Detection, location, and severity assessment of left anterior descending coronary artery stenoses by means of contrast-enhanced transthoracic harmonic echo Doppler

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Aims

Contrast-enhanced second harmonic Doppler (ED) is a new ultrasound modality that increases the feasibility of recording blood flow velocity (BFV) in the left anterior descending coronary artery (LAD) using a transthoracic approach. Blood flow velocity convective acceleration is a reliable marker of coronary stenosis and can be used to assess the percentage area reduction at the stenosis site by applying the continuity equation. To detect, locate, and assess the severity of significant stenosis throughout the LAD by means of an ED recording of BFV acceleration at the stenosis site.

Methods and results

Fifty-three consecutive patients undergoing coronary angiography (CA) underwent a colour-guided pulsed-wave ED recording of BFV in the proximal/mid and distal portions of the LAD, and maximal and reference BFV was obtained in each of the two arterial segments. Maximal velocity was much higher in the diseased segments (≥50% lumen narrowing) than in the normal segments (143 ± 84 vs. 38 ± 20 cm/s; P < 0.001); as the reference velocity was similar (37 ± 13 vs. 31 ± 12; P = 0.03), the percentage increase in velocity was also higher (290 ± 233 vs. 20 ± 37%; P < 0.001). Using a cut-off value of an 82% increase in velocity, sensitivity and specificity vs. CA was, respectively, 86 and 95%. The reduction in the percentage area of stenosis calculated using the continuity equation agreed with that determined by means of quantitative CA (r = 0.7).

Conclusion

Blood flow velocity evaluation in the LAD by means of transthoracic ED is feasible and reliable in detecting, locating, and assessing the severity of LAD stenosis.

Keywords

Coronary flow velocity • Echo-contrast • Second harmonic Doppler

Introduction

Obstructive disease of the left anterior descending coronary artery (LAD) is a frequent occurrence,1 and has a poor prognosis as it is a major independent predictor of death regardless of the number of coronary vessels involved.2 For these reasons, a non-invasive diagnostic approach to the detection of LAD stenosis would appear to be attractive.

Absolute coronary flow reserve (CFR) can now be measured in the distal portion of the LAD by means of non-invasive transthoracic Doppler echocardiography3 but, although this aids the detection of LAD stenosis,3 its predictive power for significant LAD stenosis can be reduced in the case of an intrinsically dysfunctioning microcirculation and/or altered haemodynamics.4 Furthermore, assessing CFR requires an adenosine infusion that is contraindicated in patients whose clinical condition is unstable, and provides no information concerning the location of the stenosis.

A significant coronary stenosis accelerates flow in accordance with the continuity equation,5 and this convective acceleration...
Table 1 Demographic and clinical data

| Age, yrs | 64 ± 8 |
| Gender |
| M, # pts | 40 |
| F, # pts | 13 |
| Height, m | 1.64 ± 0.08 |
| Weight, kg | 72 ± 9 |
| BMI | 27 ± 2.9 |
| Diabetes, # pts | 10 (19%) |
| Menopause, # pts | 12 (23%) |
| Angina pectoris, # pts | 52 (98%) |
| MI, # pts | 26 (49%) |
| PTCA, # pts | 11 (21%) |
| Hypert, # pts | 1 (2%) |
| DCM, # pts | 1 (2%) |

Yrs, years; M, males; F, females; BMI, body mass index; # pts, number of patients; MI, previous myocardial infarction; PTCA, previous percutaneous coronary angioplasty; AS, aortic stenosis; Hypert, systemic hypertension; DCM, dilated cardiomyopathy.

can be exploited by Doppler in order to detect stenosis and assess its severity. A few studies have tried to use transthoracic Doppler to detect convective acceleration in coronary arteries as a means of predicting coronary stenosis, but they have a number of limitations: the small number of assessed LAD stenoses meant that the accuracy parameters had broad confidence intervals; they did not use contrast enhancement, thus leading to sub-optimal feasibility; and their clinical value was limited by the fact that they did not attempt to quantify the lumen narrowing.

