Quantitative and Qualitative Analysis of the Relationship between Exercise-induced R Wave Amplitude Changes and Severity of Coronary Artery Disease

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Summary

The correlation between R wave voltage variations (ΔR) and the angiographic severity of coronary artery disease (CAD) at progressively increasing heart rate (HR) steps was evaluated in 51 patients (pts) without CAD (OV), in 42 pts with single (SVD), in 43 with double (DVD) and in 59 pts with triple vessel disease (TVD).

At the end of stress the sensitivity of ΔR was higher in DVD and TVD pts than in SVD pts. There was no clear correlation between exercise-induced R wave changes and the angiographic severity of CAD, since the qualitative and quantitative ΔR evaluation during effort showed similar changes in ΔR for a wide range of HR's in the entire study population.

Since different degrees of exercise tolerance were found in pts with SVD, DVD and TVD, we hypothesize that the correlation between ΔR and the severity of CAD at the end of stress testing may be artifactual.

It has been suggested that the evaluation of stress-induced R wave voltage variations (ΔR) could improve both the specificity and sensitivity of exercise stress test in patients with coronary artery disease (CAD).[1),2)] It is still unclear whether the ΔR criterion has any practical utility, since other authors have reported a lower sensitivity and/or specificity of the ΔR, compared to the ST criterion.[3)–7)]

Our recent study demonstrated that both specificity and sensitivity of the ΔR criterion are widely influenced by the different heart rate (HR) reached

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at the end of exercise.[8] These observations lead us to investigate further the relationship between exercise-induced R wave changes and the angiographic severity of CAD.[3),9)–13)]

The aim of our study was to evaluate R wave changes at progressively increasing HR levels and at the end of exercise in patients with different degrees of coronary arterial narrowing.

Materials and Methods

Patient population: Exercise stress test records and coronary angiograms of 195 patients referred for evaluation of chest pain were reviewed retrospectively. Coronary angiograms were performed by the Sones' technique[14] and were recorded on 35 mm film in multiple projections. Coronary artery disease was defined as stenosis ≥70% of lumen diameter of at least one of the major coronary arteries. Left ventriculography was qualitatively evaluated for areas of abnormal segmental contraction. The angiograms were evaluated without prior knowledge of the exercise results. The stress test results and the angiocardiographic records were examined by 2 independent observers.

Patients with uninterpretable ST changes during effort were excluded as were patients with valvular disease, cardiomyopathy, systemic hypertension, diabetes and those taking digitalis or beta-adrenergic blocking drugs. One-hundred-forty-four patients out of the 195, 130 males and 14 females, mean age 53 years, had angiographic evidence of CAD (CAD group). Fifty-one patients, 41 males and 10 females, mean age 47 years, had normal coronary arteries and normal left ventriculography (OV group). According to the coronarographic results, these 144 patients with CAD were divided into 3 subgroups.

The triple vessel disease group (TVD) included 59 patients with significant stenosis of 3 coronary arteries; 52 of the 59 (88.1%) had abnormal left ventricular wall motion, 39 of the 59 (66.1%) had electrocardiographic sign of a previous myocardial infarction. The second group (DVD) was composed of 43 patients with ≥70% stenosis of two coronary arteries; 32 of them (74.4%) had abnormal left ventriculography and 18 of the 43 (41.8%) had a previous myocardial infarction. The third group (SVD) included 42 patients with significant stenosis of one coronary vessel; 16 of them (42%) had abnormal ventriculography and 10 of the 42 (23.8%) had an old myocardial infarction. The exercise electrocardiograms were evaluated according to the ST criterion; 46 patients (77.9%) in the TVD group, 30 (69.7%) in the DVD group and 21 (50%) in the SVD group were true positives. Seventeen of the 51 patients (33.3%) in the OV group were true negatives.

The large number of false positive patients was a consequence of our study design, since patients with positive stress tests are more frequently referred for coronary arteriography to evaluate the presence of CAD. In addition, it was of interest to evaluate the behavior of ΔR during exercise in patients without angiographic signs of CAD.

Exercise stress test protocol: Stress testing was performed using a SASME Ergo 2 bicycle ergometer. All drugs were withdrawn at least 48 hours before exercise. The patients started cycling in the sitting position with a 50 watt load, which was increased by 20 watt every 2 min. Exercise was continued until diagnostic ST depression occurred or until patients reached 90% or more of predicted maximal HR or had limiting signs or symptoms. Criteria for significant ST segment depression have been described previously.[15] Electrocardiographic leads CM4, 5, and 6 were monitored continuously (Avionics 3000) and records were made at rest, every 2 min during exercise, in the immediate post-exercise period and every minute during the first 5 min of recovery.

