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Prognostic implication of stress echocardiography in 6214 hypertensive and 5328 normotensive patients

Lauro Cortigiani[1], Riccardo Bigi[2], Patrizia Landi[3], Francesco Bovenzi[1], Eugenio Picano[3], and Rosa Sicari[3]*

[1]Division of Cardiology, Campo di Marte Hospital, Lucca, Italy; [2]Cardiology, Department of Medicine and Surgery, University School of Medicine, Milan, Italy; and [3]Institute of Clinical Physiology, CNR, Via G. Moruzzi, 1, 56124 Pisa, Italy

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Aims To compare the prognostic implication of stress echocardiography (SE) in a large cohort of hypertensive and normotensive patients with known or suspected coronary artery disease (CAD). The relative prognostic meaning of the SE result in hypertensive and normotensive patients remains to be addressed.

Methods and results The study group was formed by 11 542 patients (6214 hypertensive patients; 5328 normotensive patients) who underwent exercise ($n = 686$), dobutamine ($n = 2524$), or dipyridamole ($n = 8332$) SE for evaluation of known ($n = 4563$) or suspected ($n = 6979$) CAD. Patients were followed up for a median of 25 months (1st quartile, 7; 3rd quartile, 57). Ischaemia on SE (new wall motion abnormality) was detected in 3209 (28%) patients. During follow-up, 1587 events (924 deaths, 663 non-fatal infarctions) occurred. Patients ($n = 2764$) undergoing revascularization were censored. The annual event rate was 7.0% in hypertensive and 5.7% in normotensive patients ($P = 0.02$) with known CAD, and 3.7% in hypertensive and 2.4% in normotensive patients ($P < 0.0001$) with suspected CAD. Ischaemia on stress echo, resting wall motion abnormality (RWMA), age, male sex, and diabetes mellitus were multivariable prognostic predictors in both patient groups. Analysing data according to the interaction of prognostically important echocardiographic covariates, such as ischaemia on SE and RWMA, an effective risk assessment was obtained in hypertensive as well as normotensive patients. The annual event rate was markedly higher in hypertensive than in normotensive patients with no ischaemia and no RWMA (2.5 and 1.7%, $P = 0.0001$). Finally, the incremental prognostic value of inducible ischaemia over clinical evaluation and resting left ventricular function was greater in hypertensive than in normotensive patients both with known and suspected CAD.

Conclusion The SE result allows an effective prognostication in hypertensive and normotensive patients. However, a non-ischaemic test predicts better survival in normotensive than in hypertensive patients with no RWMA.

Keywords Hypertension • Stress echocardiography • Prognosis

Coronary artery disease (CAD) is the first cause of morbidity and mortality in hypertensive patients.[1–3] Thus, the assessment of risk with non-invasive stress testing is of major importance to optimize clinical management of these patients. Unfortunately, the use of exercise electrocardiography and nuclear techniques is burdened by a high rate of false-positive response in the hypertensive population[4] due to reduced coronary flow reserve in the absence of obstructive CAD.[5,6] Compared with exercise electrocardiography, stress echocardiography (SE) provides similar sensitivity but superior diagnostic specificity.[7–11] Moreover, SE tests have proved to have a higher specificity than perfusion scintigraphy (91–100 vs. 36–47%), with comparable sensitivity (88–78 vs. 98–100%).[12,13] The prognostic value of SE is well established in hypertensive patients with suspected CAD[14–16] as well as in unselected cohorts of hypertensive patients.[17–19] It has been demonstrated that in patients with known or suspected CAD, SE is an

* Corresponding author: Tel: +39 050 3152397, Fax: +39 050 3152374, Email: rosas@ifc.cnr.it

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independent predictor of cardiac death, incremental to other parameters: patients with a negative stress echo are at very low risk for death (<1%/year), whereas in those with a positive test, the more severe the inducible ischaemia (i.e. the higher the rest stress variation in wall motion score index (WMSI) or the lower the dose achieved) the worse is the outcome.[20]

The present multi-centre, observational study was aimed at assessing if the established SE parameters related to outcome showed a different behaviour in normotensive and hypertensive patients with known or suspected CAD.

Methods

Patients

From the prospective data bank of three different Italian institutions (Lucca, Pisa, Milan), 11 831 patients tested with SE between 1995 and 2007 were initially selected. No patient had significant valvular or congenital heart disease, significant co-morbidity reducing life expectancy to <1 year, and an inadequate acoustic window. The number of patients excluded from data analysis due to poor images was <2%. We excluded from the analysis 210 patients who did not enter the data bank due to a poor acoustic window, which was an exclusion criteria for study enrolment. Two hundred and eighty-nine (2%) patients were lost to follow-up. The remaining 11 542 patients, 6214 (54%) of whom were hypertensive,[1] formed the study population. Indication to SE was suspected CAD in 6979 (60%) and risk stratification of known CAD [i.e. history of acute coronary syndromes (ST elevation myocardial infarction or Non-ST elevation myocardial infarction)] or coronary revascularization and/or angiographic evidence of >50% diameter coronary stenosis) in 4563 (40%) individuals. The stressor used (686 exercise, 2524 dobutamine, and 8332 dipyridamole) was chosen on the basis of specific contraindications, local facilities, and physicians' preferences. Pharmacological SE was used when the exercise electrocardiography result was unfeasible, non-diagnostic, or inconclusive. The choice of the pharmacologic stressor was made on the basis of potential relative contraindications of one over the other and on the basis of a gradient of tolerability, dipyridamole being safer[21] and more feasible than dobutamine, particularly in patients with hypertension.[22] The diagnosis of hypertension was based on at least two blood pressure measurements per visit and at least two to three visits, although in particularly severe cases, the diagnosis was based on measurements taken at a single visit.[1] Stress echocardiography was performed on anti-anginal medical therapy in 3872 (34%; β-blockers in 2129, calcium antagonists in 1784, or nitrates in 1947) and off therapy in 7670 (66%) patients. Informed consent was obtained from all patients before testing, and the study protocol was approved by the institutional Ethics Committee. Stress echo data were collected and analysed by stress echocardiographers not involved in patient care. All investigators of the contributing centres passed quality control criteria for regional wall motion prior to entering the study as previously described.[23] Diabetes mellitus[24] and hypercholesterolaemia[25] were defined according to standard definitions.

