

REVIEW PAPER

Non-invasive assessment of coronary flow and coronary flow reserve by transthoracic Doppler echocardiography: a magic tool for the real world

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Transthoracic Doppler echocardiography, introduced in the echo-lab in recent last years, to measure coronary flow and coronary flow reserve, is a very attractive tool, totally non-invasive, and easily available at bedside. This review summarizes the actual possibilities of this tool, its multiple potential clinical applications and diagnostic insights, and its arising prognosis value, in coronary artery disease as in various settings affecting the coronary microcirculation.

Introduction

Several tools have already measured coronary flow and coronary flow reserve (CFR), including coronary sinus thermodilution, cardiac nuclear imaging, inert gas washout method, cardiac magnetic resonance, and intracoronary Doppler flow wire, for decades.¹ However, these methods, although helpful for research, have limited clinical applications, being complex, time-consuming, expensive, not easily available, or invasive. Transthoracic Doppler echocardiography (TDE), to measure coronary flow and CFR, is non-invasive, easily available at bedside, not expensive, and without radiation exposure, with multiple potential clinical applications.^{2–86} This review describes why the echo-lab should reconcile clinicians to CFR, which is dimensionless, and defined as the maximal increase in coronary blood flow (by using a strong coronary vasodilator) above its basal level for a given perfusion pressure.⁸⁷

Technical considerations

The best sampling site of the coronary flow, for assessing the functional significance of a stenosis, is the distal tract of the vessel which could be easily obtained with TDE. Proximal to the stenosis CFR may be normal as there are side branches between the sampling site and the stenosis, which reflects

perfusion in normal territories. Furthermore, at the level of the stenosis, coronary flow accelerates to compensate for the lumen loss, which prevents reliable measurement of CFR.⁴⁶ Indeed, the resting flow aliasing at the site of the stenosis has already been assessed using TDE, to diagnose coronary stenosis, by comparing the adjacent segments.^{20,70,71} However, several factors, apart from the stenosis, could modify baseline coronary flow velocity (see below), and long segments of the tree should be visualized to detect the site of a stenosis, which is time-consuming.^{70,71}

The mid-distal part of the left anterior descending coronary artery (LAD) could be visualized^{2–19,36} using TDE, in a modified low parasternal view, with the patient in the left lateral decubitus position. Briefly, from the short-axis parasternal view, the probe slides laterally in order to visualize the anterior interventricular groove. The artery is searched using colour Doppler flow mapping guidance, with a velocity range defined from 12 to 16 cm/s. A slight anticlockwise rotation of the transducer to obtain the best LAD long-axis view is then performed (*Figure 1*). Blood flow velocity is measured by pulsed wave Doppler echocardiography, using a sample volume of 3–4 mm, placed on the colour signal in the LAD, which is oblique. The angle correction is redundant given that CFR is the ratio between hyperemic and baseline flow velocity, and it is not affected by the actual flow velocity. However, the angle has to be kept as small as possible (below 40°). A more distal part of the LAD can be recorded in a modified three-apical chamber view.

The posterior interventricular descending artery (PDA) is visualized from a modified apical two-chamber view

