The measurement of collateral flow reserve (CFR; the hyperemic/baseline collateral flow velocity ratio) in patients with chronic total coronary occlusion requires invasive and expensive techniques. Noninvasive transthoracic coronary Doppler echocardiography may be an alternative option. Fifty-one patients with chronic total coronary occlusion were evaluated by transthoracic coronary Doppler echocardiography and venous adenosine infusion to measure CFR in occluded coronary arteries (the left anterior descending artery in 44 patients and the artery supplying the posterior descending artery in 7 patients). CFR data were plotted against 3 angiographic parameters: (1) grade of the epicardial filling of the occluded artery (1 = absent, 2 = partial, 3 = complete), (2) stenosis of the donor artery, and (3) the extent of coronary artery disease (vessels with $\geq 70\%$ stenosis). Collateral flow was maintained at stress in 34 patients (CFR $> 1$, range 1.0 to 2.2) but was withdrawn in 17 patients (CFR $< 1$, range 0.25 to 0.90). CFR increased with the degree of angiographic collateral flow (grade 1: 0.73 ± 0.29; grade 2: 1.16 ± 0.31; grade 3: 1.34 ± 0.49; $F = 5.31$, $p = 0.008$). A multivariate model of CFR prediction showed a direct relation with angiographic collateral grade and the number of diseased vessels and an inverse relation with stenosis of the donor artery. In conclusion, CFR measurement is feasible by transthoracic coronary Doppler echocardiography. One third of the patients with chronic total coronary occlusion had collateral flow withdrawal at stress, which occurs when collateral circulation is poor and when the donor artery is stenotic. CFR correlates with angiographic collateral grade and with the extent of coronary artery disease. © 2006 Elsevier Inc. All rights reserved. (Am J Cardiol 2006;98:197–203)
between flow and the Doppler beam. Imaging of the epicardial collaterals was attempted by angling the transducer lateral to the interventricular sulcus and imaging of the intramyocardial collaterals by focusing on perforating branches.

**Coronary flow velocity and flow reserve:** Flow direction in the occluded epicardial vessel was assessed by TDE and defined as normal (anterograde) or inverted (retrograde) (Figure 2).9 Similarly, flow direction in perforating branches was defined as normal (anterograde) or inverted (retrograde).10 Coronary flow velocity was measured by pulsed Doppler ultrasound under color-coding guide. Coronary flow reserve of the collateral-dependent circulation was measured as the ratio between hyperemic and baseline diastolic velocities of the occluded artery. Blood flow velocities were recorded at baseline and during venous adenosine infusion (140 μg/kg/min over 90 seconds), within 24 to 48 hours of diagnostic coronary angiography. Peak and mean diastolic flow velocities were measured on the diastolic phase of the pulsed Doppler ultrasound curve. All studies were continuously recorded on S-VHS videotape for offline analysis. Heart rate was continuously monitored. Blood pressure was recorded at baseline, during adenosine infusion, and at recovery. For each test, the 3 greatest Doppler velocities were computed and averaged. CFR was calculated by the same operator performing the test, blind to the angiographic data, using peak diastolic values.

**Angiography:** Patients underwent left-sided cardicatheterization with biplane left ventricular and coronary angiography. Coronary occlusion was estimated as the focal absence of anterograde flow. Angiographic collateral flow was determined according to the Rentrop classification,11 which takes into consideration the degree of the epicardial filling of the occluded artery (1 = filling of small side branches, 2 = filling of major side branches with partial filling of the main epicardial vessel, 3 = total filling of the main epicardial vessel). Patients were grouped according to angiographic collateral grade: group 1: grade 1 collaterals; group 2: grade 2 collaterals; and group 3: grade 3 collaterals. The sources of collaterals (single or multiple) and the direction of collateral flow in the occluded artery (anterograde, retrograde, or mixed) were also considered and computed. The described characteristics of the collateral circulation were analyzed independently by 2 observers unaware of the Doppler results, and a consensus was reached in cases of disagreement. The interaction of the donor artery with CFR was assessed according to its anatomy proximal to the takeoff of the collateral vessels, stratifying the patients as follows: no significant stenosis (0% to 49%), intermediate stenosis (50% to 69%), and significant stenosis (≥70%). In case of multiple sources of collaterals, the artery with the greatest stenosis was considered. We also considered the
impact on CFR of the extent of coronary artery disease, computing the number of remote arteries with ≥70% luminal narrowing.