We have shown that contrast-enhanced transthoracic Doppler echo in second harmonic mode greatly increases the feasibility of detecting flow in the distal and mid-LAD, and it has also been shown that transthoracic echocardiography can visualize the proximal portion of LAD. We formulated a dual hypothesis: (i) contrast-enhanced transthoracic echo in harmonic mode can detect flow throughout the LAD, thus allowing detection and location of a significant stenosis by evaluating its effect on blood flow dynamics (i.e. flow acceleration at the stenosis site) and (ii) the percentage reduction in the cross-sectional area (CSA) of the stenosis can be assessed by means of this Doppler approach using the continuity equation.

Methods

Over an 8 month time period (from July 1999 to March 2000), a total of 59 patients were recruited, of whom 6 were considered ineligible (4 did not undergo angiography and 2 had a partially missing Doppler recording); therefore, the final study group consisted of 53 consecutive patients scheduled for coronary angiography (CA) whose demographic and relevant clinical findings are summarized in Table 1. Because of the exploratory nature of the study, sample size was not formally computed but was decided a priori to be around 60 patients. Consecutive enrolment meant that patients with a large body habitus or chronic obstructive pulmonary disease were also included. All of the patients were informed of the purpose and the nature of the study, and gave their informed consent.

Contrast-enhanced transthoracic Doppler echocardiography

Ultrasound equipment and technologies

Echocardiography was performed using an Acuson Sequoia™ ultrasound unit (C256 Echocardiography System, Acuson, Mountain View, CA, USA) and a broadband transducer with second harmonic capability (3V2c). Colour Doppler signal (velocity encoded) was attained in fundamental (2.5 MHz); during contrast administration, however, it was also attained in harmonic mode (1.7 MHz transmitting and 3.5 MHz receiving). Spectral Doppler, instead, was performed only in fundamental mode (2.5 MHz).

Ultrasound setting

Before the contrast was administered, the colour-coded Doppler setting was adjusted to maximize scanning sensitivity (pulse repetition frequency was reduced by setting the velocity range at 16–30 cm/s and maximizing the sample volume of colour flow mapping) without significantly reducing the frame rate (the colour box size was reduced to remain in keeping with a frame rate of >30 Hz). All of the studies were continuously recorded onto a half-inch S-VHS videotape.

Left anterior descending coronary artery segmentation and anatomy

Colour Doppler detection of LAD flow was attempted throughout the LAD by sequentially scanning the proximal/mid and the distal portion of the vessel. The proximal/mid-portion included (i) the strictly retro-pulmonary portion of the vessel extending from the left main coronary artery bifurcation to the pulmonary valve plane running horizontally behind the posterior wall of the pulmonary artery (Figure 1 and see Supplementary material online, Clip S1); (ii) the first part of the interventricular portion that is still spatially oriented as the strictly retro-pulmonary part running beyond the pulmonary valve plane along the left border of the anterior wall of the right outflow tract (Figure 2 and see Supplementary material online, Clips S2 and S3). The distal segment was considered the strictly vertically oriented portion of the interventricular segment.

Ultrasound plane orientations

The retro-pulmonary portion was visualized as described previously. The short axis of the aorta, the left coronary fossa was identified as the echo-dense region adjacent to the left coronary sinus delimited by the left pulmonary artery above and the summit of the left ventricle below. It was then attempted to visualize the LAD in this area by slight angling the transducer up and down, and then gradually rotating it clockwise in order to cope with the variable inclination of the vessel in the vertical plane (a 0–90° angle). Once identified in B-mode and then with colour Doppler, the course of the LAD was followed as far as possible (Figure 1 and see Supplementary material online, Clip S1).

The approach to the mid-LAD (the upper part of the interventricular portion) has been previously described. Briefly, after obtaining the short axis of the aorta, the left coronary fossa was identified as the echo-dense region adjacent to the left coronary sinus delimited by the left pulmonary artery above and the summit of the left ventricle below. It was then attempted to visualize the LAD in this area by slight angling the transducer up and down, and then gradually rotating it clockwise in order to cope with the variable inclination of the vessel in the vertical plane (a 0–90° angle). Once identified in B-mode and then with colour Doppler, the course of the LAD was followed as far as possible (Figure 1 and see Supplementary material online, Clip S1). The approach to the mid-LAD (the upper part of the interventricular portion) has been previously described. Briefly, the upper mid-LAD was visualized using a low parasternal short-axis view of the base of the heart modified by a slight clockwise rotation of the transducer beam (Figure 2 and see Supplementary material online, Clips S2 and S3), which allows the transection of the upper interventricular portion of the artery running laterally to the right ventricular outflow tract before it becomes completely vertical (i.e. while it still...
shares a similar horizontal course to that of the retropulmonary part) (Figure 2).