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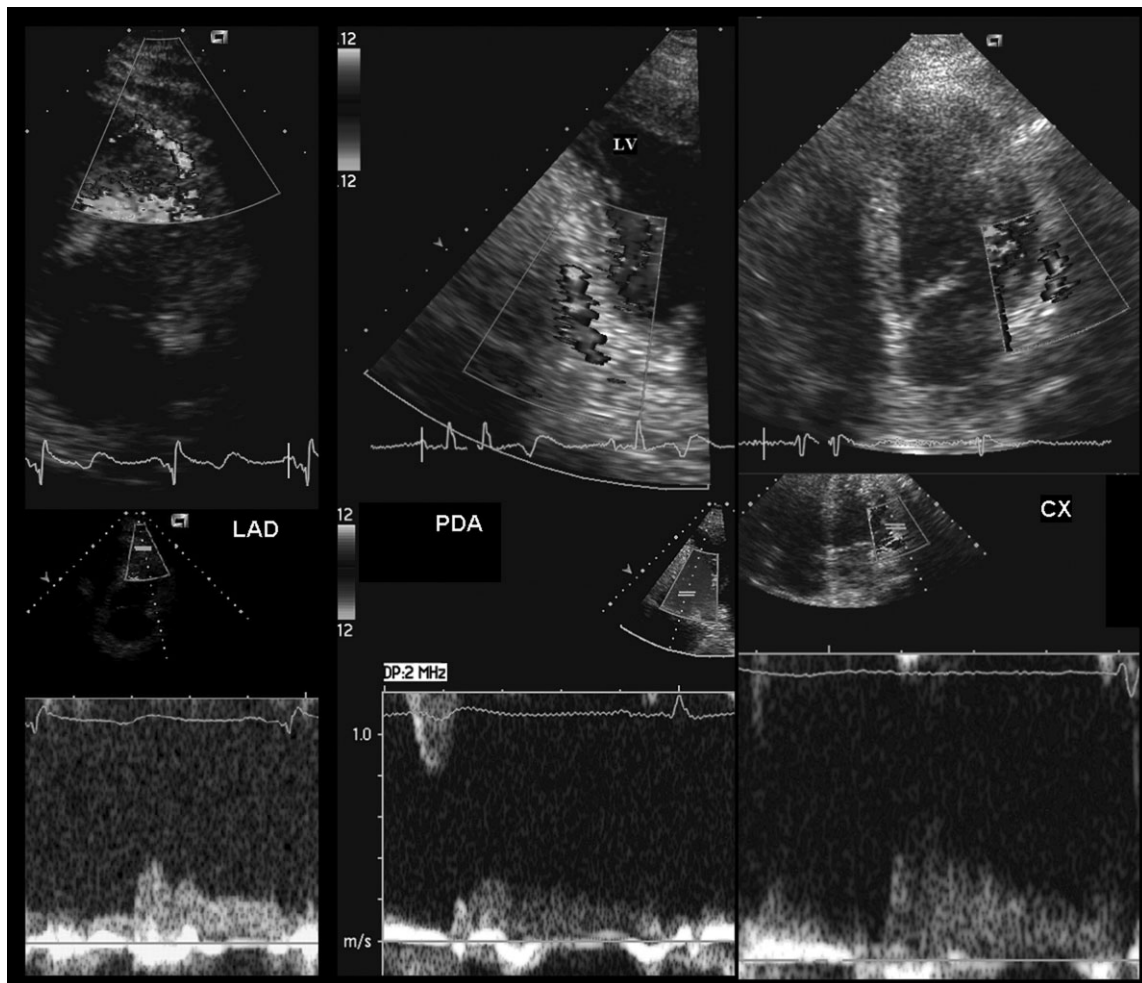


Figure 1 Illustration of artery visualization in each coronary territory using colour Doppler flow mapping, the mid-distal part of the LAD in a modified parasternal view (in left), the PDA in a modified two-chamber view (middle), and the CX artery in the modified four-apical view (in right) could be visualized. In each artery, the flow is biphasic with diastolic predominance (bottom).

showing the posterior interventricular groove, adjacent to the ostium of the coronary sinus.^{21–27} The distal part of the circumflex coronary artery (CX) (or its marginal branches) is searched on the epicardial layer of the basal and mid-portion of the left ventricular lateral wall in the apical four-chamber view.^{28,29} These arteries are searched using colour Doppler mapping guidance with the same methodology as for LAD (Figure 1).

The pattern of coronary flow velocity is biphasic with a large diastolic predominance (Figure 1). However, it is sometimes difficult to obtain complete Doppler spectral envelopes throughout the cardiac cycle as a result of cardiac motion. Therefore, only the diastolic component of the flow is usually measured with the TDE.^{36,39,46,52}

Blood flow velocity measurements are performed offline by contouring the spectral Doppler signals, using the integrated software package of the ultrasound system. Final values of flow velocity represent an average of three cardiac cycles.

TDE-CFR is defined as hyperemic diastolic mean (or peak) flow velocity divided by baseline flow velocity (Figures 2 and 3). It is important to underscore that during administration of the vasodilating agent, the transducer probe is in the same position as baseline, and machine settings including

size of sample volume and velocity scale are not changed. Other than stenosis, several factors could influence baseline flow velocity including myocardial oxygen demand, vasodilator or vasoconstrictor drug, vasomotor tone, regional left ventricular mass,⁸⁸ ageing,⁸⁹ and the angle between the Doppler beam and the artery. Hyperemic coronary flow depends on total coronary resistance and is linearly correlated to coronary perfusion pressure. The mean time required to complete a CFR test is around 10–15 min.