**Statistical analysis:** Data are expressed as mean ± SD, except for data expressed as percentages or proportions, for which SEs are used. Only average data are presented for dichotomous (0 = absent, 1 = present) variables. One-way analysis of variance was used to analyze hemodynamic changes (basal vs adenosine) as distributed among groups (BMDP-7D, University of California Press, Berkeley, California). Two-way analysis of variance was used to analyze hemodynamic changes (basal vs adenosine) as distributed among groups (BMDP-7D, University of California Press, Berkeley, California). Two-way analysis of variance was used to analyze hemodynamic changes (basal vs adenosine) as distributed among groups (BMDP-7D, University of California Press, Berkeley, California). Two-way analysis of variance was used to analyze hemodynamic changes (basal vs adenosine) as distributed among groups (BMDP-7D, University of California Press, Berkeley, California). Two-way analysis of variance was used to analyze hemodynamic changes (basal vs adenosine) as distributed among groups (BMDP-7D, University of California Press, Berkeley, California).

### Table 1

<table>
<thead>
<tr>
<th>Variable</th>
<th>Collateral Grade (Rentrop Classification)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 (n = 6)</td>
</tr>
<tr>
<td>Demographic variables</td>
<td></td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>60 ± 9</td>
</tr>
<tr>
<td>Gender (0 = female; 1 = male)</td>
<td>0.83</td>
</tr>
<tr>
<td>Body surface area (m²)</td>
<td>1.89 ± 0.15</td>
</tr>
<tr>
<td>Risk factors (yes/no)</td>
<td></td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>2/6 (33%)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1/6 (17%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.6 (17%)</td>
</tr>
<tr>
<td>Smoking habits</td>
<td>4/6 (66%)</td>
</tr>
<tr>
<td>Non–Q-wave myocardial infarction</td>
<td>5/6 (83%)</td>
</tr>
<tr>
<td>Baseline hemodynamic and angiographic variables</td>
<td></td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>64 ± 7</td>
</tr>
<tr>
<td>Mean arterial blood pressure (mm Hg)</td>
<td>103 ± 4</td>
</tr>
<tr>
<td>Peak flow velocity (cm/s)</td>
<td>24 ± 10</td>
</tr>
<tr>
<td>Mean flow velocity (cm/s)</td>
<td>19 ± 8</td>
</tr>
<tr>
<td>Diseased coronary vessels (n)</td>
<td>1.66 ± 0.81</td>
</tr>
<tr>
<td>Stenosis of the donor artery (%)</td>
<td>25 ± 16</td>
</tr>
</tbody>
</table>

Risk factors (0 = absent, 1 = present, based on standard cut-off values). One-factor analysis of variance was used to test significance. In presence of a significant (p < 0.05) F test, pairwise comparisons were performed using Bonferroni’s correction.

* p < 0.05 collateral grade 1 versus 2.

† Epicardial coronary artery.

### Results

**Feasibility and patients characteristics:** Adequate baseline and hyperemic Doppler recordings of the collateral-dependent circulation were obtained in 51 of 56 patients (92%): 44 of 44 in the LAD and 7 of 12 in the PD. There were no statistically significant differences among groups regarding gender, body surface area, coronary risk factors, and baseline hemodynamic factors, whereas there was a greater prevalence of non-Q-wave myocardial infarction in remote areas in patients with grade 1 collaterals (Table 1).

**Angiographic characteristics:** According to angiographic collateral grade, 6 patients (12%) had grade 1, 16 (31%) grade 2, and 29 (57%) grade 3 collateral flow. Thirty-seven patients (72%) had single sources of collaterals, whereas 14 (28%) had multiple sources. Fifteen patients (30%) had single-vessel disease (i.e., the occluded coronary artery), 14 (27%) had 2-vessel disease, and 22 (43%) had 3-vessel disease (mean vessel disease 1.98 ± 0.75). Regarding the anatomy of the donor artery proximal to the takeoff of the collateral vessels, 32 patients had no significant stenosis (average percentage stenosis 3.12 ± 1.76%), 8 had intermediate stenosis (53.75 ± 1.83%), and 11 had significant stenosis (79.1 ± 2.5%). Collateral flow was anterograde in 21 patients, retrograde in 16, and mixed (anterograde and retrograde) in 14.

**Collateral flow and flow reserve:** On TDE, collateral flow in the epicardial occluded artery was anterograde in 28 patients (55%), retrograde in 22 (43%; Figure 3), and mixed in 1, whereas intramyocardial flow, as detected in perfor-
branches, was inverted in 20 patients (40%), normal in 22 (43%), and undetectable in 9 (17%). A direct epicardial collateral connection was visualized in 12 patients (24%), by color TDE (Figure 3), and the corresponding spectral Doppler ultrasound always showed a chaotic, high-velocity (>50 cm/s) flow signal (Figure 3). Collateral-dependent flow reserve was <2 in most of the patients (45 of 51). Collateral flow withdrawal at stress (CFR <1; Figure 4) was observed in 17 patients (30%). CFR significantly increased with the grade of angiographic collateral flow (Figure 5): it was 0.73 ± 0.29 in grade 1, 1.16 ± 0.31 in grade 2, and 1.34 ± 0.49 in grade 3 (F = 5.31, p = 0.008; Figures 6 and 7). Multiple sources of collaterals slightly but nonsignificantly increased CFR (single source = 1.15 ± 0.47, multiple sources = 1.37 ± 0.39; F = 2.21, p = 0.14; Figure 8).