Patients were followed up for a median of 25 months (1st quartile, 7; 3rd quartile, 57) with a minimum pre-defined follow-up time of 3 months.

Stress protocol

Exercise stress echo was conducted using a semi-supine bicycle ergometer with 25 W incremental loading every 2 min. Dipyridamole (up to 0.84 mg over 10 min with co-administration of atropine up to 1 mg, or up to 0.84 mg over 6 min) and dobutamine (up to 40 mg/kg/min with co-administration of atropine up to 1 mg) stress echo were performed according to the well-established protocols.[26]

Echocardiographic analysis

Echocardiographic images were semi-quantitatively assessed using a 17-segment, four-point scale model of the left ventricle.[27] *During the procedure, blood pressure and electrocardiogram were recorded each minute.* A WMSI was derived by dividing the sum of individual segment scores by the number of interpretable segments. Ischaemia was defined as stress-induced new and/or worsening of pre-existing wall motion abnormality, or biphasic response (i.e. low-dose improvement followed by high-dose deterioration). Necrotic pattern was akinetic or dyskinetic myocardium with no thickening during stress. A test was normal in case of no rest and stress wall motion abnormality. A test was considered positive when at least two adjacent segments of the same vascular territory showed an increment of WMSI (worsening of regional function) of at least 1 point at peak stress.

Follow-up

The outcome was determined from patients' interview at the outpatient clinic, hospital chart reviews, and telephone interviews with the patient, his/her close relative, or the referring physician. Death and non-fatal myocardial infarction (MI) were registered as clinical events. Coronary revascularization (surgery or percutaneous interventions) was also recorded. To avoid misclassification of the cause of death,[28] overall mortality was considered. Myocardial infarction was defined by typical symptoms, electrocardiographic, and cardiac enzyme changes. Follow-up data were analysed for the prediction of hard events (death or non-fatal MI).

Statistical analysis

Continuous variables are expressed as mean ± SD. Two-sample comparisons were performed using the *t*-test if variables were normally distributed, Mann–Whitney *U* test for not normally distributed data, and χ^2 test for categorical data. Death/MI rates were estimated with Kaplan–Meier curves and compared by the log-rank test. Patients undergoing coronary revascularization were censored at the time of the procedure. Only the first event was taken into account. Annual event rates were obtained from Kaplan–Meier estimates to take censoring of the data into account. The association of selected variables with the outcome were assessed with the Cox's proportional hazard model using univariate and stepwise multivariate procedures. A significance of 0.05 was required for a variable to be included into the multivariate model, while 0.1 was the cut-off value for exclusion. Hazard ratios (HR) with the corresponding 95% confidence interval (CI) were estimated. Statistical significance was set at $P < 0.05$. Moreover, clinical findings, resting WMSI, and ischaemia on stress echo were sequentially included into the model. The global χ^2 value of the model was calculated from the log likelihood ratio; a significant increase after the addition of further variables indicated an incremental prognostic value. A receiver operating characteristic (ROC) analysis was used to obtain the best prognostic predictor for peak WMSI. Statistical Package for the Social Sciences (SPSS release 13.0, Chicago, IL, USA) was used for analysis.

Results

Stress echocardiography

Clinical and echocardiographic characteristics of the study population are reported in *Table 1*. Hypertensive patients were tested

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Table 1 Clinical, baseline, and stress echocardiography characteristics for hypertensive and normotensive patients

	Hypertensives ($n = 6214$)	Normotensives ($n = 5328$)	*P*-value
Clinical findings			
Age (years)	65 ± 10	61 ± 12	<0.0001
Males	3722 (60)	3425 (64)	<0.0001
Prior myocardial infarction	1912 (31)	1881 (35)	<0.0001
Prior surgery	343 (5)	270 (5)	0.28
Prior angioplasty	960 (15)	521 (10)	<0.0001
Known CAD	2412 (39)	2151 (40)	0.09
Left bundle branch block	293 (5)	199 (4)	0.006
Diabetes mellitus	1514 (24)	724 (14)	<0.0001
Hypercholesterolaemia	3160 (51)	2135 (40)	<0.0001
Smoking habit	1996 (32)	2342 (44)	<0.0001
Anti-anginal therapy			
β-blockers	1467 (24)	662 (12)	<0.0001
Calcium antagonists	1167 (19)	617 (12)	<0.0001
Nitrates	1118 (18)	829 (16)	0.0001
At least one medication	2505 (40)	1367 (26)	<0.0001
Resting echocardiogram			
WMA	2360 (38)	2514 (47)	<0.0001
WMSI	1.19 ± 0.32	1.23 ± 0.35	<0.0001
Stress echocardiography			
Exercise	390 (6)	296 (5)	0.10
Dobutamine	1158 (19)	1366 (26)	<0.0001
Dipyridamole	4666 (75)	3666 (69)	<0.0001
Normal result	3138 (50)	2255 (42)	<0.0001
Ischaemic result	1609 (26)	1600 (30)	<0.0001
Necrotic pattern	1468 (24)	1472 (28)	<0.0001
Peak WMSI	1.25 ± 0.35	1.30 ± 0.37	<0.0001

