Increased Thrombolysis in Myocardial Infarction Frame Counts in Patients with Chronic Aortic Regurgitation

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ABSTRACT

Aim: *The effects of chronic aortic regurgitation (AR) on coronary blood flow of systolic/diastolic phase and phase and coronary reserve have been shown. Whereas thrombolysis in myocardial infarction (TIMI) frame count, which incorporates coronary blood flow and a higher TIMI frame count (TFC) is reflect disordered resistance vessel function, has not yet been evaluated in chronic AR.*

Method: *33 patients with isolated chronic AR diagnosed by echocardiography and angiography, and 22 control groups with no coronary or valvular disease who underwent angiography for atypical chest pain were included in our study. Coronary blood flow was measured using TFC.*

Result: *Coronary blood flow, echocardiographic and demographic parameters were compared between the two groups. The mean TFC is found to be higher in AR patients when compared to the control group. (left anterior descending coronary artery (LAD) TFC, 43±7.3 vs. 30±5.9 frames/s, p<0.001; Corrected LAD (cLAD) TFC, 25.0±4.3 vs. 17.6 ± 3.5 frames/s, p< 0.001; Left circumflex artery (LCx) TFC, 27.0±6.4 vs. 19.9±3.4 frames/s, p<0.001; and Right coronary artery (RCA) TFC, 25.8±5.5 vs. 19.9±4.7 frames/s, p<0.001; mean TFC, 26.3±5.4 vs.19.1±3.9 frames/s, p<0.001).*

Conclusion: *This is the first study showing increase of TFC in chronic AR patients without CAD. It is thought to show impaired coronary blood flow, and may explain angina symptoms in chronic AR patients. At the same time, it could be used as a parameter showing severe AR.*

Key words: *Chronic Aortic Regurgitation, Coronary Blood Flow, TIMI Frame Count*

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Kronik Aort Yetersizliği Hastalarında Artmış Thrombolysis in Myokardial İnfarktüs Kare Sayısı

Amaç: *Kronik aort yetersizliği (AY) koroner kan akımının sistolik/diastolik fazı ve koroner akım rezervini etkilemektedir. Thrombolysis in myocardial infarction (TIMI) kare sayı koroner kan akımı ile korele olup, yüksek TIMI kare sayısı (TKS) prekapiller arteriyol damar fonksiyon bozukluğunu göstermesine rağmen AY'e hastalarında araştırılmamıştır.*

Metod: *Çalışmaya ekokardiyografi ve anjiografi ile tanı konulan 33 izole kronik aort yetersizliği hastası ile atipik göğüs ağrısı nedeniyle koroner anjiogarfi yapılıp koroner ve valvüler hastalığı olmayan 22 kontrol grubu dahil edilmiştir. Koroner kan akımı TKS ile değerlendirilmiştir. İki grubun koroner kan akımı, ekokardiyografi ve demoğrafik parametreleri karşılaştırılmıştır.*

Bulgular: *Aort yetersizliği hastalarında ortalama TKS'e kontrol grubuna göre daha yüksek olarak saptanmıştır. Düzeltilmiş LAD TKS, 25.0±4.3 vs. 17.6 ± 3.5 kare/s, p<0.001; LCx, 27.0±6.4 vs. 19.9±3.4 kare/s, p<0.001; and RCA kare sayısı, 25.8±5.5 vs. 19.9±4.7 kare /s, p<0.001].*

Sonuç: *Koroner arter hastalığı olmayan kronik AY'de ortalama TKS daha yüksektir. Bununla birlikte TKS'nin klinik önemi belirlenmelidir.*

Anahtar kelimeler: *Kronik Aort Yetersizliği, Koroner Kan Akımı, TIMI Kare Sayısı*

INTRODUCTION

The purpose of this study is to assess if coronary blood flow velocity determined by TIMI frame count (TFC) is decreased in patients with AR compared to control subjects with normal coronary arteries. Chronic severe AR has been reported to be associated with angina pectoris even in the absence of obstructive CAD. In previous studies, rest and exercise induced perfusion defect was detected by thallium-201 single-photon emission computed tomography (SPECT) in AR patients (1, 2). As known, the major portion of coronary blood flow depends on diastolic blood pressure. As diastolic blood pressure is reduced in AR, coronary perfusion pressure is lower in these patients (3). On the other hand, total myocardial oxygen requirement is augmented by the increase in left ventricular mass (4). The result, a combination of increased oxygen demand and reduced supply, sets the stage for development of myocardial ischemia (5).

