Non-invasive Diagnostic and Prognostic Assessment of Single-vessel Coronary Artery Disease: Focus on Stress Echocardiography

R. Bigi*, L. Cortigiani and A. Desideri

Cardiovascular Research Foundation, ‘S. Giacomo’ Hospital, Castelfranco Veneto, Italy

**Aims:** Revascularization procedures are increasingly applied in patients with single-vessel coronary artery disease in spite of the fact that a prognostic benefit has been proved only for soft end-points. This review summarizes the results of stress echocardiography in the diagnostic and prognostic assessment of these patients.

**Methods and Results:** The diagnostic and prognostic assessment of patients with single-vessel disease using stress (exercise, dobutamine, adenosine and dipyridamole) echocardiography are focused upon in the light of pathophysiological considerations and the results of clinical studies. Factors affecting test accuracy are individually addressed and comparisons made with different stress testing modalities, including exercise electrocardiography and nuclear techniques. Finally, therapeutic options are discussed and the superior accuracy of the physiological assessment of coronary stenosis as compared to the simple anatomic evaluation emphasized.

**Conclusions:** Patients with single-vessel disease represent an anatomically heterogeneous group. Although the sub-optimal performance of any technique in their evaluation has to be acknowledged, stress echocardiography can effectively contribute to selection of the management strategy.

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**Key Words:** single-vessel disease; coronary artery disease; stress echocardiography.

**Introduction**

Single-vessel coronary artery disease (CAD) is a puzzling clinical setting from both the diagnostic and the prognostic point of view. It may present with variable functional expressions, but is generally associated with a favourable outcome[1–3]. Nevertheless, percutaneous transluminal coronary angioplasty (PTCA) is increasingly applied in these patients despite the fact that a prognostic benefit has been proved only for soft end-points, like recurrence of symptoms[4], and in spite of the superiority of physiological assessment of coronary stenosis compared to angiographic evaluation[5].

In the last few years echocardiographic imaging, combined with exercise or pharmacological stimuli, has been increasingly used for the diagnosis of CAD[6]. The aim of the present article is to summarize the results of this imaging technique in the diagnostic and prognostic assessment of single-vessel disease.

**The Pathophysiological Rationale**

Non-invasive stress tests are often performed not only to detect coronary stenosis, but also to determine the physiological importance of angiographically identified coronary lesions[7,8]. Baptista et al.[9] reported that the minimal lumen diameter was the best angiographic predictor of a positive dobutamine stress test. However, the results of functional testing are even better related to the physiological impairment in coronary flow reserve. Bartunek et al.[10] did not find any relation between the qualitative descriptors of stenosis morphology and the degree of dobutamine-induced dyssynergy. On the other hand, Picano et al.[11] compared the results of dipyridamole stress echocardiography with the severity of CAD, as assessed by quantitative angiography, and the regional coronary reserve, as assessed by dynamic positron emission tomography. They found patients with positive stress echocardiography to have significantly greater area reduction in stenotic vessel and significantly lower maximal regional blood flow in stenotic vessel.

*Corresponding author: R. Bigi, Via Visoli 1, 23037 Tirano, Italy.
area, thus providing evidence of both anatomical and functional correlates of the stenotic lesion. More recently, Danzi et al.[12] reported that stenotic flow reserve, assessed by intracoronary Doppler, is the variable that best describes the functional significance of an isolated lesion of the left anterior descending coronary artery. Even in the case of moderate coronary stenosis, a detailed physiological assessment by means of myocardial fractional flow reserve correlates closely with the results of non-invasive stress tests[13].

All these results are in keeping with previous reports on exercise ECG[14] and nuclear techniques[15-17] and confirm the close correlation between the physiological significance of coronary lesions and the non-invasive assessment of myocardial ischaemia.

### Diagnostic Assessment

Many studies have addressed the issue of the diagnosis of single-vessel disease by exercise ECG with or without radionuclide ventriculography, but almost general agreement exists on the insufficient sensitivity of ECG signal[18] and the poor reproducibility and specificity of radionuclide ventriculography[19].