Multivariate prediction of CFR: In the 51 patients with adequate Doppler recordings, CFR was 1.21 ± 0.46 (range 0.25 to 2.27; coefficient of variation 0.38). The prediction of CFR was good (multiple r = 0.65, multiple r² = 0.42, F = 8.28, p <0.0001) on the basis of independent variables considered. However, only percentage stenosis of the donor artery (coefficient −0.0047, t = −2.63, p <0.012), the number of diseased vessels (coefficient 0.27, t = 3.27, p <0.002), and the type of collateral circulation (coefficient 0.21, t = 2.75, p <0.009) did contribute significantly. The multivariate intercept was 0.23. Therefore, to predict CFR in a patient with 30% stenosis of the donor artery (proximal to the takeoff of the collateral branch), 3-vessel coronary artery disease, and Rentrop 2 collateral circulation, the back application of these multivariate results gives an approximate CFR = 0.23 + (−0.0047 × 30 + (0.27 × 3) + (0.21 × 2)] = 1.32. In contrast, in a patient with 70% stenosis of the donor artery, 2-vessel coronary artery disease, and Rentrop 1 collateral circulation, CFR = 0.23 + (−0.0047 × 70) + (0.27 × 2) + (0.21 × 1)] = 0.65. Thus, in this model, the greater the stenosis of the donor artery, the smaller the CFR, whereas

![Figure 3](image1.png)

**Figure 3.** Top panel, coronary angiography of a patient with proximally occluded LAD coronary artery and anterograde flow, supplied by huge collaterals from the right coronary artery. Arrow, the tip of the coronary catheter, placed in the right coronary ostium. Middle panel, a large collateral is visible by color Doppler ultrasound. Flow in the LAD is anterograde (red). Bottom panel, pulsed Doppler wave ultrasound shows high-velocity (1 m/s) continuous collateral flow.

![Figure 4](image2.png)

**Figure 4.** Top panel, coronary angiography of a patient with proximally occluded LAD coronary artery and Rentrop grade 1 collaterals from the right coronary artery. Bottom panel, flow in the LAD measured by transthoracic Doppler ultrasound is retrograde, and CFR is 0.8.

![Figure 5](image3.png)

**Figure 5.** CFR of the 51 patients with chronic total occlusion of the coronary artery grouped according to Rentrop collateral flow classification.
the larger the number of diseased vessels and the greater the collateral grade, the greater the CFR. Hemodynamic variables: Adenosine infusion induced similar changes in all groups of heart rate, which increased \((p < 0.0001)\), and of mean arterial pressure, which decreased \((p < 0.0001)\). Two-way analysis of variance interaction terms were \(p = 0.13\) and \(p = 0.59\) for heart rate and mean arterial pressure changes, respectively. Moreover, there was no statistical difference between rate-pressure product at rest \((6,608 \pm 795\) for collateral grade 1, \(6,816 \pm 1,409\) for collateral grade 2, and \(6,428 \pm 969\) for collateral grade 3) and during adenosine infusion \((6,820 \pm 1,270\) for collateral grade 1, \(6,344 \pm 1,195\) for collateral grade 2, and \(6,460 \pm 1,189\) for collateral grade 3). Variability: To check intraobserver variability, 1 operator duplicated measurements of baseline and adenosine peak diastolic velocities in frozen, digital images from 51 patients. To check interobserver variability, a second observer made the same measurements, unaware of the results from the previous analysis. Variability was computed by calculating the technical error (coefficient of variability) for duplicate velocity measurements and for coronary flow reserve. We used the formula \(\sigma = \sqrt{\frac{\text{sum}(x_1 - x_2)^2}{2(n - 1)}}\), and variability was expressed as a fraction of the mean from all duplicate observations. Intraobserver variability \((2n - 1 = 101)\) for baseline velocity, adenosine velocity, and coronary flow reserve was \(3.49\% \pm 1.02\) \(cm/s\), \(2.90\% \pm 1.10\) \(cm/s\), and \(2.15\% \pm 0.026\) \(U\), respectively. Interobserver variability \((2n - 1 = 101)\) for baseline velocity, adenosine velocity, and coronary flow reserve was \(3.57\% \pm 1.05\) \(cm/s\), \(3.38\% \pm 1.29\) \(cm/s\) and \(2.74\% \pm 0.033\) \(U\), respectively.