Data presented are mean value ± SD or number (%) of patients.
CAD, coronary artery disease; WMA, wall motion abnormalities; WMSI, wall motion score index; ECG, electrocardiographic.

more frequently under anti-anginal therapy than normotensive patients (40 vs. 24%, $P < 0.0001$; *Table 1*). Ischaemia was assessed in 3209 (28%) subjects: 1929 (17%) with resting wall motion abnormalities (RWMA) and 1280 (11%) without RWMA. Ischaemia was less frequent in hypertensive than in normotensive patients (26 vs. 30%; $P < 0.0001$; *Table 1*); however WMSI at the peak of ischaemia was similar in the two populations both in the presence (1.67 ± 0.34 vs. 1.66 ± 0.33; $P = 0.36$) and in the absence (1.32 ± 0.19 vs. 1.32 ± 0.21; $P = 0.92$) of RWMA. A necrotic pattern was found in 2940 (25%) subjects: 24% of hypertensive and 28% of normotensive patients ($P < 0.0001$; *Table 1*). Peak WMSI was 1.49 ± 0.36 in the former and 1.51 ± 0.37 in the latter ($P = 0.07$). A normal test was detected in 5393 individuals (47%), being more frequent in those with hypertension (50 vs. 42%; $P < 0.0001$; *Table 1*).

Outcomes

During follow-up, 1587 (14%) patients had a cardiac event (924 deaths, 663 non-fatal MIs). According to the physician's judgement, 2764 (24%) patients underwent coronary revascularization (1042 surgery and 1722 percutaneous intervention) after a median of 55 days (1st quartile 7, 3rd quartile 235) from the index stress echo. The rates of revascularization were similar in patients with and without hypertension, both considering the group with ischaemia and the group without ischaemia on stress echo (*Figure 1*).

Outcome prediction

Annual event rate was 7.0% hypertensive and 5.7% in normotensive patients ($P = 0.02$) with known CAD, and 3.7% in hypertensive and 2.4% in normotensive ($P < 0.0001$) with suspected CAD.

The univariable and multivariable prognostic indicators in the whole population are shown in *Table 2*: hypertension was an independent predictor of outcome.

The univariable and multivariable prognostic indicators in patients with and without hypertension are shown in *Table 3*. Ischaemia at stress echo, RWMA, age, male sex, and diabetes mellitus independently predicted future events in both patient groups. Additional independent prognostic predictors were prior percutaneous coronary intervention in hypertensive patients and peak WMSI in normotensive patients (*Table 3*).

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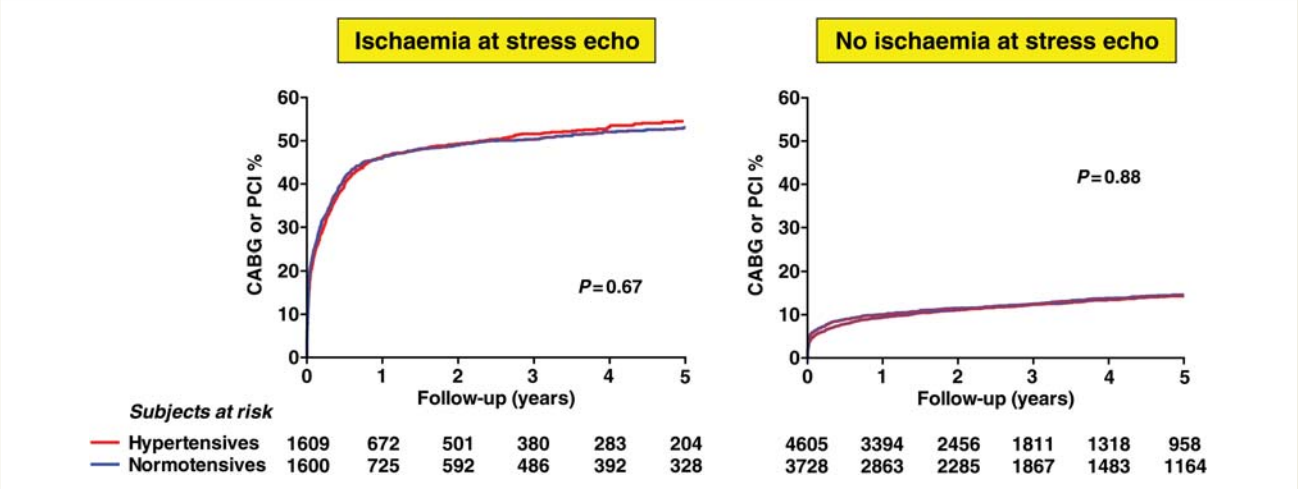

Figure 1 Revascularization rate for hypertensive and normotensive patients with and without ischaemia at stress echocardiography. Number of patients per year is shown.

Table 2 Univariable and multivariable predictors of death or myocardial infarction in the whole study population

	Univariable		Multivariable	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Age	1.04 (1.04–1.05)	<0.0001	1.04 (1.03–1.04)	<0.0001
Male sex	1.6 (1.4–1.8)	<0.0001	1.4 (1.2–1.6)	<0.0001
Hypertension	1.3 (1.2–1.4)	<0.0001	1.1 (1.0–1.3)	0.022
Smoking habit	1.1 (1.0–1.2)	0.044		
Diabetes	1.9 (1.7–2.2)	<0.0001	1.6 (1.4–1.9)	<0.0001
Left bundle branch block	1.2 (0.9–1.6)	0.098		
Hypercholesterolaemia	1.2 (1.0–1.3)	0.003		
Previous myocardial infarction	2.0 (1.8–2.2)	<0.0001		
Previous percutaneous intervention	1.6 (1.4–1.8)	<0.0001		
Previous coronary artery bypass grafting	1.5 (1.2–1.8)	<0.0001		
RWMA	2.4 (2.1–2.6)	<0.0001	1.7 (1.6–1.9)	<0.0001
Rest WMSI	2.9 (2.6–3.3)	<0.0001		
Peak WMSI	3.6 (3.2–4.0)	<0.0001		
Ischaemia at stress echo	2.5 (2.2–2.7)	<0.0001	2.1 (1.8–2.3)	<0.0001
Medical therapy at time of testing	1.6 (1.4–1.7)	<0.0001	1.2 (1.1–1.3)	0.003

Other abbreviations as in *Table 1*.
HR, hazard ratio; CI, confidence intervals.