Studies comparing stress echocardiography and perfusion scintigraphy for assessing single-vessel CAD have been reviewed recently by Geleijnse et al.[20]. Irrespective of the stressor used, perfusion scintigraphy proved to be the more sensitive test (78% vs. 67% with exercise; 78% vs. 69% with dobutamine; 76% vs. 61% with dipyridamole and 81% vs. 51% with adenosine), with a marginally superior specificity using the echocardiographic technique.

The accuracy of stress echocardiography for detecting single-vessel CAD is affected by several factors (Table 1), the majority of which are discussed below.

### Table 1. Factors influencing the diagnostic sensitivity of stress echocardiography in single-vessel disease.

| 1. | Type of stressor. |
| 2. | Severity and location of stenosis. |
| 3. | Effect of anti-ischaemic drugs. |
| 4. | Lesion morphology. |
| 5. | Test protocol. |
| 6. | Collateral circulation. |
| 7. | Status of distal myocardium. |

Critical stenosis by vasodilators, which can lead to inappropriately negative results, particularly in the case of single-vessel disease.

### Severity and Location of CAD

The diagnostic accuracy of dobutamine stress echocardiography depends strongly on the number of diseased coronary arteries[21], with a mean sensitivity of 74% for single-vessel as compared to 86% for double-vessel and 92% for triple-vessel disease. Nevertheless, the degree of difference is smaller as compared with exercise electrocardiography, in which sensitivity for single-vessel disease ranges from 25 to 60%[22]. Moreover, even though coronary angiography is generally considered the gold standard for assessing the diagnostic accuracy of non-invasive tests, visual assessment of stenosis is limited by substantial interobserver variability[23], particularly in the case of intermediate lesions (lumen reduction of 50-70%), where stress echocardiography can contribute to identify the physiological significance of coronary narrowings[24].

The stenosis location also affects the accuracy of stress echocardiography. Mean sensitivity and specificity for individual vessels reported in eight studies[25-32] were as follows: left anterior descending coronary artery 69% and 91%, circumflex coronary artery 43% and 92%, right coronary artery 69% and 88%, respectively.

### Anti-ischaemic Drugs

Anti-ischaemic drugs decrease the sensitivity of both physical and pharmacological stressors[29,33].

The sensitivity of dipyridamole stress seems to be more influenced in both echocardiographic[35-37] and nuclear[36] studies as compared to dobutamine stress. In a placebo-controlled, cross-over study[33], 91% of 57 patients with significant (>70% diameter stenosis) CAD undergoing dipyridamole stress echocardiography developed ischaemia off therapy, whilst only 65% of them did so on therapy (P<0.01). The effect was most marked for the combination of beta-blockers and nifedipine.

The effect of beta-blockade on dobutamine stress echocardiography has been a matter of debate. In experimental single-vessel disease in an animal model, beta-blockers attenuated the ability of dobutamine stress to detect a significant coronary lesion[37,38]. This has been attributed to the reduced increase in heart rate and left ventricular pressure, improvement of regional coronary flow per heart beat and attenuation of regional ischaemic lactate production[39]. Surprisingly, no effect of beta-blockers on the accuracy of dobutamine stress was reported in some clinical studies[39-41], whilst a correlation of this therapy with false negative results was reported by others[42]. A possible explanation of this discrepancy is that more symptomatic CAD, which is therefore more severe and more likely to precipitate
ischaemia, is more frequently on treatment. On the other hand, non-beta-blocker antianginal therapy showed only a modest effect[43]. However, additional atropine co-administration can effectively counterbalance the limiting effect of both beta-blocker and non-beta-blocker therapy on diagnostic sensitivity of dobutamine stress[28,41,64].

The influence of drugs on the ischaemic response at stress echo can be also used to control anti-ischaemic drug effects[45]. This can be of interest in patients with single-vessel disease who most benefit from appropriate medical treatment.

**Lesion Morphology**

The accuracy of stress echocardiography generally parallels the severity of CAD[46]. However, the importance of plaque morphology has also been emphasized by recent studies[47-49]. Complex lesions (angiographic characteristics suggestive of thrombi and/or ulcer) were associated with higher sensitivity (85% vs. 53% in simple lesions, P<0.001) using dipyridamole[47-48]. This result was not confirmed in a later study with dobutamine[50]. The pathophysiological background for the better correlation of dipyridamole echo and stenosis morphology could be related to the more extensive endothelial involvement in the case of complex stenosis[48].

