knowledge test	58/58 (100%)	56/59 (95%)
First examination	51/57 (89%)	40/59 (68%)
Second examination	7/7 (100%)	16/17 (94%)
Pass first procedural assessment¹	48/56 (86%) ²	52/59 (88%) ³
Scrubbing and donning	51/52 (98%)	58/58 (100%)
Local anaesthesia	53/54 (98%)	58/58 (100%)
Incision/Excision	50/52 (96%)	54/54 (100%)
Suturing skills	52/56 (91%)	52/59 (88%)

¹ Students failing a station of the procedural assessment were not allowed to complete their assessment

² One student stopped during the course, one student did not attend the assessment

³ One student did not attend the assessment

Knowledge and skill acquisition

Internal consistency for the knowledge tests, i.e. whether items of the knowledge test measured the same general construct, was poor to moderate, see Table 2, and higher for cohort 2016 – 2017 compared to cohort 2015 – 2016. Item-total correlations ranged from -0.058 to 0.445 for cohort 2015 – 2016 and from 0.18 to 0.55 for cohort 2016 – 2017, indicating that some items had poor ability to discriminate poor from good performing students, while other items had very good ability to discriminate. Internal consistency measured with omega was lower for both tests compared with Cronbach's alpha and less sensitive to removing poor performing items.

Internal consistency was acceptable to high for suturing for both Cronbach's alpha and omega. It was fair to good for incision/excision and poor to acceptable for local anaesthesia and this varied depending on the internal consistency measure used, see Table 2. For scrubbing, Cronbach's alpha was very small and negative for the long version including all 11 items, indicating negative inter-correlations between the individual items. Univariate analysis showed no significant prediction of technical skills score from the knowledge test, $F(1,113) = 3.335$, $p = 0.07$.

In 2015 – 2016, significant lower grades were given on the second assessment day (Thursday) for scrubbing and donning (10.0 vs 9.0, $U = 182$, $p = 0.005$), local anaesthesia (7.0 vs 8.0, $U = 181$, $p = 0.001$) and excision/incision (8.0 vs 7.5, $U = 220.5$, $p = 0.04$). Both local anaesthesia (7.0 vs 7.5, $U = 289$, $p = 0.03$) and excision/incision (7.0 vs 7.5, $U = 210.5$, $p = 0.009$) scored lower on the second assessment day in 2016 – 2017.

An overview of median grades per skill assessment station is given in Table 3 and Figure 3. There was no difference in grading between timeslots within a day (no rater drift) as determined with mixed model analysis (Figure 3). Only the 2016 – 2017 excision/incision assessment on Thursday showed a significant drift (Figure 3D, $F(4,23) = 4.388$, $p = 0.009$).

Table 2 Quality of assessments of procedural assessment and knowledge test

	Cohort 2015 – 2016		Cohort 2016 – 2017	
	Cronbach's alpha	Omega (wh)	Cronbach's alpha	Omega (wh)
Knowledge test				
Original test (21 questions in 2015 – 2016, 18 questions in 2016 – 2017)	0.48	0.36	0.78	0.36
Test 2015 – 2016, without poor performing items (8 questions)	0.66	0.31	-	-
Procedural assessment				
Scrubbing and donning	-0.01	N/A ¹	-0.29	N/A ¹
Local anaesthesia	0.55	0.56	0.71	0.43
Incision/Excision	0.85	0.67	0.63	0.41
Suturing skills	0.94	0.85	0.79	0.54

¹ Four items had no variation and hierarchical omega (wh) could not be calculated for all 11 items of the scrubbing checklist. These items were removed from further analysis.

Results post-course questionnaire

Out of 71 students from cohort 2015 – 2016, 27 (38%) filled in the post-test questionnaire after 1 [1 – 2] clinical rotation. For cohort 2016 – 2017, 21/84 (25%) filled in the questionnaire after 3 [2 – 3] rotations. Mean age was 23 ± 1.1 years and 69% was female and is in line with the male to female ratio of medical students in the Netherlands [13].

Most students handled sterile instruments during their clinical rotations (52 – 59%), whereas performing local anaesthesia (4 – 24%) and incision/excision (14 – 18%) were rare, see Figure 4A. There was no significant difference in number of procedures between cohorts, except for local anaesthesia ($U = 229$, $p = 0.05$) where more procedures were performed in cohort 2016 – 2017.

Female students performed a higher number of technical skills than male students for scrubbing and donning ($U = 160$, $p = 0.04$), sterile instrument handling ($U = 160.5$,

Table 3 Median grades per skills station per assessment day for both cohorts

	2015 – 2016			2016 – 2017		
	Day 1	Day 2	P value	Day 1	Day 2	P value
Scrubbing/donning	10 [9 – 10]	9 [8 – 10]	0.005	10 [9 – 10] ¹	10 [9 – 10] ¹	0.57
Local anaesthesia	7 [6.5 – 7.5]	8 [7.5 – 8]	0.001	8 [8 – 8]	7.5 [7 – 8]	0.03
Excision/Incision	8 [7 – 9]	7.5 [6 – 8]	0.04	7.5 [7 – 8]	7 [6.75 – 7.5]	0.009
Suturing	7.75 [7.38 – 8.5]	8 [7 – 8]	0.54	8 [7 – 8]	8 [7 – 8]	0.70

Median [IQR]

¹ Scrubbing and donning was transformed from a grade to a pass/fail criterium in 2016 – 2017 where 100% of the students obtained a pass.

$p = 0.04$), incision/excision ($U = 187.5$, $p = 0.04$) and suturing ($U = 168.5$, $p = 0.049$) but not for local anaesthesia ($U = 202.5$, $p = 0.08$), see Supplementary Figure 3.

In ordinal regression analysis, the odds of male students reporting fewer frequencies for scrubbing and donning were 1.40 (95% CI, 0.12 to 2.7) times that of female students, a statistically significant effect, Wald ($\chi^2(1) = 4.595$). The odds for reporting fewer frequencies by male students for suturing were 1.41 (0.001 to 2.8), $p = 0.05$, and 1.30 (0.08 to 2.5), $p = 0.04$ for sterile instrument handling. Male students reported not performing incision/excision or local anaesthesia during their clinical rotations.

Preparation for clinical practice

Only 10% of the students received OR introduction at all clinical rotations, while 10% received this sometimes and 58% never received an instruction. Others described that they not yet attended the OR (17%) or received more tailored instructions (4%).

There was no significant difference in course feedback questions between cohorts. Most students were confident about attending a surgery (20% completely agreed, 41% agreed) and agreed about having a professional attitude in the operating room (24% completely agreed, 37% agreed), see Figure 4B. Furthermore, students asserted that knowledge on patient safety is important (13% completely agreed, 57% agreed). Half of the students were able to acquire new variations on technical skills (13% completely agreed, 37% agreed).

In the sensitivity analysis using ordinal coding, a significant higher proportion of cohort 2015 – 2016 reported that they were unable to apply knowledge and skills at the OR, compared to cohort 2016 – 2017 ($U = 84$, $p = 0.03$). There was no significant difference in course feedback questions between cohorts for the other questions.

Two thirds of the male students reported they are able to act as a professional (0% completely agreed, 67% agreed), while female students responded more neutral (16% completely agreed, 29% agreed), $p = 0.02$ (Cramer's $V = 0.47$). The sensitivity analysis confirmed this finding ($U = 105.5$, $p = 0.03$) and demonstrated that male students attend the OR with more confidence than female students ($U = 117$, $p = 0.03$). No other statistically significant differences in responses between male and female students were found.

Discussion

Proficiency-based, simulation-based surgical skills training is recommended, however, implementation is not always straightforward [29]. In this paper, a balanced basic surgical skills curriculum was described that adequately prepared students for their clinical rotations.

The surgical skills curriculum was anchored to surgical patient flow focusing on knowledge, technical and non-technical surgical skills. Also, assessors were trained to prevent biased judgments before they assessed students on basic surgical skills. Afterwards, sterile instrument handling, scrubbing and donning and suturing skills were often performed during clinical rotations. The majority of students felt confident during their clinical rotations about attending a surgery and stated they could show a professional attitude in the operating room.

