Current perspectives
Diagnosing coronary artery disease in patients with hypertension: a resolved dilemma?

Gabriele Fragasso

Department of Cardiology and Cardiovascular Sciences, Clinical Cardiology Unit, Hospital "San Raffaele", Milan, Italy

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Patients with hypertension frequently complain of chest pain and exhibit ischemic-like ST segment changes on exercise electrocardiogram. However, the specificity of such changes for predicting significant coronary artery disease is very low, since these patients often exhibit a normal coronary angiogram. Several alternative non-invasive tests have been proposed and, recently, the relative performance of the available techniques has been systematically assessed.

The purpose of this article is to review the relevant literature on the diagnostic tests employed in the clinical setting. Recent evidence suggests that stress echocardiography yields a better diagnostic accuracy than perfusion scintigraphy in identifying significant epicardial coronary artery disease in patients with hypertension. The low specificity of myocardial scintigraphy probably relates to the fact that this method traces perfusion abnormalities, not necessarily caused by epicardial coronary artery disease, possibly due to microvascular disease, and not axiomatically causing obvious wall motion abnormalities.

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Address:

Dr. Gabriele Fragasso

Dipartimento di Cardiologia e Scienze Cardiovascolari
Unità di Cardiologia Clinica
Istituto Scientifico "San Raffaele"
Via Olgettina, 60
20132 Milano
E-mail: fragasso.gabriele@hsr.it

Introduction

The relation between hypertension and coronary atherosclerosis is well recognized[1-3]. Hypertension is a major risk factor for coronary artery disease (CAD), since it accelerates atherogenesis. On the other hand, CAD is the major cause of morbidity and mortality in hypertensive patients. Therefore, the accurate diagnosis of CAD in patients with arterial hypertension bears important therapeutic and prognostic implications. Both diseases may result in similar clinical events and frequently occur in the same patient[4,5]. If the presence of epicardial CAD can be excluded by non-invasive means, the risks and costs of coronary arteriography can be avoided. Yet, the non-invasive detection of CAD in hypertensive patients with chest pain remains an unresolved issue[5]. The use of exercise electrocardiography is limited by its low specificity, regardless of whether hypertension is associated with left ventricular hypertrophy or not[6]. In this context, myocardial perfusion scintigraphy has been proposed as a more specific alternative, but its specificity is far from being ideal[7-10]. Recently, both dipyridamole and dobutamine stress echocardiography have been proposed as useful tools for the diagnosis of CAD in hypertensive patients[11,12].

The purpose of this article is to review the relevant literature on the diagnostic tests employed in the clinical setting. Recent evidence suggests that stress echocardiography yields a better diagnostic accuracy than perfusion scintigraphy, which is penalized by a fairly low specificity, in identifying significant epicardial CAD in patients with hypertension[13]. Clinical implications of these findings are discussed.

Exercise electrocardiography

The use of exercise stress testing for determining the probability of obstructive epicardial CAD in hypertensive patients lacks specificity[5,6]. Undiagnosed hypertrophy may be present even in the absence of electrocardiographic signs[14], and exercise-induced diagnostic ST segment depression may result from transmural flow redistribution due to increased left ventricular mass rather than to obstructive epicardial CAD[15]. For these reasons, it has been suggested that the use of exercise stress testing to diagnose CAD in hy-

pertensive patients with chest pain should be abandoned[5]. However, considering its very high sensitivity, we believe that this simple procedure should be performed in all hypertensive patients with chest pain as a first screening test. In fact, exercise testing provides several additional information, useful for the management of the hypertensive patient and, when negative, it is sufficient to reassure both the doctor and the patient. Conversely, when positive, the presence of CAD must be excluded with a supplementary non-invasive test. This is why a number of non-invasive investigations have been proposed, in an attempt to overcome the limited significance of a positive exercise test.

