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Current opinion

# Coronary flow: a new asset for the echo lab?

**Paolo Voci[a,*], Francesco Pizzuto[a], Francesco Romeo[b]**

[a] *Institute of Cardiology, University of Rome, ''La Sapienza'', Rome, Italy*
[b] *Institute of Cardiology, Department of Internal Medicine, University of Rome, ''Tor Vergata'', 00100 Rome, Italy*

## Introduction

Non-invasive imaging of coronary blood flow by transthoracic Doppler echocardiography is an emerging diagnostic tool to study the left anterior descending (LAD)[1–11] and posterior descending (PD) coronary arteries.[12–15] With this new clinical application of echocardiography, we can directly measure changes in coronary flow velocity reserve (CFVR) at the very beginning of the ischaemic cascade, instead of looking at the consequences of ischaemia on myocardial contraction, as it is routinely done with dobutamine stress echocardiography and other stress tests.

Since its introduction in 1997,[1,2] it has been clear that transthoracic coronary Doppler ultrasound could provide useful information in the diagnosis of coronary artery disease (CAD)[3–15] follow-up of percutaneous coronary interventions,[16–21] coronary recanalization in acute myocardial infarction (AMI),[22–26] and coronary microcirculation.[27–33].

The importance of measuring CFVR in routine clinical practice has been anticipated over 20 years ago by the physiologist Carl Honig: ''One of the principal tasks of a physician is to estimate the patient's reserves... Prognosis is an estimate of the rate at which this reserve may disappear, and therapy is designed to increase this reserve and to prevent or eliminate stresses that might compromise it''.[34] With this teaching in mind we have planned our seven-year work on transthoracic coronary Doppler ultrasound. In this review we will focus on the main clinical applications of transthoracic coronary Doppler ultrasound, and discuss the advantages, limitations and technical pitfalls of the method.

* Correspondence to: Paolo Voci, Institute of Cardiology, University of Rome, Via San Giovanni Eudes, 27, 00163 Rome, Italy. Tel.: +39 06 6615 8122; fax: +39 06 2090 0382.
*E-mail address:* voci@uniroma1.it (P. Voci).

## Before holding the probe

Some basic yet simple concepts should be assimilated before beginning this new technique, in order to reduce errors and misinterpretations.

### The window

Coronary blood flow velocity should be measured from an apical window by pulsed Doppler ultrasound under colour-coding guide. The best long axis view in colour flow imaging should be obtained to maintain a <30° angle between flow and the Doppler beam. Correction for the theta angle may be used,[5–7] but it is a redundant operation, since CFVR is not an absolute, but a derived value (ratio between hyperaemic and baseline coronary blood flow velocity).

### Proximal or distal?

The sampling site is critical for correct coronary flow measurements because the results may be very different when CFVR is measured proximal to the stenosis, at the level of the stenosis or distal to it.

Proximal to the stenosis, CFVR may be perfectly normal, as it reflects perfusion in normal territories (Fig. 1). It may be altered only in the rare case there are no side branches between the sampling site and the stenosis. This is one of the reasons why transoesophageal echocardiography, which allows imaging of the left main and the very initial tract of the LAD,[35] has been abandoned for the study of CFVR in CAD.

At the level of the stenosis, baseline coronary flow accelerates to 40–50 cm/s or more[21] to compensate for lumen loss and maintain the coronary output constant. This accelerated baseline flow prevents reliable calculation of CFVR.

Coronary flow should therefore be measured at the distal tract of the coronary artery for three main

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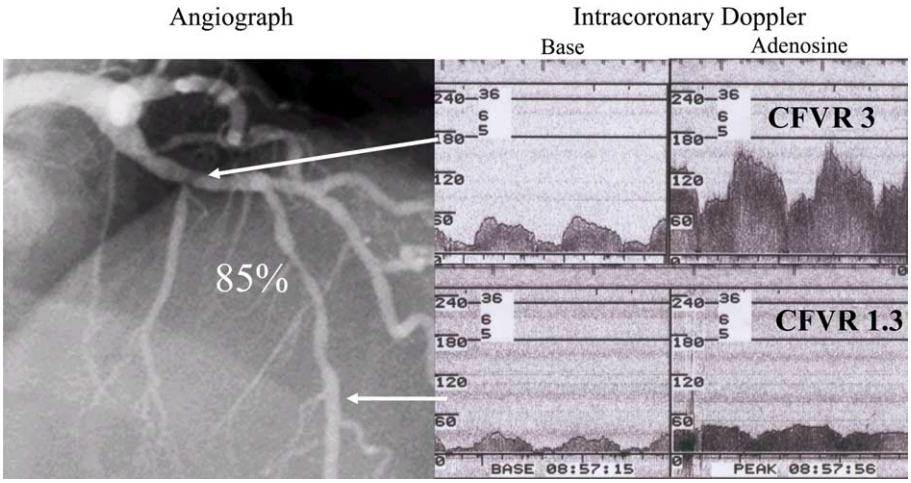


**Fig. 1** The importance of measuring CFVR distal to the stenosis. Before the stenosis CFVR measured by intracoronary Doppler ultrasound is normal (upper panels) whereas distal to the stenosis it is significantly reduced (lower panels).

reasons: (1) The effect of flow acceleration from a proximal or mid coronary stenosis is minimal; (2) The cumulative effect of sequential stenoses can be assessed, because all end in alteration of distal flow; (3) Compared to the proximal and middle tract of the coronary artery, the capacitance of the distal tract is minimal, and changes in velocity best reflect changes in vital, intramural flow.[36]

## Baseline flow velocity

Myocardial metabolism is characterised by a high baseline (often inappropriately called ''resting'') metabolic state, and very steep intramyocardial oxygen gradients. Therefore, the myocardium can incur only a small oxygen debt, and myocardial oxygen consumption is strictly flow-dependent. For this reason, baseline coronary blood flow may be readjusted on a beat-by-beat basis, and baseline coronary flow velocity may change from one beat to the other of even 5–10 cm/s. It is therefore important, in case of significant variability of baseline flow velocities, to average values obtained from at least three beats, in order to prevent misinterpretations.