Figure 3 Grading per skill assessment per time slot of maximum 8 students for both cohorts. **ACEG** Assessment grading of cohort 2015 – 2016; **BDFH** Assessment grading of cohort 2016 – 2017. Top p values depict grades per assessment day, p values within branches depict grading differences within a day. Measurements in green are for day 1, in blue for day 2. Horizontal line is median. 5 = insufficient, 6 – 10 = pass according to Dutch grading scale [20]

Curriculum redesign

The main learning goal of this course was to develop knowledge, understanding and (non) technical skills in surgery that matches daily practice. Graduate students were able to reach proficiency level in a simulation-based basic surgical skills course. Students stated to go with confidence to the operating room and felt competent in performing four basic surgical skills. Some U.S. medical students attend surgical boot camps where they increase suturing and knot tying skills and confidence [30]. Unfortunately, these boot camps do not guarantee minimum skills for all medical students as these camps are voluntary. Minimum quality of surgical skills in a mandatory simulated environment is guaranteed for all students with a pass on the surgical skills course described in this study.

Most residency programs assess surgical skills at the end of the rotations and generally with subjective evaluations [4] while these skills were already performed on patients. Furthermore, surgical skills are not acquired by all students and many medical students are not able to show sufficient surgical skills after completing a 3rd-year surgery clerkship [16]. This surgical skills course is compulsory next to other skills courses on vein-puncture and peripheral catheterisation, advanced life support and endoscopic skills. This curriculum might be more difficult to apply for programs without these skills courses. Nevertheless, aspects of this curriculum following surgical patient flow are usable for all programs. A minimum quality of surgical skills in a mandatory simulated environment is guaranteed for all students with a pass on the surgical skills course described in this study.

The redesign of our SBT was in accordance with three out of four principles described elsewhere [31], to be mandatory participation, proficiency-based, and a distributed training schedule.

Figure 4 Post-course questionnaire 2015 – 2016 ($n = 27$) and 2016 – 2017 ($n = 21$) **A** Amount of technical surgical skills performed in early clinical rotations **B** Course feedback of students during clinical rotations. OR = operating room

Our SBT lacked a component of overtraining. This seems acceptable at graduate level for Technical Medicine students, because the program aims for adaptive rather than routine skills development [21]. In retrospect, the principles of developing and refining a surgical curriculum as recently described were followed [32].

Based on internal course evaluations, local anaesthesia wet lab time was reduced (academic year 2017 – 2018) because Technical Medicine students tend not to perform these skills during rotations. More recently, more time was allocated to post-operative care such as wound healing (2018 – 2019) and enhanced recovery after surgery (2019 – 2020).

Course redesign evaluation

Surgical knowledge as deemed necessary by assessors was tested in a theoretical assessment. The majority of students passed this test on first examination (68 – 89%) and almost all students on second examination (94 – 100%). For the two cohorts described in this paper, technical skills were outstanding [20] for scrubbing and donning (10 [9 – 10]), good for local anaesthesia (8 [7 – 8]), very satisfactory to good for incision/excision (7.5 [7 – 8]) and good for suturing (8 [7 – 8]).

Internal consistency was poor to acceptable for local anaesthesia, fair to good for incision/excision and acceptable to high for suturing. For scrubbing, Cronbach's alpha was very small and negative because of little variation for the majority of items (see Supplementary Table 1).

A possible bias in the pass/fail decisions for the course was compensated by testing knowledge and skills separately with equal weighing, by using multiple assessors and by assessing a variety of surgical skills [33]. To improve reliability we propose more rigorous and repeated assessor training and exclude assessors who do not meet the standards for examination.

In this study around 80 students per academic year were assessed for technical skills in 1 – hour blocks of maximum 8 students for two days by four unique assessors. This study is among the largest study groups described [30]. A total of 48 man-hours was necessary for assessment because of parallel assessment of students. The 3 ECTS course was time consuming only to two course coordinators and to a lesser extent for guest lecturers. This curriculum is thus suitable for large student cohorts.

Previous work suggested rater drift between assessment sessions [17]. No drift in grading was observed for all skills stations in both cohorts except for excision in 2016 – 2017 on day 2 (Figure 3D). The impact of assessor training is reduced as early as 4 months after in-depth training [17] and may have resulted in more drift during the second academic cohort. Annual training before starting the course is thus recommended for consistent assessment.

Post-course evaluation and student perceptions

An important aspect of SBT is to give confidence to learners. The majority of students in this study stated to go with confidence to the operating room and felt competent in performing four basic surgical skills. Some studies have used validated confidence scores [30], while a wide range of questions were asked in this study (Figure 4B). Validated confidence scores should be implemented pre- and post a surgical skills course.

Students struggled most with clinical reasoning for complex cases and taking patient safety into account while performing a basic procedure. Furthermore, students reported that they were least confident about performing basic surgical tasks during their clinical rotations the way they were taught (Figure 4B). Demonstrating more surgical technique variations in daily practice might improve adaptivity of students.

Limitations and possible improvements

Many surgical education studies show confounders and lack a pre-test, comparator or relevance [34]. Students in Technical Medicine had no expected previous surgical skills experience and a pre-test on technical skills was not deemed necessary. A validated pre- and post-test on self-reported confidence [30] could be implemented to improve course evaluation. This study did not compare to the previous surgical skills curriculum or other programs. Therefore, effects on knowledge and skills acquisition cannot with certainty be attributed to our redesign only. Finally, it is likely that passing this course results in safe patient care as students demonstrated all-round technical and non-technical surgical skills making this course highly relevant.

The effects of redesign on patient outcomes (Kirkpatrick level 4) were not evaluated. The self-reported clinical performance (Kirkpatrick level 3) has limitations. Future studies should ask surgeons in a pre- and post-questionnaire on differences in clinical behaviour and skill transfer of students. Patient-centred medical education should be about patients, with patients and for patients [35]. Simulated patients are embedded in undergraduate Technical Medicine education. This course is about and for patients and has a patient surgical journey as backbone, but needs patient participation such as simulated patients for surgical ward training.

Gender subgroup analysis is endorsed by many organisations and studies [28, 30]. An unplanned gender analysis showed more procedures in female students for all technical skills except for local anaesthesia which was not often performed among all students (Supplementary Figure 1). An interaction was found between gender and technical skills in ordinal regression analysis with fewer reported frequencies in scrubbing and donning, sterile instrument handling and suturing. No difference was found in the behavioural questions except for acting as a professional where female students answered more neutral. These gender differences are in contrast with others where lower scores in self-efficacy for female students disappeared after a surgical boot camp [30]. Future cohort studies should include prespecified and well-designed [36] gender subgroup analysis to investigate potential gender related differences.

Conclusion

Acquiring basic surgical knowledge and skills is feasible in a 10 week, 3 ECTS, simulation-based and proficiency-based course for graduate students. Trained and committed faculty, mandatory participation and a proficiency-based program, determine the effectiveness of a course to a large extent.

By evaluating the course at the level of knowledge, skills and students' perceptions, areas for improvement of a basic surgical skills course at the graduate level were identified and applied to following courses.

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Declaration of interest

The authors report no declarations of interest.

