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Comparison of cardiac time intervals between echocardiography and impedance cardiography at various heart rates

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Abstract
The non-invasively measured initial systolic time interval (ISTI) reflects a time difference between the electrical and pumping activity of the heart and depends on cardiac preload, afterload, autonomic nervous control and training level. However, the duration of the ISTI has not yet been compared to other time markers of the heart cycle. The present study gauges the duration of the ISTI by comparing the end point of this interval, the C-point, with heart cycle markers obtained by echocardiography. The heart rate of 16 healthy subjects was varied by means of an exercise stimulus. It was found that the C-point, and therefore the end point of ISTI, occurred around the moment of the maximum diameter of the aortic arch in all subjects and at all heart rates. However, while the time difference between the opening of the aortic valves and the maximum diameter of the aortic arch decreased significantly with decreasing RR-interval, the time difference with respect to the moment of the C-point remained constant within the subjects. This means that the shortening of the ISTI with increasing heart rate in response to an exercise stimulus was caused by a shortening of the pre-ejection period (PEP). It is concluded that the ISTI can be used as a non-invasive parameter indicating the time difference between the electrical and mechanical pumping activity of the heart, both inside and outside the clinic.

Keywords: Impedance cardiography, ISTI, echocardiography, preload, autonomic nervous control, PEP, heart cycle

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Introduction

When measuring the electrical impedance of the human thorax, a distinct variation can be observed, synchronous with the activity of the heart. The time derivative of this variation is called the impedance cardiogram (ICG) and was introduced by Kubicek and Patterson in 1966 in an effort to determine cardiac stroke volume (SV) [1]. Their paper has initiated numerous studies that aimed to use the amplitude of the minimum value (C-point or $[dZ/dt]_{min}$) of the declining wave (C-wave) in the ICG during the systolic phase to assess SV. To this end, various physiological models and algorithms were used, e.g. by Sramek et al. and Bernstein [2-4]. Most of the estimates of SV were essentially based on the assumptions that the C-wave originates from small fluctuations in a simply distributed electrical field caused by blood volume changes or velocity changes in the aorta. Meanwhile, several studies have shown that these assumptions are too simplistic [5-9]. Therefore, it appears to be futile to make an interpretation of the *amplitude* of the ICG-signal based on simplistic models.

A relevant property of the ICG-signal, however, can be found in the *time relationships*, especially when compared to specific marker points in the electrocardiogram (ECG). Regardless of the multiple sources of the signal, the ICG reflects the mechanical/hydrodynamical aspects of the cardiac cycle, while the ECG reflects the electrical aspect of the cardiac cycle [10, 11]. The variation in the ICG is believed to be the result of two physiological effects [10]. Firstly, the diameters of the aorta and other contributing blood vessels vary within a heartbeat. Since blood plasma is an electrical conductor, the impedance of the thorax varies with varying blood volume in these vessels. This is called the volume effect. Secondly, the orientation of erythrocytes changes the electrical conductivity of the blood in the major vessels. The shear stress, present in flowing blood plasma, causes the disk-shaped erythrocytes to change their orientation parallel to the velocity vectors of the blood. This causes the resistivity of the blood to decrease in the direction of the flow, which may result in a pulsating decrease in thoracic impedance. This is called the orientation effect. The relative contributions of both effects to the ICG have been reported to be comparable in magnitude by some investigators [10, 12].

A parameter that links electrical and mechanical cardiac activity in time is the widely used pre-ejection period (PEP) [13, 14]. The PEP is an index of contractility, which is influenced by sympathetic but not by parasympathetic activity in humans. PEP is defined as the interval from the onset of left ventricular depolarization, reflected by the Q-wave onset in the ECG, to the opening of the aortic valves, reflected by the B-point in the ICG signal [14-16]. However, despite efforts to improve the quality of the signal by ensemble averaging over multiple beats, time locked to the R-peak, substantial uncertainties in positioning of the Q-wave onset and of the B-point remain [16-19]. It has also been reported that the B-point in the ICG does not reflect a well-defined point but rather an intersection between two waves, one of which is associated with the left ventricular ejection and the other is of unknown origin [20, 21]. The two waves become apparent in elderly, under pathologic cardiac conditions, and at higher heart rates in young, healthy volunteers during an exercise test. This phenomenon could reflect an asynchrony between the right and left part of the heart.