Elevated resting flow velocities may occur in several cardiac and non-cardiac conditions increasing oxygen consumption at rest, including tachycardia, anaemia, hyperthyroidism, severe left ventricular hypertrophy, valvular diseases, etc. Even anxiety, which is common in patients undergoing a diagnostic ''coronary'' test, may increase baseline coronary flow velocity due to an enhanced sympathetic drive.

On the other hand, coronary vasodilators such as nitrates or calcium antagonists increase the diameter of the epicardial artery and reduce baseline flow velocity. $\beta$-Blockers may also reduce baseline coronary flow velocity, mainly by decreasing heart rate and blood pressure, and hence oxygen consumption.

## The magic couple: adenosine and Doppler

Hyperaemic flow is obtained by venous infusion of adenosine (140 $\mu$cg/kg/min), a pure and strong dilator of the coronary microcirculation, having little or no effect on the epicardial artery.[37] Coronary flow is the product of velocity and the cross-sectional area of the vessel. Because the diameter of the epicardial artery does not change significantly during adenosine infusion[37] (Fig. 2), velocity can be used as an acceptable surrogate of flow. This is an important prerequisite for any drug used to study CFVR, because according to the Poiseuille's law, even small variations in calliper may cause large variations in velocities and hence in flow. Compared to dipyridamole, adenosine is more potent and more versatile, as it can be repeatedly infused just after coronary flow velocity returns to baseline.

## Safety

The safety profile of adenosine is excellent even in patients with AMI,[38] if used appropriately. In this view, we suggest to infuse adenosine for no more than 90 s, for three main reasons: (1) the maximal hyperaemic effect is already reached at 30–60 s;[39] (2) short infusion times prevent the development of myocardial ischaemia, which may occur for more prolonged infusion; (3) the costs are significantly reduced.

Small bolus injection is safe and effective. The adenosine dose may actually be reduced to a minimum of 2.5 mg bolus injection, which produces an increase in CFVR similar to that obtained by 3 min venous infusion, and has no significant side-effects,[40] with important practical and economical implications. In our series of more than 1000 patients studied with either short infusion or bolus injection, including those with acute coronary syndromes, we had only one episode of transient atrial fibrillation in a patient with poor left ventricular function and

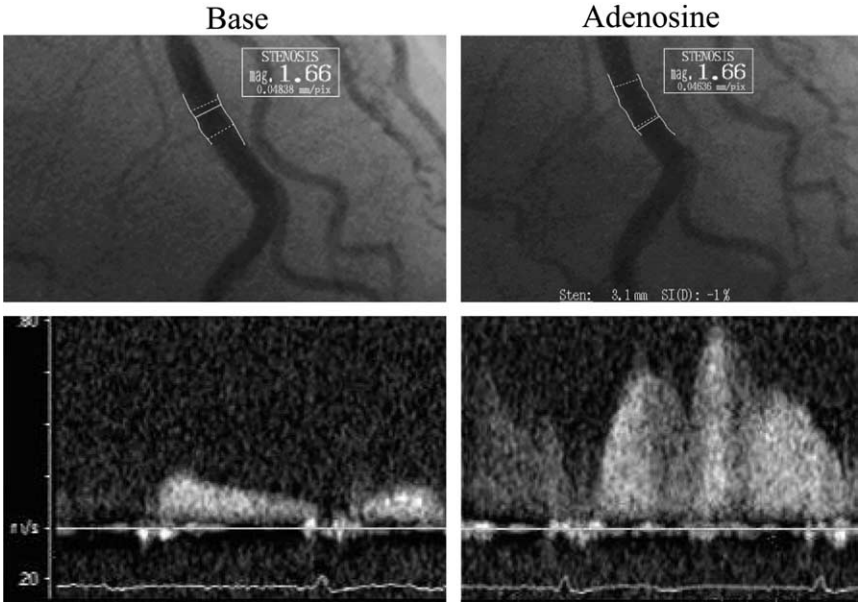


**Fig. 2** Adenosine is the drug of choice to measure coronary flow velocity reserve by Doppler, because it is a pure microvascular dilator and does not significantly alter the calliper of the epicardial coronary artery. Therefore, relative changes in velocity can be used as surrogate measures of flow.

recurrent episodes of paroxysmal atrial fibrillation. Nevertheless, some authors still use infusion times of up to 5–6 min,[5–7] which may cause significant side-effects, and may result in myocardial ischaemia in critical patients.

### Is there a role for systole?

It may be difficult to record both diastolic and systolic flow in the same cardiac cycle in all patients, because rotational and translational movements of the heart displace the coronary artery from the ultrasound beam in systole. However, compared to the diastolic, systolic flow is a less important and less stable measure. Diastolic flow is anterograde in both epicardial and intramural vessels, whereas systolic flow is anterograde in epicardial but retrograde in intramural vessels, where blood is squeezed backwards by myocardial contraction. As a result of the two opposite forces, the magnitude of systolic flow velocity may change along the coronary tree and close to the origin of a perforator there might be a watershed area with stagnation of systolic flow.[22] Therefore, the epicardial anterograde systolic flow is mainly a capacitance, rather than a nutrient flow, and does not reflect myocardial perfusion.

## Diagnosis of coronary artery disease

### Coronary stenosis

CFVR reflects the impact on total coronary resistances of: (1) The patency of the epicardial coronary artery, and (2) The vasodilator capacity of the microcirculation. In normal coronary arteries, CFVR entirely describes the resistances of the microcirculation. A flow-limiting stenosis introduces a strong proximal resistance that is higher than that opposed by the microcirculation, as demonstrated by the early normalization of CFVR after the mechanical relief of the stenosis by coronary stenting.[17] Therefore, the impact of microcirculation on CFVR is of secondary importance, compared to that of a significant epicardial stenosis.