References

1. Kohn LT, Corrigan J, Donaldson MS. *To err is human : building a safer health system*. Washington, D.C. ; [Great Britain]: National Academy Press; 2000.
2. Eden J, Berwick DM, Wilensky GR, Institute of Medicine (U.S.). Committee on the Governance and Financing of Graduate Medical Education. *Graduate medical education that meets the nation's health needs*. Washington, D.C.: The National Academies Press; 2014.
3. Jen MH, Bottle A, Majeed A, Bell D, Aylin P. Early in-hospital mortality following trainee doctors' first day at work. *PLoS one*. 2009;4:e7103.
4. Bhatti NI. Assessment of Surgical Skills and Competency. *Otolaryngol Clin North Am*. 2017;50:959-965.
5. Gostlow H, Marlow N, Thomas MJ, et al. Non-technical skills of surgical trainees and experienced surgeons. *Br J Surg*. 2017;104:777-785.
6. Stefanidis D, Cochran A, Sevdalis N, et al. Research priorities for multi-institutional collaborative research in surgical education. *American journal of surgery*. 2015;209:52-58.
7. American Board of S, American College of S, Association of Program Directors in S, Association for Surgical E. Statement on surgical preresidency preparatory courses. *J Surg Educ*. 2014;71:777-778.
8. Satava RM. Assessing surgery skills through simulation. *The Clinical Teacher*. 2006;3:107-111.
9. Stefanidis D, Sevdalis N, Paige J, et al. Simulation in Surgery What's Needed Next? *Annals of surgery*. 2015;261:846-853.
10. Ahmed K, Amer T, Challacombe B, Jaye P, Dasgupta P, Khan MS. How to develop a simulation programme in urology. *Bju Int*. 2011;108:1698-1702.
11. Lammers RL, Davenport M, Korley F, et al. Teaching and Assessing Procedural Skills Using Simulation: Metrics and Methodology. *Acad Emerg Med*. 2008;15:1079-1087.
12. Gallagher AG, Ritter EM, Champion H, et al. Virtual reality simulation for the operating room - Proficiency-based training as a paradigm shift in surgical skills training. *Annals of surgery*. 2005;241:364-372.
13. Erasmus V, Otto S, De Roos E, et al. Assessment of correlates of hand hygiene compliance among final year medical students: a cross-sectional study in the Netherlands. *BMJ Open*. 2020;10:e029484.
14. Cooper AB, Tisdell EJ. Embodied aspects of learning to be a surgeon. *Medical Teacher*. 2020;42:515-522.
15. Brunt LM, Halpin VJ, Klingensmith ME, et al. Accelerated skills preparation and assessment for senior medical students entering surgical internship. *J Am Coll Surg*. 2008;206:897-904; discussion 904-897.
16. Pender C, Kiselow V, Yu Q, Mooney J, Greiffenstein P, Paige JT. All for knots: evaluating the effectiveness of a proficiency-driven, simulation-based knot tying and suturing curriculum for medical students during their third-year surgery clerkship. *American journal of surgery*. 2017;213:362-370.
17. Gawad N, Fowler A, Mimeault R, Raiche I. The Inter-Rater Reliability of Technical Skills Assessment and Retention of Rater Training. *J Surg Educ*. 2019;76:1088-1093.
18. Knowles MS. *The modern practice of adult education: from pedagogy to andragogy*. Rev. and Updated. ed. Wilton, Conn. Chicago: Association Press ; Follett Pub. Co.; 1980.
19. Weggemans MM, van Dijk B, van Dooijeweert B, Veenendaal AG, Ten Cate O. The postgraduate medical education pathway: an international comparison. *GMS J Med Educ*. 2017;34:Doc63.

20. Netherlands Organization for International Cooperation in Higher Education (NUFFIC). Grading systems in the Netherlands, the United States and the United Kingdom. The Hague 2009:4.
21. Groenier M, Pieters JM, Miedema HAT. Technical Medicine: Designing Medical Technological Solutions for Improved Health Care. *Medical Science Educator*. 2017;27:621-631.
22. Miedema HAT. *Arts en ingenieur, and ever the twain shall meet* [PhD Thesis - Research UT, graduation UT]. Enschede: Analyse en ontwerp van de opleiding Technische Geneeskunde, Universiteit Twente; 2015.
23. Kottner J, Audige L, Brorson S, et al. Guidelines for Reporting Reliability and Agreement Studies (GRRAS) were proposed. *J Clin Epidemiol*. 2011;64:96-106.
24. Groenier M, Brummer L, Bunting BP, Gallagher AG. Reliability of Observational Assessment Methods for Outcome-based Assessment of Surgical Skill: Systematic Review and Meta-analyses. *J Surg Educ*. 2020;77:189-201.
25. Bates R. A critical analysis of evaluation practice: the Kirkpatrick model and the principle of beneficence. *Evaluation and Program Planning*. 2004;27:341-347.
26. Sijsma K. On the Use, the Misuse, and the Very Limited Usefulness of Cronbach's Alpha. *Psychometrika*. 2008;74:107.
27. Revelle W, Zinbarg RE. Coefficients Alpha, Beta, Omega, and the glb: Comments on Sijsma. *Psychometrika*. 2008;74:145.
28. Institute of Medicine (US) Board on Population Health and Public Health Practice. *Sex-Specific Reporting of Scientific Research: A Workshop Summary*. Washington (DC) 2012.
29. Hosny SG, Johnston MJ, Pucher PH, Erridge S, Darzi A. Barriers to the implementation and uptake of simulation-based training programs in general surgery: a multinational qualitative study. *The Journal of surgical research*. 2017;220:419-426 e412.
30. Bevilacqua LA, Simon J, Rutigliano D, et al. Surgical boot camp for fourth-year medical students: Impact on objective skills and subjective confidence. *Surgery*. 2020;167:298-301.
31. Zevin B, Aggarwal R, Grantcharov TP. Surgical Simulation in 2013: Why Is It Still Not the Standard in Surgical Training? *J Am Coll Surg*. 2014;218:294-301.
32. Sell NM, Phitayakorn R. Developing and refining a surgical curriculum. *Surgery*. 2020;167:528-531.
33. van der Vleuten CP, Schuwirth LW. Assessing professional competence: from methods to programmes. *Med Educ*. 2005;39:309-317.
34. Corsini EM, Antonoff MB. Surgical education research: How to move beyond the survey. *Surgery*. 2020;167:269-272.
35. Hearn J, Dewji M, Stocker C, Simons G. Patient-centered medical education: A proposed definition. *Med Teach*. 2019;41:934-938.
36. Barraclough H, Govindan R. Biostatistics primer: what a clinician ought to know: subgroup analyses. *Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer*. 2010;5:741-746.

Supplements

Supplement 1: Course overview

Technical Medicine is a 6-year health care education program including two years of clinical rotations. A description of the curriculum and goals can be found in Groenier et al. [1] In the Master program students take four simulation-based clinical skills courses to prepare them for their clinical rotations: injections and catheterisations, advanced life support, endoscopic skills and surgical skills. This manuscript focuses on the latter of these skill courses.

The surgical skills course includes a theoretical part about the surgical patient flow and rationale of various surgical skills and a practical part where students practice various technical skills in a simulated environment. The theoretical part was assessed with an online knowledge test and the practical part with a procedural skill assessment.

The test covered the following subjects: preoperative optimisation of patients, use of evidence based surgery in clinical decision making, operative procedures, skin suture techniques and advanced suturing (anastomosis, tissue sealing, stapling), electrosurgery, wound management, instrument handling, local and general anaesthetics and hygiene.

For pre-operative surgical skills, lectures addressed pre-operative assessment (problem based learning), optimising patient conditions and anaesthesiology. Group meetings included interpretation of medical imaging and surgical guidelines in a multidisciplinary council and dry lab simulation of local anaesthesia administration.

For peri-operative care, lectures included surgical time-out procedure, general surgical techniques and surgical complications. Hygiene and safety, scrubbing and electrosurgery were covered in lectures/group meetings. Wet lab simulation on porcine tissue (skin, lung, heart) included instrument handling, suturing and incision/excision. A live heart surgery was attended to experience patient centred care.

Post-operative care included wound healing and infection management. Assessment was both on technical skills (scrubbing, suturing, local anaesthesia, incision/excision) and a knowledge/surgical principles test.

References

1. Groenier M, Pieters JM, Miedema HAT. Technical Medicine: Designing Medical Technological Solutions for Improved Health Care. *Medical Science Educator*. 2017;27:621-631.