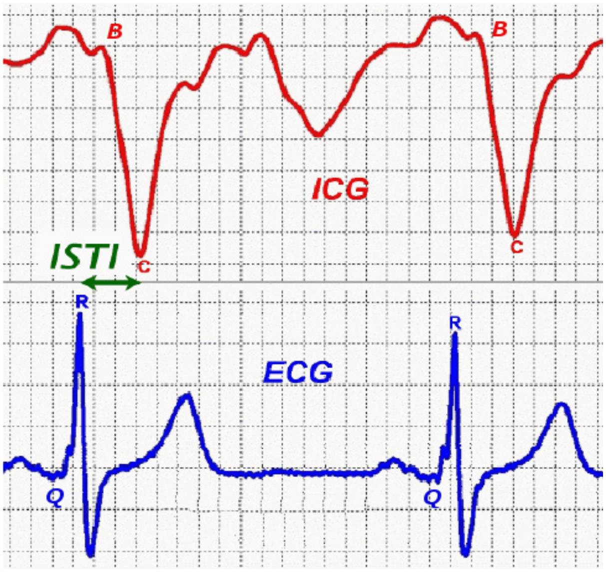

Fig.1: ISTI is defined as the dime delay between the R-peak of the ECG signal and the C-point in the ICG registration.

To find a solution to these problems, the initial systolic time interval (ISTI) was introduced as an indicator for the time delay between electrical and mechanical pumping activity of the heart [17, 19]. This parameter is defined as the time difference between the C-point in the ICG signal, also known as $[dZ/dt]_{min}$ – a minimum of the dZ/dt-signal during systole – and the preceding R-peak in the simultaneously measured ECG (see Figure 1). Both begin and end points of the ISTI can be detected robustly. Several studies reported significant trends in ISTI during fluid administration to hypovolaemic patients at the intensive care unit after cardiac surgery [22] and during excess fluid withdrawal in patients during haemodialysis [23]. Respiratory arrhythmic deviations in ISTI were observed in patients suffering from Parkinson’s disease [24]. Hoekstra et al. investigated the dependence of ISTI on heart rate and physical training [25]. These studies demonstrated a dependence of ISTI on circulating blood volume, central nervous control and on physical training. However, despite the clinically and physiologically relevant variations in ISTI, no studies are known that position the moment of occurrence of the C-point, the end marker of the ISTI, in the cardiac cycle in healthy humans and over a range of heart rates. A limited number of studies report observations during surgery, in animals, in an isolated test, or at single unknown heart rates [4, 9, 11, 26-28]. Therefore, the aim of the present study was to establish the timing of the C-point in healthy humans and at various heart rates. The moment of the C-point was compared with the timing of four other cardiac cycle markers obtained from echocardiography, in order to facilitate an interpretation of the timing of the ISTI within the cardiac cycle. To this end, the moments of opening and closing of the aortic valves, the moment of maximum diameter of the aortic arch, and the moment of maximum diameter of the descending aorta, just below the sternum, were determined simultaneously with the moment of the C-point in the ICG in 16 healthy subjects. The heart rates of the subjects were varied using an exercise stimulus on a stationary bicycle. All moments were synchronized with respect to the R-peak of the ECG. Additionally, the timing of the C-point with respect to the opening of the aortic valves was also established at various heart rates from the same recordings.

Materials and methods

Subjects

Sixteen students participated in this study. All subjects were healthy volunteers, aged between 18 and 28. The characteristics of the subjects are presented in Table 1.

Table 1: Subjects' characteristics (mean ± S.D.).