Lance Gould established in his seminal experimental work that a CFVR of 2 discriminates significant ($\geqslant$70%) from non-significant (<70%) coronary stenoses.[41,42] Human studies using single photon emission computed tomography[43,44] and intracoronary[45] and transthoracic coronary Doppler ultrasound [3–8,11,17,46] have confirmed these findings, and a cut-off value of 2 has been widely adopted as the ''magic number'' discriminating significant impairment of coronary flow that should be treated invasively by mechanical removal of the stenosis. Translated into clinical practice, transthoracic coronary Doppler ultrasound helps deferring revascularization in patients with CFVR above 2,[47] with important economical, ethical and social implications, particularly in the light of the recent concern about the excess of unnecessary invasive treatment in patients with CAD.

In keeping with the experimental findings,[41,42] transthoracic coronary Doppler ultrasound correlates well with the angiographic degree of the stenosis.[3–8,11,17] This is true for non-significant (<50%) and significant ($\geqslant$70%) coronary lesions, but data on intermediate (50–69%) lesions[10] are more dispersed. This is not surprising, since intermediate lesions are difficult to quantify even with quantitative coronary angiography, which in fact cannot reliably predict the physiological impact of these stenoses.[48] In intermediate stenoses, coronary Doppler ultrasound may guide our clinical decision

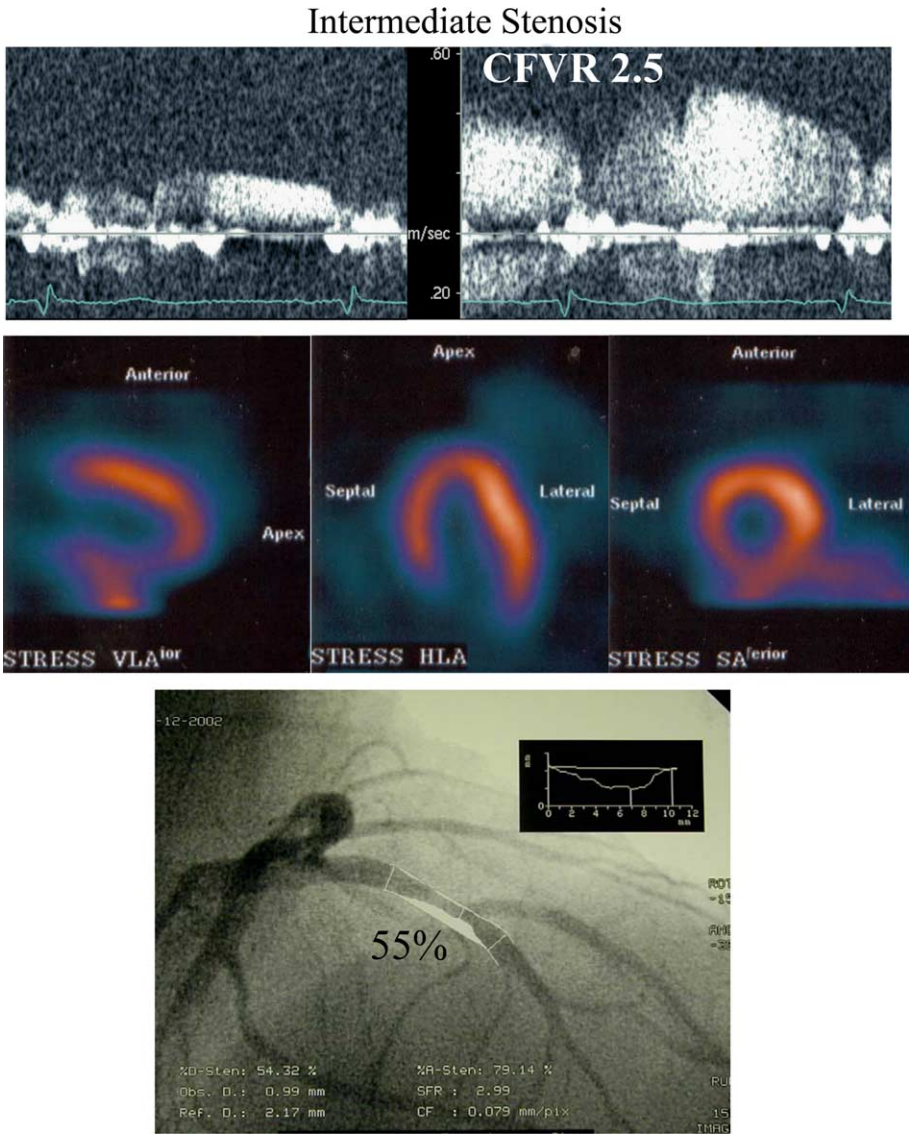


**Fig. 3** Transthoracic coronary Doppler ultrasound helps evaluating the physiological impact of intermediate coronary stenoses. In this case, a good CFVR is in accordance with myocardial scintigraphy, showing no perfusion defects at stress.

making, reserving percutaneous coronary interventions only to patients with reduced CFVR.[47] Fig. 3 shows a patient with intermediate coronary stenosis and CFVR above 2, matching well with the absence of ischaemia at myocardial scintigraphy.

Transthoracic coronary Doppler ultrasound has several advantages over other stress tests: (1) it is accurate in detecting single vessel disease,[17,19] whereas the other available non-invasive tests for CAD such as exercise ECG, myocardial scintigraphy and dobutamine echocardiography may not perform well.[49–51] However, with the currently available technology, transthoracic coronary Doppler ultrasound cannot detect branch stenosis; (2) It is low cost in terms of drug and personnel use; (3) it is less time consuming, because theoretically only few baseline and hyperaemic diastoles are needed to measure CFVR; (4) It provides a quantitative measure of coronary blood flow, which is particularly useful for follow-up evaluation;[19] (5) It is independent of baseline ST alterations and bundle branch block; (6) Drugs such as $\beta$-blockers may not be discontinued.[52] The only contraindications to the technique are asthma, and II–III degree atrioventricular block, because of the potential detrimental effect of adenosine. Patients with short PR intervals should be studied with caution because of the rare, but threatening, complication of adenosine-induced atrial fibrillation. A relative limitation of transthoracic coronary Doppler ultrasound is that, with the state-of-the-art technology, only the LAD and PD can be studied.

