Doppler Mitral Inflow Variables Time Course After Treadmill Stress Echo with and Without Ischemic Response

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Research Article

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Abstract

This study evaluated Doppler mitral inflow variables changes from rest to post-exercise among 104 subjects with and without echocardiographic evidence of ischemic response (IR) to exercise (63.9 ± 11 years, 54% male, 32% with IR) who underwent a clinically indicated treadmill stress echo (TSE) test. The time from exercise cessation to imaging (TIME) was recorded. The changes (after TSE minus baseline values) in the peak E-wave velocity (ΔE) [34.2 vs. 24.2, p = 0.024] and E-wave deceleration rate (ΔDR) [348.0 vs. 225.7, p = 0.010] were bigger in ischemic than in nonischemic subjects, while the changes in the peak A-wave velocity (ΔA) did not differ [7.9 vs. 15.0, p = 0.082]. The correlations between Doppler variables and IR, TIME, and TIME*IR interaction were analyzed. We observed a significant interaction between TIME and IR regarding ΔE and ΔDR. The differences in the regression line slopes of time courses for ΔE and ΔDR based on IR were significant: ΔE (−0.09 vs. −8.17, p = 0.037) and ΔDR (11.23 vs. −82.60, p = 0.022). Main findings: 1. Time courses after exercise of ΔE and ΔDR in subjects with and without IR were different. 2. ΔE and ΔDR did not differ between subjects with and without IR at exercise cessation (TIME = 0). 3. The simple main effect of ischemia on ΔE and ΔDR was significant at TIME of ≥3 min. Divergent time courses of ΔE and ΔDR after exercise might be promising for detecting diastolic dysfunction caused by ischemia.

Introduction

Diastolic stress echocardiography has emerged during the last two decades to detect diastolic dysfunction. The Doppler mitral inflow pattern (DMIP) is associated with physiological factors ((the left ventricle (LV) relaxation rate and stiffness, the left atrial (LA) stiffness and contractility, filling volumes, diastolic filling time, mitral valve area and inertance [5, 24] that determine the diastolic oscillatory atrioventricular pressure gradient (AVPG). The corresponding constitutive equations define the LA and LV pressures in terms of stiffness, instantaneous volume, and probably the volume change rate. Knowing the time variation of the LA and LV pressures, by that the AVPGs, it is possible to calculate DMIP variables ((peak E-wave velocity (E), E-wave deceleration rate (DR), and peak A-wave velocity (A)). Inversely, obtaining values of crucial physiological parameters only from DMIP is impossible [18]. The number of pieces of information we can extract from the DMIP is too small to determine all unknowns.

Physiological considerations:

Strong LV relaxation, high LA pressure, and a compliant LA generate steep initial AVPGs, and tall E [11]. LV stiffness has a contrasting effect on E; generally, a stiff LV indirectly increases LA pressure, by that E [23, 25]. However, steep increase in LV pressure quickly overshoots the equilibrium AVPG and blocks further growth of the E-wave [26]. Simultaneous echocardiography-catheterization studies and mathematical modeling showed that E is not a good predictor of LA pressure [5, 23–26, 28]. High filling volumes superimposed on stiff LV induce a steep increase in reverse AVPG that is positively associated with DR [6, 26]. LV stiffness at the time of LA contraction is negatively associated, while HR and left atrial contractility are positively associated with A.

Exercise physiology:

During exercise, diastolic filling time shortens and filling volumes increase. LV relaxation rate and LA pressures adjust their values to increase AVPGs and stroke volumes, which leads to more restrictive DMIPs (higher E, DR, and E/A). Adequate relaxation requires quick detachment of calcium from actin-myosin filaments, and any event that suppresses this process will decelerate the relaxation. Until recently, the prevailing opinion was that the hallmark of normal diastolic function is the maintenance of normal LA pressure during exercise and that higher AVPG is predominantly achieved through higher LV relaxation rates [2]. However, recent studies have shown a substantial increase in LA pressure during exercise, even in middle-aged healthy individuals [7, 19, 27]. High filling volumes stretch the myocardium in the relaxation process, which slows down the LV relaxation rate and increases its duration [10, 14]. Myocardial viscosity (ratio of LV pressure change and filling rate) possibly also comes into play [8, 13]. The final result of these processes is the high apparent LV stiffness [17]. This phenomenon is more pronounced in the elderly because their pressure-volume curve moves to the right and operates at higher pressures [3, 14, 22].