Myocardial perfusion scintigraphy

According to previous studies[7-10], in patients with hypertension and chest pain symptoms, stress-rest myocardial perfusion scintigraphy frequently yields false positive results, possibly due to microvascular abnormalities[16,17]. Indeed, microvascular dysfunction, which has been previously hypothesized to be the cause of ST segment abnormalities during dipyridamole administration in patients with arterial hypertension and chest pain[11], may be the cause of inhomogeneous myocardial perfusion both at rest and during stress. Increased medial thickness has been reported in coronary arterioles from hypertensive patients undergoing endomyocardial biopsy[18]. This could explain the reduction in coronary reserve and maximal flow capacity consistently observed in these patients, whose flow response to atrial pacing is blunted and is further decreased by the administration of ergonovine[19]. Thus, besides structural alterations, the microvasculature may also show functional derangements leading to abnormal vasoconstriction in response to vasoactive stimuli[20-22]. The reduction in coronary flow reserve is unrelated to the presence of left ventricular hypertrophy[23,24]. Accordingly, no relation between left ventricular mass and exercise-induced perfusion defects has been observed[13], which further supports the hypothesis that a microvascular disorder is present in the coronary circulation of patients with hypertension[25].

Stress echocardiography

Transient myocardial wall motion abnormalities induced by different pharmacological and physiological stressors are usually the earliest and most evident signs of acute myocardial ischemia[26]. Wall motion abnormalities can be identified promptly by means of cardiac ultrasound examination. As a consequence, stress echocardiography has become a worldwide adopted method for the evaluation of patients with suspected CAD and inconclusive plain exercise testing[27,28]. Specifically, both dipyridamole and dobutamine stress echocardiography have been reported to be useful for the detection of obstructive epicardial CAD in hypertensive patients[11,12]. Even when patients with left ventricular hypertrophy are excluded, exercise electrocardiography remains a poor predictor of CAD. Conversely, dobutamine echocardiography is a powerful predictor, in patients both with and without left ventricular hypertrophy. It has been shown that only patients with severe left ventricular hypertrophy (left ventricular mass index > 200 g/m^2) may have the potential for ischemia due to abnormalities of coronary flow reserve and under conditions of extreme oxygen demand[15]. Thus, the specificity of dobutamine stress echocardiography might be impaired only in patients with gross left ventricular hypertrophy.

Comparison of non-invasive tests

Comparative studies using all the previously cited techniques have not been performed. In a recent paper[13] we reported the results of a study performed in 101 consecutive patients with arterial hypertension referred to our cardiology outpatient clinic for rest and/or effort typical angina and a positive exercise test. None of the patients had had a previous myocardial infarction. In order to avoid interference with the study investigations, all anti-ischemic drugs, such as nitrates, beta-blockers and calcium antagonists were discontinued for the whole study duration. In order to control blood pressure during the study period, patients were given ACE-inhibitors and/or diuretics, as necessary. All study subjects had a reproducible positive exercise test. They all underwent stress-rest myocardial single photon emission computed tomography with 99mTc-MIBI, dipyridamole and dobutamine stress echocardiography and coronary angiography. Head-to-head comparison of these tests was performed.

Of the 101 patients studied, 57 (56%) had significant CAD, while the remaining 44 (44%) exhibited either angiographically smooth coronary arteries (34 patients) or minor vessel wall irregularities (10 patients). Twenty patients had one-vessel, 26 two-vessel and the remaining 11 three-vessel disease. Dipyridamole and dobutamine stress echocardiograms and perfusion scintigrams identified respectively 35, 50 and 56 of the 57 patients with CAD, with a relative sensitivity of 61, 88 and 98%. The three tests correctly identified respectively 40, 35 and 16 of the 44 patients with normal coronary arteries, yielding a specificity of 91, 80 and 36%. The negative predictive value was highest (94%) for MIBI while the positive predictive value was greatest for dipyridamole (90%). Dobutamine had similar positive and negative predictive values (85-83%). As a result, overall diagnostic accuracy for dipyridamole-dobutamine and perfusion scintigraphy was 74, 84 and 71%, respectively (Fig. 1)[13]. The results of the tests were concordant in 46 patients (32 with CAD and 12 with normal coronary ar-