The approach to the vertically oriented interventricular LAD (i.e. the entire distal portion) has also been described previously. Briefly, after obtaining a short axis of the left ventricle at papillary level, the area of the interventricular sulcus was identified and colour Doppler scanning started. Once a prevalent diastolic flow had been identified in the anterior sulcus area, the probe was rotated in order to optimize the long-axis transection of the distal portion of the artery. From this position, cranial angulation of the transducer was attempted to visualize the initial part of the vertically oriented LAD as far as possible. In most cases a modified two-chamber view was also attempted in order to reduce the theta angle. Given the poor spatial resolution of B-mode echocardiography, direct Doppler scanning of the interventricular part of the LAD was attempted.

The above procedure was performed twice: before and after contrast enhancement.

**Pulsed-wave Doppler mapping**

Each of the two LAD segments defined above were systematically mapped by means of colour-guided pulsed-wave Doppler echo, with the sample volume being positioned on the basis of the position of the vessel during diastole, when it is more stable (Figures 3 and 4). If aliasing was evident upon LAD colour flow mapping, we first sampled (first site) the portion in which the colour Doppler signal appeared aliased; otherwise, we sampled the whole visualized segment in order to obtain the fastest velocity possible. Secondly (second site), we recorded what became the reference blood flow velocity (BFV) in that coronary segment, which was obtained by sampling proximally (45/106 segments; 46%, Figure 3) or distally to the area with the highest recorded velocity (Figure 4), making sure that the colour did not seem to be disturbed. The mean angle of incidence between the Doppler beam and the direction of the blood flow (the theta angle) was small (18° ± 16°, range 0°–50°), and almost always the same at the first and second sites. The angle was always corrected.

**Study protocol**

After a baseline examination without contrast, contrast-enhanced Doppler scanning was always attempted using Levovist® contrast medium injected by means of an infusion pump at a concentration of 300 mg/mL and an infusion rate of 1 mL/min. Basically, two infusions of 7–8 mL each were used: one for the proximal/mid-portion as these segments have a similar plane orientation; the other for the vertically oriented interventricular LAD segment. During the administration of the contrast medium, colour Doppler was performed in a second harmonic mode. However, fundamental colour scanning and a low infusion rate (0.5 mL/min) was preferred for the retropulmonary portion in some cases because the harmonic mode signal coming from this area is greatly attenuated by the contrast-filled pulmonary infundibulum.

**Echocardiographic analysis**

All ultrasound analyses were performed in a blind manner to angiography as echocardiography was systematically performed before catheterization. The analysis was performed by segmenting the LAD in proximal–mid and distal part as largely used.
Doppler evaluation
The length of colour flow in each of the two portions of the LAD was measured before and after contrast using Callipers as described previously. If the colour flow was discontinuously visualized, the visualized length of that portion was considered as being the sum of the individual colour flow segments. The peak and time velocity integrals (TVIs) of the diastolic waves were measured at the first and second site, and the percentage increase in BFV at the first site with respect to the second site was calculated as
\[
\frac{\text{diastolic peak at the first site} - \text{diastolic peak at the second site}}{\text{diastolic peak at the second site}} \times 100
\]
The variability of these two measurements has been reported previously.6,18