Some individuals have an ischemic response (IR) to exercise with a blunted increase of the LV relaxation rate [9], increased LV stiffness and LA pressures, and restrictive DMIP [7, 19, 27]. Ischemia induces diastolic dysfunction through ATP depletion, abnormal calcium handling, persistent actomyosin bridging, and active diastolic tone throughout diastole [15].

Not surprisingly, there are circumstances where DMIPs may be similar between individuals who have an IR to exercise versus those that do not. For example, nonischemic patients with a high LV relaxation rate and a modest increase in LA pressures and ischemic patients with a blunted increase in the LV relaxation rate and a substantial increase in LA pressures may have similar DMIPs. An infinite number of combinations of physiological parameter values can result in similar AVPGs and DMIPs. Therefore, it is uncertain whether DMIP changes during exercise are sufficient to differentiate between ischemic and nonischemic subjects.

This study tested the hypothesis that DMIP changes pre to post-exercise were more restrictive in subjects with an IR to acute exercise.

Methods

The subjects underwent a clinically indicated treadmill stress echo (TSE) test using Bruce protocol with Doppler studies of mitral inflow at rest (values denoted by an index of 1) and after exercise (an index of 2). All subjects provided verbal informed consent to participate in the study. The exclusion criteria were: patients with technical limitations in image acquisition, atrial fibrillation, left bundle branch block, moderate-to-severe mitral annular calcification, and valve disease. TSE was performed according to standard protocols by certified sonographers [1, 20]. Commercially available ultrasound machines were used. Two-dimensional echocardiographic images were recorded at rest and after exercise in four standard views (parasternal long and short axis and apical four-chamber and two-chamber views) to

determine the wall motion score index (WMSI). The heart was divided into 16 segments. Each segment was scored according to its motion and systolic thickening: 1 = normal, 2 = hypokinetic, 3 = akinetic, 4 = dyskinetic, and 5 = aneurysmal. The WMSI is the result of dividing the sum of the scores by 16. Any increase in WMSI after exercise was defined as IR. Therefore, we considered IR as a categorical variable.

After obtaining 2-D images, the patients underwent a pulsed Doppler study of mitral inflow, and the study was recorded. The recording speed was 100 mm/s. The sample volume was positioned at the tip of the mitral leaflets. The smallest sample size and lowest possible Doppler gain were used. We measured E, DR, and A off-line in three consecutive beats and calculated their mean values. The second Doppler assessment was performed after exercise, waiting until the E and A waves separated from one another so that DR could be reliably determined. The time from exercise cessation to imaging was recorded (TIME) (1–6 min). Figure 1 shows an example of Doppler mitral inflow pattern.

Statistical analysis:

We used an alpha level of 0.05 throughout the statistical analysis. Demographic, exercise, and Doppler data were reported as means ± SD for continuous variables and percentages for categorical variables. The data of each variable were divided into two groups depending on the appearance of the IR, the ischemic and nonischemic group. Levene's test for the homogeneity of variance was performed for all variables. Student's *t*-test was used to test the difference in the mean values between the two groups. After obtaining postexercise Doppler values, the changes (postexercise minus the baseline values) were calculated. *T*-test was applied to check if the changes significantly differed between the two groups. Multiple regression analysis was performed on ΔDR and ΔE to determine significant predictors. The forward selection principle was used with TIME, IR, and TIME*IR as an initial set of predictors. Because of a significant TIME*IR interaction, TIME was forced into the model. Next, we tested the effect of including age, sex, and each exercise variable on its own *p*-value and the model's explanatory power. To determine significant differences in the slopes of ΔE and ΔDR with respect to TIME between the two groups, multiple regression analysis was performed considering TIME, IR, and TIME*IR as independent variables. To test the significance of the simple main effect of ischemia on ΔDR and ΔE at each point in the TIME, a new variable (TIME – T_{shift}) was introduced, and successive multiple regression analyses were performed while changing T_{shift} from 0 to 6 min. A statistical package from Microsoft Excel and XLSTAT 2020 was used for all analyses.