A high-frequency transducer (5–7 MHz) is usually used to visualize the mid-distal LAD which is close to the chest.^{2,3,6} However, a low multifrequency transducer (3.5 MHz) with a second harmonic capability is also useful with contrast.^{4,36,39,61} The PDA and the CX are profound and are visualized with a low-frequency transducer.^{21–29}

Vasodilators for CFR measurement

The most commonly used vasodilator to assess TDE-CFR is adenosine. Given its short half life (10 s) and rapid onset of action, it allows CFR measurements more rapidly than other vasodilators.⁹⁰ Furthermore, because adenosine acts mainly at the level of the microcirculation and does not alter significantly the diameter of the coronary artery⁹¹

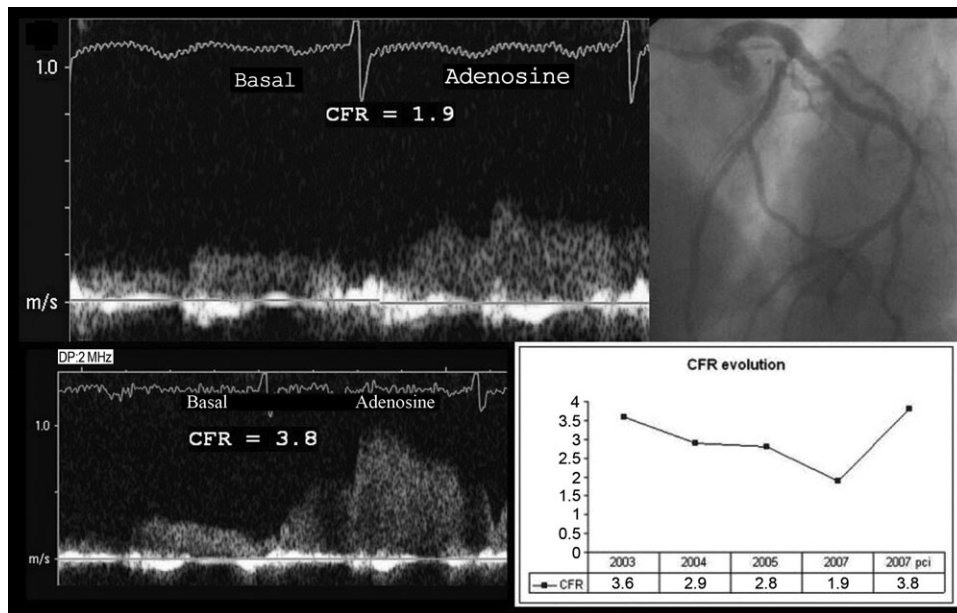


Figure 2 Illustration of TDE-CFR with adenosine in the LAD artery. Illustration of a low TDE-CFR in the distal LAD in a patient with atypical chest pain who underwent LAD angioplasty in 2003 and was followed-up with TDE-CFR. In upper left, CFR has decreased dramatically (CFR = 1.9) compared with previous measurements, as it is summarized in the graph in bottom right. The coronary angiography shows a significant proximal LAD stenosis (upper right). After successful angioplasty, CFR improves considerably (CFR = 3.8, bottom left).

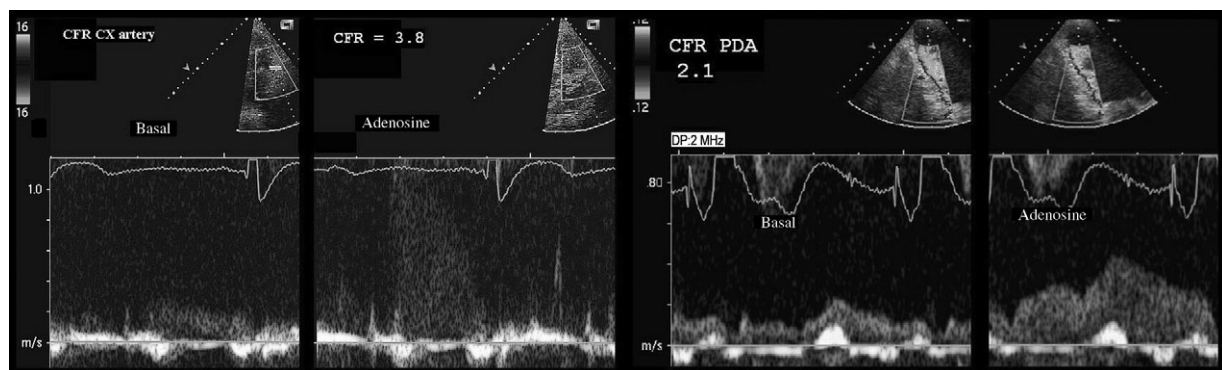


Figure 3 Illustration of TDE-CFR with adenosine in the CX and PDA arteries. In left, illustration of a normal TDE-CFR in the distal CX (CFR = 3.8) in a patient with normal angiographic CX territory. In right, TDE-CFR is 2.1 in the PDA artery in an asymptomatic patient with coronary risk factors and an intermediate stenosis of the right coronary artery.