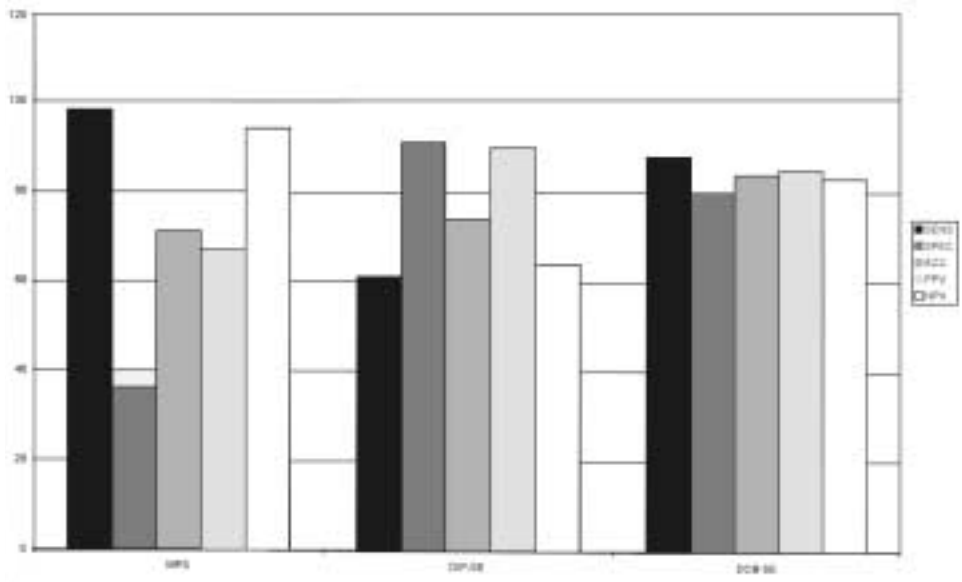

Figure 1. *Histogram showing sensitivity (SENS), specificity (SPEC), accuracy (ACC), positive (PPV) and negative (NPV) predictive values of myocardial perfusion scintigraphy (MPS), dipyridamole (DIP-SE) and dobutamine (DOB-SE) stress echocardiography, for the detection of coronary artery disease in hypertensive patients with chest pain and positive exercise test. From Fragasso et al.[13], modified.*

teries). The sensitivity to predict the presence of single, double and triple-vessel disease was 31, 69 and 82% for dipyridamole, 85, 88 and 91% for dobutamine, and 95, 100 and 100% for MIBI, respectively. Dobutamine infusion time was 13.2 ± 3.7, 13.6 ± 3.1 and 12.9 ± 2.9 min in one, two and three-vessel disease, respectively (p = NS). The sensitivity of the three tests to detect isolated left anterior descending CAD (5 patients, mean percent stenosis 71 ± 21%) was 40, 80 and 100% respectively. These figures were 78, 93 and 96% respectively, when left anterior descending CAD was present in patients with multivessel disease. All three tests were positive and concordant in 2 patients with normal coronary arteries (3 segments) and in 25 patients with CAD (37 segments). All tests were negative in 4 patients with normal coronary arteries and in none of CAD patients. Overall, they gave concordant results in 31 patients (31%).

