# Left ventricular global dyssynchrony is exaggerated with age

Gani Bajraktari[1], Per Lindqvist[2.3], Michael Y. Henein[1,3]

[1] *Department of Public Health and Clinical Medicine, Umeå University, Umeå, Sweden*
[2] *Department of Surgical and Perioperative sciences,*
[3] *Departments of Cardiology and Clinical Physiology, Heart Centre, Umeå University, Sweden*

## Abstract

**Background and Aim:** Total isovolumic time (t-IVT) and Tei index both reflect global left ventricular (LV) dyssynchrony. They have been shown to be sensitive in responding to myocardial revascularization and in predicting clinical outcome in heart failure patients. Since most these patients are senior, determining the exact effect of age on such parameters remains mandatory. The aim of this study was to investigate the effect of age on LV t-IVT and Tei index compared with conventional systolic and diastolic parameters in normal individuals.

**Methods:** We studied 47 healthy individuals, mean age 62±12 years (24 female), who were arbitrarily classified into three groups: M (middle age), S (seniors), and E (elderly), using spectral Doppler echocardiography and tissue-Doppler imaging. We studied the interrelation between age, LV systolic and diastolic function parameters as well as t-IVT [60 – (total ejection time + total filling time) in s/min], and Tei index (T-IVT/ejection time).

**Results:** LV ejection fraction was 68±6%, E/A ratio 1±0.4, filling time 538±136ms, ejection time 313±26ms, t-IVT 7.7±2.6 s/min and Tei index 0.41±0.14. Age strongly correlated with t-IVT ($r=0.8$, $p<0.001$) and with Tei index ($r=0.7$, $p<0.001$) but not with QRS duration. Age also correlated with E/A ratio ($r=-0.6$, $p<0.001$), but not with global or segmental systolic function measurements. Mean values for t-IVT were 5.5 (95% CI, 4.6-6.3 s/min) for M, 6.9 (95% CI, 6.0-7.8 s/min) for S and 9.5 (95% CI, 8.4-10.6 s/min) for E groups. The corresponding upper limit of the t-IVT 95% normal CI (calculated as mean ±2SD) for the three groups was 8.3 s/min, 10.5 s/min and 14.5 s/min, respectively. The upper limit of normal t-IVT 95% CI was significantly shorter in the S compared with the E group ($p=0.001$). T-IVT correlated with A wave ($r=0.66$, $p<0.001$), E/A ratio ($r=-0.56$, $p<0.001$), septal e' ($r=-0.49$, $p=0.001$) and septal a' ($r=0.4$, $p=0.006$), but not with QRS.

**Conclusion:** In normals, age is associated with exaggerated LV global dyssynchrony and diastolic function disturbances, but systolic function remains unaffected. The strong relationship between age and t-IVT supports its potential use as a marker of global LV dyssynchrony. In addition, variations in the upper limit of normal values, particularly in the elderly may have significant clinical applications in patients recommended for CRT treatment.

**Key words:** Total isovolumic time, age, LV dyssynchrony, Doppler echocardiography

## Introduction

Cardiac resynchronization therapy (CRT) is established as the treatment of choice for patients with chronic heart failure (CHF), low left ventricular (LV) ejection fraction and evidence of dyssynchrony, who are symptomatic despite full medical therapy [1-2]. CRT significantly reduces symptoms, improves quality of life and reduces cardiac events in these patients [3-5]. Despite such beneficial effect, more than 1/3 of patients receiving CRT do not respond, constituting a significant clinical dilemma as well as waste of resources [6]. Several studies [7-13] attempted to find accurate predictors of CRT response, in addition to ECG and clinical predictors [2]. A number of echocardiographic parameters of LV dyssynchrony have been proposed but most of them remain quite limited in their accuracy in predicting non-responders to CRT [7-13].

Most patients with dilated LV cavity have activation disturbances [14], in the form of prolonged QRS duration. Such QRS broadening has been shown to be associated with prolonged total isovolumic time (t-IVT), or the total duration when the LV is neither ejecting nor filling [15]. Hence, t-IVT has been introduced as a marker of global LV dyssynchrony, and indeed has shown a reliable predictive value in identifying early response to various treatments, medical and interventional [16-22]. Recently, t-IVT reduction by CRT was shown as a predictor of positive clinical outcomes in patients with advanced HF [23].

