Coronary Flow Velocity Reserve Does Not Correlate With TIMI Frame Count in Patients Undergoing Non-Emergency Percutaneous Coronary Intervention

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OBJECTIVES	The purpose of this research was to compare the Thrombolysis In Myocardial Infarction (TIMI) frame count (CTFC) with coronary flow velocity reserve (CFVR) in patients undergoing percutaneous coronary intervention (PCI).
BACKGROUND	The relationship between CTFC and CFVR has not been adequately assessed in patients with coronary artery disease.
METHODS	We studied 62 patients who underwent successful non-emergent PCI. All patients had Doppler evaluation of CFVR, CTFC, and quantitative coronary angiography. In an additional 17 patients, a frame count reserve was calculated as baseline CTFC/CTFC at peak hyperemia, induced by intracoronary adenosine after PCI.
RESULTS	The CTFC decreased from 27 ± 13 to 18 ± 8, and CFVR increased from 1.5 ± 0.4 to 2.6 ± 0.7 (both $p < 0.0001$). The pre-PCI CTFC and the CFVR were closely related to minimal lumen diameter ($p < 0.0001$). After PCI, there was no correlation between CFVR and CTFC. In addition, no relationship was observed between CFVR and the frame count reserve.
CONCLUSIONS	There was no significant correlation between CFVR and CTFC in patients undergoing coronary intervention. The relative utility of these measures in predicting outcomes in this setting requires further evaluation, but CTFC (or frame count reserve) does not appear to be an adequate surrogate measure of Doppler-derived CFVR. (J Am Coll Cardiol 2004;44: 778–82) © 2004 by the American College of Cardiology Foundation

The corrected Thrombolysis In Myocardial Infarction (TIMI) frame count (CTFC), which counts the number of cineangiographic frames required for dye to traverse the length of the coronary arteries, was developed by Gibson et al. (1) to provide a simple continuous index of coronary flow and microvascular perfusion. Higher CTFCs at 90 min after thrombolytic administration are related to an increased risk of early and late adverse outcomes (2). Little is known about the physiologic relevance of CTFC after non-emergent percutaneous coronary intervention (PCI) (3).

Intracoronary Doppler can determine absolute velocity in coronary arteries at rest and after a hyperemic stimulus. A coronary flow velocity reserve (CFVR) of <2.0 correlates with ischemia, predicts the need for intervention in subjects with intermediate lesions, and is associated with adverse cardiovascular events after PCI (4). However, intracoronary Doppler is not more widely used because it also has several perceived limitations, including cost (5). Both CFVR and CTFC have been used as measures of microvascular integrity and seemingly predict outcome. Therefore, we hypoth-

esized that the more easily obtained CTFC would be related to Doppler-derived CFVR in patients undergoing non-emergent PCI.

METHODS

Patient selection. The study population consisted of 62 subjects (mean age, 64 ± 10 years) who participated in the randomized multicentre study of coronary stenting or optimal balloon angioplasty, the Doppler Endpoint Stenting International Investigation (DESTINI) study (6). Exclusion criteria included chronic total occlusions, recent (<24 h) myocardial infarction (MI), or previous Q-wave MI in the territory supplied by the target vessel. The study protocol was approved by the institutional review board of participating centers, and all patients gave written informed consent.

Inclusion in this retrospectively defined substudy was based on suitability of the coronary angiograms for CTFC assessment from three of the participating centers (120 angiograms screened). All patients in this study had TIMI flow grade 3 and underwent successful non-emergent PCI without complication. All patients had Doppler evaluation of CFVR, CTFC, and quantitative coronary angiography before and after intervention.

Frame count reserve cohort. To evaluate the relationship between Doppler-derived parameters and an adenosine-

Abbreviations and Acronyms

APV = average peak velocity
CFVR = coronary flow velocity reserve
CTFC = corrected TIMI frame count
DESTINI = Doppler Endpoint Stenting International Investigation
LV = left ventricle/ventricular
MI = myocardial infarction
MLD = minimal lumen diameter
PCI = percutaneous coronary intervention
TIMI = Thrombolysis In Myocardial Infarction

Table 1. Patient Demographics

Characteristics	Number (%)
Age (yrs)	64 ± 10
Male/female	37/25
Hypertension	26 (42%)
Hyperlipidemia	23 (37%)
Diabetes mellitus	5 (9%)
Family history	23 (37%)
Cigarette smoking	24 (39%)
Previous myocardial infarction	26 (42%)
Unstable/stable coronary syndrome	30/32
Single-vessel disease	42 (67%)
Left ventricular ejection fraction	65 ± 11

induced CTFC frame count reserve, a further 17 independent patients (mean age, 60 ± 10 years) undergoing non-emergent PCI were prospectively studied. The variables measured were identical to the DESTINI cohort. In addition, a second CTFC determination was obtained at the peak of adenosine-induced (24 μg intracoronary) hyperemia. The basal/peak CTFC ratio constituted the frame count reserve (7). The peak CTFC was analyzed at a time after adenosine bolus that corresponded to the time of peak coronary velocity from the preceding adenosine injection (6 to 12 s) so as to capture peak flow and, hence, minimum CTFC.