Doppler determination of percentage area stenosis
The severity of LAD stenosis was assessed by means of transthoracic Doppler and the use of the continuity equation in 21 patients (22 narrowed LAD segments) who underwent quantitative CA. According to the continuity equation, blood flow rate should remain constant at the stenosis site \( Q_s \) and in the (proximally or distally) adjacent nonstenotic segment \( Q_{\text{ref}} \) provided that no branching occurs between the two. As blood flow is derived from the product of the Doppler curve TVI and the CSA of the vessel, then
\[
Q_{\text{ref}} = A_{\text{ref}} \times \text{TVI}_{\text{ref}} = A_s \times \text{TVI}_s = Q_i
\]
The percentage area stenosis \( \% A_i \) can be expressed as
\[
\% A_i = \frac{(A_{\text{ref}} - A_s)}{A_{\text{ref}}} \times 100 = \left( 1 - \frac{A_s}{A_{\text{ref}}} \right) \times 100
\]
Rearranging equations 1 and 2 leads to
\[
\% A_i = 100 \times \left( \frac{1 - \text{TVI}_{\text{ref}}}{\text{TVI}_i} \right)
\]
We also reassessed the data by using a corrected formula that takes into account the different flow profile in the reference and stenotic region: the first parabolic and the second flat.10,19,20 Doppler, in fact, measures peak velocity averaged over the cardiac cycle rather than average spatial velocity, but it is the latter (together with the vessel’s CSA) that is needed to calculate flow. Average spatial velocity is affected by the velocity profile and, as the blood velocity profile in the parabolically shaped reference segment can be expected to be different from that in the blunted stenotic segment,10,20 the reference TVI (derived from peak and not average spatial velocity) has to be corrected by the shape factor (0.5) for a parabolic profile.10 This avoids overestimating the reference average spatial flow velocity and consequently underestimating \( \% A_i \). Equation 3, therefore, becomes
\[
\% A_i = 100 \times \left( \frac{1 - [\text{TVI}_{\text{ref}} \times 0.5]}{\text{TVI}_i} \right)
\]

Angiographic analysis
All angiographic studies were performed and interpreted in a blind manner as they were performed as routine studies. Coronary angiography was performed using the standard Judkins method and the femoral approach, and the coronary stenosis was visually assessed on the basis of multiple projections by one investigator who was unaware of the transthoracic echocardiogram (TTE).
Doppler results. Callipers were used in the case of doubt. The proximal/mid-LAD portion was angiocardiographically defined as extending from the left main coronary artery bifurcation up to and including the origin of the last major diagonal branch, and the distal portion as the remaining part of the vessel extending from the last major diagonal branch to the apex.

In 21 of the patients with a diseased LAD, the maximum (reference) and minimum luminal diameter was assessed from digital images using an on-line analysis system (Medcom Ltd., Frankfurt, Germany), taking into account the average results obtained from two orthogonal projections or (in the case of more severe narrowing) a number of non-orthogonal projections. These diameter measurements were used to calculate the minimum and reference luminal CSA (assuming a circular cross-section), after which the percentage CSA was calculated as: 

\[
\% A_s = \frac{(A_{ref} - A_s)}{A_{ref}} \times 100.
\]

Statistical analysis

The continuous variables are expressed as mean values ± 1 SD.

The differences in colour Doppler length under two different conditions were assessed using a paired t-test.

The differences in the absolute and percentage increase in velocity (enhanced Doppler subsection) were assessed by means of a random effect model\(^{21}\) that takes into account subject-specific correlations, since multiple segments per patient were used.

The best cut-off point for dichotomizing the Doppler data (the percentage increase in velocity) was empirically estimated along with the 95% CI by means of empirical bootstrap percentile intervals (resampling 5000 times the same sample of 106 cases, the cases of each sample being randomly selected by replacement from the original sample) applied to receiver operating characteristic (ROC) curves (Figure 5). Also sensitivity and specificity with their 95% CI were estimated by the same bootstrap methodology.

Comparisons of proportions (the sensitivity and specificity of the method with and without enhancement) were made using McNemar’s test adjusted for the clustering effect\(^{22}\) as multiple LAD segments per patient were considered in this section as well.