Since most these patients are senior, the lack of precise effect of age on t-IVT remains a recognized limitation for its broad use. The aim of this study was to determine the effect of age on markers of global LV dyssynchrony, t-IVT and Tei index as well as other segmental and global function measurements in a group of normal individuals.

## Methods

### Study population

We studied 47 healthy individuals (mean age 62±12, range 40-84 years, 24 female), who were arbitrarily classified into three groups: M (middle age), S (seniors), and E (elderly). Group M (≤50 years) consisted of 10, Group S (51-65 years) 17 and Group E (>65 years) 20 subjects. All participants had: (i) no cardiovascular history and were not on any medication, (ii) normal findings on physical examination and 12-lead electrocardiogram (ECG), and (iii) sinus rhythm with a clear ECG superimposed on echo images.. The study was approved by the central ethical review board of Umeå University.

### Echocardiography

Immediately after physical examination and recording of 12-lead ECG at rest, all subjects underwent a complete M-mode, two-dimensional, and Doppler examination while lying in the left lateral decubitus position. Commercially available ultrasound system Vivid 7 (GE Medical Systems, Horten, Norway) equipped with an adult 1.5-4.3 MHz phased array transducer was used. Images were obtained during quiet expiration. LV dimensions and volumes at end-systole and end-diastole, myocardial wall thickness, LV shortening fraction and ejection fraction, were made from the left parasternal cross-sectional recording of the minor axis with the M-mode cursor positioned by the tips of the mitral valve leaflets. Ventricular long axis motion was studied by placing the M-mode cursor at the lateral and septal angles of the mitral ring (MAPSE) and the lateral angle of the tricuspid ring (TAPSE). Total amplitude of long axis motion was measured as previously described [24]. Ventricular long axis myocardial velocities were also studied using Doppler tissue imaging technique with the sample volume placed at the basal segment of LV lateral and septal segments as well as RV free wall. Systolic (s'), as well as early and late (e' and a') diastolic myocardial velocities were measured. A mean value of the lateral and septal e' velocity was calculated. Left atrial diameter was measured from aortic root recordings with the M-mode cursor positioned at the level of the aortic valve leaflets.

Doppler spectral flow velocities were obtained using pulsed and continuous wave techniques as proposed by the European Association of Echocardiography [25]. Peak LV and RV early (E wave), and late (A wave) diastolic velocities were measured and E/A ratio was calculated. Mitral and tricuspid regurgitation severity was assessed by colour and continuous wave Doppler and was graded as mild, moderate, or severe according to the relative jet area to that of the left and right atrium as well as the flow velocity profile, in line with the recommendations of the European Association of Echocardiography [25]. Retrograde transtricuspid pressure drop >35 mmHg was taken as an evidence for pulmonary hypertension, which was an exclusion criterion. All M-mode and Doppler recordings were made at a fast speed of 100 mm/s with a superimposed ECG.

**Table 1**. General characteristics of the study subjects

| Variable | All (n=47) | Group M (n=10) | Group S (n=17) | Group E (n=20) | P |
|---|---|---|---|---|---|
| Age (years) | 62±12 | 45±4 | 59±4 | 73±6 | <0.001 |
| Female (%) | 51 | 60 | 47 | 50 | 0.68 |
| Height (cm) | 171±8 | 172±6 | 170±8 | 172±9 | 0.77 |
| Weight (kg) | 73±9 | 76±11 | 68±8 | 72±8 | 0.07 |
| Body-mass index (kg/m2) | 24±2.5 | 25±3 | 23±2 | 25±3 | 0.11 |
| Body-surface area | 1.8±0.15 | 1.9±0.16 | 1.8±0.14 | 1.9±0.14 | 0.21 |
| Systolic blood pressure (mmHg) | 135±17 | 129±22 | 133±17 | 140±13 | 0.34 |
| Diastolic blood pressure (mmHg) | 76±10 | 77±12 | 77±8 | 76±11 | 0.84 |
| Heart rate (beats/min) | 63±9 | 59±6 | 62±8 | 65±10 | 0.19 |
| QRS duration (ms) | 84±13 | 79±13 | 85±14 | 87±12 | 0.31 |