These results confirm the poor diagnostic accuracy of exercise electrocardiography, since 44 patients with a positive test turned out to have angiographically normal coronary arteries. Both dipyridamole and dobutamine stress echocardiography yielded a superior diagnostic accuracy. Specifically, and in keeping with previous investigations[29,30], dipyridamole exhibited very high specificity with a relatively low sensitivity for the detection of CAD. Conversely, dobutamine yielded high sensitivity (88%) with satisfactory specificity (80%). The discrepancy between the results obtained by the two stressors probably relates to the mechanisms by which they cause ischemia. Dipyridamole induces transmural flow redistribution via the inhibition of adenosine breakdown that causes arteriolar vasodilation and subendocardial "steal". Therefore, this agent causes ischemia almost exclusively by altering coronary hemodynamics in the presence of critical epicardial disease. Indeed, in our study, the sensitivity of the test progressively increased with the progression of CAD extent. This suggests that the greater the impairment of coronary hemodynamics, the more likely dipyridamole to cause ischemia. Dobutamine increases myocardial oxygen consumption by sympathetic stimulation that causes heart rate and contractility to increase[31-33]. Like dipyridamole, this agent causes arteriolar coronary dilation (and transmural flow redistribution), due to metabolic stimulation and increased ATP breakdown; additionally, it causes oxygen demand to increase. Therefore, it is not surprising that this agent yields a greater sensitivity for detecting epicardial CAD, with very little loss in specificity and significantly greater diagnostic accuracy. Furthermore, the ability of dobutamine stress echo to detect epicardial coronary stenoses was not apparently related to the extent of the disease. In fact, the sensitivity of the test did not significantly increase with the progression of disease severity, as also evidenced by similar dobutamine infusion times in patients with one, two or three-vessel disease. This finding is at variance with previous reports, which showed a direct relation between dobutamine sensitivity and the extent of CAD[33]. It is possible that in our selected population of hypertensive patients the likelihood of a positive test may have somewhat increased, due to a reduction in the ischemic threshold induced by a greater left ventricular mass index and/or coexisting microvascular abnormalities, regardless of the extent of CAD.

Therefore, when patients with hypertension, chest pain and positive exercise test are elected to undergo further diagnostic stratification with stress echocardiography, dobutamine rather than dipyridamole should be considered as the first choice pharmacologic stressor.

However, this statement does not apply for the diagnosis of CAD in the general population, where the choice of the best stressor is still under debate. Although the American College of Cardiology/American Heart Association guidelines advocate the adoption of adrenergic stimulation[34], in some studies pharmacological stress echocardiography using vasodilator agents does appear to be valuable in detecting inducible myocardial ischemia and in determining prognosis[35].

A previous study has shown that dobutamine echocardiography and myocardial perfusion scintigraphy have similar diagnostic accuracies for the diagnosis of CAD in hypertensive patients[36]. Conversely, in our study, the diagnostic value of dobutamine stress echo also appeared to be better than that of perfusion scintigraphy. The reason for this discrepancy could depend on the fact that in the study of Elhendy et al.[36] the adoption of dobutamine, instead of exercise, in conjunction with scintigraphy might have improved the diagnostic accuracy of the nuclear test. In fact, the impact of exercise in hypertensive patients might render the test less accurate for the diagnosis of significant epicardial CAD, as already pointed out, while the stress induced by dobutamine may be more specific. Additionally, in our study we recruited only patients with a positive exercise test who are very likely to have true subendocardial ischemia and perfusion abnormalities, even in the absence of significant coronary artery stenoses.

The simple scrutiny of these figures should be enough to allow the conclusion that in patients with hypertension, angina and positive exercise test, stress-rest myocardial perfusion scintigraphy does not allow for an accurate prediction of obstructive epicardial CAD. When non-invasive assessment is envisaged, stress echocardiography should be preferred.

The choice of the stressor

Dobutamine increases oxygen demand by increasing contractility, heart rate and systolic blood pressure. These features make dobutamine an ideal stressor in hypertension. Conversely, dipyridamole produces coronary vasodilation, with little "myocardial stress" as defined by changes in rate-pressure product and lesser likelihood to cause myocardial ischemia. This is why dipyridamole yields high sensitivity when used with scintigraphy, where perfusion abnormalities are thought to represent areas of altered blood flow rather than areas of ischemia[37,38]; but this is also why its sensitivity might be low when used with echocardiography. Surely, the addition of atropine improves sensitivity[39], but leaves misdiagnosed a large proportion of patients with single-vessel disease[40-42]. On the basis of these considerations, we think that dobutamine provides the best performance for the diagnosis of CAD in hypertensive patients.

Exercise may represent a valid alternative to pharmacologic stressors, possibly yielding even better diagnostic accuracy than dobutamine, when performed by expert echocardiographers[30,40].