Subjects	Total (N=16)
Age (years)	22 ± 2
Male (m) / Female (f)	9 m / 7 f
Height (cm)	177 ± 10
Body mass (kg)	69 ± 12

Echocardiography

The ultrasound images were acquired on a Vivid 7 device from GE Healthcare with a cardiac transducer. Three different echoscope views were used, as illustrated in Figure 2. The aortic valves were imaged in the parasternal long-axis view. Subjects lay on their left side and the transducer was positioned in the 3rd or 4th intercostal space - left of the sternum. In addition, the diameter of the aortic arch was imaged in the suprasternal view. For this view, the transducer was positioned in the suprasternal notch – above the sternum – between the clavicles. Finally, the diameter of the descending aorta – just below the sternum – was imaged using the subcostal view, with the transducer positioned just below the sternum. The suprasternal and subcostal view were obtained with the subject lying in a supine position.

ECG and ICG recordings

Both the ultrasound machine and the impedance cardiograph had a facility to record ECG. The ECG recordings were obtained in accordance with Einthoven’s Lead II on both devices simultaneously. ICG recordings were obtained following the method described by Meijer et al. [17, 19]. This method uses four electrodes, as illustrated in Figure 3. Electrodes I1 and I4 apply a small, alternating electric current of 0.3 mA and a frequency of 64 kHz; I2 and I3 measure the induced voltage difference over the heart. The ICG is obtained by the impedance cardiograph by computing the time derivative of this voltage difference.

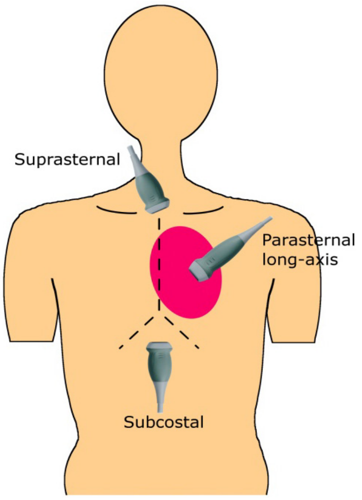

Figure 2: Positioning of the ultrasound transducer for the three views.

The impedance cardiograph used in this study was designed and built at the Department of Physics and Medical Technology of the VU University Medical Center. The signals were sampled at a frequency of 2 kHz, AD converted by means of an ADInstruments PowerLab 8SP and recorded on a PC using ADInstruments Chart 5. A typical example of a simultaneous ICG and ECG recording is presented in Figure 1.

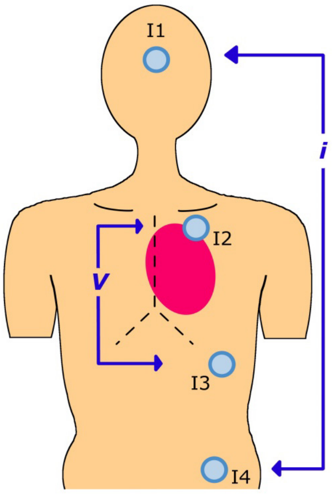

Figure 3: Electrode configuration. A small current (*i*) is applied through the outer two electrodes I1 and I4. The inner two electrodes I2 and I3 measure the impedance induced voltage difference (*V*) over the heart (indicated with an oval). The ECG is obtained from these inner electrodes simultaneously.

Procedures

To establish a baseline condition, the subjects rested for 10 minutes prior to the measurement. The subjects were also requested to fill out a questionnaire. A typical measurement routine started with a subject at rest, lying on a bed in a sideward or supine position. This position was dependent on the ultrasound registration at hand (see the section ‘Echocardiography’).

Firstly, ultrasound recordings in the parasternal long-axis, suprasternal, and subcostal view were obtained from the subject at rest, while the ICG was recorded simultaneously. Subsequently, the subject exercised on a stationary bicycle until a heart rate of approximately 170 bpm was reached. To enable ultrasound and ICG registration, the subject was positioned on the bed immediately afterwards. The heart rate typically decreased to near-resting level within a few minutes after the exercise. Therefore, the measurement procedure using the exercise stimulus on the bicycle was repeated for all three ultrasound views.

Analysis

The timing of all heart cycle markers was established with respect to the preceding R-peak in the ECG, which was recorded simultaneously on both the ultrasound machine and the impedance cardiograph. This procedure allowed for synchronization of the recordings on both devices and for beat-to-beat analysis.