### Measurements of ventricular dyssynchrony

The interventricular mechanical dyssynchrony was calculated as the difference between left and right ventricular pre-ejection intervals (LPEI and RPEI). LPEI and the RPEI were measured from the pulsed wave Doppler recording of the LV and RV outflow tract velocities, as the time from onset of the QRS on the ECG to that of the aortic and pulmonary velocities, respectively. The LV intraventricular global dyssynchrony was assessed by measuring total isovolumic time (t-IVT) and Tei Index. Total LV filling time was measured from the onset of the E wave to the end of the A wave and ejection time from the onset to the end of the aortic Doppler flow velocity. Total isovolumic time (t-IVT) was calculated as 60 - (total ejection time + total filling time) and was expressed in s/min [26]. Tei index was calculated as the ratio between t-IVT and ejection time [27].

### Reproducibility of measurements

Intra-observer and inter-observer variability were tested in all 47 subjects. Timing measurements, from which the t-IVT was derived, were repeated by one investigator and independently by a second at different times in order to determine both intra- and inter-observer variability, respectively. Results were analyzed using the method of agreement as described by Bland and Altman [28] and presented as the coefficient of variation.

### Statistical analysis

Data are presented as mean ± SD or proportions (% of patients). Correlations were tested with Pearson coefficients. Comparison between the three groups was carried out by one-way analysis of variance (ANOVA) and correlation between variables by simple linear regression analysis. Student's t-test for paired data was used where appropriate. Data analysis and calculations were performed using SPSS program (version 20, SPSS Inc., Chicago, IL, USA), and the P-value was considered statistically significant when it was <0.05.

## Results

General data (gender, age, anthropometric data, blood pressure, heart rate, QRS duration) are presented in **Table 1**. There were no significant differences between age groups.

### LV structure and function (Table 2)

LV structural measurements: systolic and diastolic dimensions, wall thickness, cavity mass as well as segmental and global minor axis and long axis systolic parameters did not differ between the three age groups, irrespective of the technique used. However, diastolic measurements differed significantly between groups, with lateral and septal e' wave velocities decreasing with age (p=0.007 and p=0.02, respectively) and septal a' velocity, increasing with age (p=0.001), resulting in increased spectral peak A wave velocity and reduced E/A ratio (p<0.001 and p<0.04, respectively). T-IVT correlated with A wave (r=0.66, p<0.001), E/A ratio (r=-0.56, p<0.001), septal e' (r=-0.49, p=0.001) and septal a' (r=0.4, p=0.006).