## Coronary subocclusion

We have learned from the Coronary Artery Surgery Study registry that patients with >90% stenosis have a 3–7.5 times higher probability to develop acute myocardial infarction than those with less severe lesions, and should deserve urgent care.[53] Unfortunately, neither the clinical

presentation, nor the currently available non-invasive tests can reliably discriminate severe from non-severe stenosis. Again in agreement with Lance Gould, who showed that the hyperaemic response disappears at 90% vessel stenosis.[54,55] a damped CFVR during adenosine infusion is consistently found in patients with severe LAD stenosis.[17,56] Three main mechanisms may be proposed to explain, isolated or in combination, why coronary flow cannot increase or may actually drop during adenosine infusion in severe stenoses: (1) In extremely tight stenoses, the microvascular reserve may already be exhausted at rest, because of maximal peripheral vasodilation, and cannot increase any further under stress; (2) An incompletely calcified coronary stenosis may maintain some degree of elasticity and may collapse during adenosine infusion[54,55,57] for a drop in intraluminal distending pressure induced by flow acceleration at the stenosis site (Venturi effect);[57] (3) Pre-stenotic collaterals may open at stress, stealing blood from the ischaemic territory to perfuse other less jeopardized segments.[58]

Other authors have postulated that a relative increase in systolic velocity at rest is a marker of severe stenosis.[59] Further studies are needed to confirm the diagnostic value of this parameter, which has the limits described above for systolic flow, but the advantage of being obtained with a simple resting exam.

## Coronary occlusion

Coronary flow can be measured by transthoracic coronary Doppler ultrasound in occluded coronary arteries receiving collateral flow. Reverse diastolic flow at rest, reflecting retrograde filling of the artery by collaterals, is a very specific marker of coronary occlusion[60] (Fig. 4) but it unfortunately has a low sensitivity, since collaterals may perfuse the vessel either retrogradely or anterogradely.

The collateral flow is routinely evaluated at rest with coronary angiography.[61] but the predictive role of this method is uncertain.[62] Conversely, the response of collateral flow to stress, which can be measured by intracoronary[63] and transthoracic Doppler ultrasound, may add useful prognostic information.

## Coronary stenting

Patients with LAD stents often present with atypical symptoms, and the standard non-invasive diagnostic tests may yield inconclusive results particularly in single-vessel disease. To complicate the clinical presentation further, studies by intracoronary Doppler ultrasound have suggested a prolonged impairment of CFVR in 30–50% of the patients treated by percutaneous coronary interventions, which was mainly attributed to microvascular dysfunction.[64–66] In contrast with intracoronary Doppler ultrasound, we have consistently found by transthoracic Doppler ultrasound an early normalization of flow after stenting,[17] and suggested that an impaired CFVR at follow-up should reflect restriction of epicardial flow due to in-stent restenosis, rather than microvascular dysfunction. In fact, an impaired CFVR (<2) at follow-up discriminates patients with ⩾70% LAD in-stent restenosis, and may essentially mean restriction of epicardial flow.[19] Patients with CFVR between 2 and 2.5 may have insignificant (intermediate) in-stent restenosis, and may be monitored, reserving angiography only

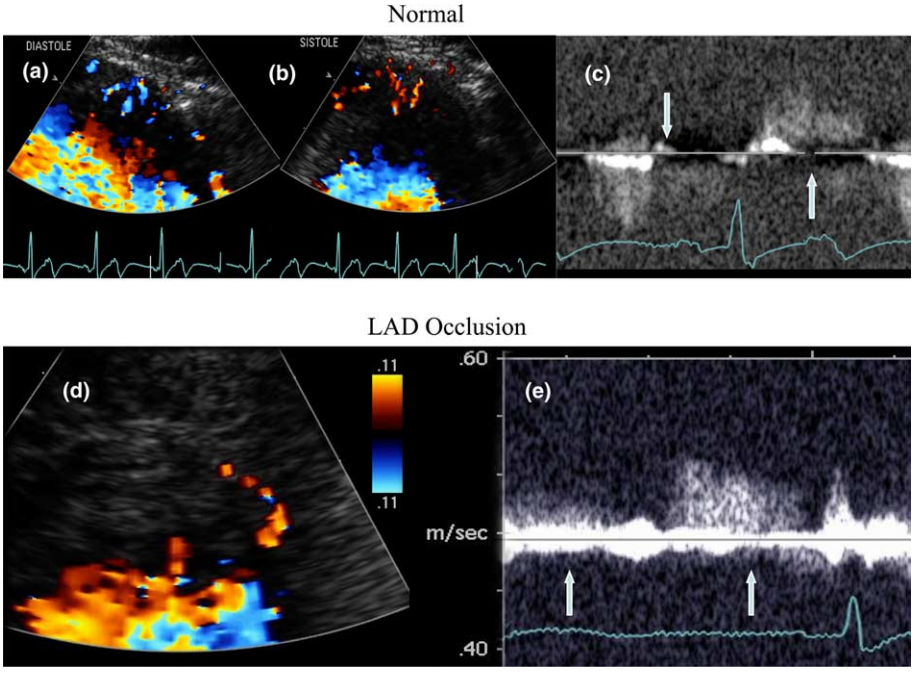


**Fig. 4** Transthoracic coronary Doppler ultrasound is a unique technique to image perforators. In normal subjects, perforators have a diastolic forward flow (panel a, coded in blue) and a systolic retrograde flow (panel b, coded in red), which is confirmed by pulsed Doppler ultrasound (panel c, arrows). In patients with coronary occlusion color Doppler ultrasound may show a characteristic flow inversion in diastole (panel d, coded in red), which is confirmed by pulsed Doppler ultrasound (panel e, arrows).

to those with symptoms, provided the safety of deferring treatment in intermediate lesions and CFVR >2.[47]

Other authors[16,21] utilized resting flow acceleration at the PTCA/stent site to predict restenosis. However, sampling at the level of the stent may be impeded by the interposition of the ribs, and resting velocities may not differentiate restenosis subgroups. Of note, acceleration at the stenosis site depends not only on the stenosis, but also on the driving pressure, metabolic demand, coronary vasomotor tone, etc, all factors altering the velocity gradient.