	1	2	3	4	5
Suturing technique selection	Student is unable to discriminate between techniques / materials	Can discriminate between suturing techniques but unable of providing a rationale for them	Selects appropriate technique but is unable to provide a rationale for instrument selection	Selects appropriate technique, superficial knowledge of materials	Selects appropriate technique immediately and able to provide a rationale for selected technique
Movement	Frequently makes unnecessary movements		Acceptable efficiency, some unnecessary movements		Economic movements, maximum efficiency
Instrument selection	Student is unable to discriminate between instruments		Selects appropriate instruments, unable to provide an adequate rationale for selection		Selects appropriate instruments immediately and provides a rationale for selected instruments
Instrument use	Repeatedly makes insecure and/or clumsy movements		Skilful use, at times a bit stiff or clumsy		Fluent movements, skilful use
Use of feedback	Ignores feedback		Uses feedback to improve performance		Requires no feedback for performance improvement
Knot tying	Knot is loose, slipping, not enough knots		Unilateral well tied knot		Right knot, right amount and right amount of alternations
Tissue sensitivity	Frequently uses unnecessary force or damages tissue due to inappropriate instrument use		Careful tissue handling, some tissue damage		Consistent, careful handling of tissue without damage
Final result	Final result not achieved	Secondary wound healing	Suture is cosmetically adequate	Suture is functionally adequate	Suture is functionally and cosmetically adequate
Safety	Disregards safety		Adequate attention to personal safety, neglects colleague / patient		Adequate attention to personal safety and safety of others

Supplementary Figure 1 Procedure-specific rating scale for suturing. Red coloured boxes represent critical errors where students fail the assessment immediately.

Supplementary Table 1 Technical skills assessment

	Cohort 2015 – 2016 n = 56	Cohort 2016 – 2017 n = 59	p value
Suturing	n = 56	n = 59	...
Suturing technique – selection	3 [3 – 3]	3 [2 – 4]	0.30
(Unnecessary) Movements	4 [3 – 4]	4 [3 – 4]	0.79
Instrument – selection	3 [3 – 3]	3 [3 – 3]	.015
Instrument handling	4 [3 – 4]	4 [3 – 4]	0.68
Use of feedback	3 [3 – 4]	3 [3 – 4]	0.87
Knot tying	4 [3 – 4]	4 [3 – 4]	0.70
Tissue handling	4 [4 – 4]	4 [3 – 4]	0.11
Final result	4 [4 – 5]	4 [3 – 5]	0.27
Safety	4 [3 – 4]	4 [2 – 4]	0.72
Final grade ¹	8.0 [7.2 – 8.0]	8.0 [7.0 – 8.0]	0.47
Incision/Excision	n = 52	n = 54	...
Handling – selection	5 [5 – 5]	4 [4 – 4]	<0.001
Instruments – selection	5 [5 – 5]	4 [4 – 4]	<0.001
Preparation	5 [3 – 5]	4 [4 – 4]	0.02
Safety	5 [3 – 5]	4 [3 – 4]	<0.001
Final result	4.5 [3 – 5]	4 [3 – 4]	0.03
Instrument handling	5 [3 – 5]	4 [3 – 4]	0.009
(Unnecessary) Movements	3 [3 – 5]	4 [3 – 4]	0.82
Final grade ¹	8.0 [7.0 – 8.5]	7.5 [7.0 – 8.0]	0.02
Local Anaesthesia	n = 54	n = 58	...
Anaesthesia technique – selection	4 [4 – 4]	4 [4 – 4]	0.02
Materials – selection	4 [4 – 4]	4 [4 – 4]	0.02
Preparation	4 [3 – 4]	4 [4 – 4]	0.44
Infiltration	3 [3 – 4]	4 [3.5 – 4]	<0.001
Safety	4 [3 – 4]	4 [4 – 4]	0.10
Tissue handling	4 [3 – 4]	4 [4 – 4]	0.53
Final result	4 [3 – 4]	4 [4 – 4]	0.009
Final grade ¹	7.5 [6.9 – 8.0]	8.0 [7.0 – 8.0]	0.02
Scrubbing and donning	n = 51	n = 58	...
No jewellery	51 (100%)	58 (100%)	1.00
Correct dressing	51 (100%)	58 (100%)	1.00
Wearing scrub cap	49 (96%)	47 (81%)	0.02
Wearing surgical mask	43 (84%)	55 (95%)	0.07
Correct order of steps	40 (78%)	58 (100%)	<0.001
Wetting hands	51 (100%)	57 (99%)	1.00
Drying hands	47 (92%)	58 (100%)	0.045
Timely use of alcohol	48 (94%)	58 (100%)	0.10
Finish in time	47 (92%)	52 (90%)	0.75
Final grade ¹	10 [10 – 10]	10 [10 – 10] ²	0.76

Median [IQR] and n (%)

¹ A fail was noted as a 5 (insufficient). Final grade is on the 1 – 10 Dutch grading scale [1]² Pass/fail scores were used in 2016 – 2017, where 100% passed scrubbing and donning

References

1. Netherlands Organization for International Cooperation in Higher Education (NUFFIC). Grading systems in the Netherlands, the United States and the United Kingdom. The Hague 2009:4.

CONSORT 2010 flow diagram – Surgical Skills

Supplementary Figure 2 Flow diagram of study

Supplementary Figure 3 More technical skills were performed by female students for all technical skills ($p = 0.037$ to $p = 0.049$) except for local anaesthesia which was not often performed among all students. In ordinal regression analysis, lower frequencies of technical skills were associated (Wald χ^2) with male students for scrubbing and donning ($p = 0.03$), sterile instrument handling ($p = 0.04$) and suturing ($p = 0.050$). Male students did not perform local anaesthesia and incision/excision.

Supplement 2 Questionnaire questions in English (original language: Dutch)

Quantitative

Number of skills performed in clinical rotations:

1. Scrubbing and donning
2. Local anaesthesia
3. Sterile instrument handling
4. Incision/Excision
5. Suturing

Students were asked to score on a 6-point Likert scale: 0 times, 1 time or 2, 3, 4 or 5+ times.

Qualitative

1. Knowledge of surgical patient flow is applicable
2. Technical skills are applicable
3. I have faith in entering OR
4. This course helped me to attain professional behaviour
5. I am able to act professionally in the OR
6. I am able to apply knowledge on patient safety
7. Patient flow helped me for better insight in the OR
8. Insight in patient flow helped me to ensure patient safety
9. Knowledge and skills are representative
10. Knowledge helped me to learn new procedures
11. Technical skills helped me to learn new procedures
12. I am unable to apply knowledge and skills as learned
13. My surgical skills as learned are appreciated in practice
14. I am able to show skills of someone else's preference
15. I am able to defend the skills I have learned

Students were asked to score on a 6-point Likert scale: Completely disagree, disagree, neutral, agree, completely agree or not applicable.

CHAPTER 9

GENERAL DISCUSSION

Abbreviations and acronyms

CABG	Coronary artery bypass graft surgery
FFR	Fractional flow reserve
LVEF	Left ventricular ejection fraction
NHR	Netherlands Heart Registry
OPCAB	Off-pump coronary artery bypass graft surgery
PCI	Percutaneous coronary intervention
QCA	Quantitative coronary analysis

General discussion and future perspectives

General discussion

Cardiac surgery is still superior on long-term clinical outcome compared to cardiological interventions. However, a major drawback of cardiac surgery is its invasiveness and related impact for patients. As a result numbers of surgical interventions are dropping and new developments are predominantly funded for interventional cardiology.

To further improve clinical outcomes of cardiac surgery, several themes were defined to make cardiac surgery sustainable for the future. The hypothesis was that cardiac surgery remains a first time right strategy for patients when these themes are adopted in clinical practice. The three themes stated in this thesis should enable combination of good outcomes and reduce drawbacks. Several aspects that improve cardiac surgery were covered in this thesis. However this thesis was not designed in a way to prove that the overall outcome is better than alternative choices or leads to an increase in surgical volume.

