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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 S_1 to the closure point of the mitral valve measured by TDI) were both measured by color TDI.

$IVCT_t$ (IVCT measured by TDI) was significantly longer than $IVCT_m$ or $IVCT_d$ (IVCT measured by M-mode or PWD) (both $P < .0001$), while EMD_t (EMD measured by TDI) was significantly shorter than EMD_m or EMD_d (EMD measured by M-mode or PWD) (both $P < .0001$). But MCT was not significantly different from EMD_m or EMD_d ($P > .05$) and ICMC did not differ significantly from EMD_m or EMD_d minus EMD_t or $IVCT_t$ minus $IVCT_m$ or $IVCT_d$ ($P > .05$), in other words, ICMC almost equaled to (EMD_m or EMD_d minus EMD_t) or ($IVCT_t$ minus $IVCT_m$ or $IVCT_d$).

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, EMDt = electric mechanical delay time measured by TDI, EMDd = electric mechanical delay time measured by PWD, IVCT = isovolumic contraction time measured by M-mode, IVCTm = isovolumic contraction time measured by M-mode, IVCTt = isovolumic contraction time measured by TDI, IVCTd = isovolumic contraction time measured by PWD, PEP = pre-ejection time, PEPm = pre-ejection time measured by M-mode, PEPt = pre-ejection time measured by TDI, 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, PIVC = pre-isovolumic contraction time, 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.[1] The IVC starts approximately at the left atrioventricular pressure crossover and ends at the diastolic ventriculoaortic pressure crossover.[2] 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.[6–12]

Many researchers attribute the discrepancies to the fact that IVCT was not measured in the same cardiac cycle.[13,14] 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).[19,20] 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

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did not close at the start of S1 based on the TDI video imaging.[25] We hypothesize that there may be a previously unidentified phase in the cardiac cycle, which occurs just before the real IVC. This phase has not been noticed due to low temporal resolution and may be the main reason causing the IVCT discrepancies by 3 echocardiographic methods.

The present study is to investigate whether there is a potentially unidentified phase causing the different results of IVCT. The electric mechanical delay time (EMD), IVCT, and pre-ejection period (PEP) obtained by M-mode, PWD and TDI, respectively, were analyzed.

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 abnormal T wave (flat, bidirectional or inverted T wave), or pathological Q wave was shown on ECG. Individuals with the change of heart shape on 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).

Table 1

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

Age, years	30 ± 6
Men/women (n)	18/12
Body surface area, m^2	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 (%)	69 ± 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.

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 image analysis and postprocessing ultrasound system was used for Echocardiography. Transthoracic imaging was performed with subjects in the left lateral position. All recordings were made with a simultaneous superimposed ECG to identify the electrical and mechanical phases of each cardiac cycle. Recordings were made at sweep speeds of 100 mm/s. By adjusting the ECG, the lead with an obvious Q wave was selected. If no Q wave was available, the lead with a clear R wave was selected. Initially, the 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_m (EMD measured by M-mode) was measured from the onset of the QRS complex until the closure of mitral valve, and PEP_m (PEP measured by M-mode) was measured from the onset of the QRS complex until the opening of the aortic valve. $IVCT_m$ (IVCT measured by M-mode) was calculated with the formula of $IVCT_m = PEP_m – EMD_m$.

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. EMD_d (EMD measured by PWD) was measured from the onset of the QRS complex to the end of A_M, and PEP_d (PEP measured by PWD) was measured from the onset of the QRS complex to the onset of the spectrum of the aortic valve. $IVCT_d$ (IVCT measured by PWD) was calculated as $IVCT_d = PEP_d – EMD_d$.

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_t (EMD measured by TDI) was measured from the onset of the QRS complex to the end of A_m, and PEP_t (PEP measured by TDI) was measured from the onset of the QRS complex to the onset of S_m. $IVCT_t$ (IVCT measured by TDI) was measured from the end of A_m to the onset of $S_m$or calculated with the formula of $IVCT_t = PEP_t – EMD_t$. The starting point of the cardiac cycle segment of interest was the onset of the QRS complex. MCT was measured from the onset of the QRS complex to the closure time of the mitral valve, while ICMC was measured from the onset of IVC wave S_1 to the closure of the mitral valve (Fig. 1). Afterwards, transform velocity mode was transformed into strain mode by using update key to obtain the strains (SI) from the onset of IVC to the closure time of mitral valve. The subjects' heart rate was observed during each measurement. The measurements were used only if no more than 100 ms variation in R-R interval was observed.