The agreement between the angiographic and Doppler-determined percentage reduction in the stenosis area was evaluated using a linear regression analysis (expressed as the correlation coefficient \(r\)) and the Bland–Altman method.\(^{23}\)

Results

Coronary angiography

Coronary angiography revealed at least one significant stenosis (diameter lumen narrowing ≥50%) in 40 of 53 patients and 44 of 106 segments (38 proximal/mid and 6 distal); no significant stenosis was found in 13 patients and 62 segments (15 proximal/mid and 47 distal). Two of the 40 patients with a diseased LAD also had a mid-coronary occlusion.
No adverse event was noted after contrast administration, which is in line with the result of large-scale safety studies and our extensive previous experience. The quality of the B-mode visualization was poor and so it was not analysed, but the colour-flow Doppler recordings were greatly improved by the use of contrast combined with harmonic technology. Colour Doppler length in the proximal/mid and distal...
segments was, respectively, 16 ± 11 and 5 ± 8 mm before enhancement, and 33 ± 11 and 21 ± 7 mm after enhancement (P < 0.001); and the overall length of LAD colour flow was 22 ± 15 mm before enhancement and 56 ± 14 mm after enhancement (mean difference 32 ± 16 mm; 95% CI 27–37 mm; P < 0.001) (see Supplementary material online, Table).

Enhanced Doppler

Higher velocity at the first site was recorded in the 44 angiographically diseased segments than in the 62 non-diseased segments (143 ± 84 vs. 38 ± 20 cm/s; P < 0.001), whereas velocity at the reference sites was similar (37 ± 13 vs. 31 ± 12; P = 0.03) (Figures 3 and 4 and see Supplementary material online, Table). Consequently, the percentage increase in velocity at the first site with respect to the reference site was much higher in the angiographically diseased segments (290 ± 233 vs. 20 ± 37%, P < 0.001) (Figure 5). A localized aliased colour signal at the first site was more frequently detected in the diseased segments: 38 segments (86%) vs. 7 segments (11%) (P < 0.01).

Enhanced Doppler diagnostic accuracy

Using the best cut-off point (>82%; 95% CI = 65–90) identified by means of the bootstrapped ROC curve analysis (area under the curve = 0.94 [95% CI = 0.87–0.99], P < 0.0001, Figure 5), the dichotomised percentage increase in velocity at the first site proved to be a good predictor of CAD: 38 of 44 stenotic segments and 59 of 62 non-stenotic segments were correctly detected yielding a bootstrapped sensitivity and specificity at, respectively, 86% (95% CI = 75–95) and 95% (95% CI = 89–100) (Figure 6).

Only one of the six angiographically diseased segments with a ≤82% increase in velocity at Doppler scanning showed a very tight stenosis at the beginning of the vertically oriented portion not visualized by colour (see Supplementary material online, Table); four of the remaining five segments had a medium–severe stenosis (a reduction in diameter of between 65 and 50%) and one was occluded. In the other patient with a mid-coronary occlusion (correctly detected), uniformly abnormally high velocities were recorded probably in a collateralized big intermediate branch (see Supplementary material online, Table).

None of the three non-significantly diseased segments with a >82% increase in velocity at the first site (see Supplementary material online, Table) had entirely normal angiographic findings: two had lumen irregularities that caused luminal narrowing of 20–40%, and the third (distal segment) was part of a severely diseased LAD with post-angioplasty re-stenosis (correctly detected by Doppler) in the adjacent mid-LAD segment.

Non-enhanced Doppler

Doppler detection of flow acceleration was greatly improved by the use of contrast and harmonic technology because of the stronger Doppler signal and the additional segment of colour flow visualized after enhancement. Flow acceleration was detected by Doppler in only 15 of the 44 diseased segments before enhancement, but in 38 after enhancement (P < 0.003). Enhancement thus increased sensitivity from 34 to 86% (P < 0.003), although specificity did not change (see Supplementary material online, Table).
Stenosis severity: transthoracic echocardiogram Doppler vs. quantitative coronary angiography

The 21 patients with 22 diseased LAD segments (10 proximal, 11 mid, and 1 distal) who underwent quantitative angiography were randomly selected on the basis of the availability of catheterization laboratory access to a digital image on-line analysis system.

The quality of the Doppler curve was adequate for calculation in all segments (feasibility 100%). There was good correlation and agreement between the Doppler-derived and angiographic percentage CSAs of stenosis over values ranging from intermediate to severe, with a maximum difference of 10% in all but four patients (Figure 7) using the corrected formula.4 Overall, the limits of agreement (95%) of the individual differences were 16.9% (95% CI 23–10%) and −16.6% (95% CI, −23 to −10), and the correlation coefficient \( r \) was 0.7. On the contrary, the non-corrected formula systematically underestimated the QCA % cross-sectional stenosis area, thus giving the same correlation as the corrected formula but with worse agreement (see Supplementary material online, Figure).