Analysing data according to prognostically important echocardiographic parameters, such as ischaemia at stress echo and RWMA, an effective risk stratification was obtained both in hypertensive as well as normotensive patients (*Figure 2*). However, the event rate associated with the ischaemic test was similar ($P = 0.16$) in hypertensive with and without RWMA, but lower ($P = 0.002$) in normotensive patients without RWMA (*Figure 2*). An effective risk stratification, using the same parameters as *Figure 2*, was obtained when individual endpoints, death, and non-fatal MI were analysed separately (*Figures 3* and *4*).

With a ROC analysis, peak WMSI >1.4 in patients with no RWMA [area under curve 0.54 (95% CI 0.51–0.57) sensitivity 34%, specificity 76%], and peak WMSI >1.95 in patients with RWMA [area under curve 0.57 (95% CI 0.55–0.60) sensitivity 28%, specificity 83%] were the best predictors of hard events both in hypertensive and normotensive patients. Kaplan–Meier survival estimates reported in *Figure 5* show the differences between the two groups separated on the basis of the cut-offs obtained at ROC analysis. The annual event rate was comparable among the subsets analysed and separated on the basis of the presence or absence of medical therapy at the time of testing (*Figure 6*).

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Table 3 Univariable and multivariable predictors of death or myocardial infarction in hypertensive and normotensive patients

	Hypertensives				Normotensives			
	Univariable		Multivariable		Univariable		Multivariable	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Age	1.0 (1.03–1.04)	<0.0001	1.02 (1.03–1.04)	<0.0001	1.05 (1.04–1.06)	<0.0001	1.03 (1.04–1.05)	<0.0001
Male sex	1.6 (1.2–1.9)	<0.0001	1.4 (1.2–1.6)	<0.0001	1.6 (1.4–1.9)	<0.0001	1.3 (1.1–1.6)	0.001
Smoking habit	1.1 (1.0–1.3)	0.03			1.1 (0.9–1.3)	0.14		
Diabetes	1.6 (1.4–1.9)	<0.0001	1.44 (1.2–1.7)	<0.0001	2.4 (2.0–2.9)	<0.0001	1.7 (1.5–2.1)	<0.0001
Left bundle branch block	1.3 (0.97–1.8)	0.08			1.05 (0.7–1.6)	0.82		
Hypercholesterolaemia	1.2 (1.02–1.3)	0.02			1.1 (0.9–1.3)	0.20		
Previous myocardial infarction	1.9 (1.7–2.2)	<0.0001			2.2 (1.9–2.6)	<0.0001		
Previous percutaneous intervention	1.6 (1.3–1.9)	<0.0001	1.28 (1.1–1.5)	0.006	1.5 (1.2–1.9)	0.001		
Previous coronary artery bypass grafting	1.4 (1.06–1.8)	0.02			1.6 (1.2–2.1)	<0.0001		
RWMA	2.2 (1.9–2.5)	<0.0001	1.6 (1.4–1.8)	<0.0001	2.8 (2.4–3.3)	<0.0001	1.4 (1.1–1.7)	0.003
Rest WMSI	2.5 (2.2–3.0)	<0.0001			3.6 (3.1–4.3)	<0.0001		
Peak WMSI	3.3 (2.8–3.8)	<0.0001			4.1 (3.5–4.8)	<0.0001	2.3 (1.80–2.8)	<0.0001
Ischaemia at stress echo	2.9 (2.6–3.4)	<0.0001	2.5 (2.1–2.8)	<0.0001	2.1 (1.8–2.4)	<0.0001	1.4 (1.2–1.6)	<0.0001
Medical therapy at time of testing	1.4 (1.20–1.6)	<0.0001			1.8 (1.6–2.1)	<0.0001		

All abbreviations as in *Table 1*.