**Table 2**. Echocardiographic data in age study groups

| Variable | All (n=47) | Group M (n=10) | Group S (n=17) | Group E (n=20) | P |
|---|---|---|---|---|---|
| **LV dimension and mass** | | | | | |
| Left atrial diameter (mm) | 35±8 | 34±11 | 33±9 | 38±5 | 0.12 |
| LV mass (g) | 162±39 | 162±39 | 161±44 | 164±36 | 0.98 |
| LV mass index (g/m2.7) | 21±5.5 | 19±4.6 | 21±5.4 | 21±6.1 | 0.67 |
| LV EDD (mm) | 50±4 | 50±4 | 50±3 | 49±5 | 0.69 |
| LVESD (mm) | 31±4 | 31±4 | 31±4 | 31±4 | 0.87 |
| Stroke volume | 81±16 | 85±12 | 82±15 | 78±18 | 0.53 |
| **LV systolic function** | | | | | |
| LV ejection fracion (%) | 68±6 | 70±6 | 67±6 | 68±6 | 0.53 |
| LV shortening fraction (%) | 38±5 | 38±5 | 38±5 | 38±5 | 0.65 |
| Lateral s' (cm/s) | 5.5±1.3 | 5.2±1.5 | 6±1.4 | 5.1±1.0 | 0.12 |
| Septal s' (cm/s) | 5.2±1 | 5.5±1.3 | 5.4±0.9 | 4.8±0.8 | 0.09 |
| MAPSE lateral (cm) | 1.42±0.3 | 1.47±0.3 | 1.45±0.3 | 1.36±0.2 | 0.44 |
| MAPSE septal (cm) | 1.2±0.2 | 1.3±0.3 | 1.2±0.2 | 1.1±0.1 | 0.06 |
| E/e' | 10±2.7 | 10.5±2.8 | 8.9±3.2 | 10.8±1.9 | 0.09 |
| **LV diastolic function** | | | | | |
| E wave (cm/s) | 63±13 | 71±11 | 62±14 | 60±12 | 0.98 |
| A wave (cm/s) | 67±17 | 53±14 | 64±15 | 76±15 | 0.001 |
| E/A | 1±0.4 | 1.4±0.4 | 1±0.4 | 0.8±0.2 | <0.001 |
| E wave deceleration time (ms) | 211±51 | 187±45 | 202±48 | 230±52 | 0.06 |
| Lateral e' (cm/s) | 7.3±2.5 | 6.8±3.2 | 8.7±2.5 | 6.3±1.3 | 0.007 |
| Lateral a' (cm/s) | 8.5±2.7 | 7.8±2.7 | 8.4±2.7 | 8.9±2.7 | 0.61 |
| Septal e' (cm/s) | 6±1.9 | 6.9±1.7 | 6.4±2.2 | 5.1±1.3 | 0.02 |
| Septal a' (cm/s) | 8.1±1.5 | 7.3±1.7 | 7.9±1.3 | 8.7±1.4 | 0.04 |
| **RV function** | | | | | |
| RV diameter (mm) | 24±5 | 22±7 | 23±4 | 26±5 | 0.14 |
| E wave (cm/s) | 54±14 | 61±8 | 51±15 | 53±14 | 0.17 |
| A wave (cm/s) | 46±11 | 47±10 | 49±13 | 44±8 | 0.46 |
| E/A | 1.9±0.3 | 1.3±0.3 | 1.1±0.4 | 1.2±0.3 | 0.13 |
| E wave deceleration time (ms) | 218±60 | 214±57 | 211±47 | 227±73 | 0.71 |
| Right e' (cm/s) | 10±2.8 | 12±3 | 9.8±1.9 | 9.8±3 | 0.17 |
| Right a' (cm/s) | 12.9±2.8 | 11.8±3.9 | 13.7±2.2 | 12.9±2.5 | 0.25 |
| Right s' (cm/s) | 10.2±1.7 | 9.7±1.3 | 10.4±1.5 | 10.2±2 | 0.59 |
| TAPSE (cm) | 2.4±0.4 | 2.3±0.4 | 2.5±0.3 | 2.4±0.4 | 0.36 |
| PA acceleration time (ms) | 119±26 | 131±15 | 127±29 | 105±20 | 0.004 |
| **Ventricular dyssynchrony** | | | | | |
| FT (ms) | 538±136 | 612±104 | 545±146 | 493±129 | 0.07 |
| t-IVT (s/min) | 7.7±2.6 | 5.5±1.4 | 6.9±1.8 | 9.5±2.5 | <0.001 |
| Tei index | 0.41±0.14 | 0.32±0.13 | 0.34±0.13 | 0.51±0.15 | <0.001 |
| LPEI – RPEI | 8.1±8 | 4.7±3 | 5.8±5 | 11.8±10 | 0.018 |

LV: left ventricle; RV: right ventricle; A: atrial diastolic velocity; E: early diastolic filling velocity; EDD: end-diastolic dimension; ESD: end-systolic dimension; T-IVT: total isovolumic time; s':systolic myocardial velocity, e': early diastolic myocardial velocity; a': late diastolic myocardial velocity; MAPSE: mitral annular plane systolic excursion; TAPSE: tricuspid annular plane systolic excursion; PA: pulmonary artery; IVRT: isovolumic relaxation time; FT: filling time; LPEI: left pre-ejection interval; RPEI: right pre-ejection interval.

### RV structure and function (Table 2)

None of the RV structural, systolic or diastolic function measurements was different between the three groups. Pulmonary artery acceleration time was the only measurement significantly shortened with age (p=0.004).

### Effect of age on ventricular dyssynchrony (Table 2)

The difference between LV and RV pre-ejection time significantly increased with age (p=0.018). Also, t-IVT and Tei index increased significantly with age (p<0.001, for both; **Fig.1**).