Results

One hundred and four subjects (: 63.9 ± 11 years, 54% male) underwent clinically indicated TSE, with Doppler studies of mitral inflow performed at rest and after exercise.

The subjects were categorized into two groups depending on the appearance of ischemia, which was defined as an increase in the WMSI from pre to post-exercise.

Table 1 presents the baseline summary statistics of DMIP variables, heart rate, age and sex. Ischemia developed in 33 (32%) subjects. The ischemic subjects were older [$t(96) = -2.37$, $p = 0.020$] and predominantly males [$F(1,102) = 5.03$, $p = 0.027$]. None of the baseline DMIP values or HR (denoted by an index of 1) differed significantly between the two groups: E_1, $t(102) = -0.12$, $p = 0.903$; DR_1, $t(102) = -0.02$, $p = 0.981$; A_1, $t(102) = -1.57$, $p = 0.119$; HR_1, $t(46) = -0.13$, $p = 0.900$.

Table 2 presents the summary statistics of the exercise variables and changes (postexercise–baseline) in E, DR, and A. The duration of exercise [$t(102) = 0.44$, $p = 0.664$; peak HR: $t(102) = 1.72$, $p = 0.088$] and TIME [$t(102) = -0.57$, $p = 0.572$] were not statistically different between the two groups. ΔHR was significantly higher in patients without ischemia [$t(102) = 2.85$, $p = 0.005$].

The ΔE [$t(102) = -2.29$, $p = 0.024$] and ΔDR [$t(102) = -2.64$, $p = 0.010$] were significantly higher in the ischemic subjects than in the nonischemic subjects. The changes in A were not statistically different between the ischemic and nonischemic subjects [$t(47) = 1.78$, $p = 0.082$].

Table 1
Baseline Summary Statistics of Doppler and Clinical Variables

	Group 1 nonischemics	**Group 2 ischemics**	***p*-value**
N	71 (68%)	33 (32%)	-
Age, years	62.5 ± 12.0	67.0 ± 7.2	0.020
Males	33 (47%)	23 (70%)	0.027
E_1, cm/s	72.3 ± 21.4	72.8 ± 21.4	0.903
A_1, cm/s	68.2 ± 17.5	74.4 ± 21.1	0.119
DR_1, cm/s^2	388.6 ± 177.2	389.5 ± 194.8	0.981
HR_1, beat/min	61.3 ± 8.5	61.6 ± 12.7	0.900
Values are mean ± SD or N (%)			

The *p*-value indicates the significance of the differences in the mean values between the two groups. N = number of subjects; E = E-wave peak velocity; A = A-wave peak velocity; DR = E-wave deceleration rate; HR = heart rate. Index 1 denotes baseline values.

Table 2
Summary Statistics of Exercise Variables and Changes (Postexercise – Baseline) in Doppler Variables

	Group 1 nonischemics	Group 2 ischemics	*p*-value
ΔE ($E_2 - E_1$), cm/s	24.2 ± 21.6	34.2 ± 19.4	0.024
ΔA ($A_2 - A_1$), cm/s	15.0 ± 14.8	7.9 ± 20.9	0.082
ΔDR ($DR_2 - DR_1$), cm/s^2	225.7 ± 234.5	348.0 ± 183.9	0.010
Duration of exercise, min	7.9 ± 2.7	7.7 ± 2.5	0.664
Peak HR, beats/min	141.1 ± 21.7	133.7 ± 17.0	0.088
ΔHR ($HR_2 - HR_1$), beats/min	26.3±10.7	19.5±12.9	0.005
TIME, min	2.9 ± 1.1	3.1 ± 1.1	0.572
Values are the mean ± SD			
p-values for the differences in the means between the two groups			
Δ = difference between postexercise and baseline values; Index 2 denotes postexercise, and index1 baseline values; E = E-wave peak velocity; A = A-wave peak velocity; DR = E-wave deceleration rate; HR = heart rate; Peak HR = HR at cessation of exercise; TIME = time of obtaining Doppler variables measured from the cessation of exercise.			