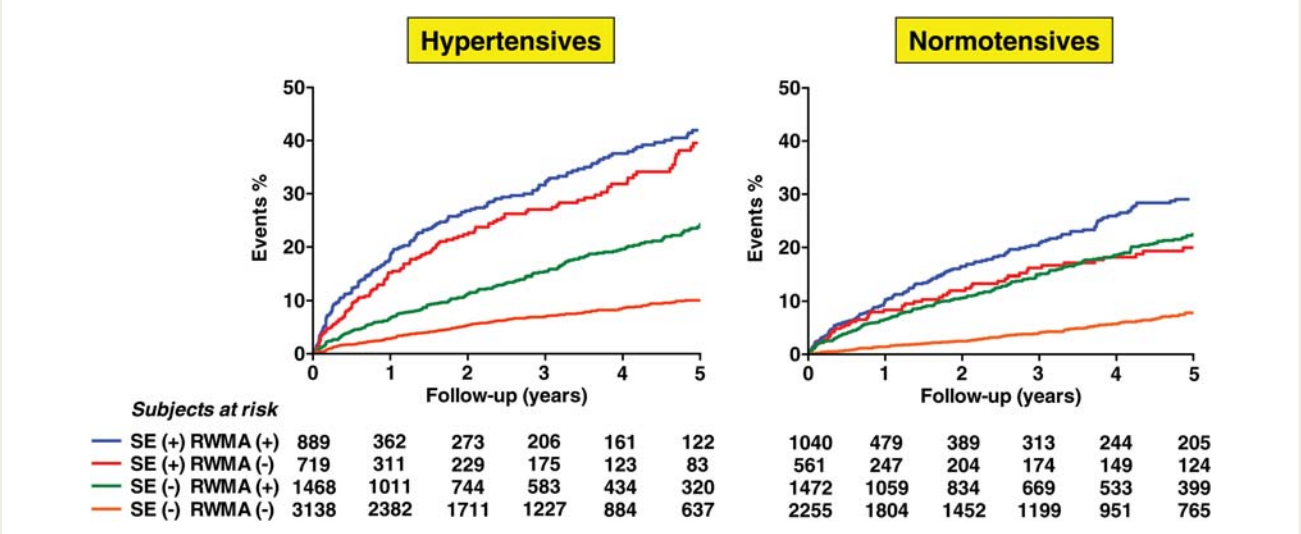

Figure 2 Death/myocardial infarction rates for hypertensive and normotensive patients separated on the basis of presence (+) or absence (−) of ischaemia at stress echocardiography, and presence (+) or absence (−) of resting wall motion abnormality. Number of patients per year is shown.

A positive test result and negative test result without RWMA were predictive of a markedly higher annual event rate in patients with hypertension, while the necrotic pattern was associated with a comparable outcome in hypertensive and normotensive patients (*Figure 6*). The annual event rate in normotensive and hypertensive patients older than 65 years was higher than in the younger subsets; however hypertensive patients showed a higher incidence rate of events in both age groups (*Figure 7*).

In patients with known CAD, global χ^2 of the clinical model for predicting outcome was 60.9 ($P < 0.0001$) in hypertensive and

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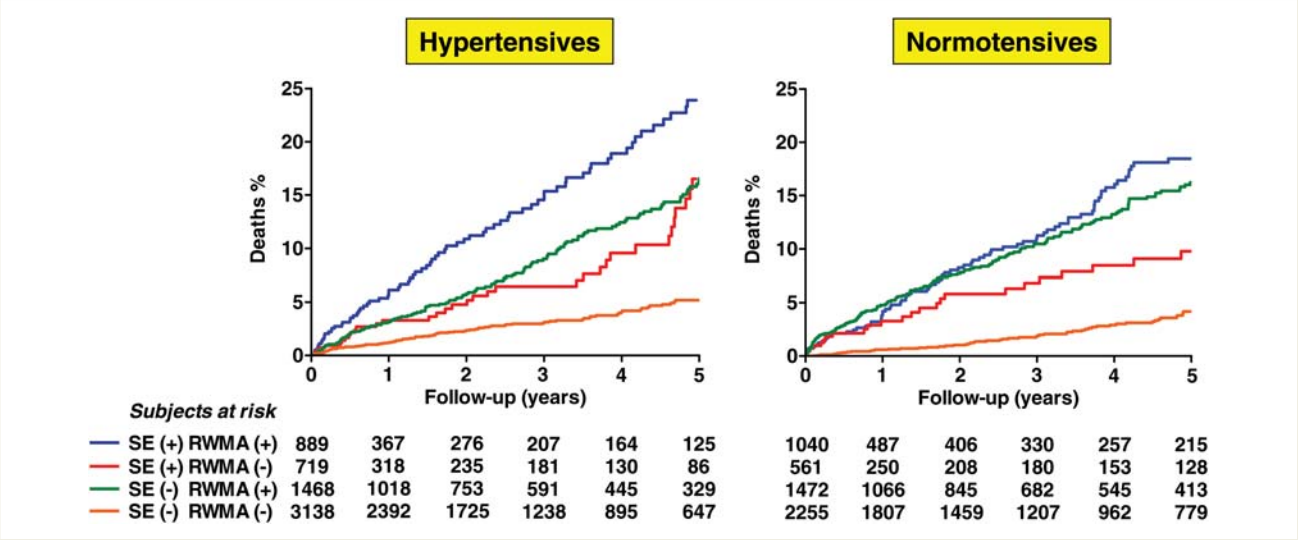

Figure 3 Death rates for hypertensive and normotensive patients separated on the basis of presence (+) or absence (−) of ischaemia at stress echocardiography, and presence (+) or absence (−) of resting wall motion abnormality. Number of patients per year is shown.