where the pulsed wave Doppler sample is positioned during CFR measurement, the relative changes in velocity can be used as a surrogate measures of flow (product of velocity and cross-sectional area of the vessel).⁴⁶ However, adenosine, although safe, is contraindicated in bronchial asthma or poorly tolerated in others due to side effects.⁹² Furthermore, intravenous adenosine at doses usually used to assess CFR (0.14 mg/kg/min) does not produce a maximal hyperemic flow in minority of patients.⁹⁰ In this subset of patients and others, intravenous dobutamine could be a good alternative to assess CFR during dobutamine stress echocardiography (DSE).³⁷⁻³⁹ CFR with DSE is obtained by calculating peak diastolic flow velocity divided by baseline diastolic flow velocity (Figure 4).³⁷⁻³⁹ However, dobutamine increases coronary flow via different mechanisms as adenosine,^{93,94} and CFR during DSE is not widely used. High-dose (0.84 mg/kg) intravenous dipyridamole induces a CFR to the same extent as intravenous adenosine, whereas a standard dose

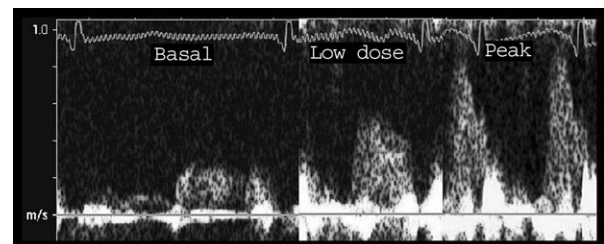


Figure 4 TDE-CFR with dobutamine. The flow is recorded in the distal LAD during DSE. There is a progressive increase of the flow velocity during DSE with a final ratio (between peak and baseline) of 3.6 in a patient with normal wall motion response with DSE at 100% of the predicted heart rate.

(0.56 mg/kg) is less efficient.⁴⁰ However, dipyridamole is less compelling and flexible than adenosine given its longer half-life for similar adverse effects. Nonetheless, it

is possible to assess wall motion simultaneously to coronary flow during dypiridamole infusion^{41–43,68,77} as during dobutamine infusion.^{37–39}

Feasibility and variability of TDE-CFR

The feasibility of TDE-CFR for LAD artery is very high, with more than 90% in experienced hands,^{2,4,5,7,36,41} and nearly ~100% with the use of intravenous contrast agents.⁵ Indeed, even in difficult cases (~10%), the use of low dose of an intravenous contrast agent (one or repeated bolus of 0.1 ml of Sonovue) would help to improve visualization of the colour Doppler signal and/or to obtain clear spectral Doppler signals in the artery. The feasibility is less in the PDA artery, between 54 and 86%,^{21–27} due to technical limitations.

The measurements of TDE-CFR, in the LAD as in the PDA arteries, are closely correlated with invasive measurements using a Doppler flow wire.^{3,4,23,24,44,45} The feasibility of TDE-CFR in the circumflex artery in our experience is more challenging given the particular anatomy of this artery and the poor resolution of the lateral wall. In fact, the distal tract of the circumflex artery cannot be sampled easily unless it is the PDA. However, in two recent Japanese reports, the feasibility compared to nuclear cardiac imaging was 72 and 73%,^{28,29} respectively.