Part I: The first part of this thesis focuses on minimally invasive cardiac surgery. By reducing the impact of the heart-lung machine outcomes for large groups of patients will improve. Other patient groups can profit from off-pump surgery even when inoperable for cardiac surgery with a heart-lung machine.

Part II: Besides minimal invasive surgery, technological innovations in cardio-thoracic surgery such as improved biomaterials and devices are necessary to further improve surgical outcome.

Part III: A multidisciplinary approach with teamwork and shared decision making from patients, (technical) medical specialists, nurses, physiotherapists and other professionals will optimise treatments in cardio-thoracic surgery. Good professional behaviour starts with proper training in a simulated environment.

Future perspectives

Available knowledge for decision making

After 115 randomised trials to compare on-pump coronary artery bypass surgery (CABG) to off-pump CABG (OPCAB) on short and long term outcome controversy on benefits for patients persists [1]. A summary of unquestioned advantages of OPCAB, heterogeneous or no advantages of OPCAB and disadvantages of OPCAB is described in Table 1.

Other uncertain decision making exists for patients aged 60 – 65 with severe aortic stenosis where both biological and mechanical heart valves are (un)suitable [2] and different rates of structural valve deterioration and reintervention [3] should determine patient specific treatment.

Patient specific decision making is performed daily in heart team discussion between cardiac surgeons and cardiologists according to international guidelines [4]. Here patient characteristics determine decision making for a surgical, percutaneous or conservative treatment. Combining patient characteristics with procedural characteristics could further tailor treatment and thus improve outcome.

Table 1 Specific subsets of patients and procedural aspects that benefit, not benefit or are harmed when using off-pump CABG

Benefit	No benefit/No harm determined	Harm
Low LVEF	Advanced age	Inexperience of surgeon
Women	Neurological risk	Incomplete revascularisation
	Anaortic technique	Saphenous vein grafts
	End-organ failure	Emergency intraoperative conversion
	Cost-effectiveness	
	Minimally invasive access	
	Total endoscopic CABG	
	Hybrid coronary revascularisation	

CABG = Coronary artery bypass surgery; LVEF = Left ventricular ejection fraction. Table based on [1]

Information on (non-) treatment options, potential complications and outcomes of surgery is discussed between patients and health professionals during informed consent discussion. While a CABG improves physical quality of life one year after surgery for the majority of patients [5], 1 out of 3 patients over 80 years reported a reduced mental health. As this information might influence decision making for patients, quality of life after surgery should be discussed during preoperative counselling.

Furthermore, intraoperative techniques such as orientation of the aortic cannula impacts blood flow to the brain [6] with short and long-term effects on the brain. Combining both intraoperative techniques such as correct placement of the cannula and preoperative imaging of patients aortic arch branches will result in optimal perfusion during cardiopulmonary bypass.

Next, patients are often not involved in shared decision making for type of CABG or valve prosthesis, because they lack sufficient time or knowledge on e.g. different aortic valve prostheses [7]. An online patient decision aid increased preoperative mental health, yet is not persistent after aortic valve replacement [8]. To improve individual quality of life after surgery, patient preference should be taken into account after heart team discussion and tools should be developed to support shared decision making. Online decision tools and 3D imaging and printing might assist in truly informed consent for treatments.

Professional information for decision making is scattered. Direct comparison between competing treatments or diagnosis modalities are often lacking. For assessing coronary artery stenosis, visual eyeballing by a cardiologist is most common, although high intra- and interobserver variability exists for many years with low concordance around clinical relevant cut-off points [9, 10]. Quantitative coronary analysis (QCA) with 2D or 3D reconstruction using cardiac angiography is used in some centres to analyse degree of stenosis but is still not suitable for graft patency prediction compared to functional assessment using the more invasive fractional flow reserve (FFR) [11]. Here, clinical cut-off values are also debated and might even differ between percutaneous coronary intervention (PCI) or CABG. Future studies should investigate the cut-off values of FFR or QCA for PCI and CABG to optimize outcome for patients.

National registries were developed to show transparent outcomes, inter centre variation and ultimately improve outcome for patients. The Netherlands Heart Registry (NHR) was founded in 2018 to make outcomes of cardiac surgery, interventional cardiology and electrophysiology publicly available. At this moment the focus is on individual registries and comparisons between competing treatments are not made. For instance, a clear difference in 5-year mortality after PCI or CABG is visible when two graphs are placed next to each other (Figure 1) with only minor differences in baseline characteristics.

Inter centre variation is dependent on quality of care, but even more on interpretation of quality indicators or data registration. Other surgical disciplines developed textbook outcomes as a composite measure of quality indicators [12, 13]. Textbook outcomes for cardiac surgery are not developed yet, but might be interesting for aortic valve replacement or CABG to allow for benchmarking between hospitals and improve patient

Figure 1 Long-term mortality of Dutch heart centres after PCI or CABG, with transparent publication of inter centre variation. A higher mortality is observed in the PCI group. **A** PCI; **B** CABG. Adapted from [14]

CABG = Coronary artery bypass surgery; PCI = Percutaneous coronary intervention

care. Indeed, because interpretation is difficult, outcome-based quality improvements based on NHR data are still limited [15]. A systematic approach to identify improvement potential and implementation of initiatives should follow. Hospitals then should also gain from improvement initiatives. Now a paradoxical system exists that e.g. reduction of intensive care unit stay reduces income for hospitals. The introduction of bundled payments for pre, per and postoperative care might deal with this problem.

Simulation training

A variety of simulation models for training in cardio-thoracic surgery exists [16]. Effectiveness of simulation in cardio-thoracic surgery on surgical training and patient safety is yet to be determined. Three out of four factors that harm patients when using OPCAB (Table 1) are related to training. A long learning curve of 80 – 240 patients [17] should not be accepted in 21st century medical education. Unfortunately OPCAB training in a simulated environment is not appreciated by residents or junior surgeons and

techniques vary between countries, hospitals and even individual surgeons. Efforts to share personal experience with OPCAB are limited [18, 19] and demand more insights in human factors in OPCAB.

Limited evidence is available to support no-touch aorta techniques as to prevent neurological events [20, 21] and randomised studies in direct comparison with PCI are thus justified. Safety margins during OPCAB are reduced and can lead to hemodynamic instability because of increase in systemic arterial pressure or rise in pulmonary arterial pressure [22]. This might result in emergency intraoperative conversion with associated risks for myocardial infarction and early mortality.

Simulation training does improve OPCAB skills [23], but simulators are expensive, provide ample feedback on haemodynamics to trainees and impact on clinical outcome is often lacking [24, 25]. Future research should focus on development of an OPCAB simulator and training program that acknowledges training needs from surgeons and residents, has functional fidelity based on scenario design and has a specified simulator design [26]. Strong proficiency-based, simulation-based courses on all aspects of cardiac surgery e.g. OPCAB or aortic valve replacement should be standard before practice on patients.

The Technical Physician – A high tech health professional

In the Netherlands a new professional with technical medical expertise was added to the pallet of healthcare providers: the Technical Physician.

Technical Physicians are experts in applying, improving and designing complex medical technology in patient care by combining knowledge of medicine and engineering [27, 28]. Five years of temporary independent authority to perform reserved procedures were followed with independent authority as of 2020 in the Dutch Individual Healthcare Professions Act. As more and more technological innovations enter hospitals, technology-enabled endpoints of clinical trials will and should be developed as well [29]. This shift to novel endpoints require understanding anatomy, (patho)physiology and medical technological concepts. A Technical Physician combines these concepts and “contributes to improved, more efficient and safer health care” [27] for patients.

Close collaboration between cardio-thoracic surgeons and Technical Physicians will accelerate innovations in cardio-thoracic surgery. The future is for predicting and optimising outcome with state of the heart technology. A multidisciplinary approach with efforts from patients, (technical) medical specialists, nurses, physiotherapists and other professionals can bring treatments in cardio-thoracic surgery further.

The Technical Physician is thus the right person to improve outcomes of cardio-thoracic surgery by performing minimally invasive techniques in the operating room, with strong technological designs and working together with other allied professionals and patients.