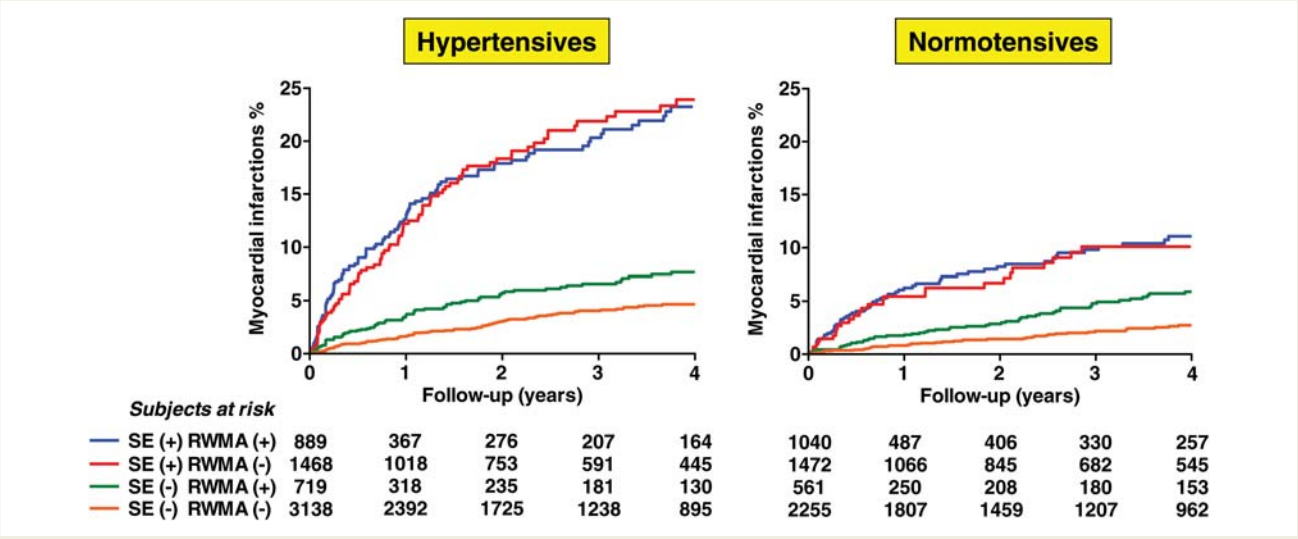

Figure 4 Myocardial infarction rates for hypertensive and normotensive patients separated on the basis of presence (+) or absence (−) of ischaemia at stress echocardiography, and presence (+) or absence (−) of resting wall motion abnormality. Number of patients per year is shown.

104.7 ($P < 0.0001$) in normotensive patients. Sequential inclusion of resting WMSI and ischaemia on stress echo increased it by 41% (89.0; $P < 0.0001$) and 70% (151.4; $P < 0.0001$) in hypertensive and by 52% (160.2; $P < 0.0001$) and 10% (175.8; $P < 0.0001$) in normotensive patients, respectively. The same dynamic of stratification also applies to patients with suspected CAD.

Discussion

The burden of cardiovascular disease and mortality attributable to an elevated blood pressure was estimated from the Global Burden of Disease 2001 study.[29] Therefore, the prognostic assessment of hypertensive patients is of primary clinical importance since hypertension is associated with an almost double risk of developing CAD.[1] The results of this study indicate that SE is a useful prognostic tool in hypertensive patients. A normal study with any type of stressor is a marker of low risk; however, in the hypertensive group the risk is higher. Inducible ischaemia on SE is an independent predictor of hard cardiac events, and the level of risk is related to the extent of the inducible abnormality as expressed by the peak WMSI. However, the presence of RWMA is an independent predictor of outcome in both patient groups.

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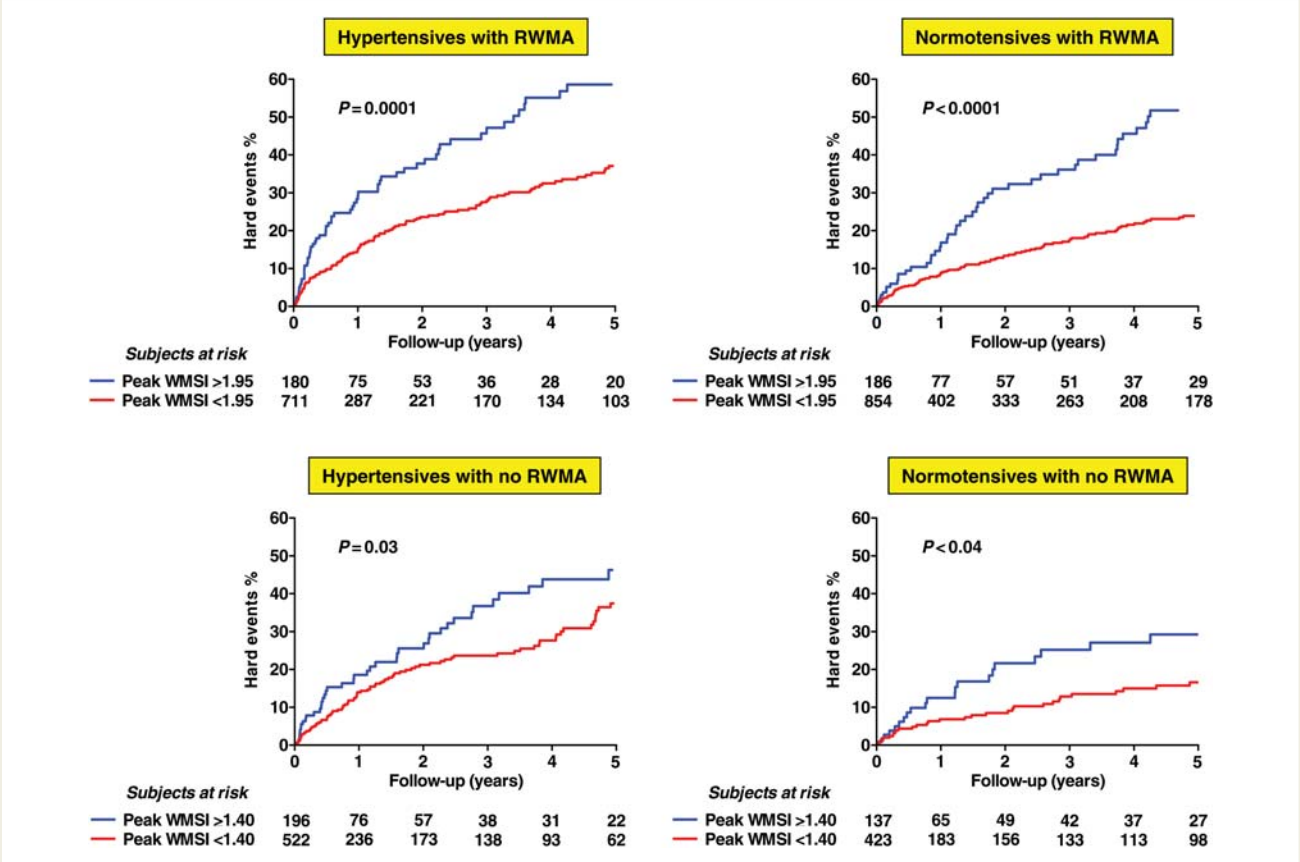

Figure 5 Death/myocardial infarction rates for hypertensive and normotensive patients separated on the basis of peak wall motion score index > or <1.4 with no rest wall motion abnormalities at stress echocardiography, and peak wall motion score index > or <1.95 with resting wall motion abnormality. Number of patients per year is shown.