## Coronary grafts

It is very easy to measure flow in the left and right internal mammary arteries (Fig. 5) both at the origin[67–69] and at the level of the suture over the LAD[1,2,70] with important perioperative and follow-up information on the functional status of the graft. For saphenous vein grafts it is possible to measure flow at the level of the suture over the LAD. Imaging of grafts to other coronary arteries is a matter of further research.

## The posterior descending and the squaring of the circle

Despite the prominent importance of the LAD in the prognosis of coronary artery disease, the evaluation of other coronary arteries is also important. As most of the infarctions occur either in the LAD or in the PD distribution territories, we have recently concentrated on PD flow.[12] In our experience, it is feasible to measure CFVR in the PD in around 50% of the patients regardless of its origin from the right or circumflex coronary artery,[12] but others have reported higher figures.[15] The lower success rate of imaging the PD compared to the LAD (feasibility 98%) depends on four main factors: (1) The PD runs deep into the chest (7–8 cm) while the LAD is more superficial (~2 cm); (2) The PD runs close to the right ventricular inflow tract and to the mid-cardiac vein, which generate strong and disturbing diastolic and systolic flow signals;[12] (3) Adenosine-induced hyperventilation interferes more with PD than with LAD imaging; (4) A dedicated transducer has been designed for the LAD, whereas the PD is studied with a conventional transducer.

Imaging of the PD can be improved in several ways: (1) The use of ultrasound contrast agents improving the signal-to-noise ratio; (2) The use of specific $A_{2A}$ adenosine receptor agonists reducing side effects as hyperventilation;[71] (3) The design of specific probes and software; (4) Reducing the heart rate to minimize wall motion artifacts on Doppler sampling.

## Acute coronary syndromes

Transthoracic Doppler echocardiography can be used to non-invasively detect effective, intramural recanalization in anterior AMI.[22] We have hypothesized that recanalization of perforators emerging from the LAD reflects adequate reperfusion in AMI and have a positive impact on left ventricular function at follow-up. Perforators bridge the large epicardial artery and the microcirculation, and their patency in AMI may yield the same information about the status of local nutrient perfusion as myocardial contrast echocardiography. With myocardial contrast echocardiography, a >50% increase in perfusion in the risk area has been proposed as an indicator of successful reperfusion in anterior AMI.[72] Similarly, we have shown that recanalization of >50% segments in the anterior apical wall predicts good recovery of left ventricular function after anterior AMI.[22]

Adenosine can be safely used during AMI[38] and may add important functional information about microcirculation viability. It has been reported that a CFVR $\geqslant$1.6 in the infarct-related artery predicts recovery of regional left ventricular function.[23,72] Therefore an integrated morphological and functional approach by transthoracic coronary Doppler ultrasound (recanalization of perforators and measurement of CFVR) may be a key prospective tool for clinical decision making and prognostic stratification in AMI.

Fig. 6 shows a patient with anterior AMI, treated with an apparently successful intravenous thrombolysis (early ST normalization, clinical stability) 30 min after the onset of symptoms.[73] However, transthoracic coronary Doppler ultrasound failed to show recanalization of perforators, and LAD flow velocity failed to increase during

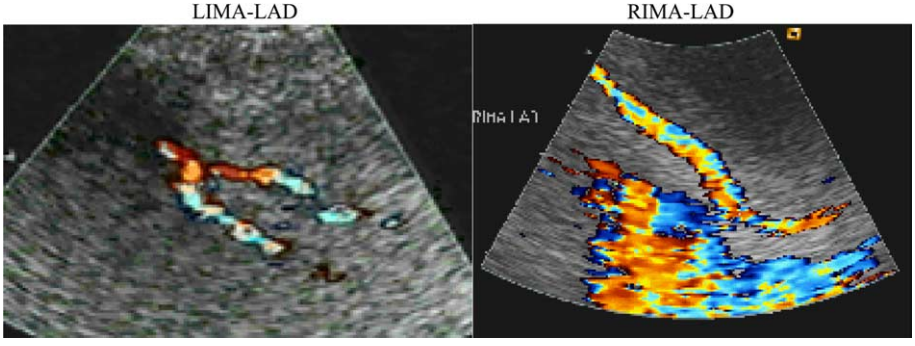


**Fig. 5** Transthoracic colour-Doppler imaging of the left internal mammary artery (LIMA) and the right internal mammary artery (RIMA) grafted over the left anterior descending coronary artery (LAD).

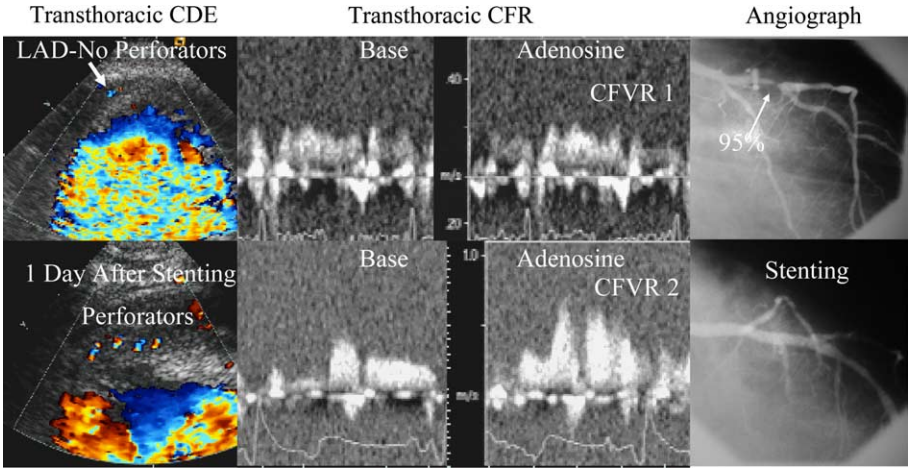


**Fig. 6** Patient with acute anterior myocardial infarction treated with intravenous thrombolytics 30 min after the onset of symptoms. Upper panels: Transthoracic coronary Doppler echocardiography (CDE) failed to show recanalization of perforators in the territory of the left anterior descending (LAD) coronary artery. CFVR was 1, and coronary angiography showed LAD subocclusion. Lower panels: After successful LAD stenting there was an early restoration of perforators' patency in the anterior apical wall and a marked improvement in LAD flow (CFVR = 2), predicting recovery of wall motion at follow-up. Modified from reference.[73]

venous adenosine infusion (CFVR = 1). Coronary angiography showed LAD subocclusion, that was successfully treated by stenting, and colour Doppler ultrasound showed early restoration of perforators' patency in the anterior apical wall, and improvement in LAD flow (CFVR = 2), predicting recovery of left ventricular function at follow-up.

