A potentially new phase of the cardiac cycle
Pre-isovolumic contraction recognized by echocardiography

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Abstract
Clinically the isovolumic contraction time (IVCT) can be measured by 3 echocardiographic methods of M-mode, pulse-wave Doppler (PWD), and tissue Doppler imaging (TDI). But IVCT can be clinically different by the 3 methods. This study is to investigate whether there is a potentially unidentified phase causing the discrepancies by analyzing electric mechanical delay time (EMD), IVCT, and pre-ejection period (PEP).

A total of 30 healthy subjects were recruited for the study. EMD, IVCT, and PEP were obtained by the 3 methods, respectively. MCT (the interval from the onset of the QRS wave to the closure point of the mitral valve measured by TDI) and ICMC (the interval from the onset of IVC wave S1 to the closure point of the mitral valve measured by TDI) were both measured by color TDI. IVCT (IVCT measured by TDI) was significantly longer than IVCTm or IVCTd (IVCT measured by M-mode or PWD) (both \( P < .0001 \)), while EMD, (EMD measured by TDI) was significantly shorter than EMDm or EMDd (EMD measured by M-mode or PWD) (both \( P < .0001 \)). But MCT was not significantly different from EMDm or EMDd (\( P > .05 \)) and ICMC did not differ significantly from EMDm or EMDd minus EMDt or IVCTt minus IVCTm or IVCTd (\( P > .05 \)), in other words, ICMC almost equaled to (EMDm or EMDd minus EMDt) or (IVCTt minus IVCTm or IVCTd).

There may be an unidentified phase between the end of atrial contraction and the closure of mitral valve causing the discrepancies in IVCT, which is named as the pre-isovolumic contraction phase. It is a non-isovolumic phase and is included in the traditional isovolumic contraction phase.

Abbreviations: TDI = tissue Doppler imaging, PWD = pulse wave Doppler, EMD = electric mechanical delay time, EMDm = electric mechanical delay time measured by M-mode, EMDd = electric mechanical delay time measured by PWD, IVCT = isovolumic contraction time measured by M-mode, IVCTm = isovolumic contraction time measured by M-mode, IVCTd = isovolumic contraction time measured by TDI, PEP = pre-ejection time, PEPm = pre-ejection time measured by M-mode, PEPd = pre-ejection time measured by PWD, MCT = the interval from the onset of the QRS wave to the closure point of the mitral valve measured by TDI, ICMC = the interval from the onset of IVC wave S1 to the closure point of the mitral valve measured by TDI, ICC = intraclass correlation coefficient.

Keywords: cardiac cycle, echocardiography, pre-isovolumic contraction, tissue Doppler imaging

1. Introduction
Isovolumic contraction (IVC) is the early phase of systole. During this time period, the myocardial fibers begin to contract but have not developed enough pressure in the ventricles to overcome the aortic and pulmonary end-diastolic pressures in order to open the valves and consequently the ventricular volumes remain unchanged.[11] The IVC starts approximately at the left atrioventricular pressure crossover and ends at the diastolic ventriculoaortic pressure crossover.[12] The isovolumic contraction time (IVCT) is defined as the interval between the closing of the atrioventricular valves and the opening of the semilunar valves.[1] It can be measured by 3 echocardiographic methods of M-mode, pulse-wave Doppler (PWD), and tissue Doppler Imaging (TDI).[3–5] Clinically, the IVCT obtained by these methods for the same patients is not consistent and has caused misunderstanding (or confusions) in clinical diagnosis and treatment.[6–13]

Many researchers attribute the discrepancies to the fact that IVCT was not measured in the same cardiac cycle.[11,14] The start of IVC wave S1 on TDI represents the end of atrial muscle contraction and the beginning of voluntary ventricular muscle contraction, whereas the end of the IVC wave S1 represents the end of IVC along with opening of aortic valve and beginning of ventricular pumping.[15–18] In addition, it has been confirmed that IVC wave S1 on TDI is synchronous to the first derivative of the left ventricular pressure (dP/dt). Thus, the period of S1 has been considered as the IVCT over years in clinical practice.[21–24] However, our data indicated that the mitral valve...
The electrocardiogram
Inclusion criteria: no family history of coronary heart disease.

EMD (EMD measured by M-mode) was measured from the short-axis plane. Sweep speeds were kept high at 100 mm/s across the mitral and aortic valves in the parasternal long- or routine diagnostic images of color-flow mapping and continuous-wave Doppler spectrum were obtained. Ejection fraction was measured in all subjects by the biplane modified Simpson method.