Discussion

Our results demonstrate that contrast-enhanced transthoracic Doppler echocardiography is capable of detecting, locating and, most importantly, assessing the severity of lumen narrowing throughout the LAD by evaluating its haemodynamic effects on blood flow dynamics. Taking a flow acceleration of \( \geq 82\% \) of the reference value as a Doppler criterion of significant stenosis, the sensitivity and specificity of the method in identifying all diseased segments was 86 and 95% (Figure 6). The assessments of stenosis severity (expressed as the percentage reduction in CSA) made using the two methods were comparable (limits of agreement: 16.8 to −16.6%; \( r = 0.7 \)).

Stenosis detection and location by Doppler

Flow acceleration at a site of lumen narrowing (convective acceleration) is an example of basic hydraulic behaviour designed to maintain a constant flow.5 This physical principle (which is expressed by the continuity equation) derives from the principle of mass conservation, and previous animal and human studies have clearly shown that Doppler can precisely evaluate convective acceleration in coronary arteries.26

We accurately evaluated stenoses throughout the LAD by acquiring physiological information that can characterize them on the basis of their fundamental effects on blood flow. A cut-off point based on a \( \geq 82\% \) increase in BFV proved to be the best predictor of significant CAD (a \( \geq 50\% \) reduction in lumen diameter) with relatively narrow 95% empirical bootstrap percentile confidence intervals (65–90). These results are substantially in agreement with previous findings showing best cut-off values in the range of 45–50%.6,11

Assessment of stenosis severity using the continuity equation

In comparison with quantitative CA, the diagnostic method using the corrected continuity equation provides a good estimate of the severity of lumen narrowing, whereas the non-corrected equation systematically underestimates severity. This is totally in line with the findings of a previous Doppler study10 and may be explained by the presence of different velocity profiles in the two sampling regions, which has been experimentally demonstrated.19,20 Although the assumption of a fully blunted profile (shape factor = 1) at the stenosis site used in the corrected equation may not be true for all degrees of stenosis severity,20 it does work for clinical applications.
This non-invasive quantitative approach is attractive for a number of reasons: it is totally non-invasive; stenosis severity can be assessed throughout the LAD (we analysed four proximal, 17 mid and 1 distal stenosis); it has a high success rate (100% in our consecutive series of patients selected on the basis of catheterisation laboratory logistics); and it works over a wide range of stenoses (from mild to severe).

The other approaches proposed for clinically applying the continuity equation as a means of estimating the severity of coronary stenosis are those based on an intravascular Doppler flow wire and transoesophageal Doppler. However, the first is limited by the fact that it is invasive and not very feasible in severe grade stenosis, and the second by the fact that it is semi-invasive and can only explore the proximal portion of the LAD.

**Previous studies**

A few studies have attempted to evaluate the convective acceleration of flow in coronary arteries by means of transthoracic Doppler. However, their clinical value is limited by a number of methodological flaws: (i) the small number of LAD stenoses assessed meant that the accuracy parameters had broad confidence intervals; (ii) the feasibility of such non-enhanced Doppler methods was sub-optimal; (iii) they did not attempt to quantify the stenoses; (iv) they did not report the severity of the stenoses, or it was so slight as to raise doubts concerning the potential of the method in the case of more severe narrowing; and (v) they did not describe a systematic procedure (in terms of echocardiographic views) for assessing flow throughout the LAD, nor report any parameters that could express it in a certain manner (e.g. the total length of colour flow). Most of these limitations have been overcome by our enhanced Doppler method.

**Clinical implications**

Although limited to assessing LAD, the method may have considerable clinical implications. Its great appeal lies in the fact that it provides a non-invasive, hydraulic insight into the specific level of the epicardial stenosis that is totally independent from the microcirculation and haemodynamics.