The interobserver and intraobserver reproducibility of TDE-CFR have been described in various studies, not exceeding ~5 and 5%, respectively.^{36,39,61} However, few data reported the intra-individual variability of TDE-CFR.^{8,9,47,48,61} In a series of 10 volunteers who repeated TDE-CFR 3 weeks apart, and in 11 patients who repeated the test 20 min apart, we found that the between-measure interval of agreement using the Bland-Altman method was from –10 to +12% and –9 to +11%, respectively, indicating that individual variability of TDE-CFR is low with adenosine.⁶¹ One study demonstrated that in 14 patients the variability in the PDA is also low with adenosine.²³

Comparison with other stress tests

The accuracy of TDE-CFR with adenosine is not limited by concurrent medication such as beta-blocking agents, the patient's ability to exercise, baseline wall motion, or ECG abnormalities.⁴⁶ It is less time-consuming, low cost than other stress tests, easily and serially available, and without irradiation. In contrast to wall motion analysis, during stress echo, which is qualitative or semi-quantitative and sometimes difficult to interpret, TDE-CFR provides a quantitative interpretation of a Doppler signal (the magic number, the measure of CFR). It is accurate for detecting single-vessel disease but the assessment of multivessel disease is more challenging compared with other stress tests, because the feasibility is far from being equivalent for each coronary territory.

The magic number

The cut-off value of 2 of CFR for detecting significant epicardial coronary stenosis or to predict ischemia in the underlying territory has been demonstrated in various studies.^{2,5–7,21,36,49,64} A significant coronary stenosis induces a very high proximal resistance to flow which is otherwise mainly

determined by the coronary microcirculation in the absence of epicardial coronary stenosis. Even in patients with various coronary risk factors which could influence the coronary microcirculation, the cut-off value of <2 of CFR is precise with a high sensitivity (90%) and specificity (93%) for detecting significant LAD stenosis.⁴⁹ However, there is no clear cut-off value when dealing with the coronary microcirculation.^{9,50–61} In patients with truly normal epicardial arteries, TDE-CFR explores the coronary microcirculation, under stable haemodynamic conditions.^{9,50–61} In this setting, the mean value of CFR varies widely in different studies according to the population studied,^{9,48,51,52} the presence and extent of risk factors for vascular dysfunction,^{52–55} the concomitant medical therapy,^{48,74,75} and the habits such as coffee or tea intake,⁵⁶ or even cigarette smoking⁵⁷ and the type of meal⁵⁸ before the test. Ageing is also an important factor affecting CFR by increasing baseline flow velocity without change in hyperaemic flow velocity.⁸⁹ For example, the mean value of CFR is 5.9 ± 1 in endurance athletes,⁵⁹ 4.5 ± 0.9 in healthy male subjects with a mean age of 26 years,⁵⁶ and 3.3 ± 0.4 in elderly people with a mean age of 66 years.³⁶ In women without coronary risk factors, sexual hormones also influence CFR which increases significantly during the follicular phase than the menstrual phase [4.8 ± 0.4 vs. 3.7 ± 0.8] and decreases after the menopause.⁹ In a study population, the comparison of CFR before and after an event, or before and after a therapeutic intervention, or to a control group is the usual way to interpret the value of CFR. For example, in patients with aortic stenosis and normal coronary angiogram, undergoing aortic valve replacement, the mean CFR is 1.8 ± 0.5 , and 6 months after surgery it increases significantly to 2.6 ± 0.7 .⁶⁰ In patients with tako-tsubo cardiomyopathy, CFR is transiently impaired with a mean value of 2.2 ± 0.3 at the acute phase, and 2.9 ± 0.3 after the recovery ($P < 0.01$).⁶¹ Acute cigarette smoking in healthy young smokers induced marked reduction in CFR from 3.6 ± 0.6 to 2.8 ± 0.7 .⁵⁷ In patients with pre-hypertension, TDE-CFR is impaired compared to controls but higher than hypertensive (2.5 ± 0.5 vs. 2.9 ± 0.5 vs. 2.2 ± 0.5 , respectively).⁵² In the subgroup of patients with angina-like chest pain and with no evidence of obstructive epicardial coronary atherosclerotic plaques (syndrome X), a reduction of TDE-CFR has been shown, compared to a control group, suggesting that coronary microvascular dysfunction is a plausible cause of angina (microvascular angina).⁶³

Indications for coronary flow and CFR by TDE

A lot of potential indications for non-invasive evaluation of coronary flow and CFR have been demonstrated in the previous years in various settings, and Table 1 presents these various conditions.