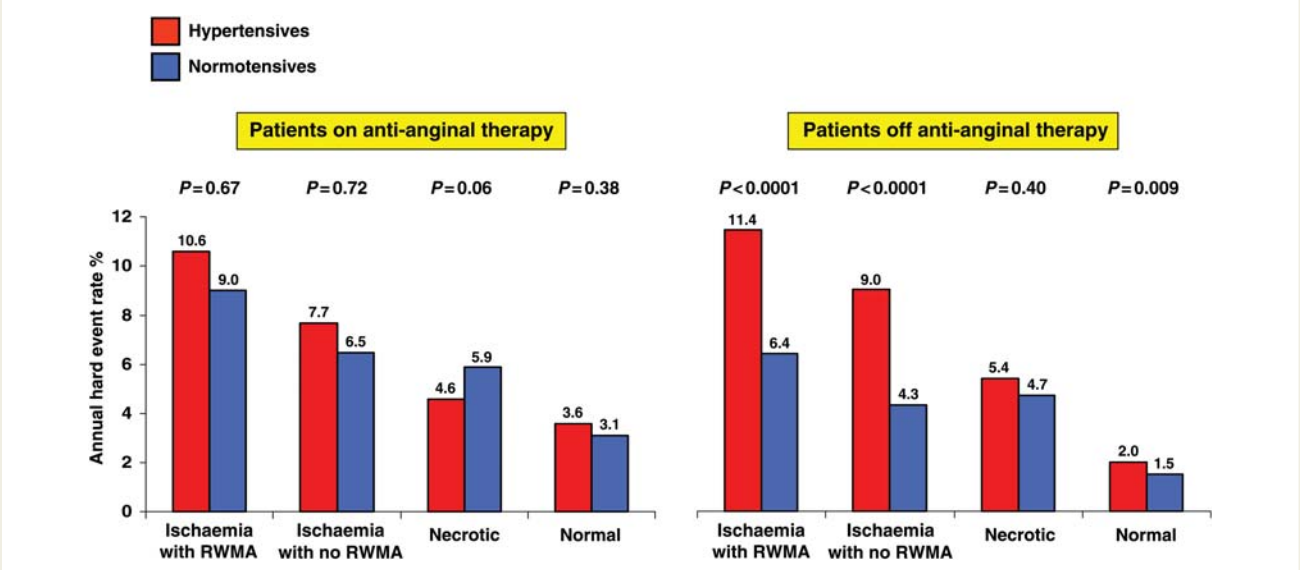

Figure 6 Annual death/myocardial infarction rates for hypertensive and normotensive patients according to stress echocardiography results. The groups tested off and on anti-anginal therapy were separately analysed.

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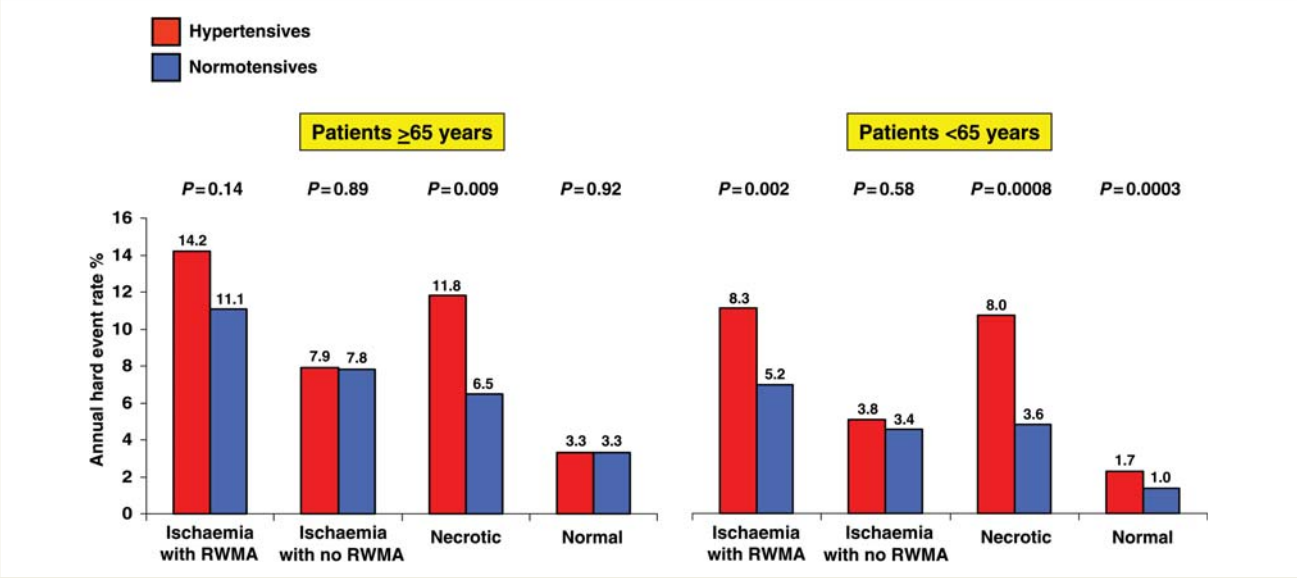

Figure 7 Annual death/myocardial infarction rates for hypertensive and normotensive patients according to stress echocardiography results. The groups are separately analysed on the basis of age <65 or >65 years.