MATERIALS AND METHODS

Thirty-three patients with severe AR and otherwise normal coronary arteriograms and 22 subjects with atypical chest pain and normal coronary arteriograms (the control group) were included in this study. All of the patients had transthorasic echocardiographic examination before coronary aniography. The echocardiographic examinations including M-Mode, two-dimensional and color Doppler evaluations were performed with Vivid 5 system (GE Vingmed Ultrasound Horten, Norway, 2-4 MHz phased array transducer). Measurements were made according to the American Society of Echocardiography guidelines by a single cardiologist (6, 7). AR was evaluated by transthoracic echocardiography (TTE) but quantification was made by aortography. M-Mode recordings obtained in the parasternal long-axis view were used for determination of left ventricular (LV) dimensions, LV wall thickness, and left atrial (LA) dimension. Left ventricular ejection fraction (LVEF) was measured from the American Society of Echocardiography guidelines (7). In the presence of tricuspid regurgitation, the pulmonary artery systolic pressure (PASP) was calculated from the sum of the estimated mean right atrial pressure, and the maximum pressure difference between the right ventricle and right atrium, as determined by continuous wave Doppler echocardiography (8).

The subjects with AR underwent routine coronary arteriography for evaluation of coronary artery status before surgery. The control group consisted of the patients with atypical chest pain who underwent coronary angiography because their symptoms could not be adequately clarified with noninvasive tests. Coronary arteriography was performed with a femoral approach in multiple angulated views using the standard Judkins technique and iopromide (Ultravist-370, Schering AG, Berlin, Germany) as the contrast agent. Coronary flow rates of all subjects were documented by TFC. The TFC for each coronary artery was determined according to a distal marking point specific for the coronary artery of interest (9). The left anterior descending coronary artery (LAD) frame count was corrected by dividing with 1.7 to derive a corrected TFC (cTFC) as described previously (9).

AR was quantified angiographically. Patients with 3+ and 4+ AR were included in the study (10). Patients with any of the followings were excluded from the study: concomitant severe aortic stenosis, mitral regurgitation, mitral stenosis, a prosthetic heart valve, a history of surgical or percutaneous aortic valvuloplasty, anemia,

***Table 1**. The baseline characteristics of the study groups (mean ± SD)*

Variables	*Group I*	*Group II*	*p values*
Male/Female (n)	*17/16*	*10/12*	*ns*
Age (years)	*51±10*	*52±12*	*ns*
Heart rate (beats/minute)	*84±13*	*71±13*	*0.008*
Systolic blood pressure (mmHg)	*146±12*	*125±15*	*0.001*
Diastolic blood pressure (mmHg)	*62±8*	*80±9*	*0.001*
Diabetes mellitus (n)	*2*	*1*	*ns*
Smokers (n)	*9*	*6*	*ns*
Total cholesterol (mg/dl)	*195±68*	*188±55*	*ns*
Triglycerides (mg/dl)	*136±90*	*122±75*	*ns*

Group I: Aortic regurgitation patients, Group II: Control groups, ns: Statistically non-significant.

coronary artery disease including spasm, plaque, ectasia, or an obstructive lesion, and cardiac Syndrome X.

Statistical analysis

Statistical analysis was performed with SPSS for Windows, version 11.0 (SPSS Inc. Chicago, Illinois). Data is presented as mean ± SD. For continuous variables, the unpaired Student t-test and for categorical changes, the Chi-square test was used. Variances of variables were homogenous between groups according to the Levene's test. A p value of < 0.05 was considered to indicate statistical significance.

RESULTS

The baseline characteristics, the echocardiographic parameters and mean TFC of the study groups are shown in table 1. 19 of AR patients had 4+ and14 had 3+AR. There was no difference between the two groups in terms of sex, age, CAD risk factors, and laboratory findings. Sixteen patients were under medication with angiotensin-converting enzyme (ACE) inhibitors and 9 with nifedipine in AR group. None of AR patients was taking beta-blocking drugs. Twenty-seven AR patients were referred for surgery. Seven patients in the control group had hypertension; 3 patients were using ACE inhibitors, 2 patients using calcium channel blocker and 1 patient using angiotensin-II receptor blocker.