Intermediate coronary stenosis

Evaluation of patients with angiographic intermediate coronary artery stenosis is challenging. Neither visual assessment of an angiogram nor quantitative coronary angiography can accurately predict the significance of most intermediate stenoses (50–70%).⁹⁵ As resting coronary flow is preserved until severe narrowing occurs (85% stenosis), CFR declines earlier when stenosis is still moderate (40–50%). This progressive decrease in vasodilator reserve resulting in reduction in

Table 1 Various settings in which TDE-CFR and flow velocity measurements can be useful

Measurement of flow velocity
Diagnosis of reperfusion in the acute phase of myocardial infarction ^{11,13}
Evaluation of no reflow after recanalization of myocardial infarction ^{15,17,18}
Diagnosis of severe coronary stenosis (the diastolic component of the flow D is decreased compared to the systolic component S; ratio D/S ^a) ^{10,73,86}
Diagnosis of upstream coronary occlusion (reverse diastolic flow) ^{31–33}
Evaluation of intra-aortic balloon pumping ⁶⁷
Evaluation of coronary bypass graft ^{34,35}
Understanding the physiology and pathophysiology of various conditions ^{76,83}
Measurement of TDE-CFR
Diagnosis of significant coronary stenosis (CFR < 2): sensitivity ~89% and specificity ~93% for LAD ^{2,5,21,49} and sensitivity ~88% and specificity ~90% for PDA ^{21,25–27}
Follow-up after coronary angioplasty ^{8,44,64}
Evaluation of coronary stenosis of intermediate severity ^{36,65}
Assessment of viability, prediction of improvement of regional left ventricular function after myocardial infarction ^{14,16b}
Evaluation of coronary bypass graft ^{34,35}
During stress echocardiography: coupling the perfusion and function (dobutamine or dipyridamole) ^{37–39,41–43,68}
Evaluation of the coronary microcirculation
Hypertension, cardiomyopathies, valvular heart diseases ^{12,48,51,52,55,60,61,72}
Understanding the physiology and pathophysiology of various conditions ^{9,53,56–59,63,81,82,84}
Evaluation of a therapeutic intervention ^{48,60,69,74,75}
Prognosis-risk stratification (dilated cardiomyopathy, cardiac transplantation, coronary artery disease) ^{68,77–79}

^aD/S < 1.5–1.6 when left ventricular systolic function and size are normal and D/S < 1.8 in the setting of left ventricular dilatation and systolic dysfunction (all in sinus rhythm).

^bCFR > 1.5, 24 h after reperfusion predict recovery of regional LV function with a sensitivity of 91% and specificity of 94% in a study of 29 patients with anterior myocardial infarction.

hyperaemic blood flow with increasing stenosis severity has been demonstrated in animal models and human beings.^{87,96} TDE-CFR is a very useful tool to assess the functional significance of such stenoses and for deferring revascularization (when CFR > 2), given its high negative predictive value to detect ischemia, either with DSE (97%)³⁶ or with nuclear cardiac imaging.⁶⁵ In patients with intermediate stenosis, TDE-CFR reduction is located upstream in the classical ischemic cascade, and it can well detect stenosis that is unable to induce wall motion abnormalities during stress echo.⁶⁸ In patients with a wide range of stenosis, other studies have demonstrated the usefulness of TDE-CFR for detecting significant coronary stenosis, compared to nuclear perfusion imaging,⁷ wall motion assessment,^{41,42} and invasive Doppler flow wire.^{3,4,6,23} At the end of the spectrum, coronary sub-occlusion could also be detected by TDE showing a damped CFR.⁶⁶

Angioplasty and restenosis

When TDE-CFR is <2 during follow-up after angioplasty, the restenosis in the LAD is detected with high sensitivity (from

78 to 89%) and specificity (from 90 to 93%).^{8,44,64} These values are identical to those obtained with stress tests such as stress echocardiography or nuclear perfusion imaging. The cut-off value of 2 for CFR at a time point is useful but probably less sensitive than its evolution over time to detect restenosis after angioplasty or the progression of an intermediate stenosis in a given patient. Like other tools, such as the mean gradient in patients with valvular prosthesis, a reference value of CFR should be established in a given patient to assess the follow-up in this setting.