To describe the relationship between the time interval of the C-point with respect to the R-peak (the ISTI) on the one hand and the RR-interval on the other hand, a linear regression model was used in accordance with the method used by Hoekstra et al. [25]. The time delays of the four echocardiographic heart cycle markers with respect to the R-peak were also analyzed with linear regression models. To compare ISTI with these four heart cycle markers, a two-sided, paired t-test with unequal variances was applied at two chosen values of the RR-interval (500 ms and 1000 ms). These RR-interval values were within the measuring range for all subjects.

An additional analysis was made to determine the moment of occurrence of the C-point and the echocardiography markers in the ejection phase. The regression line of the opening of the aortic valves was subtracted from all other regression lines, for each subject. This yielded four regression lines per subject, representing the moment of occurrence for each heart cycle marker with respect to the opening of the valves. Two-sided, one-sample t-tests were applied to investigate whether the slopes of the regression lines differed from zero.

Results

The measurements resulted in a dataset of heart cycle marker moments at varying heart rates for each subject. The relationship of each marker moment with the RR-interval was established by means of linear regression. All linear relationships were found to be significant (all $R > 0.86$, all $p < 0.005$). A typical example of these relationships in one of the subjects is shown in Figure 4, in which the moment of occurrence after the R-peak of the markers is presented

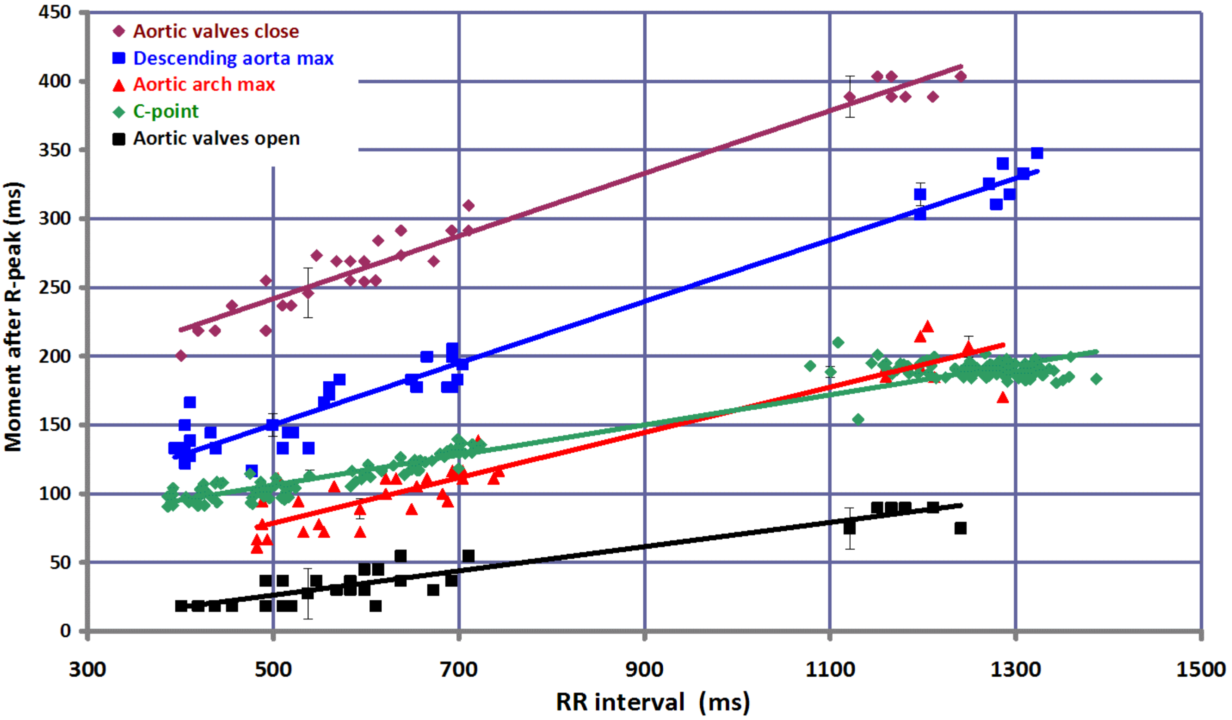

Figure 4: Typical example of results from a subject: the moments of occurrence for each heart cycle marker are presented at various RR-intervals. Shown are from bottom to top: opening aortic valves, C-point ICG, maximum diameter aortic arch, maximum diameter descending aorta and closing aortic valves. Least squares linear regression was used to fit the data. All coefficients of correlation were r > 0.97 (p<0.005). The error bars of C-point indicate the standard deviation at a constant heart rate. For all other markers, the error bars indicate the measurement's time resolution.