### Correlation between age and ventricular structure and function (Table 3)

In the study group as a whole, age did not bear any relationship with LV structure or markers of global or segmental systolic function. However, it strongly correlated with t-IVT (r=0.8, p<0.001) as well as with Tei index (r=0.7, p<0.001). Age correlated, to a lesser extent, with LA diameter (r=0.3, p=0.04), septal e' (r=-0.45, p=0.002), and septal a' (r=0.41, p=0.005). It also correlated with markers of diastolic LV function, particularly A wave (r=0.66, p<0.001), E/A ratio (r=-0.58, p<0.001), filling time (r=-0.47, p=0.001) and ejection time (r=-0.49, p<0.001). The rest of LV and RV structural and functional measurements did not correlate with age. Total IVT itself correlated with systolic blood pressure (r=-0.56, p<0.001) and stroke volume (r=0.34, p=0.02). QRS duration had no significant relationship with age, t-IVT or Tei index.

### Upper 95% normal limit for total isovolumic time in age groups

Mean t-IVT values were 5.5 (95% CI, 4.6-6.3 s/min) for M, 6.9 (95% CI, 6.0-7.8 s/min) for S and 9.5 (95% CI, 8.4-10.6 s/min) for E groups. The corresponding upper limit of the t-IVT 95% normal CI (calculated as mean ±2SD) for the three groups was 8.3 s/min, 10.5 s/min and 14.5 s/min, respectively. The upper limit of normal t-IVT 95% CI was significantly shorter in the S compared with the E (p=0.001) group (**Fig.2**).

### Reproducibility of measurements

The intra-observer mean difference of filling time was 1.66 ms and the intra-class correlation coefficient was 0.997 (95%CI, 0.995-0.999). Respective values for the inter-observer measurements were 1.72 ms and 0.960 (95%CI, 0.929-0.978).

**Table 3**. Correlation of total isovolumic time with clinical and echo data

| Variable | R | P |
|---|---|---|
| Age | 0.80 | <0.001 |
| Systolic blood pressure | 0.52 | 0.004 |
| Diastolic blood pressure | 0.07 | 0.71 |
| LV mass index | 0.16 | 0.31 |
| Left atrial diameter | 0.27 | 0.07 |
| LV ESD | 0.23 | 0.12 |
| LV ejection fraction | -0.22 | 0.13 |
| Stroke volume | -0.34 | 0.02 |
| E/A ratio | -0.56 | <0.001 |

LV: left ventricle; atrial diastolic velocity; E: early diastolic filling velocity; ESD: end-systolic dimension;

**Fig1**: Correlation between T-IVT and age in study subjects

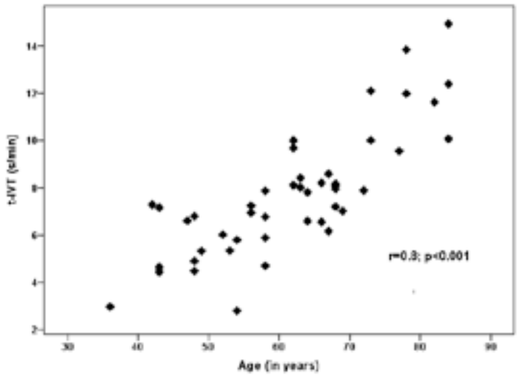
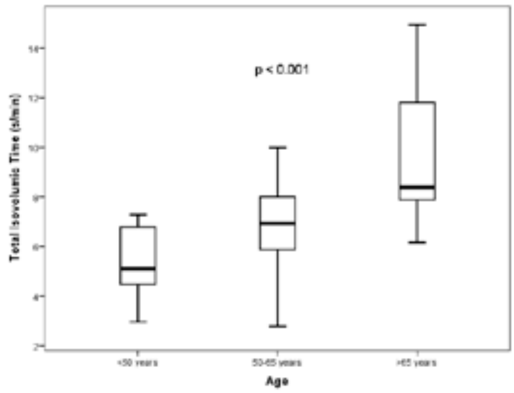



**Fig2**: The pattern of change in Total Isovolumic Time with increasing age (p<0.001)




## Discussion

**Findings:** Our results show no significant effect of age on right or left ventricular structure or systolic function, but a modest direct correlation with left atrial diameter and ventricular diastolic function changes. In particular, the myocardial e' velocities drop and a' velocities increased with age. These alterations resulted in respective changes in the pattern of LV filling, E/A, which inversely correlated with age. Furthermore, with age the inter-ventricular and intra-ventricular dyssynchrony increased, particularly the prolongation of t-IVT which strongly correlated with age and itself correlated with diastolic LV function changes but not with QRS duration. Finally, our results suggest an upper limit of normal t-IVT of 14.5 ms, specific for individuals above 65 year of age, which is significantly longer than that of middle aged.