**Miscellaneous Factors**

Conditions reducing compensatory microvascular dilatation (such as left ventricular hypertrophy, arterial hypertension or increased low-density-lipoprotein cholesterol) and left anterior descending location of coronary stenosis may inflate the sensitivity of stress echocardiography. Increasing stenosis severity has a similar effect, whilst milder stenosis, even limiting peak hyperaemic flow, may produce little or no ischaemia[51]. Similarly, the presence of collaterals and submaximal tests may underscore sensitivity, particularly in the case of moderate stenosis. Finally, resting echocardiographic aspects related to the pathophysiological status of the myocardium may decrease (scar) or increase (viable) diagnostic sensitivity.

**Prognostic Assessment**

Patients with single CAD and positive stress tests are frequently revascularized. Consequently, the prognostic value of any stress testing modality is difficult to assess. Although exercise-dependent techniques convey prognostic information in patients with multivessel disease, a similar evidence in patients with single-vessel disease was not definitely proved[52,55,58-63]. Moreover, single-vessel disease population was not separately analysed in a consistent proportion of studies. In order to verify whether pharmacological stress echocardiography could contribute to risk stratification in this clinical setting, Cortigiani et al.[59] analysed data from 754 single-vessel disease patients. On multivariate analysis, positive stress echo was the only independent predictor of death and myocardial infarction (odds ratio = 2.9) in medically treated patients. Moreover, a significantly higher 4-year event-free survival was found in invasively versus medically treated patients with a positive (P=0.012) but not with a negative (P=0.853) stress result, thus emphasizing the superior benefit from an ischemia-guided therapeutic strategy.

Detection of myocardial viability after acute uncomplicated infarction with low dose dobutamine has been shown to predict unstable angina[59]. Moreover, we recently demonstrated that ischaemia in dys-synergic but viable segments can predict cardiac events[60]. The clinical impact of these data in the subset of patients with single-vessel disease is still unknown.

**Therapeutic Options**

Historical data of the CASS Study show that medically treated patients with single-vessel disease had a 10-year survival rate not statistically different than those undergoing surgery[63]. These findings have been confirmed by the Duke Data Bank Registry[64]. The ACME study[4] randomized 328 patients with a positive exercise ECG, 166 to PTCA and 162 to medical treatment. Five-year results revealed that more patients were angina-free and drug-free with PTCA than with medical treatment. However, the number of events and hospitalizations in the two groups was similar. Even in patients with proximal left anterior descending coronary artery involvement, no differences were found in terms of incidence of infarction and death between medically treated and revascularized patients in the MASS Study[65]. Moreover, broad basis clinical practice failed to demonstrate a reduction of subsequent myocardial infarction or death even with use of coronary stenting[66]. Stress echocardiography has been demonstrated to be a reliable method to detect relevant restenosis after PTCA, and helps to select patients who may benefit from repeated angiography[67-69].

**Conclusions**

The practice of performing coronary revascularization purely on the basis of the anatomic data, with no knowledge of their functional correlates, is a frequent but inadequate therapeutic option. Patients with single-vessel disease are an anatomically heterogeneous group as regards location and severity of stenosis, plaque morphology, collateral circulation and presence of viable or infarcted myocardium. This heterogeneity explains the difficulties in demonstrating the superiority of an ischaemia-guided strategy as compared to a direct
referral to revascularization. Indeed, the suboptimal performance of any technique in the evaluation of single-vessel disease has to be acknowledged: 75–80% for perfusion imaging and 65–70% for stress echocardiography. In particular, the pharmacological stressor (adenosine) or the anatomical location of the disease (circumflex coronary artery) can negatively affect the performance of stress echocardiography (52% and 43%, respectively). Nevertheless, this technique provides a panoramic view on the main markers of risk (i.e., resting function, viability and ischaemia) and, therefore, may be of help in selecting the management strategy for the individual patient.

References


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