The LVEF was significantly lower in AR patients than control subjects. The LV end-systolic dimensions (LVSD), LV end-diastolic dimensions (LVDD), LV wall thickness, LA dimensions, and PASP were significantly higher in AR patients than control group. In both groups, TIMI-III flow was present in each artery at the time of arteriography and the coronary arteries were entirely normal. The LAD TFC, cLAD TFC (Figure 1A), LCx TFC (Figure 1B), RCA TFC (Figure 1C) and mean TFC of AR patients were significantly higher than the control groups (43±7.3 vs. 30±5.9 frames/s, p<0.001; 25.0±4.3 vs. 17.6±3.5 frames/s, p<0.001; 27.0±6.4 vs. 19.9±3.4 frames/s, p<0.001; 25.8±5.5 vs. 19.9±4.7 frames/s, p<0.001, 26.3±5.4 vs.19.1±3.9 frames/s, p<0.001, respectively).

***Table 2**. The echocardiographic characteristics of the two groups (mean± SD)*

Variables	*Group I*	*Group II*	*p values*
LVEF (%)	*55±8*	*67±3*	*0.001*
LVDD (cm)	*6.2±0.9*	*4.7±0.4*	*0.001*
LVSD (cm)	*4.3±0.8*	*2.8±0.4*	*0.001*
Left atrial dimensions (cm)	*4.3±0.6*	*3.7±0.4*	*0.001*
Ventricular septal thickness (cm)	*1.2±0.1*	*1.0±0.1*	*0.001*
Posterior wall thickness (cm)	*1.2±0.1*	*1.0±0.1*	*0.001*
SPAP (mmHG)	*44±10*	*25±7*	*0.034*

Group I: Aortic regurgitation patients, Group II: Control groups, LVEF: Left ventricular ejection fraction, LVDD: Left ventricular end-diastolic dimensions, LVSD: Left ventricular end-systolic dimensions, SPAB: Systolic pulmonary arterial pressure.

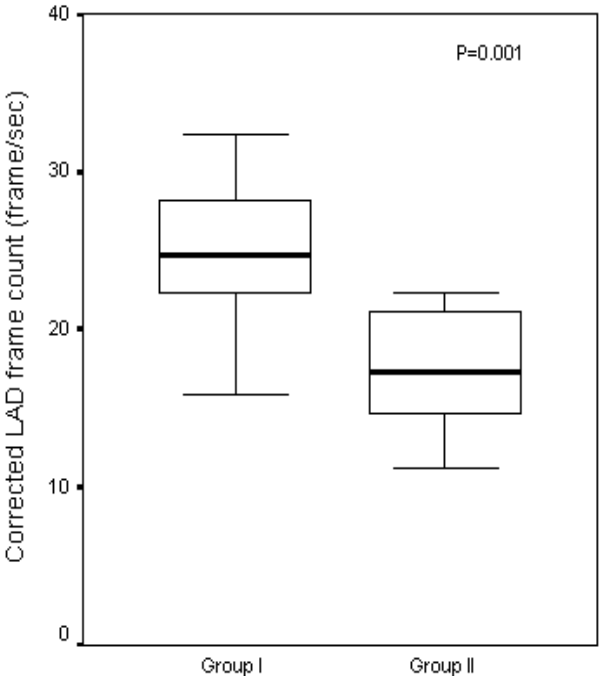

***Figure 1 A**. Corrected LAD frame counts of the two groups are shown.*

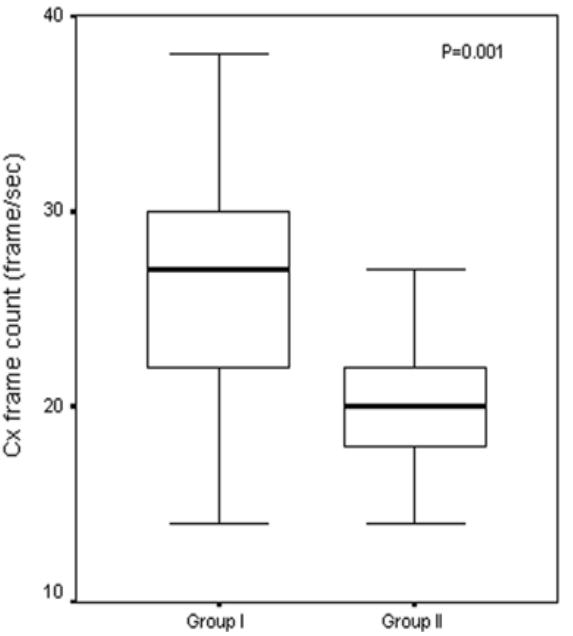

***Figure 1 B**. Cx frame counts of the two groups are shown.*

DISCUSSION

In this study, we found that TFC was increased in AR patients. To our knowledge, this is the first study showing the increase of TFC in AR in the absence of coronary stenosis.

