

Original Article

Decreased coronary blood flow velocity in patients with aortic insufficiency but normal coronary arteries: the use of TIMI frame count in aortic insufficiency cases

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Received July 6, 2015; Accepted September 6, 2015; Epub September 15, 2015; Published September 30, 2015

Abstract: Patients with aortic insufficiency (AI) may suffer from angina pectoris in the absence of obstructive coronary artery disease. In this study, we aimed to investigate coronary blood flow using the thrombolysis in myocardial infarction (TIMI) frame count (TFC) method in patients with AI and normal coronary arteries. The study included 64 patients (Group 1; mean age 62.4 ± 13.2 years) with moderate to severe AI who had undergone coronary angiography that resulted in angiographically normal coronaries, and 42 patients with a typical chest pain and angiographically normal coronary arteriogram (Group 2; mean age 58.8 ± 9.8 years). All patients underwent coronary angiography either to exclude coronary artery disease or to evaluate their coronary anatomy before aortic valve replacement. TFC was calculated and compared for each artery, including the left anterior descending (LAD), circumflex (LCX), and right coronary artery (RCA) in both groups. The baseline characteristics of the study groups were similar. In both groups, TIMI-3 flow was present in each artery at the time of arteriography, and the coronary arteries were entirely normal. LCx and RCA frame counts and corrected LAD frame counts were significantly higher in Group 1 than in Group 2 (26.4 ± 2.1 vs. 24.3 ± 3.6 , $P < 0.05$; 22.1 ± 2.3 vs. 20.5 ± 2.9 , $P < 0.05$; and 22.5 ± 1.8 vs. 20.5 ± 2.4 , $P < 0.05$, respectively). The TFC method may be used as a marker for coronary flow velocity in patients with aortic insufficiency and angiographically normal coronary arteries to estimate decreased coronary blood flow velocity.

Keywords: Thrombolysis in myocardial infarction frame count, aortic insufficiency, coronary blood flow velocity

Introduction

Aortic insufficiency (AI) is characterized by diastolic reflux of blood from the aorta into the left ventricle (LV) due to malcoaptation of the aortic cusps [1]. Several studies have investigated the influence of AI on coronary blood flow (CBF) and myocardial oxygen consumption, and the effect of regurgitation on CBF phases is well known [2]. Although a few invasive techniques (such as coronary sinus thermodilution, the use of Doppler guide wires, and transesophageal Doppler echocardiography) that evaluate CBF are in use [3, 4], these modalities have not found widespread application in the assessment of microvascular perfusion. Such techniques demand excessive effort, are highly costly and time-consuming, and are not readily available in all coronary laboratories. Fur-

thermore, the diagnostic value of these methods in the assessment of blood flow is limited by low sensitivity and specificity [5].

The thrombolysis in myocardial infarction (TIMI) frame count (TFC) method, developed by Gibson et al. [6] is a quantitative method that counts the number of cineangiographic frames required for dye to travel from the ostium to standardized distal landmarks of the coronary artery [6]. The TFC is a simple, reproducible, objective and quantitative index of coronary flow velocity.

In this paper, using the TFC method, we sought to determine whether or not coronary flow velocity is affected in patients with AI but without obstructive coronary artery disease.

Materials and methods

The study included 64 patients (Group 1; mean age 62.4 ± 13.2 years) with moderate to severe AI who had undergone coronary angiography that resulted in angiographically normal coronaries, and 42 patients with atypical chest-pain and angiographically normal coronary arteriogram (Group 2; mean age 58.8 ± 9.8 years).

Patients with AI were included in the study if they had moderate or severe regurgitation and completely normal coronary arteries. Patients with mild AI; aortic stenosis; severe mitral regurgitation or stenosis; a prosthetic heart valve; coronary artery disease including coronary spasm, plaque, ectasia, or an obstructive lesion; cardiac syndrome X; a history of surgical or percutaneous aortic valvuloplasty; and/or atrial fibrillation were excluded from the study. AI was also evaluated with aortography. The patients took no medications (such as beta blockers, nitrates, or digoxin) for two days before angiography. The present study was approved by the local ethics committee.