Evaluation of exercise-induced R wave amplitude changes: R wave amplitude changes and ST segment depression were measured in the CM5 lead. In any single patient, R wave changes were calculated in millimeters from the isoelectric line to the peak of the R wave for at least 10 or more consecutive beats;[1] the average value was used to minimize respiratory variations. ΔR was measured by comparing the R wave amplitude at rest with the values found during exercise and immediately at the end of the stress test.

The values of ΔR were calculated during effort at each of 8 increasing HR steps: 100–110, 111–120, 121–130, 131–140, 141–150, 151–160, 161–170, and ≥171 beats/minute (b/m). We considered ΔR values equal to or greater than zero to be significant for CAD, while ΔR values lower than zero were considered as normal.[1] The influence of HR on the relationship between ΔR and the severity of CAD was studied by considering the percentages of ΔR values ≥ 0 and < 0, in CAD patients and in OV group at increasing HR steps. Furthermore, we calculated at each HR step the mean ΔR value of patients with and without CAD, including patients who stopped their exercise at that HR and those who were able to progress to higher HRs.

Not all patients are included in each HR step. Many patients skipped one or two steps within the 2 min between the two electrocardiographic recordings; thus, it is possible to find different numbers of patients in one HR step compared to other HR steps. However, the trend was towards a decrease in number of patients with progressively increasing HR because many more patients stopped their exercise because of symptoms or ST depression.

The statistical analysis and comparisons between patients with and without CAD were performed by Fisher's exact test, unpaired Student's *t*-test, one-way analysis of variance and Duncan's test.[16]

Results

Correlation between R values at the end of stress and the severity of CAD: The evaluation of ΔR at the peak of exercise showed that this criterion had a sensitivity of 61.1% and a specificity of 74.5% (Table I). The sensitivity of ΔR was higher in patients belonging to the TVD and DVD groups, who showed a $\Delta R \geq 0$ in 69.4 and 60%, respectively (Table I).

Patients with double and triple vessel disease more frequently stopped their exercise at HRs lower than 140 b/m (62.7 and 71.1% of the cases, respectively) (Table II). Among these patients, the incidence of $\Delta R \geq 0$ at the

Table I. Sensitivity and Specificity of ΔR Criterion at the End of Exercise in Patients with CAD and in Angiographically Normal Patients (OV)

		$\Delta R \geq 0$	%	$\Delta R < 0$	%
TVD	n= 59	41	69.4°♀	18	80.6
DVD	n= 43	26	60.4°	17	39.6
SVD	n= 42	21	50.0	21	50.0
Tot.	n=144	88	61.1	56	38.9
OV	n= 51	13	25.5	38	74.5

TVD=patients with triple vessel disease; DVD=patients with double vessel disease; SVD=patients with single vessel disease; Tot.=all CAD patients.
° $p<0.001$ versus OV, ♀ $p<0.05$ versus SVD.
Statistical analysis performed by Fisher's exact test.

Table II. Number of Patients (STOP) with CAD Interrupting Their Exercise at Each HR Step (HR), Number of Patients with $\Delta R \geq 0$ at the End of Stress ($\Delta R \geq 0$) in Each HR Step, and Incidence of Values of $\Delta R \geq 0$ (%)

HR (b/m)	TVD (59)			DVD (43)			SVD (42)		
	STOP	$\Delta R \geq 0$	%	STOP	$\Delta R \geq 0$	%	STOP	$\Delta R \geq 0$	%
100–110	6	5	83.3	4	3	75	3	3	100
111–120	7	5	71.4	6	4	66.6	4	3	75.0
121–130	11	10	90.9	4	4	100	4	2	50.0
131–140	18	13	72.2	13	8	61.5	10	5	50.0
141–150	13	6	46.1	10	6	60	11	5	45.5
151–160	4	2	50.0	3	1	33.3	2	=	0
161–170				3	=	0	8	3	37.5
≥171									

end of stress testing was 78.5 and 70.3% in the TVD and DVD groups (Table II). Over 141 b/m, the percentages of $\Delta R \geq 0$ at peak exercise in DVD and TVD patients were 43.7 and 47%, respectively (Table II). In the SVD group, 21 patients (50%) stopped their exercise at HRs between 100 and 140 b/m, 13 of them (61.9%) showing a $\Delta R \geq 0$; the frequency of $\Delta R \geq 0$ was 38% among the 21 patients (8/21) with less severe CAD who stopped their exercise at HRs ≥141 b/m (Table II). Table III shows that the frequency of $\Delta R < 0$ at the end of stress testing was higher in OV patients who stopped their exercise at very high HRs (≥161 b/m) than in patients who stopped their exercise at HRs lower than 160 b/m.