CFVR and quantitative coronary angiography. The details of the study have been previously described (6). An 0.014-inch Doppler guidewire (Volcano Therapeutics, Rancho Cordova, California) was advanced 2 cm distal to the stenosis, and the Doppler signal was optimized. Basal velocity was recorded, and 12 or 24 μg of adenosine was injected into the right or left coronary artery, respectively. In 42 subjects, a determination of CFVR was made in a non-PCI artery for the determination of relative CFVR (CFVRculprit/CFVRnormal). Duplicate CFVR measurements were performed, and the average of the two measurements was used. All procedural angiograms were analyzed independently in a core laboratory using a quantitative angiographic system (CMS MEDIS version 4.0, Leiden, the Netherlands).

CTFC. The number of cineframes was measured using a frame counter according to the method of Gibson et al. (1) by two experienced blinded observers. The unadjusted TIMI frame count for left anterior descending artery culprits was corrected to account for its longer length by dividing by 1.7.

Statistical analysis. Data are presented as mean ± SD. Serial measurements were analyzed by repeated measures analysis of variance. Correlation between CTFC and hemodynamic and Doppler parameters were determined by linear regression analysis (SPSS v.11.5, Chicago, Illinois) and included the 62 subjects from the DESTINI cohort. The results were no different regardless of whether or not the additional 17 patients from the frame count reserve cohort were included in the analysis. In addition, the relative CFVR was used as an end point in the analysis. Because the results were no different from the results obtained when CFVR was used, these were not reported. When the two observers independently evaluated CTFC on a series of angiograms, the interobserver variability was 2.7 ± 1.8 frames. All statistical tests are two-tailed, and a value p < 0.05 was considered significant.

RESULTS

Patient characteristics. The clinical characteristics of the study population are shown in Table 1. The majority of patients had single-vessel coronary disease with preserved left ventricular (LV) function. Almost one-half (42%) had a previous MI.

CTFC. Percutaneous coronary intervention increased minimal lumen diameter (MLD) from 0.94 ± 0.32 mm to 2.78 ± 0.54 mm (% stenosis: 69 ± 10% to 15 ± 11%). All subjects had TIMI flow grade 3 both before and after procedure. The CTFC decreased (Table 2) from 27 ± 13 to 18 ± 8 (p < 0.0001). The predictors of CTFC are shown in Table 3. There was a very significant relationship between the pre-procedure CTFC and the MLD (p < 0.0001) as shown in Figure 1. After the procedure, the only multivariate predictor of CTFC was the pre-procedure value (p = 0.003). There was no relationship (Table 3) between LV function, number of vessels diseased, previous MI, or cardiovascular risk factors and CTFC.

Doppler-derived CFVR. After PCI (Table 2), both the baseline average peak velocity (APV) and the CFVR increased significantly (p = 0.012 and p < 0.0001, respectively). Pre-procedure CFVR was related to MLD (Fig. 1B) (p < 0.0001) and the reference vessel diameter (p = 0.02). By multivariate analysis, only pre-MLD remained a significant predictor of pre-CFVR (p < 0.0001). After the

Table 2. Doppler Data and CTFC Data

	Before PCI	After PCI	p Value
APV (cm/s)	15.6 ± 9.9	19.2 ± 8.8	0.012
CFVR	1.5 ± 0.4	2.6 ± 0.7	<0.0001
MLD (mm)	0.94 ± 0.32	2.78 ± 0.54	<0.0001
Stenosis (%)	69 ± 10	15 ± 11	<0.0001
CTFC	27 ± 13	18 ± 8	<0.0001

APV = average peak velocity; CFVR = coronary flow velocity reserve; CTFC = corrected TIMI frame count; MLD = minimal lumen diameter.

Table 3. Correlates of CTFC

	r	p Value
Pre-PCI CTFC		
Univariate		
Pre-MLD	0.55	<0.0001
Stenosis (%)	0.55	<0.001
Previous MI		0.89
CFVR	0.20	0.117
APV	0.06	0.66
Multivariate	0.55	for model
Pre-MLD		<0.0001
Post-PCI CTFC		
Univariate		
Post-MLD	0.05	0.70
Stenosis (%)	0.03	0.79
Previous MI		0.70
CFVR	0.14	0.28
APV	0.18	0.16
Pre-PCI CTFC	0.37	0.003
Multivariate	0.37	for model
Pre-PCI CTFC		0.003

APV = average peak velocity; CFVR = coronary flow velocity reserve; CTFC = corrected TIMI frame count; MLD = minimal lumen diameter; MI = myocardial infarction; PCI = percutaneous coronary intervention.