Multiple linear regression was calculated to predict ΔE and ΔDR from age, sex, peak HR, ΔHR, exercise duration, IR (IR = 0 for nonischemics, and IR = 1 for ischemics), TIME, and the TIME*IR interaction. Table 3 presents a summary of this regression analysis. Forward selection criteria were applied with IR, TIME, and TIME*IR as an initial set of predictors. Except for age, none of the other independent variables introduced one by one and in various combinations contributed significantly on their own.

Table 3
Summary of Regression Analysis for Variables Predicting Changes in E and DR

	ΔE	ΔDR
Age	NS⇑ (p = 0.065)	⇑
IR	NS⇓ (p = 0.242)	NS⇓ (p = 0.206)
TIME	⇓⇓⇓	⇓⇓
TIME*IR	⇑	⇑
Adjusted R^2	0.162	0.175
Directions of arrows indicate direction of association (upward means positive)		
⇑: p < 0.05; ⇑⇑: p < 0.01; ⇑⇑⇑: p < 0.001		
NS = nonsignificant (p > 0.05)		
IR = ischemic response: for nonischemics IR = 0, and for ischemics IR = 1; TIME = time of obtaining Doppler variables measured from the cessation of exercise; R^2 = coefficient of determination; Δ = difference between postexercise and baseline values; E = E-wave peak velocity; and DR = E-wave deceleration rate.		

This model showed a marginally significant influence of age on ΔE [F(4,99) = 5.972, sig. F < 0.001, coeff. 0.336, p = 0.065, 95% CI: −0.021–0.694]. Age was a significant predictor of ΔDR [F(4,99) = 6.479, sig. F < 0.001, coeff. 3.989, p = 0.038, 95% CI: 0.232–7.745]. The main effect of ischemia on ΔE and ΔDR was not significant. The main effects of TIME on ΔDR [F(4,99) = 6.479, sig. F < 0.001, coeff. −80.445, p = 0.001, 95% CI: −125.319 to −35.571] and on ΔE [F(4,99) = 5.972, sig. F < 0.001, coeff. −7.988, p < 0.001, 95% CI: −12.262 to −3.714] were statistically significant. The values of ΔE and ΔDR obtained later were lower than those obtained earlier.

There was no correlation between IR and TIME (r = 0.06, p = 0.57), and the frequency distribution of ischemics was not statistically different between and within groups of TIME (1–6 min) [F(5,98) = 1.49, p = 0.20)]. There was no bias in collecting data regarding TIME between ischemics and nonischemics.

The TIME*IR interaction was statistically significant for ΔDR [F(4,99) = 6.479, sig. F < 0.001, coeff. 90.473, p = 0.025, 95% CI: 11.832–169.113] and for ΔE [F(4.99) = 5.972; sig. F < 0.001; coeff. 7.799; p = 0.041, 95% CI: 0.309–15.289]. The effect of IR on the values of ΔE and ΔDR relied on the time after cessation of exercise at which data were collected.

To determine the time course of $\Delta E = E_2 - E_1$ and $\Delta DR = DR_2 - DR_1$ after the exercise, multiple linear regressions were performed to predict ΔE and ΔDR from the IR, TIME, and TIME*IR interaction as predictors. The general form of the regression function was as follows:

$$Y = C_0 + C_1 \cdot \left(\text{TIME} - T_{\text{shift}}\right) + C_2 \cdot \text{IR} + C_3 \cdot \text{IR} \cdot \left(\text{TIME} - T_{\text{shift}}\right)$$

where Y represented either ΔE or ΔDR, T_{shift} is the time shift (T_{shift} = 0 denotes linear regression with respect to the end of the exercise, T_{shift} = 1 min denotes linear regression with respect to the time coordinate having zero in the first minute, continuing similarly for later times). The outcome of the multiple regression model for nonischemics (IR = 0) was calculated according to

$$Y_{nonischemic} = \left[C_0 -- C_1 \cdot T_{shift}\right] + C_1 \cdot TIME$$

where, coefficient C_1 denotes the slope.