Echocardiography

Standard echocardiographic examinations were performed with a Vingmed Vivid System 5 (General Electric, Horten, Norway). For Doppler examinations, 2.5-MHz probes and second harmonic echocardiographic imaging were used. Standard parasternal long and short axes and apical 4- and 2-chamber windows were used in two-dimensional (2D) imaging. LV systolic, diastolic, aortic, and left atrial diameters were measured with 2D and M-mode imaging examinations. The aortic velocities were measured with continuous wave Doppler. The LV ejection fraction was calculated using the modified Simpson method using 2D imaging [7]. The echocardiographic techniques and calculations were performed in accordance with the recommendations of the American Society of Echocardiography [9]. The grading of AI severity was based on a number of echocardiographic and Doppler parameters, as previously described [9].

Coronary angiography

All patients underwent coronary angiography on multiple orthogonal views using the Judkins technique. Cineangiography was performed by

hand injection through diagnostic 6 Fr Judkins catheters. Iopromide contrast (Ultravist-370, Schering AG, Berlin, Germany) was used in all of the patients.

Thrombolysis in myocardial infarction frame count

The TIMI frame count was measured with digital cardiac image sequence acquisitions (Advantx LC and DLX, GE Medical Systems, Chicago, IL, USA). The first frame in the TFC was defined by a column of contrast extending across > 70 percent of the arterial lumen with anterograde motion, as reported previously [11]. The last frame counted was that in which contrast entered into the distal arterial landmark branch; full opacification of the branch was unnecessary [6]. As defined by Gibson et al. [6], the distal coronary landmarks used for the analysis were the distal bifurcation at the apex of the LAD (the mustache, pitchfork, or whale's tail); the distal bifurcation of the major obtuse marginal, or the main Cx (which ever was larger); and the site of origin of the first branch at the crux or its posterolateral extension for RCA.

If one of these landmarks was not well visualized, another nearby well-visualized landmark was chosen instead. The TFCs of the LAD and the LCx are often best assessed in either the right or left anterior oblique views with caudal angulation, while the RCA is often best assessed in the left anterior oblique projection with steep cranial angulation. The TFC could be measured in 95 percent of the patients. The TFC was measured blindly by two medically qualified observers (SMD, MRS). Because of its higher length, corrected TFC for LAD was calculated by dividing by 1.7.

Statistical analysis

All statistical analyses were performed with SPSS for Windows, version 10.0 (SPSS, Chicago, IL, USA). All quantitative values are expressed as mean \pm SD. Statistical analysis was performed using the unpaired Student's *t*-test and the Mann-Whitney U test when appropriate. Two observers independently measured the TFC, and inter observer correlation was assessed by linear regression analysis. A *P* value of less than 0.05 was considered to indicate statistical significance.

Table 1. General characteristics of the groups*

| | Group 1 (n=64) | Group2 (n=42) | P |
|---------------------------------|-------------------|------------------|------|
| Age (years) | 62.4 ± 13.2 | 58.8 ± 9.8 | 0.12 |
| Sex (male/female) | 38/26 | 24/18 | 0.84 |
| BMI (kg/m ²) | 28.3 ± 3.3 | 27.1 ± 2.1 | 0.27 |
| Systolic blood pressure (mmHg) | 134 ± 26 | 121 ± 33 | 0.09 |
| Diastolic blood pressure (mmHg) | 65 ± 9 | 66 ± 12 | 0.63 |
| Heart rate (beats/min) | 83 ± 9 | 78 ± 9 | 0.04 |
| Hypertension (n) | 27 | 13 | 0.31 |
| Diabetes mellitus (n) | 16 | 9 | 0.29 |
| Smokers (n) | 25 | 17 | 0.52 |
| Total cholesterol (mg/dl) | 180 ± 50 | 196 ± 25 | 0.11 |
| Triglyceride level (mg/dl) | 138 ± 72 | 158 ± 108 | 0.34 |
| LDL (mg/dl) | 105 ± 44 | 117 ± 31 | 0.24 |
| HDL (mg/dl) | 46 ± 19 | 45 ± 11 | 0.89 |

*Data presented as mean ± standard deviation. BMI: Body mass index, LDL: Low density lipoprotein, HDL: High density lipoprotein, NS, not significant..