Table 4. Correlates of CFVR

|	r	p Value
Pre-PCI CFVR		
Univariate		
Pre-MLD	0.48	<0.0001
Stenosis (%)	0.39	0.002
Ref. diameter	0.29	0.02
Previous MI		0.24
Multivariate	0.48	for model
Pre-MLD		<0.0001
Post-PCI CFVR		
Univariate		
Post-MLD	0.26	0.04
Stenosis (%)	0.145	0.26
Ref. diameter	0.31	0.015
Previous MI		0.48
Pre-PCI CFVR	0.31	0.014
CTFC/MLD ratio	0.26	0.04
Multivariate	0.39	for model
Pre-CFVR		0.018
CTFC/MLD ratio		0.05

CFVR = coronary flow velocity reserve; CTFC = corrected TIMI frame count; MI = myocardial infarction; MLD = minimal lumen diameter; PCI = percutaneous coronary intervention.

procedure, a weak relationship remained between MLD, the reference diameter, and the post-CFVR. There was no effect (Table 4) of risk factors, LV function, or previous MI on the CFVR. There was no relationship with any of the Doppler-derived parameters including CFVR, either before ($p = 0.12$) or after the procedure ($p = 0.29$) and the CTFC. The pre- and post-procedure APV were not related to their respective CTFCs ($p = 0.66$ and $p = 0.16$, respectively). The post-procedure CFVR was weakly related to the post-CTFC/MLD ratio, but this relationship was no stronger than the relationship to MLD alone in a univariate analysis (Fig 2) ($p = 0.04$). However, in a multivariate analysis, the predictors of post-procedure CFVR were pre-procedure CFVR ($p = 0.018$) and the CTFC/MLD ratio ($p = 0.05$).

Frame count reserve. After an intracoronary bolus of adenosine, the CTFC decreased from 29 ± 14 to 19 ± 8 ($p = 0.005$), after stenting ($n = 17$), yielding a calculated frame count reserve of 1.6 ± 0.6. The CFVR was 3.3 ± 1.2

in these patients. There was no relationship between the frame count reserve and the CFVR ($p = 0.7$).

DISCUSSION

We demonstrated the following key findings: 1) in patients with TIMI flow grade 3, pre-PCI CTFC was closely related to the MLD and decreased significantly after PCI; and 2) there was no strong relationship between CTFC or the frame count reserve and Doppler-derived basal velocity or CFVR. A weak relationship with CFVR and the CTFC/ MLD ratio was observed.

The CTFC is a surrogate measure of coronary blood flow under resting conditions, whereas CFVR reflects both resting and hyperemic flow with their determinants being complex and probably different in acute and stable conditions. Despite this, CTFC and CFVR are both integrated measurements of coronary flow integrity, and both seemingly predict outcomes. However, in the present study, a
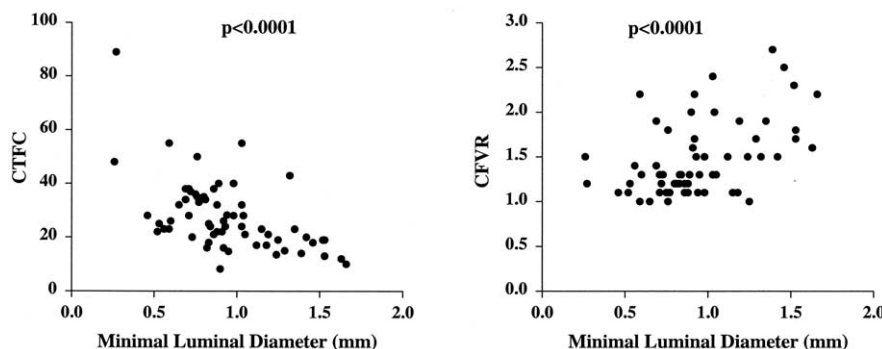
Figure 1. Scatter diagram showing relationship between corrected TIMI frame count (CTFC) and minimal luminal diameter (MLD) **(A)** and coronary flow velocity reserve (CFVR) and MLD **(B)** before intervention. The estimated regression equations are: 1) CTFC = $-22.6 \pm$ MLD $+ 48.9$ ($p < 0.0001$); 2) CFVR = $0.63 \pm$ MLD $+ 0.88$ ($p < 0.0001$).
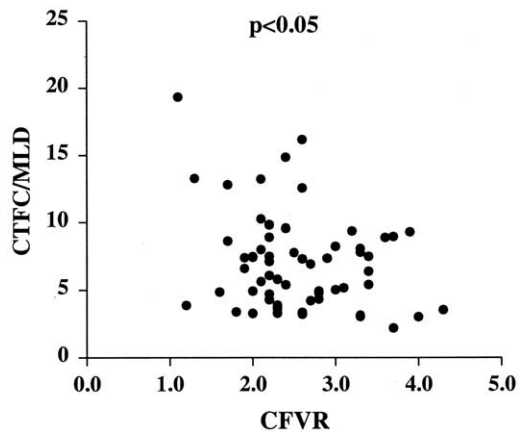
Figure 2. Scatter diagram showing relationship between corrected TIMI frame count (CTFC)/minimal luminal diameter (MLD) ratio and coronary flow velocity reserve (CFVR) after intervention. The estimated regression equation is: CTFC/MLD = −1.31 CFVR + 10.3 (p = 0.04).