We performed M-mode measurements by placing the cursor across the mitral and aortic valves in the parasternal long- or short-axis plane. Sweep speeds were kept high at 100 mm/s. EMD (EMD measured by M-mode) was measured from the onset of the QRS complex until the closure of mitral valve, and PEP (PEP measured by M-mode) was measured from the onset of the QRS complex until the opening of the aortic valve. IVCT (IVCT measured by M-mode) was calculated with the formula of 

$$\text{IVCT}_m = \text{PEP}_m - \text{EMD}_m.$$ 

PWD across the mitral and aortic valves was assessed in each subject. The usual size of the pulsed Doppler gate was 2 mm. For optimal acquisition, care was taken to direct the transducer beam as close as possible to the flow direction <20° in selected planes. 

2. Materials and methods

2.1. Clinical data of subjects

The study recruited 30 healthy individuals, including 18 men and 12 women, with mean age of 30±6 years (range 20–40 years). Inclusion criteria: no family history of coronary heart disease. The electrocardiogram (ECG) was normal and the heart rate was 60 to 100 times/min, without arrhythmia. The cardiac x-ray examination was normal. (4) Blood pressure <140/90 mm Hg (18.62/11.97 kPa). (5) Individuals that could withstand strenuous physical exertion. Exclusion criteria: A low ST segment, or pathological Q wave was shown on ECG. Individuals with the fl at, bidirectional or inverted T wave, or abnormal T wave (at, bidirectional or inverted T wave), or the X-rays. The underlying diseases such as cardiovascular diseases were excluded. High-quality echocardiographic imaging was performed in these individuals. The clinical data of patients were listed in Table 1. All subjects signed the informed consent and this study was approved by the Institutional Review Board at the Affiliated Hospital to Changchun University of Traditional Chinese Medicine (Ethical approval number CCZYFYLL2012[K]001).

2.2. Echocardiography

The GE Vivid 7 Dimension echocardiography system (General Electric Healthcare Vingmed Ultrasound, Horten, Norway) with a 1.5 to 4.3 MHz transducer, a built-in work station, and an aortic valve. IVCT was measured from the onset of the spectrum of the aortic valve. IVCT was measured by PWD was calculated as the start point of the cardiac cycle segment of interest was continuously positioned within the interrogated segment. The tissue velocity curve was obtained. EMD (EMD measured by TDI) was measured from the onset of the QRS complex to the end of Aa, and PEP (PEP measured by TDI) was measured from the onset of the QRS complex to the onset of S or calculated with the formula of IVCT = PEP – EMD.

TDI was conducted using the same equipment. Color TDI was superimposed on the underlying two-dimensional gray-scale images (four-chamber apical views). At least ten consecutive beats were recorded, and the images were analyzed by EchoPac software (General Electric Healthcare Vingmed Ultrasound). The region of interest was continuously positioned within the interrogated segment. The tissue velocity curve was obtained. EMD (EMD measured by TDI) was measured from the onset of the QRS complex to the end of Aa, and PEP (PEP measured by TDI) was measured from the onset of the QRS complex to the onset of S or calculated with the formula of IVCT = PEP – EMD.

2.3. Statistical analysis

For each echocardiographic parameter, the mean over at least 3 heart beats was calculated. All results were expressed as mean ± standard deviation. Statistical analysis was performed using SPSS software (Version 15.0, SPSS, Chicago). As tested by one sample K-S test, EMD, PEP and IVCT values were in normal distribution. Thus, one-way ANOVA was used to compare EMD, PEP, and IVCT values obtained by each of the 3 measurement methods, as well as to compare MCT, EMD, and EMD, ICMC, (EMD – EMD), and (EMD – EMD), ICMC, (IVCT – IVCT), and (IVCT – IVCT). Pearson’s correlation analysis was used to define relationships of MCT with EMD and EMD and those of ICMC with EMD and EMD. P<.05 was considered to be statistically significant. Two independent observers analyzed all the recordings and the inter-observer variability was analyzed by intraclass correlation coefficient.