Acute coronary syndrome, myocardial infarction

Few studies have tested the usefulness of TDE-CFR to predict recovery of left ventricular regional function in patients with reperfused anterior myocardial infarction (MI).^{14,16} However, TDE-CFR has not really been validated in this situation, and the best time to perform TDE-CFR after reperfused acute MI is questionable given the dynamic and complex anatomic and functional change that occurred in the coronary microcirculation in this setting. A particular coronary flow pattern with a short diastolic deceleration time (DDT) of flow velocity, an early systolic retrograde flow, and diminished systolic anterograde flow is suggestive of the no reflow phenomenon, early after reperfused acute MI (Figure 5).^{15,17,18} Immediately after the successful primary angioplasty in patients with first anterior MI (<24 h), a DDT of <185 ms detects the no reflow better than the TIMI frame count, the absence of ECG ST resolution, and peak creatine kinase-MB in one study,¹⁸ and a DDT of >600 ms on day 1 predicts improvement of regional LV systolic function at 1 month in another study.¹⁵ A systolic flow reversal (≥ 10 cm/s and ≥ 60 ms) identified 48 h after reperfusion in a recent report has a 100% positive predictive value to detect irreversible myocardial damage, and it seems more specific than DDT and peak creatine kinase.¹⁷ However, recent papers criticized the importance of reduced DDT and systolic flow reversal to identify no reflow.^{46,97} According to these papers, this pattern might be the result of wall motion artefact. The recanalization of intramural perforators emerging from the LAD reflects adequate reperfusion in patients with acute MI, and the recanalization score is the best predictor of recovery of LV function, in a multivariate model including the TIMI frame count.¹¹

Bypass grafts

The patency of coronary bypass grafts and their anastomosis could be easily evaluated with TDE using various views coupled with colour Doppler flow mapping (Figure 6).^{34,35} The flow pattern of the distal part of a graft is usually biphasic with a diastolic predominance (similar to a native coronary artery). In cases of graft dysfunction, the diastolic component is reduced or disappears. The flow reserve gives complementary information about the status of the graft.³⁴ However, as several factors including a competitive flow from the native artery could influence measurements performed in the graft alone, and may be misleading, the best sampling site to explore the entire arterial conduit is the distal part of the native coronary artery downstream to the anastomosis of the graft.³⁵

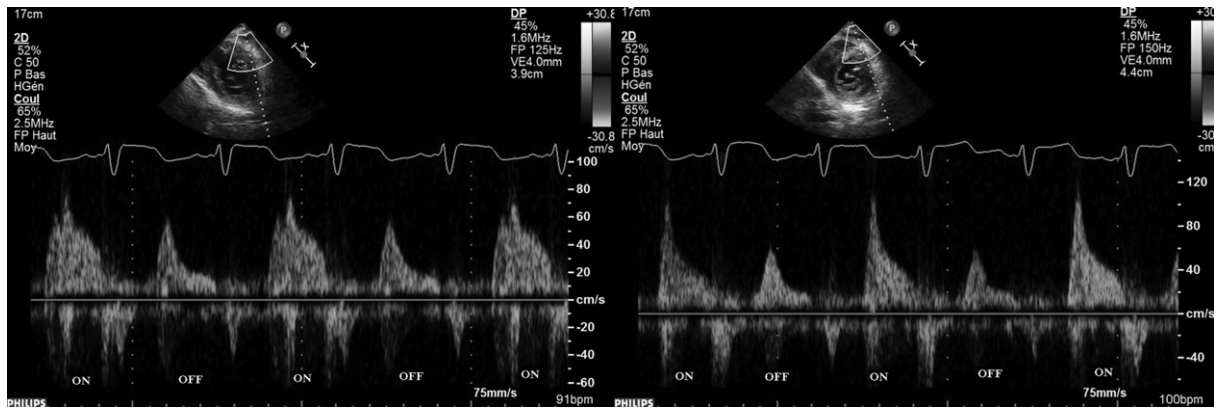


Figure 5 Illustration of the coronary flow pattern in a patient with an intra-aortic balloon pumping and a no reflow. Phasic coronary flow velocity (CVF) during 1:2 balloon pumping in a 70-year-old woman with reperfused anterior myocardial infarction complicated by ventricular septal rupture. Diastolic CVF is enhanced during balloon inflation as seen in the first, third, and fifth beats (left and right panel). However, in left panel, the balloon is inflated too late as suggested by the notch between diastolic deceleration flow and augmentation flow. In right panel, after optimal timing of balloon inflation: the diastolic flow augmentation coincides with the upstroke of diastolic acceleration flow velocity. In both panels, a no reflow is strongly suggested by the coronary flow pattern with a rapid deceleration of the diastolic component and an early systolic retrograde flow.