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_d, and EMD_m, ICMC, (EMD_m–EMD_t), and (EMD_d–EMD_t), ICMC, ($IVCT_t$–$IVCT_d$), and ($IVCT_t$–IVCTm). Pearson's correlation analysis was used to define relationships of MCT with EMDd and EMDm and those of ICMC with EMDm–EMDt, ICMC and EMDd–EMDt, IVCTt–IVCTd, and IVCTt–IVCTm. A P-value < .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

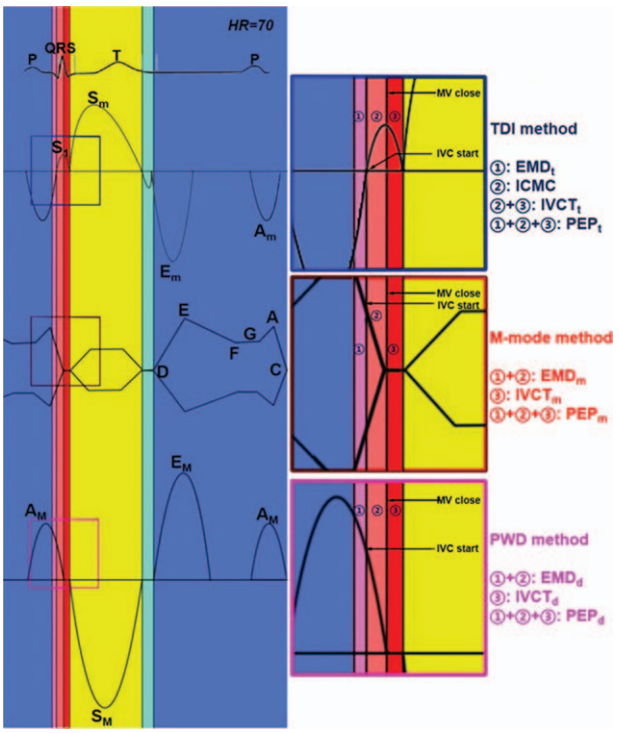

Figure 1. TDI, M-mode, and PWD schematic graph. $IVCT_t$ = ICMC+ $IVCT_m$ or $IVCT_d$. EMD_m or EMD_d = EMD_t +ICMC = MCT. $IVCT_m$ or $IVCT_d$ is IVCT in its true sense. PEP (PEP_t, PEP_m, and PEP_d) contains 3 parts: EMD_t, ICMC, and IVCT in its true sense. ICMC is an unidentified phase prior to IVCT in systolic phase. TDI: tissue Doppler imaging; PWD: pulse wave Doppler; EMD: electromechanical delay; EMD_t: EMD measured by TDI; EMD_m: EMD measured by M-mode; EMD_d: EMD measured by PWD; IVCT: isovolumic contraction time; $IVCT_t$: IVCT measured by TDI; $IVCT_m$: IVCT measured by M-mode; $IVCT_d$: IVCT measured by PWD; PEP: pre-ejection period; PEP_t: PEP measured by TDI; PEP_m: PEP measured by M-mode; PEP_d: PEP measured by PWD; ICMC: pre-isovolumic contraction time—the interval from the onset of IVC wave S_1 to the closure point of the mitral valve on TDI; MCT: the interval from the onset of the QRS wave to the closure point of the mitral valve on TDI.

(ICC) test. An ICC score ≥ 0.75 was considered as good reliability.