Table III. Number of Patients (STOP) without CAD Interrupting Their Exercise at Each HR Step (HR), Number of Patients with $\Delta R < 0$ at the End of Stress ($\Delta R < 0$) in Each HR Step, and Incidence of Values of $\Delta R < 0$ (%)

HR (b/m)	OV		
	STOP	$\Delta R < 0$	%
100–110			
111–120			
121–130	2	=	0
131–140	9	5	55.5
141–150	7	5	71.4
151–160	8	5	62.5
161–170	15	13	86.6
≥171	10	10	100

Table IV. Values of HR and Incidence of $\Delta R \geq 0$ in Patients with CAD and of $\Delta R < 0$ in the OV Group Patient, Divided According to the Exercise-Induced ST Segment Depression Changes

	n	$\Delta R \geq 0$	%	HR (mean±SD)
CAD				
True Positives	97	67	69.1♀	130±16°
False Negatives	47	21	44.6	146±13
	n	$\Delta R < 0$	%	HR (mean±SD)
OV				
True Negatives	17	15	88.2	167±11°
False Positives	34	23	67.7	145±16

♀ $p < 0.005$ versus false negatives.
Statistical analysis performed by Fisher's exact test.
° $p < 0.001$ versus false negatives and false positives.
Statistical analysis performed by unpaired Student *t*-test.

If we divide the CAD population into true positives and false negatives by exercise test results, true positive patients stopped their exercise at significantly lower HRs than those with false negative electrocardiograms, and showed, compared to false negatives, a higher incidence of $\Delta R \geq 0$ (Table IV); these differences were not statistically significant. Similar subdivision of OV group in true negative and false positive patients showed that the true negatives had a higher incidence of $\Delta R \geq 0$ and were able to reach higher values of HR than were false positive patients (Table IV).

Qualitative and quantitative ΔR changes during exercise. Angiographic correlations: Tables V and VI show the variations of R wave amplitude at progressively increasing HRs during stress testing in patients with and without angiographic evidence of CAD. The patients with single and multivessel CAD show similar incidences of $\Delta R \geq 0$ at the same HR steps; only at HRs between 131–140 b/m, was a significantly higher frequency of $\Delta R \geq 0$ found between

Table V. Exercise-Induced R Wave Changes in Patients with Triple (TVD), Double (DVD), and Single Vessel Disease (SVD)

HR (b/m)	100–110	111–120	121–130	131–140	141–150	151–160	161–170
TVD							
$\Delta R \geq 0$	21/27	20/26	26/32	19/23♀	8/17	2/4	
%	77.7	76.9	81.2	82.6	47.0	50.0	
DVD							
$\Delta R \geq 0$	18/23	18/22	19/22	13/21	6/15	3/6	1/3
%	78.2	81.8	86.3	61.9	40.0	50.0	33.3
SVD							
$\Delta R \geq 0$	20/23	24/32	18/28	13/24	11/19	4/10	3/8
%	86.9	75.0	64.3	54.1	57.8	40.0	37.5

♀ $p<0.05$ versus SVD.
Statistical analysis performed by Fisher's exact test.

Table VI. Sensitivity and Specificity of ΔR Criterion in Patients with CAD and in Angiographically Normal Patients (OV) at Progressively Increasing HR Levels

HR (b/m)	100–110	111–120	121–130	131–140	141–150	151–160	161–170	≥171
CAD								
$\Delta R \geq 0$	59/73	62/80	63/82	45/68	25/51°	9/20°	4/11°	
%	80.8	77.5	76.8	66.1	49.0	45.0	36.3	
OV								
$\Delta R < 0$	6/22	6/22	9/33	9/20	13/27♀	17/23°	18/20°	10/10°
%	27.3	27.3	27.3	45.0	48.2	73.9	90.0	100

♀ $p<0.05$ versus 100/110, ° $p<0.001$ versus 100/110.
Statistical analysis performed by Fisher's exact test.

SVD and TVD subgroups (Table V). All CAD patients, independent of the severity of disease, had the highest percentages of $\Delta R \geq 0$ at HRs between 100 and 140 b/m; in contrast, at rates over 141 b/m, the sensitivity of the ΔR criterion decreased significantly (Tables V and VI).

In the OV group, the specificity, which was very low between 100–140 b/m, significantly increased at HR over 141 b/m (Table VI). The OV group showed mean values of ΔR significantly lower than those found in the total CAD population only at HRs higher than 151 b/m (Table VII). In contrast, the average values of ΔR were not statistically different between OV patients and CAD subgroups, even at the highest HR, probably due to a considerable decrease in SVD, DVD, and TVD population at HRs higher than 151 b/m (Table VIII).