References

1. Gaudino M, Angelini GD, Antoniadou C, et al. Off-Pump Coronary Artery Bypass Grafting: 30 Years of Debate. *J Am Heart Assoc*. 2018;7:e009934.
2. Baumgartner H, Falk V, Bax JJ, et al. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. *Eur Heart J*. 2017;38:2739-2791.
3. Dvir D, Bourguignon T, Otto CM, et al. Standardized Definition of Structural Valve Degeneration for Surgical and Transcatheter Bioprosthetic Aortic Valves. *Circulation*. 2018;137:388-399.
4. Neumann FJ, Sousa-Uva M, Ahlsson A, et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. *Eur Heart J*. 2019;40:87-165.
5. Blokzijl F, Houterman S, van Straten BHM, et al. Quality of life after coronary bypass: a multicentre study of routinely collected health data in the Netherlandsdagger. *European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery*. 2019;56:526-533.
6. Kaufmann TA, Hormes M, Laumen M, et al. Flow distribution during cardiopulmonary bypass in dependency on the outflow cannula positioning. *Artificial organs*. 2009;33:988-992.
7. Korteland NM, Bras FJ, van Hout FM, et al. Prosthetic aortic valve selection: current patient experience, preferences and knowledge. *Open Heart*. 2015;2:e000237.
8. Korteland NM, Ahmed Y, Koolbergen DR, et al. Does the Use of a Decision Aid Improve Decision Making in Prosthetic Heart Valve Selection? A Multicenter Randomized Trial. *Circ Cardiovasc Qual Outcomes*. 2017;10.
9. Leape LL, Park RE, Bashore TM, Harrison JK, Davidson CJ, Brook RH. Effect of variability in the interpretation of coronary angiograms on the appropriateness of use of coronary revascularization procedures. *American heart journal*. 2000;139:106-113.
10. Sen T, Kilit C, Astarcioğlu MA, et al. Comparison of quantitative and qualitative coronary angiography: computer versus the eye. *Cardiovasc J Afr*. 2018;29:278-282.
11. Glineur D, Grau JB, Etienne PY, et al. Impact of preoperative fractional flow reserve on arterial bypass graft anastomotic function: the IMPAG trial. *Eur Heart J*. 2019;40:2421-2428.
12. Poelemeijer YQM, Marang-van de Mheen PJ, Wouters M, Nienhuijs SW, Liem RSL. Textbook Outcome: an Ordered Composite Measure for Quality of Bariatric Surgery. *Obes Surg*. 2019;29:1287-1294.
13. Karthaus EG, Lijftogt N, Busweiler LAD, et al. Textbook Outcome: A Composite Measure for Quality of Elective Aneurysm Surgery. *Annals of surgery*. 2017;266:898-904.
14. Netherlands Heart Registry (NHR). Netherlands Heart Registry (NHR) Annual Report 20192020.
15. van Veghel D, Daeter EJ, Bax M, et al. Organization of outcome-based quality improvement in Dutch heart centres. *Eur Heart J Qual Care Clin Outcomes*. 2019.
16. Villanueva C, Xiong J, Rajput S. Simulation-based surgical education in cardiothoracic training. *ANZ J Surg*. 2020;90:978-983.
17. Bougioukakis P, Kluegl SJ, Babin-Ebell J, et al. Presentation of a quality management program in off-pump coronary bypass surgery. *Innovations (Phila)*. 2014;9:317-321.
18. Taggart DP. How I deploy arterial grafts. *Ann Cardiothorac Surg*. 2018;7:690-697.
19. Zenati MA. Off Pump Coronary Artery Bypass (OPCAB). Vol 2019: CTSNet; 2012.
20. Zhao DF, Edelman JJ, Seco M, et al. Coronary Artery Bypass Grafting With and Without Manipulation of the Ascending Aorta: A Network Meta-Analysis. *Journal of the American College of Cardiology*. 2017;69:924-936.

21. Arrigoni SC, Mecozzi G, Grandjean JG, Hillege JL, Kappetein AP, Mariani MA. Off-pump no-touch technique: 3-year results compared with the SYNTAX trial. *Interactive cardiovascular and thoracic surgery*. 2015;20:601-604.
22. Do QB, Goyer C, Chavanon O, Couture P, Denault A, Cartier R. Hemodynamic changes during off-pump CABG surgery. *European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery*. 2002;21:385-390.
23. Cristancho S, Moussa F, Dubrowski A. Simulation-augmented training program for off-pump coronary artery bypass surgery: developing and validating performance assessments. *Surgery*. 2012;151:785-795.
24. Ribeiro IB, Ngu JMC, Lam BK, Edwards RA. Simulation-Based Skill Training for Trainees in Cardiac Surgery: A Systematic Review. *Ann Thorac Surg*. 2018;105:972-982.
25. Feins RH, Burkhart HM, Conte JV, et al. Simulation-Based Training in Cardiac Surgery. *Ann Thorac Surg*. 2017;103:312-321.
26. Meurs Wv. *Modeling and simulation in biomedical engineering : applications in cardiorespiratory physiology*. 1 ed. New York: McGraw-Hill; 2011.
27. Groenier M, Pieters JM, Miedema HAT. Technical Medicine: Designing Medical Technological Solutions for Improved Health Care. *Medical Science Educator*. 2017;27:621-631.
28. de Haan M, van Eijk-Hustings Y, Bessems-Beks M, Dirksen C, Vrijhoef HJM. Facilitators and barriers to implementing task shifting: Expanding the scope of practice of clinical technologists in the Netherlands. *Health Policy*. 2019;123:1076-1082.
29. Marquis-Gravel G, Moliterno DJ, Francis DP, et al. Improving the Design of Future PCI Trials for Stable Coronary Artery Disease: JACC State-of-the-Art Review. *Journal of the American College of Cardiology*. 2020;76:435-450.

List of publications and activities

List of publications

Journal papers

1. Halfwerk, F.R., Groot Jebbink, E. & Groenier, M. Development and evaluation of a proficiency-based and simulation-based surgical skills training for Technical Medicine students, submitted
2. Halfwerk, F.R.[†], Spoor, P.[†], Mariani, S., Hagmeijer R. & Grandjean J.G. Intraoperative Transit Time Flow Measurements: The Impact of Coronary Stenosis on Competitive Flow, submitted
3. Ploumen, E.H.[†], Halfwerk, F.R.[†], van der Kolk, R., Grandjean, J.G., von Birgelen, C. & van Til, J.A. Use of the Radial Artery as Access for Coronary Angiography and as a Bypass Conduit: a Clinical Dilemma, submitted
4. Halfwerk, F. R., Mariani, S., Boudrie, S. & Grandjean, J. G. Downsizing is not enough: Minimal Invasive Extracorporeal Circulation is more than just a Circuit, Annals of thoracic surgery, accepted
5. Sokolski, M., Gajewski, P., Zymlinski, R., Biegus, J., ten Berg, J.M., Bor, W., Cuculi, F., D'Elia, E., Ferenc Édes, I., Garus, M., Greenwood, J.P., Halfwerk, F.R., (...), Bax, J.J. & Ponikowski, P. Impact of coronavirus disease 2019 (COVID-19) outbreak on acute admissions at the emergency and cardiology departments in Europe, The American Journal of Medicine, accepted
6. Urgert, T., Halfwerk, F. R., Hagmeijer, R., van den Heuvel, M. & Grandjean, J. G. Mechanically reducing regional left ventricular wall stress and improving ejection fraction in heart failure patients, 12 Aug 2019, International journal of artificial organs. 42, 8, p. 419-420
7. Halfwerk, F. R., Knol, K., Mariani, S., Grandjean, J. G. & Mecozzi, G. Randomized Trial of Miniaturized versus Standard Extracorporeal Circulation in Aortic Valve Surgery, 1 Jul 2019, Annals of thoracic surgery. 108, 1, p. 37-44
8. Van Veghel, D., Daeter, E. J., Bax, M., Amoroso, G., Blaauw, Y., Camaro, C., Cummins, P., Halfwerk, F. R., Wijdh-den Hamer, I. J., De Jong, J. S. S. G., Stooker, W., Van Der Wees, P. J. & Van Der Nat, P. B. Organisation of outcome-based quality improvement in Dutch heart centres, 26 Apr 2019, European heart journal. Quality of care & clinical outcomes. 6 p.
9. Aarnink, K. M.[†], Halfwerk, F. R.[†], Saïd, S. A. M., Grandjean, J. G. & Paulusse, J. M. J. Technical Feasibility and Design of a Shape Memory Alloy Support Device to Increase Ejection Fraction in Patients with Heart Failure, 15 Mar 2019, Cardiovascular Engineering & Technology. 10, 1, p. 1-9.
10. Halfwerk, F. R., Rouwkema, J., Gossen, J. & Grandjean, J. G. Supercritical carbon dioxide decellularised pericardium: Mechanical and structural characterisation for applications in cardio-thoracic surgery, 2018, J of the mechanical behavior of biomedical materials. 77, p. 400-407.
11. Wielens, N., Hulskotte, S., Halfwerk, F. R. & Grandjean, J. G. Klinische mobilisatie voor de hartchirurgische patiënt: Bewegen is Herstellen!, 5 Sep 2018, Cordiaal. 39, 4, p. 118-120.
12. Halfwerk, F.R., Damanik, F., Rouwkema, J., Moroni, L., Siddappa, R., Grandjean, J.G. State of the Heart Technology: the Potential of Decellularised Pericardium by Supercritical Carbon Dioxide Processing for Cardiothoracic Surgery, 2014, Netherlands Heart Journal, Volume 22, Suppl. pp 13