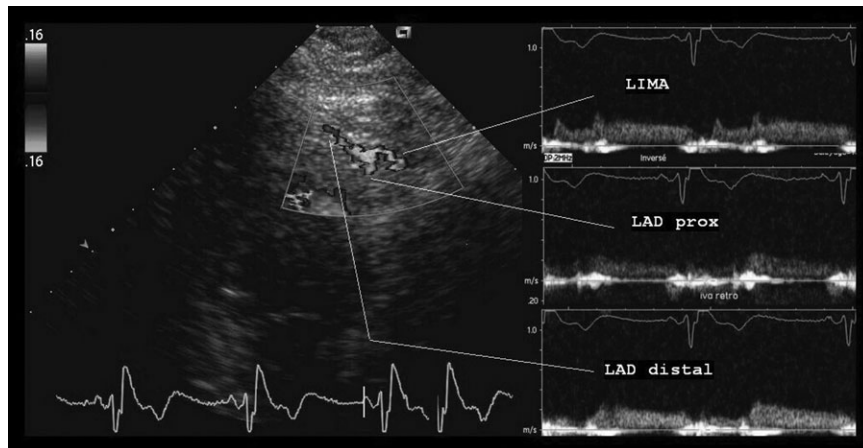


Figure 6 Left internal mammary artery graft to the LAD. Illustration of the distal part of a left internal mammary artery graft to the LAD and its anastomosis visualized with color Doppler flow. The respective flow velocities recorded with pulsed wave Doppler in the distal graft and in the distal LAD show a normal flow pattern. In the LAD proximal to the anastomosis, there is a retrograde flow as the proximal LAD is occluded.

Prognostic value of CFR

The prognostic impact of TDE-CFR is emerging as recent studies relied on the bad outcome in patients with low CFR measured in the LAD with different cardiac diseases.^{68,77-79} A reduced CFR (<2 , using dipyridamole) is an independent predictor of unfavourable outcome in patients with non-ischemic dilated cardiomyopathy, during a median follow-up of 22 months.⁷⁷ A reduced TDE-CFR (<2.6 , using adenosine) is the main independent predictor of major adverse cardiac events (relative risk = 3.1) in a series of 66 heart transplantation patients, during a mean follow-up of 19 ± 5 months.⁷⁸ In 329 patients with known or suspected coronary artery disease, a reduced CFR (≤ 1.92 using dipyridamole) is an independent indicator of a worse prognosis despite having a negative stress echocardiography by wall motion criteria.⁶⁸ The 36 months event-free survival is 68% vs. 98% for patients with a preserved TDE-CFR. In patients with an angiographic LAD stenosis of intermediate severity (50–70%), a TDE-CFR of >2 confers a

good prognosis during a mean follow-up of 15 months.⁷⁹ To summarize, the assessment of TDE-CFR in these different settings can be useful in risk stratification, but whether improving CFR in such diseases and other with coronary microvascular dysfunction would influence positively the prognosis remains to be established. Furthermore, there is no general agreement about the prognostic value of reduced CFR in patients with angiographically normal coronary arteries.^{46,98} The coronary flow velocity pattern is also of prognostic value. Twelve to 48 h after reperfused first anterior MI, DDT of ≤ 600 ms predicts not only LV remodeling, but is an independent predictor of in hospital complications.⁸⁰

TDE-CFR at bedside to reconcile the researcher and the clinician

Non-invasive coronary flow and CFR is highly feasible, reproducible, accurate, and easily available at bedside, after a

period of training. It has been performed in a lot of situations, helps to understand the pathophysiologic insight, and is useful in clinical practice in various settings as coronary artery disease.^{51,52,61,72,77,81-85} It compares favourably with invasive Doppler flow wire,^{3,4,23,24,44,45} nuclear cardiac imaging,^{7,28,47} stress echocardiography,^{36,62} and myocardial contrast echocardiography.^{63,99} As CFR could improve with various therapy or lifestyle change,^{9,48,51,54,56,60,74,75} increasing CFR would be a new target for treatment. Apart from the difficulty to assess multivessel disease, the anatomic information about the coronary tree is not routinely available with current technology. More technical advancements on ultrasound machine and transducer technology allow in routine practice direct visualization of the coronary plaque and its content; emergence of new vasodilating agents easier to use and with less adverse effects,⁹² increase the feasibility of TDE-CFR (hyperventilation caused by adenosine could prevent reliable measurement of CFR in some cases); and the development of three-dimensional echocardiography, analyses the coronary artery anatomy¹⁰⁰ and its vasodilating capacity,¹⁰¹ all of these future developments are the next step to improve and expand this fascinating tool to all the coronary territories.

Conflict of interest: none declared.

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