Beyond diagnosis: interpreting positive tests in hypertensive patients with normal coronary arteries

From the studies reviewed in the previous chapters, it appears that hypertensive patients may develop transient myocardial ischemia despite normal epicardial coronary arteries. Myocardial perfusion scintigraphy appears as a very sensitive tool to detect myocardial ischemia in these patients, whose ischemia is very likely related to hypertension-induced microvascular dysfunction. The physician in the outpatient clinic may be happy to know that his/her patient has normal coronary arteries and, for this reason, inclined to think that the evidence of ischemia is anyhow tied to a good prognosis. However, the latter assumption has not been demonstrated by any specific study, i.e. we do not know whether a hypertensive patient with normal coronary arteries but instrumental evidence of transient myocardial ischemia will bear a worse prognosis, compared to a patient without ischemia. Additionally, which therapy would be more appropriate in patients with evidence of ischemia? In arterial hypertension, cardiac remodeling comprises myocyte hypertrophy, interstitial fibrosis and functional and structural alterations of the coronary microcirculation, leading to impairment of coronary reserve[20-22], which can be already present in young patients with borderline hypertension[43,44]. Consequently, antihypertensive treatment should aim at repairing hypertensive cardiac remodeling through reversing myocyte hypertrophy, restoring myocardial structure and improving coronary flow reserve along with blood pressure normalization[3]. Preliminary clinical data indicate that, after prolonged antihypertensive treatment, coronary and peripheral flow reserve can be improved in hypertensive patients with microvascular disease[24,45]. Further studies are warranted to elucidate whether improved coronary flow reserve after medical treatment for arterial hypertension is due to an influence of myocardial factors, such as left ventricular hypertrophy or myocardial fibrosis, or to the repair of the structurally remodeled microcirculation. In a research context, the use of absolute blood flow measurements by positron emission tomography before and after interventions would certainly provide unique insights into the pathophysiology of hypertensive cardiomyopathy[46].

Conclusions

Chest pain is a common complaint among hypertensive patients. Hypertension and CAD may present

with symptoms and signs that are clinically indistinguishable. A positive exercise electrocardiogram is not reliably predictive of obstructive epicardial CAD and should prompt the physician to pursue additional noninvasive testing. For this purpose stress echocardiography appears as the most valuable tool. Among pharmacologic stressors, dobutamine stress echocardiography should be the first choice. Myocardial perfusion imaging yields a very low specificity and therefore does not help in excluding the presence of epicardial CAD in hypertensive patients with chest pain and positive exercise test. However, carefully performed prospective studies on the prognostic significance of perfusion defects in hypertensive patients with chest pain and positive exercise test are not available. Long-term follow-up of such patients would merit major consideration.