Table 2. Echocardiographic parameters of the groups*

| | Group 1 (n=51) | Group 2 (n=42) | P |
|------------------|-------------------|-------------------|--------|
| LVEDD (mm) | 54.2 ± 7.7 | 47.1 ± 2.8 | 0.005 |
| LVESD (mm) | 37.5 ± 8.5 | 30.2 ± 3.7 | 0.008 |
| LA (mm) | 43.4 ± 6.9 | 36.7 ± 2 | 0.002 |
| Aortic root (mm) | 36 ± 6.1 | 27.1 ± 2 | <0.001 |
| IVS (mm) | 12.1 ± 1.3 | 10.5 ± 0.75 | <0.001 |
| PW (mm) | 11.9 ± 1.2 | 10.1 ± 0.75 | <0.001 |
| EF (%) | 51 ± 9 | 62 ± 3 | <0.001 |

*Data presented as mean ± standard deviation. LVEDD: Left ventricle enddiastolic diameter, LVESD: Left ventricle end systolic diameter, LA: Left atrium, IVS: Interventricular septum, PW: Posterior wall, EF: Ejection fraction.

Results

The baseline characteristics of the groups are shown in **Table 1**. There were no statistically significant differences between the groups in terms of age, sex, or body mass index. All of the coronary arteries of the groups were free of atherosclerosis. The echocardiographic parameters of the groups are shown in **Table 2**. The left ventricular end-diastolic and end-systolic dimensions were significantly higher in Group 1 than in Group 2 (54.2 ± 7.7 mm vs. 47.1 ± 2.8 mm, P = 0.005 and 37.5 ± 8.5 mm vs. 30.2 ± 3.7 mm, P = 0.008, respectively). The aortic root diameter and left atrial diameter were sig-

nificantly higher in Group 1 than in Group 2 (36 ± 6.1 vs. 27.1 ± 2 mm, P < 0.001 and 43.4 ± 6.9 mm vs. 36.7 ± 2 mm, P = 0.002, respectively). The interventricular septal thickness and posterior wall diameters were significantly higher in Group 1 than in Group 2 (12.1 ± 1.3 mm vs. 10.5 ± 0.75 mm, P < 0.001 and 11.9 ± 1.2 mm vs. 10.1 ± 0.75 mm, P < 0.001, respectively). The corrected LAD frame count, and the LCx and RCA frame counts, were significantly higher in Group 1 than in Group 2 (26.4 ± 2.1 vs. 24.3 ± 3.6, P = 0.001; 22.1 ± 2.3 vs. 20.5 ± 2.9, P = 0.002; and 22.5 ± 1.8 vs. 20.5 ± 2.4, P < 0.001, respectively) (**Figure 1**).

Discussion

In the present study, we found that TFC was higher in patients with AI, but otherwise patients had normal epicardial coronary arteries when compared with those with atypical chest pain and normal coronary arteriography. Our study indicates that coronary blood flow velocity is decreased, even in the absence of apparent obstructive coronary artery disease in patients with AI.

AI is sometimes accompanied by clinical findings that suggest ischemia, including angina pectoris [12]. Although these findings may imply severe valvular disease and a poor prognosis, they do not necessarily indicate accompanying severe coronary artery disease [12]. The reason that angina accompanies AI without severe coronary disease is not fully understood, although based on previous experimental observations [2, 12, 13], altered CBF (with or without an associated increase in myocardial work) has been suggested.