3. Results

3.1. The results of EMD, IVCT and PEP obtained by the 3 methods

The 3 methods of M-mode, PWD and tissue Doppler Imaging (TDI) were performed to measure the values of EMD, IVCT, and PEP. The differences in EMD, IVCT, and PEP obtained by these 3 methods were analyzed. As listed in Table 2, EMD_t (12.20 ± 5.62 ms) was significantly lower than EMD_m (34.69 ± 9.27ms) and EMD_d (34.63 ± 10.46 ms) (both $P < .0001$). There was no significant difference between EMD_m and EMD_d ($P > .05$). $IVCT_t$ (56.24 ± 13.49 ms) was significantly higher than $IVCT_m$ (35.97 ± 9.71 ms) and $IVCT_d$ (36.05 ± 11.23 ms) (both $P < .0001$). However, $IVCT_m$ was not significantly different from $IVCT_d$ ($P > .05$). Furthermore, no significant differences were found among PEP_m (71.90 ± 18.55 ms), PEP_d (72.01 ± 17.81 ms), and PEP_t (71.76 ± 16.7 9 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 EMD_m or EMD_d ($P > .05$). ICMC (24.55 ± 10.33 ms) did not significantly differ from (EMD_m–EMD_t) or (EMD_d–EMD_t) ($P > .05$) or from ($IVCT_t$–$IVCT_d$) or ($IVCT_t$–$IVCT_m$) ($P > .05$). 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 EMD_d, MCT, and EMD_m ($r = 0.948$, 0.941, respectively) and between ICMC and (EMD_d–EMD_t), ICMC, and (EMD_m–EMD_t), ICMC and ($IVCT_t$–$IVCT_d$), and, ICMC and ($IVCT_t$–$IVCT_m$) ($r = 0.862$, 0.920, 0.885, and 0.886, respectively).

These results indicate that there is ICMC in S_1 wave, which is the possible reasons of the discrepancy between EMD_t, and EMD_m or EMD_d, between $IVCT_t$ and $IVCT_m$ or $IVCT_d$. 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 EMD_m, 0.96 for EMD_d, 0.89 for EMD_t, 0.97 for $IVCT_t$, 0.95 for PEP_m, 0.94 for PEP_d, 0.97 for PEPt, 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]

Table 2

Comparison of electric mechanical delay time (EMD), isovolumic contraction time (IVCT) and pre-ejection period (PEP) by different methods (mean ± standard deviation).

Variable	M-mode (n = 30)	PWD (n = 30)	TDI (n = 30)	*P*-value (1-way ANOVA)
EMD, ms	34.69 ± 9.27	34.63 ± 10.46	12.20 ± 5.62	<.0001*,†
IVCT, ms	35.97 ± 9.71	36.05 ± 11.23	56.24 ± 13.49	<.0001*,†
PEP, ms	71.90 ± 18.55	72.01 ± 17.81	71.76 ± 16.79	.512

* TDI vs M-mode with $P < .05$ in post-hoc analysis.

† TDI vs PWD with $P < .05$ in post-hoc analysis; one-way ANOVA = analysis of covariance, EMD = electric mechanical delay time, IVCT = isovolumic contraction time, PEP = pre-ejection period, PWD = pulse-wave Doppler, TDI = tissue Doppler imaging.