[†] Contributed equally to this paper

Conference papers and abstracts

1. Halfwerk, F.R. *, Schotanus, F. , Siesling, S. , 2013. Selective contracting in cancer care: Development of a composite measure of quality indicators for breast cancer care. Proceedings of the 22nd Annual IPSERA Conference, Nantes, France, pp 825 – 832
2. Halfwerk, F.R. *, Damanik, F. , Rouwkema, J. , Moroni, L. , Siddappa, R. , Grandjean, J.G. , 2014. State of the Heart Technology: the Potential of Decellularised Pericardium by Supercritical Carbon Dioxide Processing for Cardiothoracic Surgery. Spring Congress of the Dutch Society for Cardiology (NVVC) and the Dutch Society for Cardio-Thoracic Surgery (NVT), Amsterdam, the Netherlands
Awarded the prof. Snellen prize for best cardio-thoracic surgery presentation
3. Halfwerk, F.R. *, Damanik, F. , Rouwkema, J. , Moroni, L. , Siddappa, R. , Grandjean, J.G. , 2014. State of the Heart Technology: Decellularised Pericardium by Supercritical Carbon Dioxide Processing for Cardiothoracic Surgery Applications. Wetenschapsdag Medisch Spectrum Twente, September 17th 2014, Enschede, the Netherlands
4. Halfwerk, F.R. *, Gossen J.A. , Grandjean J. G. , 2015. State of the Heart Technology: Supercritical CO₂ Decellularisation and Sterilisation of Pericardia for Applications in Cardio-Thoracic Surgery. Oral and Poster Presentation at Annual Conference of the Dutch Society for Technical Physicians (NVvTG), Amsterdam, the Netherlands
5. Halfwerk, F.R. *, Rouwkema, J., Gossen, J. & Grandjean, J. G., 2015. Supercritical Carbon Dioxide Decellularisation of Pericardium – Mechanical and Structural Characterisation for Applications in Cardiovascular Surgery: XXV Congress of the International Society of Biomechanics, Glasgow, UK
Nominated for Young Investigator Award
6. Groenier, M. *, Groot Jebbink, E. , Halfwerk, F.R. , 2016. A Human Factors Perspective on Simulation-Based Surgical Skill Assessment: Poster Presentation at the Annual Conference of the Dutch Society for Simulation in Healthcare (DSSH), Delft, the Netherlands
Awarded as best poster presentation
7. Halfwerk, F.R. *, Rouwkema, J., Grandjean, J.G. , 2016. Characterisation of Cardiovascular Tissues after Supercritical Carbon Dioxide Decellularisation: Oral Presentation at the Annual Congress of the European Society of Biomechanics, Lyon, France
8. Groenier, M. *, Groot Jebbink, E. , Halfwerk, F.R. , 2016. Simulation-based assessment of surgical skills in graduate technical-medical education: Oral Presentation at the Annual Conference of the Association for Medical Education in Europe (AMEE), Barcelona, Spain
9. Halfwerk, F.R. *, Knol, K. , Grandjean, J.G. , Mecozzi, G. , 2017. The MECOZZI study: MECC vs Conventional ECC in Aortic Valve Replacement Surgery: Annual Meeting of the Society for Cardio-Thoracic Surgery of Great-Britain and Northern-Ireland (SCTS), Belfast, United Kingdom
10. Spoor, P. *, Halfwerk, F.R. , Hagmeijer R., Grandjean J.G., 2017. Quantitative Measurements of Competitive Flow in Left Internal Mammary Artery Bypass Grafts: Annual Meeting of the Society for Cardio-Thoracic Surgery of Great-Britain and Northern-Ireland (SCTS), Belfast, United Kingdom
Awarded the John Parker Medal for best clinical presentation
11. Halfwerk, F.R. *, Wielens, N. , Hulskotte, S. , Grandjean, J.G. , 2017. In-Hospital Early Mobilisation Measurement and Improvements After Cardiac Surgery: Poster Presentation at the International Forum on Quality & Safety in healthcare, London, UK

12. Halfwerk, F.R. *, Groot Jebbink, E. , Groenier, M. , 2017. Surgical patient Flow at the Core of Surgical Skills Training: A New Perspective on Teaching Surgical Skills: Poster Presentation at the Annual Meeting of the Society in Europe for Simulation Applied to Medicine (SESAM), Paris, France
13. Spoor, P. *, Halfwerk, F.R., Hagmeijer, R. & Grandjean, J. G., 2017. Quantitative Measurements of Competitive Flow in Left Internal Mammary Artery Bypass Grafts: International Coronary Congress, New York, U.S.A.
14. Wielens, N. *, Hulskotte, S. *, Halfwerk, F. R. & Grandjean, J. G., 2017. Bewegen is herstellen: Wetenschapsdag Medisch Spectrum Twente, Enschede, the Netherlands
15. Halfwerk, F. R. *, Knol, K., Mariani, S., Mecozzi, G. & Grandjean, J. G., 2017. Open and Closed Miniaturised Extracorporeal Circulation: A randomized Controlled Trial of Blood Loss in Aortic Valve Replacement Surgery: Wetenschapsdag Medisch Spectrum Twente, Enschede, the Netherlands
16. Halfwerk, F. R. *, Groot Jebbink, E. & Groenier, M., 2017. Surgical Patient Flow at the Core of Surgical Skills Training: A New Perspective on Teaching Surgical Skills: Wetenschapsdag Medisch Spectrum Twente, Enschede, the Netherlands
17. Spoor, P. *, Halfwerk, F. R., Hagmeijer, R. & Grandjean, J. G., 2017. Transit Time Flow Measurements of Competitive Flow in Left Internal Mammary Artery Bypass Grafts: Wetenschapsdag Medisch Spectrum Twente, Enschede, the Netherlands
18. Knol, K. *, Halfwerk, F. R., Mariani, S., Mecozzi, G. & Grandjean, J. G., 2017. Open and Closed Miniaturized Extracorporeal Circulation: A Randomized Controlled Trial of Blood Loss in Aortic Valve Replacement Surgery: Physician Assistants Invest 2017, Ede, the Netherlands
19. Halfwerk, F. R. *, Groot Jebbink, E. & Groenier, M., 2018. Development and evaluation of a proficiency-based and simulation-based surgical skills training for Technical Medicine: 10th Congress of the Dutch Society for Simulation in Healthcare, Enschede, the Netherlands
20. Uineken, R. *, Groot Jebbink, E., Halfwerk, F. R., Bulten, A., Knoben, P., Roux, M., Wicik, O. & Groenier, M., 2018. MOJECT: Motion Analysis to Support Assessment of Surgical Skills: 10th Congress of the Dutch Society for Simulation in Healthcare, Enschede, the Netherlands
21. Halfwerk, F. R. *, Hulskotte, S., Wielens, N. & Grandjean, J. G., 2018. Building Nurse leadership: Success Case of Early In-Hospital Mobilisation After Cardiac Surgery: Conference Proceedings International Forum on Quality and Safety in Healthcare 2-4 May 2018: Reclaiming the Quality in Healthcare, Amsterdam, the Netherlands. BMJ, pp 260-261
22. Groenier, M., Halfwerk, F.R. * & Groot Jebbink, E., 2018. Motion tracking to support surgical skill feedback and evaluation: Annual Meeting of the Society in Europe for Simulation Applied to Medicine (SESAM), Bilbao, Spain
23. Halfwerk, F. R. *, Knol, K., Mariani, S., Mecozzi, G. & Grandjean, J. G., 2018. MiECC for AVR Surgery: A Randomised Controlled Trial on Blood Loss: Autumn Congress of the Dutch Society for Cardiology (NVVC) and the Dutch Society for Cardio-Thoracic Surgery (NVT), Arnhem, the Netherlands
24. Moejes, D. S. *, Halfwerk, F. R., Hagmeijer, R., van Meurs, W. L. & Grandjean, J. G., 2019. A simulator for training off-pump coronary bypass surgery: Wetenschapsdag Medisch Spectrum Twente, Enschede, the Netherlands
25. Urgert, T. *, Halfwerk, F. R., Hagmeijer, R., van den Heuvel, M., & Grandjean, J. G., 2019. Mechanically reducing regional left ventricular wall stress and improving ejection fraction in heart failure patients: Wetenschapsdag Medisch Spectrum Twente, Enschede, the Netherlands
Awarded bronze medal best oral presentation