In the absence of valvular regurgitation, epicardial blood flow is characterized by the predominance of diastolic blood flow [14, 15]. In severe acute aortic regurgitation, antegrade coronary blood flow occurs predominantly in systole, and retrograde flow during diastole [14-16]. In an experimental study, Ardehali et al. suggested that acute aortic regurgitation predisposes the myocardium to ischemia due to the hemodynamic consequences of valvular regur-

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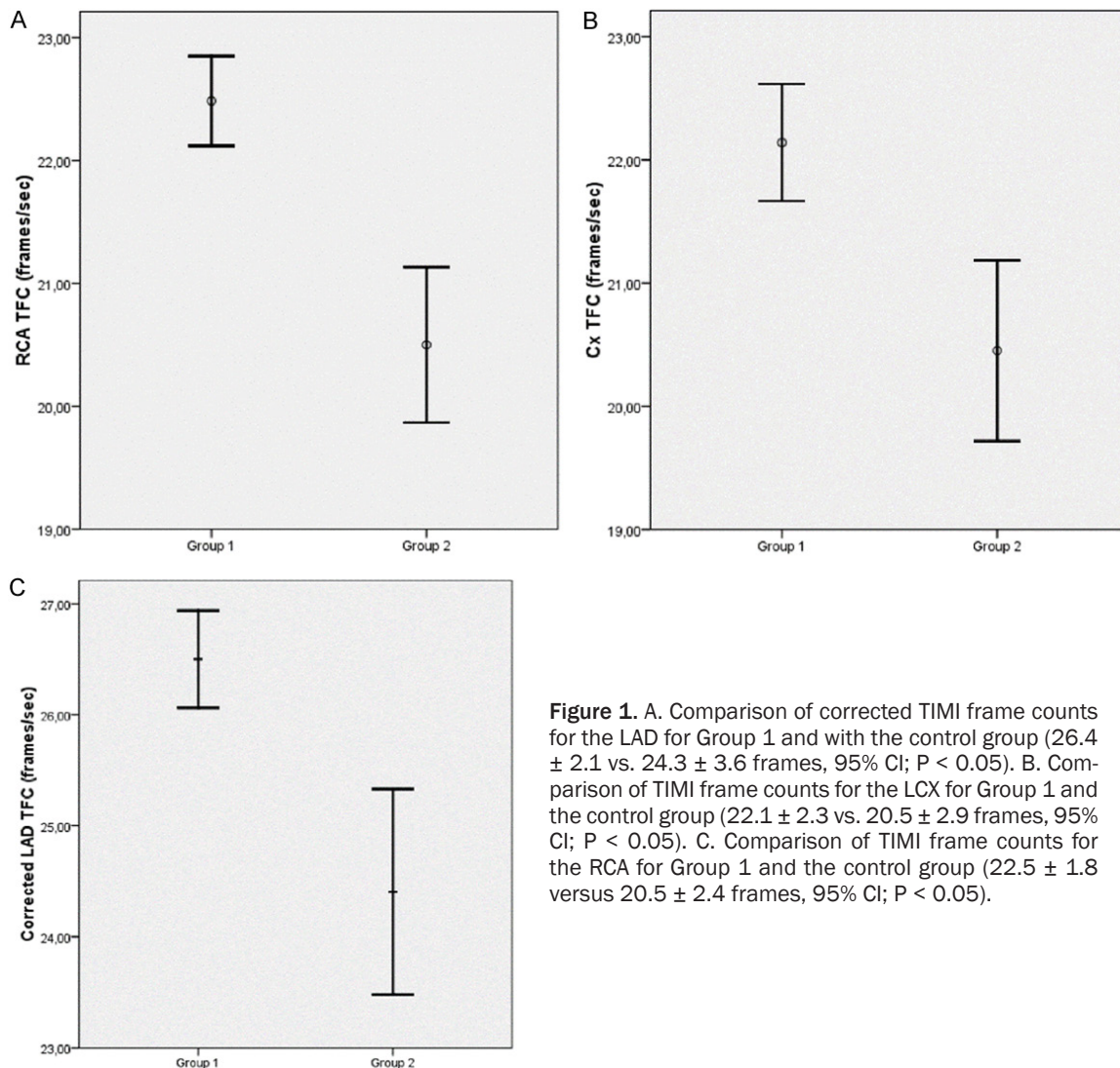


Figure 1. A. Comparison of corrected TIMI frame counts for the LAD for Group 1 and with the control group (26.4 ± 2.1 vs. 24.3 ± 3.6 frames, 95% CI; $P < 0.05$). B. Comparison of TIMI frame counts for the LCX for Group 1 and the control group (22.1 ± 2.3 vs. 20.5 ± 2.9 frames, 95% CI; $P < 0.05$). C. Comparison of TIMI frame counts for the RCA for Group 1 and the control group (22.5 ± 1.8 versus 20.5 ± 2.4 frames, 95% CI; $P < 0.05$).

gitation [16]. Experimental studies have shown that when aortic diastolic pressure decreases because of the AI, the CBF during systole increases. The decrease in flow during diastole, however, cannot be compensated; as a result, mean coronary flow decreases [14-16]. The reduction in coronary flow may reflect the decreased coronary flow velocity and increased TFC rates that we observed in our study.