as a function of the RR-interval. This figure shows that all markers, including the C-point, occurred earlier after the R-peak for smaller RR-intervals. This was observed in all subjects. The C-point occurred at about the same moment in the cardiac cycle as the moment of maximum diameter of the aortic arch. Furthermore, the slopes of the regression lines for the C-point and the opening of the aortic valves (AV open) were indistinguishable.

Table 2 presents a comparison of the moment of the C-point with the other heart cycle markers, both in rest and after exercise at the two chosen heart rates. It shows that the moment of occurrence of the C-point differed significantly from all other markers both in rest and after exercise, except the maximum diameter of the aortic arch.

Table 2: Moment of occurrence of the C-point compared with all other heart cycle markers in all 16 subjects. Paired 2-sided t-tests were applied to the C-point and all other markers to compare the means, both in rest and after exercise. All markers differed from the moment of the C-point, except the moment of maximum diameter of the aortic arch.

	C-point compared with	p-value
Rest (RR=1000 ms)	Aortic valves open	< 0.001
	Aortic arch maximum	**> 0.05**
	Descending aorta maximum	< 0.001
	Aortic valves close	< 0.001
Exercise (RR=500 ms)	Aortic valves open	< 0.001
	Aortic Arch maximum	**> 0.05**
	Descending aorta maximum	< 0.05
	Aortic valves close	< 0.001

In order to evaluate the moments of occurrence of the markers in the ejection phase, the regression line of the moments of opening of the aortic valves was subtracted from the other lines for each subject. An example of these relationships, originating from the same subject, is presented in Figure 5. Every line represents the time interval between the start of the ejection phase and the corresponding heart cycle marker.

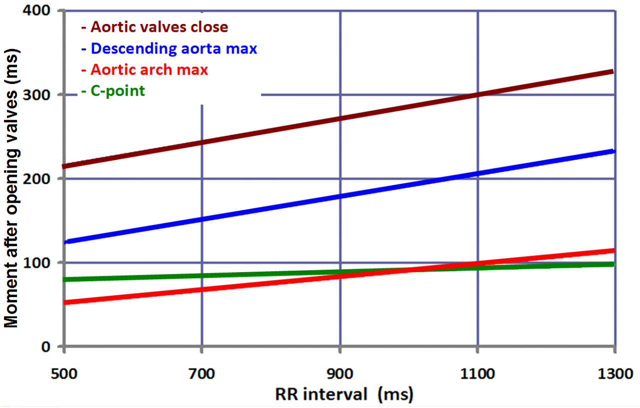

Figure 5: Typical example of the relationships of the time interval between the start of the ejection phase (opening aortic valves) and the heart cycle markers. Data from the same subject as in Figure 4 were used.

Figure 5 illustrates that the interval between the ultrasound markers and the opening of the aortic valves decreased for smaller RR-intervals, while the time interval between the C-point and opening of the aortic valves was constant and independent of the RR-interval.

The t-tests were applied to the slopes of the regression lines, shown in Figure 5, to test whether they differ from zero. As such, all markers were tested for having a constant time interval between the opening of the aortic valves and the marker. This procedure was followed for each subject. The results are shown in Table 3.

Table 3: The mean slopes and their standard deviations (SD) of the regression lines describing the time interval between the start of the ejection phase and the corresponding heart cycle marker. All slopes were found to differ from zero, except for the C-point.