Table 1: Baseline characteristics of the study population (n=30).

| Age, years | 30±6 |
|-----------|------|
| Men/women (n) | 18/12 |
| Body surface area, m² | 1.86±0.14 |
| Heart rate, beats/min | 67±8 |
| Peak E velocity, cm/s | 79±14.5 |
| Peak A velocity, cm/s | 46.7±8.3 |
| E/A | 1.7±0.3 |
| LVEF (%) | 60±5 |

Note: Peak E velocity, peak early diastolic transmitral flow velocity; Peak A velocity, peak late diastolic transmitral flow velocity; E/A, peak early to late diastolic transmitral flow velocity; LVEF, left ventricle ejection fraction.
methods were analyzed. As listed in Table 2, EMD (12.20 ± 5.62 ms) was significantly lower than EMDm (34.69 ± 9.27 ms) and EMDd (34.63 ± 10.46 ms) (both P < .0001). There was no significant difference between EMDm and EMDd (P > .05). IVCTd (36.24 ± 13.49 ms) was significantly higher than IVCTm (35.97 ± 9.71 ms) and IVCTd (36.03 ± 11.23 ms) (both P < .0001). However, IVCTm was not significantly different from IVCTd (P > .05). Furthermore, no significant differences were found among PEPm (71.90 ± 18.55 ms), PEPd (72.01 ± 17.81 ms), and PEP (71.76 ± 16.79 ms) (P > .05).

3.2. The results of MCT, ICMC, and the SI of mitral valve closure point obtained by TDI

To determine the possible reasons of the discrepancy, color TDI was performed. MCT (33.50 ± 10.06 ms) measured by TDI was not significantly different from EMDm or EMDd (P > .05). ICC (24.55 ± 10.33 ms) did not significantly differ from (EMDm - EMDd) or (EMDd - EMDm) (P > .05) or from (IVCTm - IVCTd) or (IVCTd - IVCTm) (P > .05). Strain curve on apical 4-chamber view demonstrated that myocardium of the basal septum had shortened at the time of mitral valve closing, and the SI of mitral valve closure point was -1.31 ± 0.29% (Figs. 1 and 2). We also found a strong positive correlation between MCT and EMDm, MCT, and EMDm (r = 0.948, 0.941, respectively) and between ICMC and (EMDm - EMDd), ICMC, and (EMDm - EMDd), ICMC and (IVCTm - IVCTd), and, ICMC and (IVCTd - IVCTm) (r = 0.862, 0.920, 0.885, and 0.886, respectively).

These results indicate that there is ICMC in S1 wave, which is the possible reasons of the discrepancy between EMDm and EMDd, between IVCT, and IVCTm or IVCTd. ICMC is considered as the time of pre-isovolumic contraction (PIVC).

3.3. The results of inter-observer variability analysis

The individual variability of the interobserver was calculated. The ICC was 0.94 for EMDm, 0.96 for EMDd, 0.89 for EMDm, 0.97 for IVCT, 0.95 for PEPm, 0.94 for PEPd, 0.97 for PEP, 0.91 for MCT, and 0.90 for ICMC, respectively. These results indicate that there was no significant difference between the two observers.

4. Discussion

In this study, the age group of 20 to 40 years was selected to ensure normal reference index. Clinically, physiological condition and systolic function of the heart are optimal in this age group. We set the region of interest on the basal septum to obtain the parameters of TDI according to the fact that the mechanical activity of the heart ends at the basal myocardial wall.[26]
The IVC refers to the state where the mitral valve is closed and the aortic valve is not opened, that is, no blood is flowing from the left atrium to the left ventricle.\(^1\) However, we observed that the mitral valve did not close at the onset of IVC wave S\(_1\) in clinical practice when reviewing each frame of the video of the color TDI step by step. In fact, some researchers have also noticed this phenomenon. For example, Yellin et al.\(^2\) found negative flow at the mitral orifice during IVC. They interpreted this finding as an artificial effect and assumed that the mitral valve must already have been closed at the onset of IVC. Vogel et al.\(^3\) also found that IVC started at or just before mitral valve closure in pigs, however, they did not study this further. Similarly, Goetz et al.\(^4\) reported that the mitral valve was still open at the beginning of IVC in sheep. However, their discussion focused on isometric contraction. They believed that IVC were not discernable by echocardiography, because echocardiography was unable to give precise distances between two moving points due to the considerably longer temporal resolution (30 ms).

In our study, 3 parameters of EMD, PEP, and IVCT were obtained by M-mode, PWD and TDI echocardiography, respectively. The results found that EMD was significantly shorter than EMD\(_m\) or EMD\(_d\) while IVCT\(_m\) was significantly longer than IVCT\(_d\) or IVCT\(_m\). In addition, PEP values obtained by these 3 methods were not significantly different.