Discussion

This study shows for the first time that the function of collateral-dependent circulation is measurable with TDE. Our findings are similar to those recently reported by Werner et al\(^{12}\) by intracoronary Doppler ultrasound, with the difference that they found collateral flow withdrawal mainly in patients with Rentrop grade 2 collaterals rather than grade 1 (Figure 5). We may therefore suggest that a poorly developed collateral circulation is more prone than a well-developed collateral circulation to withdraw its flow support to the occluded coronary artery under stress. Unfortunately, our population contained few patients in grade 1 collaterals to confirm this finding.

Werner et al\(^{12}\) also found small baseline Doppler velocities (approximately 10 \(cm/s\)) in the collateral-dependent circulation in most patients, whereas we consistently...
found normal velocities, similar to those reported by Watanabe et al9 (26.4 ± 9.8 and 28.1 ± 7.4 cm/s, respectively).

Therefore, it appears to be a difference between invasive and noninvasive studies. A possible explanation may be that Werner et al12 included patients with previous myocardial infarctions of the index artery, whereas Watanabe et al9 and we studied only patients without previous infarctions of the myocardium distal to the occluded artery. In addition, there may be some pitfalls in the measurement of collateral flow by intracoronary Doppler flow wire: (1) it is technically demanding, (2) the position of the tip of the wire relative to the occlusion and to the input of collateral flow may be suboptimal, (3) sampling too close to the occlusion site may result in small coronary flow velocity recordings, (4) artifacts may be generated by guidewire motion and inadvertent contact with the vessel wall,13 and (5) placing the Doppler wire requires a previous opening of the vessel with a stiff wire, which creates a new channel, potentially altering collateral flow dynamics. Conversely, TDE measurements are obtained in a more physiologic, no-touch way, in the distal tract of the vessel, in which coronary flow velocity likely recovers to its normal value.

Several investigators have interpreted the reduction of collateral flow at stress in patients with chronic total coronary occlusion as “coronary steal.”12,14 However, because collateral flow toward the occluded artery is actually a gift of the “donor” artery, the accusation of theft is unfair, and the term “coronary flow withdrawal” may be more appropriate.

Recent studies with TDE have shown that LAD occlusion was invariably associated with retrograde flow9 in the index artery and/or in its perforating branches.10 However, angiographic experience teaches that collateral flow may be anterograde, retrograde, or mixed. In fact, in our patients with chronic total coronary occlusion, inverted flow in the distal LAD was found at TDE in only 43% of the patients, whereas preserved anterograde flow was found in 55%. Flow direction was undetectable in the remaining 2%. Similarly, normal intramyocardial anterograde flow direction was preserved in more than half of the cases. Nevertheless, the TDE finding of retrograde diastolic flow, either in the epicardial vessel or in perforating branches, is a useful and specific sign of coronary occlusion. The reasons for the discrepancy between our data and those of others9,10 are not clear, but patient selection, racial difference in chest wall acoustic impedance, and coronary flow sampling site by TDE may play a role. In our population, there was also some discrepancy between the direction of flow when detected at angiography or by TDE. This is mainly due to the high prevalence of mixed flow (n = 14) at angiography that may be classified by TDE as either retrograde or anterograde, because ultrasound still has no panoramic view of the coronary tree.

An additional peculiar finding of the collateral circulation detected by TDE is the high blood flow velocity in the collateral pathways (Figure 3). In fact, collateral vessels have an intrinsic resistance to flow that is comparable to a 70% coronary artery stenosis.15 This resistance may produce flow acceleration at rest (as a mechanism to keep the coronary output constant) and may prevent the adequate increase of flow at stress in the recipient artery (CFR < 2), as found in most of our cases with chronic total coronary occlusion. Interestingly, coronary flow reserve < 2 also characterizes patients with significant coronary artery stenosis.16,17 Unfortunately, direct imaging of the collateral pathways, using the available TDE technology, is feasible in only 1/4 of the cases.

A direct relation between the resistance of the donor artery and the ability of the collateral-dependent circulation to increase flow during vasodilation has been found using intracoronary Doppler ultrasound and pressure wires.12,14 In our study, we did not measure the resistances but evaluated the degree of the stenosis of the donor coronary artery proximal to the collateral takeoff, which inversely correlated with the CFR (the greater the stenosis, the smaller the CFR). An interesting new finding of our study is that CFR proportionally increased with the number of diseased vessels, suggesting a chronic stimulus to create more connections within the myocardium in case of diffuse atherosclerotic narrowing of the epicardial coronary arteries.

1. Hozumi T, Yoshida K, Akasaka T, Asami Y, Ogata Y, Takagi T, Kaji S, Kawamoto T, Ueda Y, Morioka S. Noninvasive assessment of...