26. Moejes, D. S. *, Halfwerk, F.R., van Meurs, W. L., Hagmeijer, R., Groenier, M., Grandjean, J. G., 2020. Design of a simulator for training off-pump coronary bypass surgery: Accepted for short communication at the annual Meeting of the Society in Europe for Simulation Applied to Medicine (SESAM), Milan, Italy

*Presenting author

List of activities

Invited presentations

1. Halfwerk, F.R., 2016. Technology in Heart Surgery: Follow Your Heart, Use Your Head: Science Meets Business Event, Nijmegen, the Netherlands
2. Halfwerk, F.R., 2016. Surgical Skills: De Technisch Geneeskundige aanpak, Shaping the future of medicine: 10 Years ECTM, Enschede, the Netherlands
3. Halfwerk, F.R., 2016. Technology in Heart Surgery: Follow Your Heart, Use Your Head: MIRA day 2016, Enschede, the Netherlands
4. Halfwerk, F.R., 2017. Peri-operatieve keuzes in de cardio chirurgie: Hartsymposium Twente Hart in Actie 2017, Enschede, the Netherlands
5. Halfwerk, F.R., 2017. Bewegen is herstellen! Klinische mobilisatie voor de hartchirurgische patiënt: Dag van de fysiotherapeut 201, Barneveld, the Netherlands
6. Halfwerk, F.R., Wietsma, N., 2018. Bloedproducten: niet altijd de oplossing: Symposium Hart in Actie 2018, Enschede, the Netherlands
7. Wielens, N., Halfwerk, F.R., 2019. Bewegen is herstellen! Klinische mobilisatie voor de hartchirurgische patiënt: Landelijke hoofddag cardiochirurgie, Amsterdam, the Netherlands
8. Halfwerk, F.R., 2019. Twente, Thoraxchirurgie en Techniek: Een gouden combinatie: Voorjaarsvergadering Nederlandse Vereniging voor Thoraxchirurgie 2019, Utrecht, the Netherlands
9. Halfwerk, F.R., 2020. Uitkomsten hartzorg Thorax Centrum Twente: Bijeenkomst voor verwijzend cardiologen MST, Gorssel, the Netherlands
10. Halfwerk, F.R., 2020. Ontwikkeling van het vak Technische Geneeskunde: Innovaties en actuele ontwikkelingen in- en rond de artsenopleiding, opleidingsbijeenkomst stichting topklinische ziekenhuizen, digitaal

Grants

1. Wielens, N., Halfwerk, F.R., 2018. Bewegen is herstellen! Keten zorg na hartchirurgie: Fonds op Naam – Regionaal Genootschap Fysiotherapie Twente en IJsselzoom
2. Saïd, S.A.M., Paulusse, J.M.J., Grandjean, J.G., Halfwerk, F.R., Teeuw, W.B. & Brinks, G., 2018. Electro-mechanical resynchronisation therapy with a smart material for patients with heart failure: Pioneers in Health Care
3. Van Haaren, J., Halfwerk, F.R., Wielens, N., Grandjean, J.G., 2020. MOVeMeNT: Bewegen is Herstellen! Objectief meten van beweging na hartchirurgie: Stichting Hartcentrum Twente

Conference organisation

1. H. van der Kooij (General Chair), H.F.J.M. Koopman (Finance Chair), S. Misra (Program Chair), F.R. Halfwerk (Treasurer), E.H.F. van Asseldonk (Chair), Raffaella Carloni (Chair), J. van der Lek (Organiser), A. Forner Cordero (Chair), Petrus H. Veltink (Member of programme committee), Lorenzo Masia (Member of programme committee), Sunil L. Kukreja (Chair), A.Q.L. Keemink (Chair), M. Sartori (Chair), Heike Vallery (Chair), 2018. 7th IEEE RAS & EMBS International Conference on Biomedical Robotics and Biomechatronics, BioRob 2018, Enschede, the Netherlands
2. Jan G. Grandjean, Ab G. Hensens, Frank R. Halfwerk, Kees Knol, Yvonne Weggen, Esther de Jong, Esther Polman, Monique Aink, 2018. Symposium Hart in Actie 2018, Enschede, the Netherlands

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Curriculum vitae

Frank Ruben Halfwerk (1989) obtained a Bachelor (2010) and Master (2014) degree in Technical Medicine, with a specialisation in reconstructive medicine from the University of Twente (supervisor: prof. Grandjean). In addition, he also finished a Master in Health Sciences (2014) with a specialisation in health services and management from the same university (supervisors: prof. Schotanus, prof. Siesling).

He started as a technical physician in cardio-thoracic surgery at Thorax Centrum Twente (Medisch Spectrum Twente) and as parttime doctoral candidate in the department of Biomechanical Engineering in the 'Technology in cardiac surgery' group of prof. Grandjean.

As of 2020, he is appointed assistant professor technology in cardiac surgery and continues his work in Thorax Centrum Twente.

His research focus is both on technical and applied innovations in cardio-thoracic surgery. He was awarded the prof. Snellen Award (2014) from the Dutch Society for Cardiology / Dutch Society for Cardio-Thoracic Surgery, and the prof. Schuijjer Campus Culture Prize (2012) for 'combining excellent cultural performance with good study results'. His research was nominated for the prof. David Winter Young Investigator Award from the International Society of Biomechanics (2015). The work of Frank, his co-workers and students is often presented at (inter)national conferences and received awards from time to time.

Frank is involved in the healthcare programmes Technical Medicine, Health Sciences and Biomedical Engineering of the University of Twente with a great enthusiasm for teaching. He is co-applicant and project manager of awarded research projects and supervised over 70 bachelor and master students. Multiple clinical studies were initiated as a (local) principle investigator.

Other interests include dancing in national and international ballroom competitions, playing chess, organising events, politics and health care policy.