Furthermore, the status and, in particular, any spontaneous or medically induced evolution in the obstructive plaque may theoretically be more easily detected by this method than any other non-hydraulic method (i.e. angiography, CT, and MRI). Flow velocity through the stenosis is inversely related to the lumen diameter raised to the power of two, and so even a small change in vessel area at the stenosis site may have a significant impact on flow velocity but not be detected by other morphological methods. This theoretical concept is supported by an invasive intracoronary Doppler study of post-angioplasty patients in which, despite good post-procedural ‘luminology’ results (no significant residual lumen narrowing), 38% of the patients showed flow acceleration at the stenosis site (>50% than at the reference site), and this acceleration was the strongest independent predictor of restenosis after 6 months’ follow-up. Moreover, as our method is non-invasive and quantitative (Figure 7), it is ideal for serial repeated studies.

This new method can add very important information to non-invasively assessed absolute CFR in the LAD. Microcirculation and haemodynamic abnormalities can reduce absolute CFR, and very often co-exist in patients with suspected CAD. The direct non-invasive assessment of a coronary stenosis can help to clarify whether the impaired CFR is essentially related to non-stenotic factors (as in the case of patients with microvascular disease in whom stenosis has been excluded) or coronary stenosis (the strongest factor in reducing reserve), as well as add information concerning the location of the stenosis, which certainly has very important clinical and prognostic implications. In case of coexistence of severe microcirculatory dysfunction and CAD, serial evaluation of CFR and LAD mapping before and after coronary angioplasty may discriminate between the two conditions. Thus, flow mapping the entire LAD together with non-invasively assessing CFR can weigh the relative impacts of coronary stenosis and microcirculatory dysfunction on coronary physiology.

This important integration of CFR and convective acceleration assessment may play a pivotal role in clinical decision-making in patients with effort angina (revascularisation or an aggressive medical approach to reversing atherosclerosis) because revascularization improves survival in patients with two- or three-vessel disease only if the proximal LAD is involved.

**Limitations**

Nevertheless, the method also has a number of limitations.

The lack of a common point of reference with angiography (particularly, echocardiography’s lack of constant visualisation of diagonal branches) hampers the establishment of precise Doppler–angiographic correlations.

The method’s potential in diagnosing left main coronary artery stenosis was not explored because none of the patients in our consecutive series showed significant lumen narrowing in this part of the coronary tree. Further studies are needed to address this issue.

Coronary artery occlusion may be difficult to detect, although reverse flow in the LAD and a high degree of flow velocity reversal in intra-myocardial branches may be a marker of occlusion. However, once again, this requires further study.

It can sometimes be difficult to visualize tortuous segments (more common in the elderly), and so some portions of the vessel may not be explored. This may explain some of the false-negative cases (Figure 6 and see Supplementary material online, Table).

The quantitative assessment validation has some limitations: (i) the regression has quite a large confidence interval for the population because of the relatively small sample size, although the limits of agreement are narrow enough to be clinically useful in all but four cases (Figure 7); (ii) the gold standard (CA) based on orthogonal measurements of minimum lumen diameter and the assumption of a circular shape are not ideal for evaluating severity, especially when the lesion is eccentric and/or complex; (iii) the reference velocity used by the continuity equation to assess the percentage reduction in CSA could be critical because, as branches are not detectable, a major undetected branch between the sample volume and the stenosis would disintegrate the equation’s basic assumption. To reduce the risk of including branches between the reference and the stenosis, reference sampling must be made in the immediate proximity of the acceleration while, of course, trying to avoid pre- or post-stenotic jets. In the case of...
the first two points, the quantitative data may be considered only preliminary and exploratory, and need to be confirmed by a larger prospective validation study, possibly using a more appropriate gold standard such as intravascular echocardiography.

Finally, specific training is necessary, and a thorough knowledge of coronary anatomy and its variation is essential.15

Conclusions

The use of contrast-enhanced transthoracic Doppler echocardiography to evaluate BFV throughout the LAD coronary artery is a feasible and reliable means of detecting, locating, and preliminarily assessing the severity of LAD stenoses as it identifies the effect of a stenosis on blood flow dynamics. Further studies are needed to verify the usefulness of the method in specific clinical settings.

Supplementary material

Supplementary material is available at European Heart Journal online.

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References