Comparison with previous studies

The use of exercise or pharmacological SE in the setting of arterial hypertension has been addressed in previous studies.[14–19] In particular, stress-induced wall motion abnormality during pharmacological testing was a strong multivariable predictor of future cardiac events in hypertensive patients with chest pain of unknown origin,[14] including those with left ventricular hypertrophy,[15] and added prognostic information on top of clinical and exercise electrocardiography.[16] Moreover, the result of test was independently associated with cardiac death in an unselected cohort of hypertensive patients with known or suspected CAD.[17] However, mortality was predicted by inducible ischaemia in exercise-tested patients and by the presence of any stress echocardiographic abnormality in those undergoing the dobutamine challenge.[18] Inducible ischaemia at inotropic stress was also associated with unfavourable outcome in the high-risk population of hypertensive patients unable to exercise.[18] Exercise-induced change in left ventricular ejection fraction proved to be a multivariable predictor of mortality incremental to clinical findings, left ventricular mass index, and resting left ventricular function among hypertensive patients with left ventricular hypertrophy.[19] Finally, echocardiographic left ventricular wall motion abnormalities in adults without overt cardiovascular disease were associated with 2.4- to 3.4-fold higher risks of cardiovascular morbidity and mortality, independent of established risk factors.[30] Our findings reinforce previous reports on the capability of SE to effectively stratify risk in hypertensive patients. Multivariable analysis in the present study, including a very large number of patients, showed similar results in hypertensive and normotensive patients despite a worse outcome in the group of hypertensive patients with known or suspected CAD.

Anti-anginal therapy lowers the sensitivity of exercise echocardiography as it does with vasodilator stress testing. The beneficial effect of therapy on dipyridamole time parallels variations in exercise time, providing the possibility of an exercise-independent assessment of efficacy of medical therapy.[31] The present results are consistent with our previous reports demonstrating that medical therapy at the time of testing has an ominous effect on the outcome, identifying patients at a higher risk of death.[32] A normal test on medical therapy had an event rate higher by 80% in hypertensive and by 106% in normotensive patients when compared with a test conducted off medical therapy.

Clinical implications

Information on the relative prognostic contribution of SE in the hypertensive and normotensive population could allow to optimize patient management. However, the prognostic information provided by SE shows important differences in the hypertensive and normotensive populations that should be taken into account in risk stratification.

First, a normal test result implied a less favourable outcome among hypertensive patients independently of whether or not they were studied on anti-anginal therapy. Secondly, an ischaemic test conveyed markedly lower risk in normotensive patients without than in those with RWMA, while no difference was found among hypertensive patients. Finally, the incremental prognostic value of stress-induced ischaemia over clinical data and resting left ventricular function was greater in hypertensive than in normotensive patients with known or suspected CAD. After adjusting for important confounders, hypertension was still associated with significantly increased risk, such as in patients aged <65 years with a normal test result, thus confirming its major prognostic role.[1] The presence of an abnormal stress echocardiogram indicates that the patient is at risk of experiencing hard cardiac events. Therefore, high-risk patients with inducible ischaemia should be referred to coronary angiography and ischaemia-driven

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revascularization. Conversely, optimization of blood pressure control, adequate treatment of risk factors[1] with amelioration of the profile, and watchful surveillance including periodic assessment of myocardial ischaemia should represent pivotal targets of management in hypertensive patients with a high-risk clinical profile but no evidence of ischaemia on SE. Randomized clinical trials addressing this specific issue should be designed to provide a definitive answer to the prognostic impact of medical therapy at the time of testing, with the evaluation of treatment changes during follow-up.

Study limitations

Because of the long recruitment period, the outcome based on stress test results may have been potentially influenced by evolution of methodology, technology, and expertise and advances in medical and interventional treatments. In this study, there was no central reading. Stress echocardiography was interpreted in the peripheral centres and entered directly in the database. This system allowed substantial sparing of human and technological resources, but it also was the logical prerequisite for a large-scale study designed to represent the realistic performance of the test rather than the results of a single laboratory, or even a single person, working in a highly dedicated echocardiography laboratory. Because the assessment of the echocardiograms was qualitative and subjective, variability in reading the echocardiograms might have modulated the results of individual centres.[27] However, all our readers in individual centres had a lengthy experience in echocardiography and passed the quality control in the SE reading as previously described.[24] The test results available to the referring physicians may have influenced the clinical management of the patients, especially regarding coronary revascularization, but this may have only decreased the prognostic power of the test, because patients were censored at the time of the procedure. The study was not designed to address the effect of antihypertensive therapy; therefore, enrolling centres evaluated each single patient according to the referring physician's prescriptions. We cannot also exclude the possibility that, during the follow-up period, medical therapy may have been changed to obtain optimal hypertension control. Renal function was not available in our databank but uraemic patients were not included in the study. However, renal insufficiency is an independent predictor of outcome and its potential effect on the study population should be acknowledged.[33] In our patient population, normotensive patients have a higher incidence of previous MI and a potential selection bias may have been introduced. However, the selection criteria included all patients referred for stress echo with subsequent coronary angiography within 3 months from the index test. This led to inclusion of patients with different clinical conditions and heterogeneous angiographic patterns, which, however, reflects the wide variety of patients referred to the stress echo laboratory for suspected or known CAD.

Conclusions

The results of the present study indicate that SE is a useful tool for estimating the risk of hard cardiac events in hypertensive patients with known or suspected CAD, just as it is in normotensive subjects. In case of test positivity, a spectrum of risk can be identified on the basis of the presence of concomitant medical therapy, previous MI, and the extent and severity of inducible ischaemia.

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