Resting LAD Doppler ultrasound may show LAD patency, and peak diastolic velocity may predict TIMI flow in acute myocardial infarction.[22] In fact, both Doppler ultrasound and TIMI flow are independent measures of velocity. However, the correlation between these two parameters is imperfect, probably because Doppler ultrasound is a quantitative, objective measure, whereas TIMI flow is semiquantitative and more subjective. On the other hand, baseline Doppler ultrasound velocities may be altered by the effect of local spasm, thrombosis, and drugs administered during AMI.

Other resting pulsed Doppler parameters (reverse systolic flow,[74] and short deceleration time[75]) were associated with no-reflow, but they need further clinical validation. The early systolic flow reversal detected by intracoronary Doppler ultrasound[74] may be an artefact generated by wire displacement in early systole, and may be difficult to differentiate from the early systolic flow reversal detected in approximately 20% normal patients.[76] A convincing explanation for the occurrence of systolic flow reversal is lacking. In the epicardial coronary artery red blood cells move according to a forward pressure gradient throughout the cardiac cycle, and systolic pressure in the distal coronary bed cannot overcome systolic pressure in the aorta. Coronary flow is inverted in systole only in perforating branches, where blood is squeezed backwards by myocardial contraction. During AMI the backward force of myocardial contraction is lost or severely depressed because of myocardial necrosis and stunning and systolic flow reversal is less likely to occur. As an example, Fig. 7 shows that systolic flow reversal may occur in subjects without myocardial infarction.

The reported correlation between short deceleration time and no-reflow[75] conflicts with the principles of fluid dynamics, because a rapid slope should reflect better patency of a vascular system instead of obstruction, and is probably another artifact (Fig. 7). There are several other reasons why this unusual slope is not convincing: (1) Coronary flow velocity, even in case of severe microvascular damage, is characterized by a slowly decrescendo diastolic flow, with a prolonged deceleration time. This pattern reflects high microvascular resistances at rest, which in normal subjects markedly decrease at stress, resulting in a steeper slope (Fig. 2). Conversely, in patients with significant coronary stenosis, the hyperaemic slope inversely correlates with the severity of the stenosis,[77] that is, the higher the stenosis (higher resistance) the less steep the slope at hyperaemia. (2) If a steep, early diastolic slope, is produced by microvascular obstruction, it is not clear why in mid and late diastole the curve is back to normal; (3) This altered slope is lost at follow-up, even in patients with persistent severe microvascular damage and depressed left ventricular function; (4) The altered deceleration time appears to be an all-or-none phenomenon, an unusual finding in biology; (5) Surprisingly, inferior infarction does not produce an altered slope; (6) A steep deceleration slope can be found as an artefact even in patients without myocardial infarction (Fig. 7), suggesting that it might be the result of a wall motion artefact, which may be exacerbated by ventricular dysynergy in the setting of anterior AMI.

Therefore a word of caution is necessary before considering resting Doppler ultrasound slope as a reliable marker of adequate reperfusion. In fact, other authors found that short deceleration time was associated with a good myocardial blush grade and recovery of left ventricular function, that is, good reflow.[78] Similarly, in our study with transthoracic Doppler ultrasound, we could

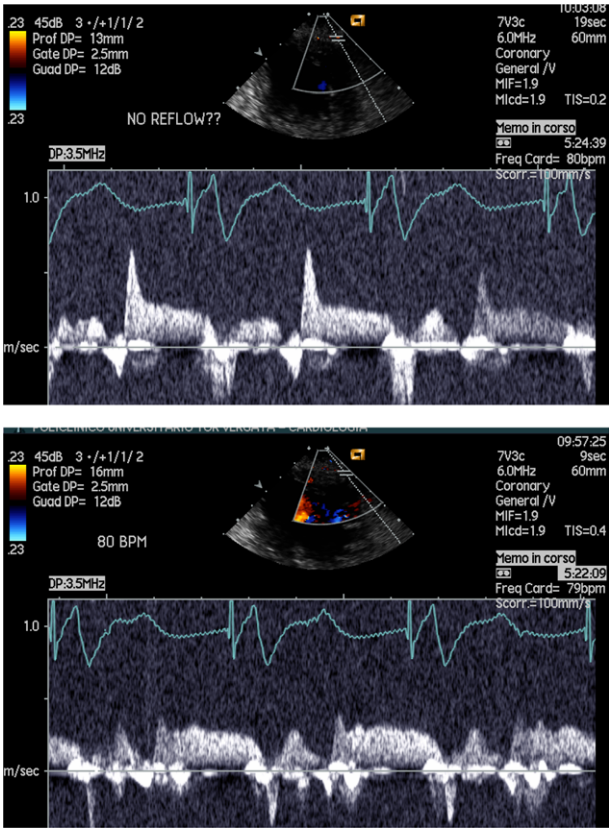


**Fig. 7** Transthoracic coronary Doppler ultrasound in a patient with normal coronary arteries, normal left ventricular function, and no history of acute myocardial infarction (AMI). Upper panel shows a pattern described as no-reflow (steep early diastolic deceleration slope and inverted systolic flow). Lower panel shows normalization of the diastolic pattern, after slightly tilting the probe, whereas it persists a retrograde early systolic signal. Therefore, these altered Doppler ultrasound signals can also be found in non AMI patients, are non-specific, and may be related to wall motion artefacts or venous flow.

not find a correlation between deceleration time and recovery of left ventricular function.[22]

## Aortic counterpulsation

The main goal of aortic counterpulsation, either internal as external, is to improve mean aortic blood pressure, coronary blood flow[79] and myocardial perfusion in critically ill patients with severe ischaemia and/or cardiac failure. Transthoracic coronary Doppler ultrasound shows, on-line and beat-to-beat, the efficacy of aortic counterpulsation on coronary blood flow velocity, helping to select the optimal setting of the device. Fig. 8 shows alternated diastolic flow velocities in a patient with 2:1 aortic counterpulsation where increased velocity is associated with the assisted beat.