strong relationship between post-PCI CTFC and CFVR has not been identified.

A similar lack of correlation has been reported in small studies (8–10). In the study by Stankovic et al. (10), there was no relationship between CTFC and CFVR. The authors introduced the concept of the CTFC/MLD ratio as a composite measure of structure and function. It was related to restenosis in that study. In the much larger Randomized Efficacy Study of Tirofiban for Outcomes and Restenosis (RESTORE) study of acute coronary syndrome, Gibson et al. (3) reported a similar relationship between the CTFC/MLD ratio and restenosis and other clinical outcomes (10). A weak relationship was also seen in our study between this ratio and CFVR, suggesting that the decrease in CTFC after PCI may be measuring a similar parameter. The long-term significance of post-PCI CTFC or CTFC/ MLD in a stable cohort remains to be determined.

The CTFC has been most studied in the acute situation and is useful in assessing outcomes after thrombolysis and PCI in acute MI. It reflects adequacy of perfusion paralleling findings from myocardial blush score and myocardial contrast echocardiographic studies. From our study, it is clear that the conduit vessel plays an important role in the CTFC given the close relationship between MLD and CTFC before the procedure. In addition, this is supported by the decrease in CTFC post-procedure when upstream stenosis is eliminated. After the procedure, CTFC reflects microvascular perfusion in a stable cohort, such as was studied here.

The concept of CFVR was introduced as a surrogate for evaluating the physiological significance of luminal narrowing and, subsequently, for determining the adequacy of a PCI result. A threshold value of <2.0 has been shown to correlate with ischemia and increased events after PCI. The Doppler Endpoints Balloon Angioplasty Trial Europe (DEBATE) study showed that post-PCI CFVR with post-PCI diameter stenosis had a modest predictive value for short- and long-term outcomes after PCI (11). The

DESTINI study has shown that CFVR-guided balloon angioplasty has outcomes comparable to coronary stenting (6). Attenuation of CFVR after successful coronary intervention is associated with adverse cardiovascular events (4,12). Causes of this abnormal microvascular function are many, but they include abnormal interactions between platelets, inflammatory cells, and the endothelium after the PCI procedure.

Because the CTFC reflects basal blood flow and not a hyperemic state, as measured by CFVR, we also compared a hyperemic frame count reserve with CFVR in 17 patients after PCI. Two previous small studies (7,9) have reported a relationship between an adenosine-induced hyperemic frame count reserve and Doppler-derived CFVR. However, in both studies insufficient numbers of patients were studied to determine whether the relationship was present after PCI. In the current study, there was no relationship between the frame count reserve and the CFVR or other Doppler indexes.

Study limitations. The study of CTFC was not a predefined end point of the DESTINI study. As such, all angiograms reviewed could not be included in the analysis. The recently reported study by Stoel et al. (7) utilized intravenous adenosine to measure the frame count reserve. It is expected that this would generate a more stable measure of the CTFC to a hyperemic response than the intracoronary bolus used here. The study was powered to detect modest correlations between CTFC and CFVR. The sample size for some of the secondary comparisons, such as post-PCI APV and CTFC (p = 0.16) should be viewed as too small to be definitive.

Conclusions. There was no statistical correlation between CTFC, the frame count reserve and CFVR after PCI in patients undergoing non-emergent coronary intervention. A weak relationship was seen between CFVR and CTFC/ MLD. The relative utility of CTFC and CFVR in predicting outcomes in this setting requires further evaluation, but CTFC (or frame count reserve) does not appear to be an adequate surrogate measure of Doppler-derived CFVR.

Acknowledgments

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