References

1. Pooling Project Research Group. Relationship of blood pressure, serum cholesterol, smoking habits, relative weight and ECG abnormalities to incidence of major coronary events: final report of the Pooling Project. J Chron Dis 1978; 31: 201-306.
2. Chobanian AV. The influence of hypertension and other haemodynamic factors in atherogenesis. Prog Cardiovasc Dis 1983; 26: 177-96.
3. Fröhlich ED, Apstein C, Chobanian A, et al. The heart in hypertension. N Engl J Med 1992; 327: 998-1008.
4. Fröhlich ED. Coexistence of hypertensive and coronary arterial disease. Hypertension 1987; 10: 473-4.
5. Prisant LM, Frank MJ, Carr AA, et al. How can we diagnose coronary heart disease in hypertensive patients? Hypertension 1987; 10: 467-72.
6. Wroblewski EM, Pearl FJ, Hammer WJ, Bove AA. False positive stress tests due to undetected left ventricular hypertrophy. Am J Epidemiol 1982; 115: 412-7.
7. Schulman DS, Francis CK, Black HR, Wackers FJT. Thallium-201 stress imaging in hypertensive patients. Hypertension 1987; 10: 16-21.
8. DePuey EG, Guertler-Krawczynska E, Perkins JV, et al. Alterations in myocardial thallium-201 distribution in patients with chronic systemic hypertension undergoing single-photon emission computed tomography. Am J Cardiol 1988; 62: 234-8.
9. Houghton JL, Frank MJ, Carr AA, et al. Relations among impaired coronary flow reserve, left ventricular hypertrophy and thallium perfusion defects in hypertensive patients without obstructive coronary artery disease. J Am Coll Cardiol 1990; 15: 43-51.
10. Prisant ML, von Dohlen TW, Houghton JL, Carr AA, Frank MJ. A negative thallium (± dipyridamole) stress test excludes significant obstructive epicardial coronary artery disease in hypertensive patients. Am J Hypertens 1992; 5: 71-5.
11. Picano E, Lucarini AR, Lattanzi F, et al. Dipyridamole echocardiography in essential hypertensive patients with chest pain. Hypertension 1988; 12: 238-43.
12. Senior R, Basu S, Handler C, et al. Diagnostic accuracy of dobutamine stress echocardiography for detection of coronary heart disease in hypertensive patients. Eur Heart J 1996; 17: 289-95.
13. Fragasso G, Lu C, Dabrowski P, Pagnotta P, Sheiban I, Chierchia SL. Comparison of stress/rest myocardial perfusion tomography, dipyridamole and dobutamine stress echocardiography for the detection of coronary disease in hypertensive patients with chest pain and positive exercise test. J Am Coll Cardiol 1999; 34: 441-7.
14. Carr AA, Prisant LM, Watkins LO. Detection of hypertensive left ventricular hypertrophy. Hypertension 1985; 7: 948-54.
15. Marcus ML, Harrison DG, Chilian WM, et al. Alterations in the coronary circulation in hypertrophied ventricles. Circulation 1987; 75 (Suppl I): I19-I25.
16. Yrenev AP, DeQuattro V, Dubov PB, et al. Silent myocardial ischemia in patients with essential hypertension. Am J Hypertens 1992; 5: 169S-174S.
17. Iriarte M, Caso R, Murga N, et al. Microvascular angina pectoris in hypertensive patients with left ventricular hypertrophy and diagnostic value of exercise thallium-201 scintigraphy. Am J Cardiol 1995; 75: 335-9.
18. Schwarzkopf B, Motz W, Frenzel H, et al. Structural and functional alterations of the intramyocardial coronary arterioles in patients with arterial hypertension. Circulation 1993; 88: 993-1003.
19. Brush JE, Cannon RO, Schenke WH, et al. Angina due to coronary microvascular disease in hypertensive patients without left ventricular hypertrophy. N Engl J Med 1988; 319: 1302-7.
20. Opherk D, Mall G, Zebe H, et al. Reduction of coronary reserve: a mechanism for angina pectoris in patients with arterial hypertension and normal coronary arteries. Circulation 1984; 69: 1-7.
21. Treasure CB, Klein JL, Vita JA, et al. Hypertension and left ventricular hypertrophy are associated with impaired endothelium mediated relaxation in human coronary resistance vessels. Circulation 1993; 87: 86-93.
22. Antony I, Nitemberg A, Foult JM, Aptecar E. Coronary vasodilator reserve in untreated and treated hypertensive patients with and without left ventricular hypertrophy. J Am Coll Cardiol 1993; 22: 514-20.
23. Camici P, Chiriatti G, Lorenzoni R, et al. Coronary vasodilation is impaired in both hypertrophied and nonhypertrophied myocardium of patients with hypertrophic cardiomyopathy: a study with nitrogen-13 ammonia and positron emission tomography. J Am Coll Cardiol 1991; 17: 879-86.
24. Parodi O, Neglia D, Palombo C, et al. Comparative effects of enalapril and verapamil on myocardial blood flow in systemic hypertension. Circulation 1997; 96: 864-73.
25. Parodi O, Sambuceti G. The role of coronary microvascular dysfunction in the genesis of cardiovascular diseases. Q J Nucl Med 1996; 40: 9-16.
26. Davies GJ, Bencivelli W, Fragasso G, et al. Sequence and magnitude of ventricular volume changes in painful and painless myocardial ischemia. Circulation 1988; 78: 310-9.
27. Picano E. Stress echocardiography. From pathophysiological toy to diagnostic tool. Circulation 1992; 85: 1604-12.
28. Marwick TH. Stress echocardiography. Its role in the diagnosis and evaluation of coronary artery disease. Norwell, MA: Kluwer Academic Publishers, 1994.
29. Margonato A, Chierchia S, Cianflone D, et al. Limitations of dipyridamole-echocardiography in effort angina pectoris. Am J Cardiol 1987; 59: 225-30.
30. Dagianti A, Penco M, Agati L, et al. Stress echocardiography: comparison of exercise, dipyridamole and dobutamine in detecting and predicting the extent of coronary artery disease. J Am Coll Cardiol 1995; 62: 18-25.
31. Tuttle RR, Mills J. Dobutamine: development of a new catecholamine to selectively increase cardiac contractility. Circ Res 1975; 36: 185-96.
32. Sawada SG, Segar DS, Ryan T, et al. Echocardiographic detection of coronary artery disease during dobutamine infusion. Circulation 1991; 83: 1605-14.
33. Mazeika PK, Nadazdin A, Oakley CM. Dobutamine stress echocardiography for detection and assessment of coronary artery disease. J Am Coll Cardiol 1992; 19: 1203-11.