## Apical thrombosis

It is clinically important to discriminate fresh from old intracavitary thrombi because of their different embolic

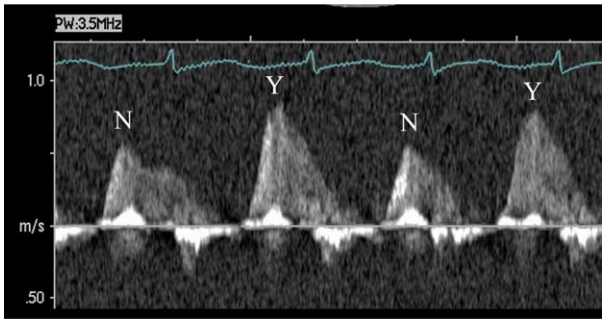


**Fig. 8** Pulsed-Doppler ultrasound of the left anterior descending coronary artery in a patient treated early after coronary surgery with 2:1 aortic counterpulsation shows a 25% increase in coronary flow velocity in the assisted (Y) compared to the non-assisted (N) beats.

potential. The growth of new vessels within an apical thrombus (Fig. 9) may be detected by transthoracic Doppler ultrasound and may be a useful additional marker of the ''stability'' of the lesion.

## Coronary vasomotor tone and the ''third dimension'' of Doppler

Time and velocity are the most commonly used parameters to extrapolate clinically useful data from Doppler spectra. However, there is a third potentially useful but often neglected piece of information in the Doppler spectrum: the intensity of the reflected signal.[80] Provided that the entire section of the coronary artery is included in the sample volume, Doppler intensity is proportional to the number of scatterers and is a measure of blood volume crossing the Doppler sample volume. Doppler intensity can be used to detect coronary vasomotion: it may decrease during handgrip in patients with coronary artery disease where the sympathetic drive increases coronary vasomotor tone, whereas it may increase or remain unchanged in normals.[80] A similar response is observed during cigarette smoke (Fig. 10) where Doppler intensity may be more sensitive than CFVR[28] to detect subtle changes in coronary vasomotor tone.

# Which role for the microcirculation?

There is no doubt that acute myocardial infarction causes a deep alteration of the coronary microcirculation, mainly due to ''hard'' events like microembolisation of plaque debris, interstitial oedema and increased vasomotor tone. However, the role of microcirculation in other clinical settings is probably more ''soft'' than expected. Transthoracic coronary Doppler ultrasound has been used to study the impact on microvascular flow in a number of settings known to, or suspected of, altering microvascular flow, such as coronary stenting,[64–66] remote coronary artery disease, sex hormones,[27] cigarette smoke,[28] left ventricular hypertrophy,[31–33] diabetes[81] and ageing.[82,83]

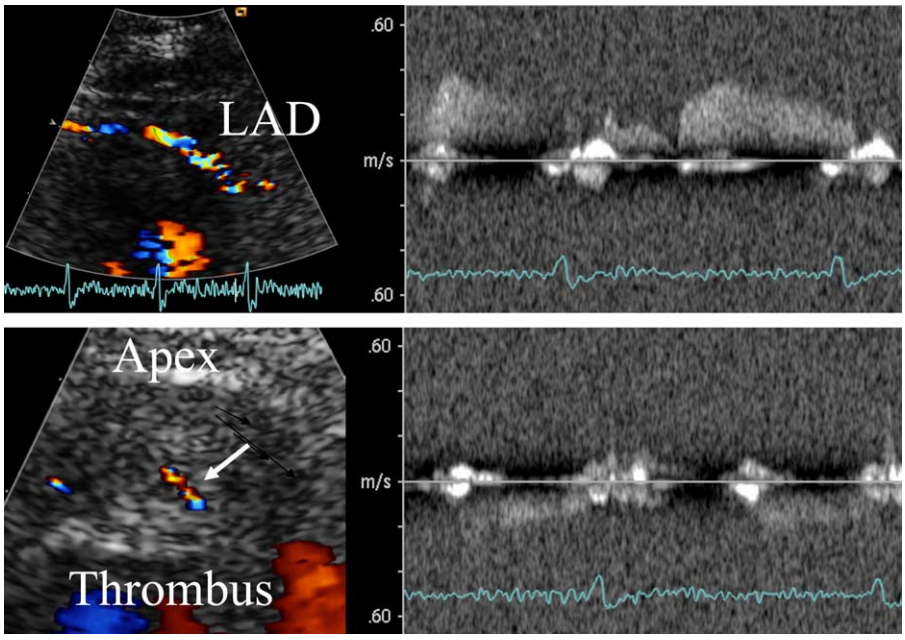


**Fig. 9** Transthoracic coronary Doppler ultrasound shows a vessel penetrating from the endocardium into an apical thrombus (arrow), indicating that the lesion is not recent. The direction of flow in the neo-vessel is opposite to the transducer, whereas in the LAD it is directed towards the transducer.