For ischemics (IR = 1), the outcome is

$$Y_{ischemics} = \left[C_0 -- C_1 \cdot T_{shift} + C_2 -- C_3 \cdot T_{shift}\right] + \left[C_1 + C_3\right] \cdot TIME$$

where the slope is $C_1 + C_3$.

Note that the intercept is a function of T_{shift} and IR: it changes from $\left[C_0 - - C_1 \cdot T_{shift}\right]$ for nonischemics to $\left[C_0 - - C_1 \cdot T_{shift} + C_2 - - C_3 \cdot T_{shift}\right]$ for ischemics.

Figures 2 and 3 show slopes for the group of ischemics (coefficients $C_1 + C_3$) and nonischemics (coefficient C_1).

The slopes of ΔE or ΔDR in ischemic subjects were not significantly different from zero. Contrarily, slopes of ΔE ($p < 0.001$) and ΔDR ($p = 0.001$) in the nonischemic subjects were significantly different from zero and negative. Our model showed that there was a significant IR*TIME interactive effect on ΔE (adj. R^2 = 0.14, $F(3,100) = 6.64$, sig., $F < 0.001$, coeff. 8.1, $p = 0.037$, 95% CI: 0.51–15.66) and ΔDR [adj. R^2 = 0.15, $F(3,100) = 6.92$, sig. $F < 0.001$, coeff. 93.8, $p = 0.022$, 95% CI: 13.9–173.7]. Consequently, regression slopes were significantly different between the ischemic and nonischemic subjects (coefficient C3 for the IR*TIME interactive effect). Figure 2 shows the measured ΔE as a function of TIME and IR and the regression lines for the ischemic and nonischemic subjects, and Figure 3 shows the same for ΔDR. At T_{shift} = 0, the intercepts of the regression lines of ΔE and ΔDR were not significantly different between the two groups. As shown by the regression lines for the ischemic group, the values of ΔE and ΔDR remain constant within the first 6 min, whereas in the nonischemic group, E and DR tend to return to the baseline values. Consequently, the differences in ΔE and ΔDR between the two groups increased in TIME; hence, the question was at what time did these differences become significant, i.e., the time at which the simple main effect of IR became relevant.

Table 4 presents the *p*-values for the simple main effect of IR on ΔE and ΔDR, calculated at different T_{shift} values. The results indicated that until the third minute, the effect of ischemia was not significant. At ≥3 min, positive associations of ischemia with ΔDR and ΔE were highly significant, which means that the

values of these variables were significantly higher in the ischemic subjects.

Table 4
P-values for the Simple Main Effect of Ischemia on ΔE and ΔDR as a Function of T_{shift}

T_{shift}, min	0	1	2	3	4	5	6
ΔE, cm/s	0.271	0.532	0.651	**0.012**	**0.001**	**0.002**	**0.005**
ΔDR, cm/s^2	0.236	0.516	0.578	**0.005**	**0.000**	**0.001**	**0.002**

T_{shift} = time shift; Δ = difference between postexercise and baseline values; E = E-wave peak velocity; and DR = E-wave deceleration rate.

Discussion

The purpose of this clinical study was to examine whether DMIPs after exercise were more restrictive in subjects with induced ischemia compared to those without ischemia. The results indicate that there is not an unambiguous answer to that question.

The key finding from our results is that ΔE and DR in the ischemic and nonischemic groups have divergent time courses after the exercise, which has two significant consequences. The first is that ΔE and DR do not differ at exercise cessation between the two groups. The second is that the influence of exercise-induced ischemia on ΔE and DR is significant only at ≥3minutes after the exercise. In the ischemic group, ΔE and ΔDR are constant in the first 6 min after exercise, whereas E and DR tend to their basal values in the same period in the nonischemic subjects.

TIME and ischemia influenced ΔE and ΔDR, and because of their significant interaction, establishing a conclusion about the influence of ischemia on ΔE and ΔDR without consideration of TIME is inappropriate. Whether ischemia is associated with changes in ΔE and ΔDR depends on TIME, and conversely, whether TIME correlates with ΔE and ΔDR depends on ischemia. For data obtained within the first 2 min after the exercise, ΔE and ΔDR were the same in both groups, so IR was not a predictor of changes. On the contrary, for data obtained at 3 min and after that, the ΔE and ΔDR were significantly higher in the ischemic group, so IR became a predictor of changes.