Slope of	Mean ± SD	p-value
C-point	0.02 ± 0.06	0.255
Aortic arch maximum	0.07 ± 0.06	< 0.001
Descending aorta maximum	0.17 ± 0.07	< 0.001
Aortic valves close	0.16 ± 0.06	< 0.001

Table 3 shows that the C-points occurred at a constant time interval after the opening of the aortic valves, independently of the RR-interval. The slopes of the regression lines for the other heart cycle markers were significantly different from zero. Thus, the time interval of these other markers after the aortic valves open decreased for decreasing RR-intervals.

Discussion

In this study a comparison was made between the timing of the C-point in the impedance cardiogram and the timing of four different cardiac cycle markers obtained from echocardiography in healthy, young volunteers at various heart rates. The study was not intended to identify the sources of the C-wave in the ICG, which may be complex, but was designed to position the moment of the C-point (minimum of the C-wave or $[dZ/dt]_{min}$) in the cardiac cycle. This provides an interpretation of the ISTI, the time difference between the R-point in the ECG and the C-point in the ICG.

It was found that the C-point occurred around the same moment in time as the maximum diameter of the aortic arch for all sixteen subjects and at all heart rates. No significant difference was found between the timing of the C-point and the moment of the maximum diameter of the aortic arch in the cardiac cycle within the time resolution of the echocardiographic recordings. This implies that the C-point occurs around the moment that the blood pressure in the aortic arch reaches its maximum.

Consistent with the observations reported by Hoekstra et al. [25], the C-point occurred earlier in the cardiac cycle for higher heart rates (shorter RR-intervals), which means that the ISTI shortened accordingly. However, the present study shows that this is entirely the consequence of a shortening of the period between the R-peak and the opening of the aortic valves, because the time interval between the opening of the aortic valves and the C-point remained constant. Thus, the latter period was independent of the heart rate in this study. This means that the regression line of the C-point with the RR-interval followed a different trend than the moment of maximum diameter of the aortic arch. A possible explanation for this observation is the erythrocyte orientation effect [5, 12], which causes thorax conductivity to decrease as a consequence of the velocity change of the blood. Aortic velocity flow patterns have recently been visualized by Tanaka et al. [29]. They used echo-dynamography to show that the blood in the aortic arch spirals during the systole; the rotation cycle of this flow is inversely correlated with the maximum velocity. These complex flow profiles may well influence the orientation of the erythrocytes for subjects in exercise. Consequently, the C-point might also coincide with the maximum velocity of aortic arch flow.

This observation also means that the shortening of the ISTI with increasing heart rate in response to an exercise stimulus can be attributed to a shortening of the pre-ejection period (PEP) in every individual subject in this study. This is not contradictory to the report of van Lien et al. [18] that concluded that ISTI and PEP were not interchangeable by one single regression equation, pooled for multiple individuals. Whether the intra-individual relationship between PEP and ISTI is fixed over a wide range of physiological and clinical conditions has to be established in future studies.

In line with the method used by Hoekstra et al. [25], the relationships between ISTI and RR-interval were described using linear regression analysis. However, despite the execution of a strict measurement protocol, it is possible that the moment of the C-point in the cardiac cycle was influenced by variables other than heart rate alone. For example, vascular tonus may be different in rest than during exercise. However, such effects on the timing of the C-point are believed to have been of minor influence on the observed relationships, since all linear fits were highly significant.

Conclusions

The moment of occurrence of the C-point in the cardiac cycle was found to be indistinguishable from the moment of the maximum diameter of the aortic arch. This means that the non-invasively measured ISTI, obtained by impedance cardiography, can be interpreted directly in terms of known events in the cardiac cycle. Therefore, the ISTI can be used as a clinical and physiological parameter indicating the time difference between the electrical activity and the pumping activity of the heart. The ISTI can be used both in intra- and extramural settings.

The time interval between the opening of the aortic valves (start of the ejection phase) and the C-point was found to be independent of the heart rate and constant within subjects, while the time interval between the opening of the aortic valves and the moment of maximum diameter of the aortic arch shortened at increased heart rates. This means that the shortening of the ISTI with increasing heart rate in response to an exercise stimulus was caused by a shortening of the pre-ejection period (PEP) in this study.

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