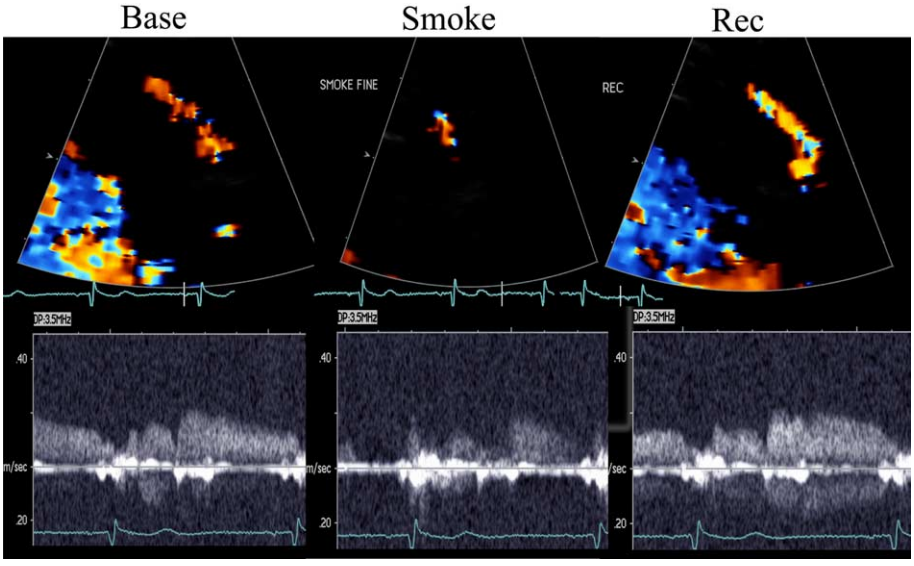


**Fig. 10** The effect of smoke on colour-Doppler ultrasound imaging and pulsed Doppler tracing. Coronary vasoconstriction caused by smoking is detected as a reduction in colour-Doppler flow signal, corresponding to a reduction in pulsed Doppler ultrasound intensity, which is followed by a recovery phase, characterized by some reactive hyperaemia.

As mentioned in a previous section, coronary stenting was believed to be followed by sustained microvascular dysfunction,[64–66] and focal coronary artery disease was supposed to generate a diffuse alteration in coronary flow involving not only the stenosed artery, but also angiographically normal (remote) coronary arteries[84] (coronary cross-talking). With regard to coronary stenting, we have shown that CFVR rapidly recovers after the procedure,[17] challenging the presence of microvascular dysfunction. With regard to remote microvascular alteration in focal CAD, we have found that CFVR in the angiographically normal coronary artery is never affected by remote coronary stenosis, AMI, or stenting.[85] These findings confirm that focal factors in each territory are the major determinants for CFVR, and impaired CFVR in one region is not a general phenomenon of the coronary circulation.

The interaction between microvascular flow and sex hormones is complex and incompletely understood. Microvascular involvement is often called to explain

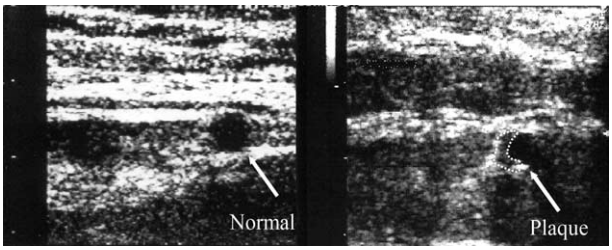


**Fig. 11** High-resolution echocardiographic short-axis imaging of a normal tract of the LAD, and a diseased tract, containing a partially calcified plaque, producing attenuation of the ultrasound beam.

cyclic chest pain and positive stress tests in fertile women with normal epicardial coronary arteries, but a definitive confirmation of this link is lacking. Moreover, despite the previous belief that hormonal replacement therapy may play a protective role in cardiovascular disease,[86,87] recent randomized trials showed no benefit at all[88–91] Accordingly, Hirata et al., found only minor changes in CFVR in relation to different hormonal exposure.[27]

Active and passive cigarette smoke may alter microvascular flow but the relative changes in CFVR[28] were, as for hormonal exposure,[27] well above the cut-off value for significant microvascular dysfunction (CFVR 2.24[92]–2.5[93]) reported in reference studies. Similarly, studies using positron emission tomography showed no difference in CFVR between smokers and non-smokers.[94]

Ageing is an important factor limiting functional reserve in many organs, and the coronary circulation makes no exception.[82,83]

In conclusion, our experience with transthoracic coronary Doppler ultrasound teaches that an altered microcirculation may decrease CFVR from a theoretical maximal value of 3–5 to not less than 2–2.5. Only in some of the patients labelled as having syndrome X, CFVR may fall below 2. Of note, our patients die of epicardial CAD, not of microvascular disease.

## A call for help

Transthoracic coronary Doppler ultrasound turns our attention from surrogate markers of atherosclerosis, such as brachial/ankle index, left ventricular mass, and carotid intima/media thickness to a direct screening modality of coronary flow.[95] The support of industries to our research is essential to pursue this ambitious goal. In magnetic resonance imaging and computed tomography, huge investments have turned the dream of non-invasive coronary imaging into reality. A much smaller investment in ultrasound may result in a more comprehensive evaluation of coronary flow physiology, which is an important complement to coronary morphology, particularly in intermediate coronary lesions and microvascular disorders.

In medicine, simple concepts work and easy techniques rapidly gain popularity. Thanks to transthoracic Doppler echocardiography, the evaluation of CFVR has migrated from the cardiac catheterization laboratory and the ''ivory research towers'' of positron emission tomography to settle in the more accessible and ''democratic'' echo lab, where the cardiologist working in the territory can build his own know-how on coronary physiology and microcirculation, based on a large population approach.

## The future

Coronary stenosis and flow reserve are two important aspects of the pathophysiology of coronary artery disease. Undoubtedly, the composition of the coronary plaque is the third important factor that may affect prognosis. High-resolution ultrasound transducers may directly image the plaque in the LAD[96] and may provide information on its calcium and lipid content (Fig. 11). Again, more research on ultrasound machines and transducer technology should be done in this field to translate another exciting potentiality into a clinical reality.

Several studies have shown that the cavitation effect of ultrasound, which is enhanced by ultrasound contrast agents containing microbubbles, facilitates clot lysis through an acceleration of the enzymatic activity of rtPA.[97,98] In AMI, direct imaging of the occluded coronary artery may enhance thrombolysis and potentially transform an emerging imaging modality into a fascinating therapeutic tool.[99]

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