DMIP changes follow the changes in AVPGs. Consequently, AVPGs should be the same in the first two minutes after exercise in persons with and without IR. Although, it is reasonable to assume that changes in relevant physiological variables and the proportional effect of each on AVPGs differed between the two groups. It is important to emphasize that AVPG can occur at any pressure, so it indicates nothing about pressure levels in the LA and LV.

After exercise, there was a gradual decrease in cardiac output (CO) in both groups because of reduced body metabolism and oxygen demand. In patients without ischemia, there was a gradual return of E, DR (Figures 2 and 3), and presumably AVPG and all relevant physiological variables (relaxation rate, filling volumes, and apparent LV stiffness) to baseline values within 6 min. Conversely, although the patients with ischemia restored the baseline coronary blood flow, postischemic diastolic dysfunction has been persistent due to processes at the molecular level (ATP depletion, calcium overload, and oxyradical formation) [6–8]. Consequently, high LV stiffness persisted with elevated LA pressure, and ΔE and ΔDR remained constant in the observed time after TSE.

We can conceptualize these findings into three hypothetical paradigmatic responses to exercise at their extremes: 1. normal response with an increase in the relaxation rate without an increase in LA pressure, 2. diastolic dysfunction without ischemia with a blunted increase in the relaxation rate, volume induced increase in apparent LV stiffness that leads to high LA pressure, 3. ischemia-induced diastolic dysfunction with a blunted increase in the relaxation rate, and high LA pressure due to increase in LV stiffness.

An initial study on the influence of exercise-induced ischemia on the diastolic function showed that in ischemics, DMIP became more restrictive [15]. Numerous studies afterward corroborated these findings. However, none of them took into consideration the importance of the time of obtaining images after exercise cessation on DMIP. It is interesting how this observation has escaped for years the attention of the researchers' community. The interpretation of the results of this study is founded on a clear physical and physiological concept. We created a new paradigm with a pathophysiological rationale based on the fact that there is a persistent high LV stiffness after cessation of exercise in patients who develop ischemia because of postischemic diastolic dysfunction. E and DR of these patients will not tend toward baseline values in the first few minutes after exercise, which is opposite to the tendency observed in patients with no ischemia.

We recommend expressing the Doppler variable values in diastolic stress echocardiographic studies by referring to the time elapsed since exercise cessation.

Limitations

We included a relatively small number of participants. The diagnosis of ischemia via stress echocardiography is a subjective assessment, estimated visually and at risk of false positive and negative results and interobserver variability.

Conclusion

In this study, we measured baseline and postexercise values of E and DR. Postexercise values were measured at a known TIME. We statistically analyzed ΔE and ΔDR in relation to TIME, IR, and their interaction. There were significant effects of the interaction of IR and TIME on ΔE and ΔDR. After the cessation of exercise, ΔE and ΔDR in nonischemic subjects, but not in ischemic subjects, quickly tend to

zero. The differences in ΔE and ΔDR between the two groups only became significant for TIME of ≥3 min. At the time of exercise cessation, the values of ΔE and ΔDR (taken from the regression lines) were not significantly different between the patients with and without IR.

This divergent response might be promising for detecting diastolic dysfunction caused by ischemia.

Declarations

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Figures

Figure 1

Doppler mitral inflow pattern

Figure 2

Regression slopes of ΔE as a function of TIME and ischemia

ΔE is the difference between the E-wave peak velocities after exercise (taken at TIME after cessation of exercise) and at baseline. Blue circles denote data for the nonischemic group, and red triangles denote data for the ischemic group. The slope of ΔE in nonischemics but not in ischemics is significantly different from zero. The difference in the slopes of the two groups is significant (p = 0.037).

Figure 3

Regression slopes of ΔDR as a function of TIME and ischemia

ΔDR is the difference between the E-wave deceleration rates after exercise (taken at TIME after cessation of exercise) and at baseline. Blue circles denote data for the nonischemic group, and red triangles denote data for the ischemic group. The slope of ΔDR in nonischemics but not in ischemics is significantly different from zero. The difference in the slopes of the two groups is significant (p = 0.022).

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