Coronary arteriography is mainly performed and interpreted in a qualitative manner. A few quantitative techniques have been developed to standardize contrast dye injections [17, 18] and to measure blood flow [6, 19, 20]. In a study on chronic AI, Nitenberg et al. investigated coronary flow reserve and coronary resistance with invasive methods (before and after

an intravenous dipyridamole infusion) in eight patients with exertional angina pectoris, normal coronary arteriograms, and chronic aortic regurgitation. They concluded that coronary reserve had decreased in those patients compared to the control groups [21]. Estimating coronary reserve flow may be time-consuming, and it requires instrumentation of the coronary arteries by experienced operators using non-reusable, expensive devices that are not readily available in all coronary laboratories [22, 23]. In addition, coronary flow reserve is dependent upon the factors influencing rest and maximal flow, such as heart rate, contractility, and end-diastolic pressure [22, 23]. Manginas et al. showed, however, that TIMI frame counts can be used reliably in the catheterization laboratory to estimate coronary flow reserve [7]. Since

coronary flow reserve detection falls outside the aim of our paper, it was not evaluated in our study. We found decreased coronary flow velocity in patients with AI using the TFC method, which is easier to implement and to apply in clinical settings.

The TFC method was proposed as a simple, quantitative, and reproducible method to assess coronary blood flow. Previously, the TFC method was used to diagnose specific disorders such as coronary ectasia [24], hypertrophic cardiomyopathy [25], isolated myocardial bridging [26], and chronic obstructive pulmonary disease [27]. In a study of patients with severe aortic stenosis expected to undergo aortic valve surgery, Barutcu et al. demonstrated higher TFC levels in patients with normal coronary arteries. The authors concluded that the decreased coronary flow was most likely related to microvascular dysfunction [5]. In our study, we observed significantly higher TFC levels in patients with moderate to severe AI and normal coronary arteries compared to a control group. In patients with moderate to severe AI, when the coronary flow decreased, the systolic to diastolic flow ratio increased. Accordingly, the coronary flow velocity decreased, and an increased TIMI frame count could be observed.

Study limitations

The main limitation of our study is that we did not measure myocardial oxygen consumption and volumetric flow to determine whether blood flow is adequate for myocardial demand. The TFC method does not assess ischemia, but only demonstrates coronary flow abnormalities. The TFC method may be affected by several factors, such as heart rate, nitrate use, and the cardiac cycle in which dye is injected [8]. We used a standard 6F Judkins catheter and the same contrast material (Ultravist-370, Schering AG, Berlin, Germany) in all patients. Injection without the use of an automatic injector is certainly an important limiting factor for the assessment of TFC; in our study, all injections were made by hand, at as close to the same injection rate as possible, and we were careful to synchronize the injections with the electrocardiographic R wave. Dipyridamole, nitroglycerin, verapamil, or other medications were not administered into the coronary arteries or intravenously before or after the angiography.

Conclusion

The TFC method may be used to estimate decreased coronary blood flow velocity in patients with aortic insufficiency and angiographically normal coronary arteries.

Acknowledgements

We thank staff of the data processing center for their kind cooperation. Author contribution: Icli A. designed and performed the research, analysed the data, wrote the paper. Karabag T. Designed and performed the research and wrote the paper. Kahraman H. Collected the data and performed the research. Mutlu H. Professional editing manuscript.

Disclosure of conflict of interest

None.

Abbreviations

LAD, left anterior descending artery; LCx, circumflex artery; RCA, right coronary artery; TFC, TIMI frame count.

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