34. Cheitlin MD, Alpert JS, Armstrong WF, et al. ACC/AHA Guidelines for the Clinical Application of Echocardiography. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Clinical Application of Echocardiography). Developed in collaboration with the American Society of Echocardiography. Circulation 1997; 95: 1686-744.
35. Picano E, Bedetti G, Varga A, Cseh E. The comparable diagnostic accuracy of dobutamine and dipyridamole stress echocardiography: a meta-analysis. Coron Artery Dis 2000; 11: 151-9.
36. Elhendy A, Geleijnse ML, van Domburg RT, et al. Comparison of dobutamine stress echocardiography and technetium-99m sestamibi single-photon emission tomography for the diagnosis of coronary artery disease in hypertensive patients with and without left ventricular hypertrophy. Eur J Nucl Med 1998; 25: 69-78.
37. Wackers FJ. Pharmacological stress with dipyridamole: how lazy can one be? J Nucl Med 1990; 31: 1024-7.
38. Kumar EB, Steel SA, Howey S, Caplin JL, Aber CP. Dipyridamole is superior to dobutamine for thallium stress imaging: a randomised cross-over study. Br Heart J 1994; 71: 129-34.
39. Picano E, Pingitore E, Conti U, et al. Enhanced sensitivity for detection of coronary artery disease by addition of atropine to dipyridamole echocardiography. Eur Heart J 1993; 14: 1216-22.
40. Beleslin BD, Ostojic M, Stepanovic J, et al. Stress echocardiography in the detection of myocardial ischemia. Head-to-head comparison of exercise, dobutamine and dipyridamole tests. Circulation 1994; 90: 1168-76.
41. Marwick T, Willemart B, D'Hondt AM, et al. Selection of the optimal non exercise stress for the evaluation of ischemic regional myocardial dysfunction and malperfusion: comparison of dobutamine and adenosine using echocardiography and 99m Tc-MIBI single photon emission tomography. Circulation 1993; 87: 345-54.
42. Previtali M, Lanzarini L, Fetiveau R, et al. Comparison of dobutamine stress echocardiography, dipyridamole stress echocardiography and exercise stress testing for diagnosis of coronary artery disease. Am J Cardiol 1993; 72: 865-70.
43. Motz W, Strauer BE. Therapy of hypertensive cardiac hypertrophy and impaired coronary microcirculation. J Cardiovasc Pharmacol 1994; 24 (Suppl 1): S34-S38.
44. Laine H, Raitakari OT, Niinikoski H, et al. Early impairment of coronary flow reserve in young men with borderline hypertension. J Am Coll Cardiol 1998; 32: 147-53.
45. Virdis A, Ghiadoni L, Lucarini A, Di Legge V, Taddei S, Salvetti A. Presence of cardiovascular structural changes in essential hypertensive patients with coronary microvascular disease and effects of long-term treatment. Am J Hypertens 1996; 9: 361-9.
46. Strauer BE, Schwartzkopff B, Kelm M. Assessing the coronary circulation in hypertension. J Hypertens 1998; 16: 1221-33.