In some studies, comparisons were done between these techniques by using the Tei index (IVCT+IVRT/ET). For instance, Meng et al.\(^5\) argued that the IVCT measured by PWD was shorter than the IVCT measured by TDI because IVCT measured by PWD was in a different cardiac cycle and the point measured by PWD was less well defined compared to TDI. Also, Rojo et al.\(^6\) found similar result that IVCT\(_d\) was shorter than IVCT\(_m\) and they thought that IVCT was obtained from tissue Doppler imaging on apical 4-chamber view: EMD\(_d\) = 90 ms, PEP\(_d\) = 90 ms, IVCT\(_d\) = PEP\(_d\)−EMD\(_d\) = 70 ms, MCT = 40 ms, ICMC = MCT−EMD\(_d\) = 20 ms, which almost equals to EMD\(_m\)=EMD\(_m\) and IVCT\(_m\)=IVCT\(_m\). The long arrow indicates the starting point of isovolumic contraction wave S\(_1\), and the short arrow indicates the closure point of mitral valve. (f) Strain curve on apical four-chamber view. SI of the closure point of mitral valve is \(-1.37\%\), which means that myocardium have shortened at the time of mitral valve closing. The arrow indicates the closure point of mitral valve. The abbreviations used were the same as that in figure legend for Fig. 1.

**Figure 2.** TDI, M-mode, and PWD echocardiograph. (A) M-mode cursor across the mitral valve in the parasternal long-axis plane view. EMD\(_m\) = 41 ms. The long arrow indicates the starting point of isovolumic contraction wave S\(_1\), and the short arrow indicates the closure point of mitral valve; (B) M-mode cursor across the aortic valve in the parasternal long-axis plane view. PEP\(_m\) = 90 ms; IVCT\(_m\) = 50 ms (PEP\(_m\)= B−EMD\(_m\) of A); (C) Pulsed Doppler flow across the mitral valve on apical 4-chamber view. EMD\(_m\) = 41 ms. The long arrow indicates the starting point of isovolumic contraction wave S\(_1\), and the short arrow indicates the closure point of mitral valve, which shows that when cardiac muscle starts to contract, the mitral valve is not yet closed. So the blood flows from the left atrium into the left ventricle continuously slowly; (D) Pulsed Doppler flow across the aortic valve on apical 5-chamber view. PEP\(_a\) = 89 ms; IVCT\(_a\) = 48 ms (PEP\(_a\)= D−EMD\(_a\) of C); (E) Color tissue Doppler imaging on apical 4-chamber view: EMD\(_a\) = 20 ms, PEP\(_a\) = 90 ms, IVCT\(_a\) = PEP\(_a\)−EMD\(_a\) = 70 ms, MCT = 40 ms, ICMC = MCT−EMD\(_a\) = 20 ms, which almost equals to EMD\(_m\)=EMD\(_m\) and IVCT\(_m\)=IVCT\(_m\). The long arrow indicates the starting point of isovolumic contraction wave S\(_1\), and the short arrow indicates the closure point of mitral valve. (f) Strain curve on apical four-chamber view. SI of the closure point of mitral valve is \(-1.37\%\), which means that myocardium have shortened at the time of mitral valve closing. The arrow indicates the closure point of mitral valve. The abbreviations used were the same as that in figure legend for Fig. 1.
observed from velocity curve and strain curve during the period. Therefore, we conclude that there may be an undefined period, which is between the end of atrial contraction and the closure of mitral valve and can be distinguished by echocardiography. We name it as PIVC (pre-isovolumic contraction). The period is not an isovolumic phase but is included in the traditional isovolumic contraction phase, in which the cardiac muscle begins to contract while the mitral valve does not close. As a consequence, the blood continues to flow slowly from the left atrium into the left ventricle as a result of inertia and a counter pressure gradient.

PEP is a composite interval consisting of two time frames delimited by changes in LV pressure, EMD, and IVCT. However, our conclusion is that PEP consisted of 3 parts: EMD, ICMC, and IVCT. The newly identified phase (ICMC) was named as PIVC. In addition, either IVCTd or IVCTm is the IVCT in its true sense. However, methods of measuring muscle contraction simultaneously in the same cardiac cycle are currently not available. Thus, future studies to further validate the potentially new phase of the cardiac cycle (PIVC) are still needed.

One limitation in our study was that the measures of EMD, PEP, and IVCT obtained using M-mode, PWD, and TDI were measured sequentially, not during the same cardiac cycle. Consequently, the accuracy of the results may be compromised by heart rate fluctuations. However, we excluded subjects with a difference more than 100 ms. Besides, ANOVA were used to analyze the heartbeats. Another limitation was that the sample size was relatively small.

To sum up, we identify a potentially new phase in the cardiac cycle, which is named as PIVC. It is not an isovolumic period. During PIVC, cardiac muscles start to contract while the mitral valve does not close and blood continues to flow slowly from the left atrium into the left ventricle as a result of inertia and a counter pressure gradient. This finding may be a complementary to the fundamental theory of heart physiology and may change and refine the traditional recognition. Further researches on the role of PIVC in heart disease are warranted.

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