**Data interpretation:** The amazing design of the human heart requires its pump function, i.e ejection fraction and fractional shortening, not to be affected by normal aging, this finding has been confirmed in different studies using various techniques for assessing systolic function[29, 30]. Diastolic function, in contrast, seems to be sensitive to aging[31]. In particular, the early diastolic myocardial velocities reduce making its respective ventricular filling velocities also fall with age. Such drop in early diastolic velocities reflect the impaired myocardial elastic recoil, known to associate aging[32], a function change that is combated by regular physical exercise[33]. The heart design also dictates atrial systolic function to accentuate, as a potential compensatory mechanism, in order to optimize ventricular filling volume, and consequently pumped stroke volume, in the succeeding cycle[34].

Furthermore, this atrioventricular interaction is also helped by the potential energy stored in the atrial myocardium which is released in due course [35]. These changes were clearly explained by the relationships we found between age and patterns of LV ventricular filling. In addition, age was associated with progressive prolongation of inter- and intra-ventricular dyssynchrony. What is more exciting was that the strong relationship we found between age and t-IVT, and to a lesser extent Tei index, which itself is an indirect reflection of t-IVT.

The prolongation of t-IVT was not an isolated finding since its two measurement components were also affected by age i.e filling and ejection times. It is unlikely that the primary change with age was the latter which resulted in prolongation of t-IVT but more likely to suggest cavity shape changes during the two isovolumic times which caused shortening of filling and ejection. Although changes in isovolumic relaxation time can be explained on the basis impaired elastic recoil and its effect on the slow intra-ventricular pressure drop, the effect of age on isovolumic contraction time is not very well understood, particularly in the absence of any relationship between its changes and QRS duration, which itself was not affected by age. These findings suggest that even in normal individuals age related changes in global LV synchronous function are not necessarily electrical in origin, hence explaining the absence of cardiac symptoms in normal individuals, but likely to be related to the same structural changes that influence diastolic function. This finding contrasts what we have previously shown in patients with dilated cardiomyopathy, in whom QRS duration correlates with the prolongation of t-IVT and Tei index [26]. As far as we know, the current study is the first that differentiates between normal electrical and mechanical changes with age and their interrelations. The progressive shortening of pulmonary acceleration time with age may reflect age related changes in the pulmonary vascular resistance as recently suggested [36].

**Limitations:** The main limitation of our study is the small number of studied individuals, despite that the strength of the relationship between age and markers of global LV dyssynchrony support the relevance of the findings, which can only be strengthened in a larger population. We did not study myocardial intrinsic properties in the form of strain and strain rate deformation and their timing, since we believe that they must be preserved in order to maintain overall systolic LV function.

**Clinical implications:** Our results confirm that t-IVT as a marker of LV synchronous function prolongs with age and hence affects Tei index. Our upper 95% CI for t-IVT also prolongs with age being significantly longer in patients >65 compared to those between 50-65 years of age. These findings should have significant clinical implications when considering patients for electrical resynchronization therapy.

**Conclusion:** Age does not affect ventricular structure or systolic function. It significantly affects diastolic function as well as prolongs inter- and intra-ventricular dyssynchrony. The strong relationship between age and total isovolumic time supports its potential use as a marker of global LV dyssynchrony. Finally, upper limit of normal values variation with age, particularly in the elderly may have significant clinical implications in patients recommended for CRT treatment.

**Correspondence to:**
Dr. Gani Bajraktari
Public Health and Clinical Medicine,
Umeå University, SE-901 87 Umeå, Sweden
E-mail: gani.bajraktari@medicin.umu.se

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