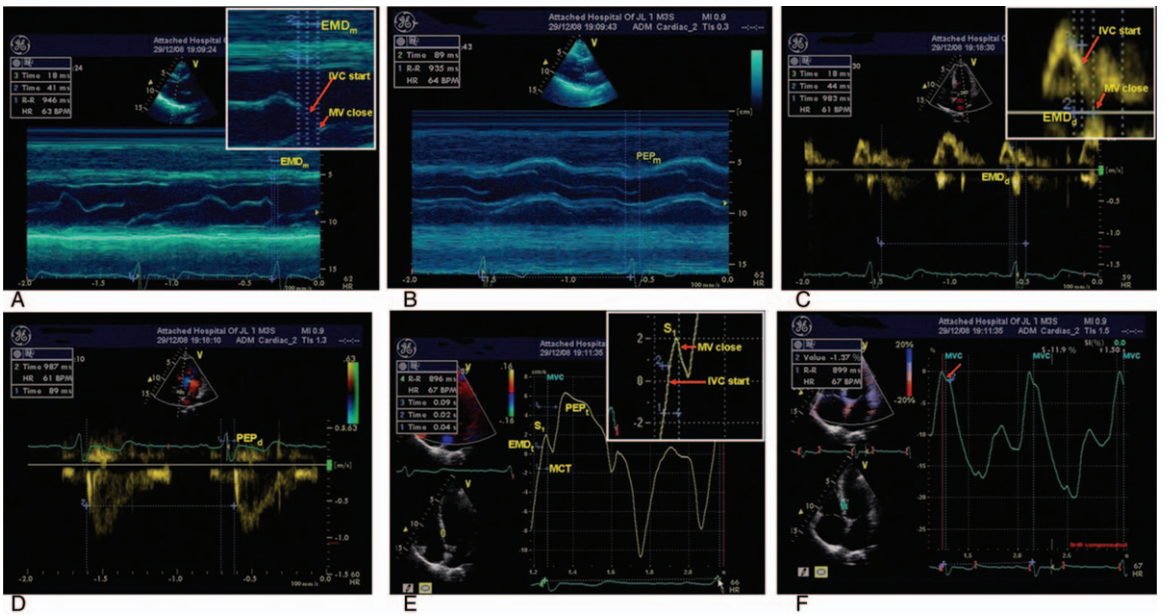

Figure 2. TDI, M-mode, and PWD echocardiograph. (A) M-mode cursor across the mitral valve in the parasternal long-axis plane view. $EMD_m = 41$ ms. The long arrow indicates the starting point of isovolumic contraction wave S_1, and the short arrow indicates the closure point of mitral valve; (B) M-mode cursor across the aortic valve in the parasternal long-axis plane view. $PEP_m = 90$ ms; $IVCT_m = 50$ ms (PEP_m of B–EMD_m of A). (C) Pulsed Doppler flow across the mitral valve on apical 4-chamber view. $EMD_d = 41$ 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 continues slowly; (D) Pulsed Doppler flow across the aortic valve on apical 5-chamber view. $PEP_d = 89$ ms; $IVCT_d = 48$ ms (PEP_d of D–EMD_d of C). (E) Color tissue Doppler imaging on apical 4-chamber view: $EMD_t = 20$ ms, $PEP_t = 90$ ms, $IVCT_t = PEP_t – EMD_t = 70$ ms, MCT = 40 ms, ICMC = MCT–$EMD_t = 20$ ms, which almost equals to $EMD_{m/d}$–EMD_t and $IVCT_t$–$IVCT_{m/d}$. 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.

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[27] 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[20] 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[28] 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_t was significantly shorter than EMD_d or EMD_m while $IVCT_t$ 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[29] 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[30] found similar result that $IVCT_d$ was shorter than $IVCT_t$, and they thought that IVCT was obtained from tissue velocity time intervals that were not exactly coincident with flow time intervals.

However, we do not believe the above explanations are adequate enough. M-mode, the simplest and oldest echocardiographic modality, with its 1000 samplings/second and discrete deflections,[31] offers a relatively accurate means of observing mitral and aortic valve opening and closure. PWD detects blood flow in the heart when the mitral valve closes and mitral valve flow ceases. Thus, the time of the mitral valve closing as measured by M-mode should be the end of A_M of PWD. In this study, EMD_m showed no significant difference from EMD_d. The same was observed between $IVCT_d$ and $IVCT_m$. TDI, because of its high temporal resolution, is one of the most techniques by which to detect small differences in myocardial timings.[32] The end of A_m of TDI represents the terminating of atrial contraction and the beginning of ventricular muscle contraction. Then, does the end of A_m of TDI occur at the same time as the end of A_M of PWD? The answer is no. We observed that the end of A_m occurred prior to the end of A_M. That is to say, the closure of the mitral valve is not synchronous with the beginning of IVC wave.

Our results also showed that MCT was not significantly different from EMD_m or EMD_d. ICMC was not significantly different from ($IVCT_t$–$IVCT_m$), ($IVCT_t$–$IVCT_d$), (EMD_m–EMD_t), or (EMD_d–EMD_t). It was observed that mitral closure fell behind the onset of IVC S_1 by 24.55 ± 10.33 ms. Moreover, an obvious myocardial displacement and shortening could be

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.[33–35] 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 $IVCT_d$ or $IVCT_m$ 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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Writing – original draft: Zhibin Cong.
Writing – review & editing: Zhibin Cong.

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