Previous studies have used some invasive techniques such as the coronary sinus thermodilu-tion technique, Doppler guide-wire, and transesophageal Doppler echocardiography to evaluate coronary blood flow in patients with AR but normal coronary angiogram (11-15) and showed increase in systolic phase and decrease in diastolic phase of coronary blood flow (12, 14), reduced coronary reserve (13), and LV diastolic dysfunction (15) in AR patients. However, these techniques are costly and time-consuming. Moreover they need good expertise, and have low sensitivity and specificity for the assessment of coronary blood flow. On the other hand, the TFC method is a simple, quantitative, and reproducible method to assess coronary blood flow in all coronary laboratories. Although TFC is a measure of epicardial flow, it is dependent on the microvasculature. It has also been suggested that a higher TFC may reflect disordered resistance vessel function (9). Previously, Senen et al. (15) showed that TFC was increased in patients with coronary artery ectasia. Tanedo et al. (17) showed that TFC is an inverted index of coronary flow velocity and correlates with Doppler-derived average peak velocity. Moreover, Manginas at al. (18) found an excellent correlation between coronary flow velocity reserves calculated with FloWire and the TFC method. A correlation was also found between volumetric flow and resting distal average peak velocity (19).

In chronic aortic regurgitation, eccentric hypertrophy, with combined concentric hypertrophy of the LV, is an important adaptive response to volume overload, which in itself is a compensatory mechanism for permitting the ventricle to normalize its afterload and to maintain normal ejection performance. However, progressive dilatation of the LV leads to depressed left ventricular contractility and myocardial structural changes, including cellular hypertrophy and interstitial fibrosis (20, 21).

Most of the patients with AR but otherwise normal coronary arteriography have suffered from angina pectoris and some ischemic findings have been shown in these patients but the reason for these findings is not fully understood. One possible mechanism may be reduced

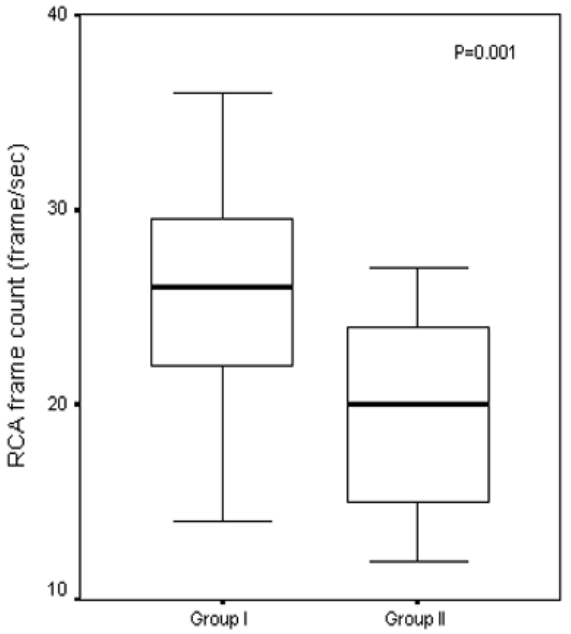

***Figure 1 C**. RCA frame counts of the two groups are shown.*

vasodilator reserve. It may be secondary to volume overload caused by ventricular hypertrophy in AR patients (12, 13). Reduced coronary vasodilator reserve is mainly attributable to a curtailment in maximal myocardial blood flow, which in the absence of epicardial stenosis reflects dysfunction of the coronary microcirculation (22, 23). In addition to these, coronary perfusion pressure is decreased in AR patients (20). It has been proposed that these changes in AR can compromise coronary blood flow leading to myocardial ischemia and angina pectoris. We assumed that decreased perfusion pressure, left ventricular remodeling, LV diastolic dysfunction and microvascular dysfunction in AR patiets were responsible for increased TFC. We also concluded that increased TFC values in AR patients indicated impaired coronary blood flow. Accordingly, TFC could be used as an angiographic parameter in explaining angina in patients. Moreover, in addition to aortography, increased TFC values can show the severity of chronic AR.

Study limitations

AR was not graded quantitatively by echocardiography. Study of the correlation between quantitative echocardiographic parameters for AR and TFC could give further valuable information. Although coronary perfusion pressure had been shown to be lower than normal in these patients in the former studies, left ventricle end-diastolic pressure was not routinely measured in our study (20). The intra-observer and inter-observer variations for TFC were less than 5%.

In conclusion, this is the first study showing increase of TFC in chronic AR patients without CAD. It is thought to show impaired coronary blood flow, and may explain angina symptoms in chronic AR patients. At the same time, it could be used as a parameter showing severe AR.

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