Fig. 1 shows R wave voltage changes in a patient without CAD (A) and in 2 patients with multivessel CAD (B and C). Patient A shows a ΔR of +2 mm at a HR of 124 b/m and a ΔR of −7 mm at a HR of 139 b/m. In patient B exercise was stopped at a HR of 125 b/m with a ΔR of +1.5 mm. Patient C shows a ΔR of +0.5 mm at a HR of 115 b/m and a ΔR of −3.5 mm at a HR of 140 b/m, at which point the exercise was interrupted.

Table VII. Quantitative Evaluation of Exercise-Induced R Wave Amplitude Changes in OV and CAD Patients

HR (b/m)	ΔR (mm, mean±SD)	
	OV	CAD
100–110	0.74±1.6	1.8 ±1.9
n	22	73
111–120	0.60±1.9	0.49±1.4
n	22	80
121–130	0.59±1.4	0.54±1.8
n	33	82
131–140	−0.13±1.8	−0.07±1.6
n	20	68
141–150	−0.6 ±1.3	−0.25±1.9
n	27	51
151–160	−1.17±1.4°	−0.35±1.1
n	23	20
161–170	−2.1 ±1.7°°	−1.06±1.6
n	20	11
171	−3.02±0.7	
n	10	

° $p<0.025$, °° $p=0.05$ versus CAD.
Statistical analysis performed by unpaired Student's *t*-test.

Table VIII. Quantitative Evaluation of Exercise-Induced R Wave Amplitude Changes in OV Patients and in SVD, DVD, and TVD Subgroups

HR (b/m)	ΔR (mm, mean±SD)			
	OV	SVD	DVD	TVD
100–110	0.74±1.6	1.25±1.6	0.69±1.8	0.87±1.9
n	22	23	23	27
111–120	0.60±1.9	0.46±1.5	0.72±1.3	0.44±1.4
n	22	32	22	26
121–130	0.59±1.4	−0.01±1.5	1.02±1.8	0.70±2
n	33	28	22	32
131–140	−0.13±1.8	−0.53±1.4	−0.17±1.9	0.50±1.5
n	20	24	21	23
141–150	−0.6 ±1.3	−0.26±1.9	−0.26±2	−0.25±2
n	27	19	15	17
151–160	−1.17±1.4	−0.3 ±1.3	−0.3 ±0.7	−0.72±1
n	23	10	6	4
161–170	−2.1 ±1.7	−0.9 ±0.6	−1.5 ±1.8	
n	20	8	3	
171	−3.02±0.7			
n	10			

Statistical analysis performed by analysis of variance and Duncan's test.

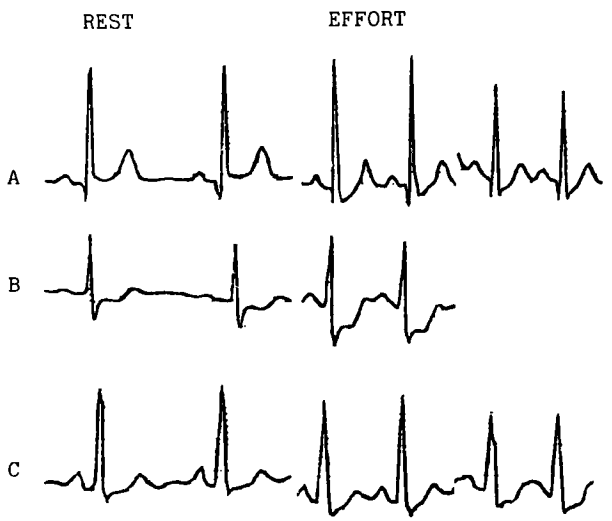

Fig. 1. R wave amplitude changes during effort in a patient without CAD (A) and in 2 patients with multivessel disease (B and C). All patients show an increase in R wave amplitude for HRs lower than 130 b/m; at a HR of 140 b/m it is possible to find a decrease of R wave amplitude in patients A and C.

Discussion

The R phenomenon, angiographic correlations and mechanism: It has been suggested that the exercise-induced R wave changes are related to the angiographic severity of CAD. In fact, patients with multivessel CAD, taken as a group, show higher percentages of $\Delta R \geq 0$ at the end of exercise than do patients with single vessel disease.[3),9),12)] Recently, the relationship between R wave changes and left ventricular impairment has been emphasized;[9)–13)] these observations are in contrast with the disappointing results when using the ΔR criterion to detect CAD.[3)–7)]

It has been demonstrated that even patients with severe CAD may show ΔR values lower than zero at the end of exercise;[3),17),18)] furthermore, Fox et al[7)] found that patients with more severe CAD behave similarly in terms of R wave changes to those with normal coronary arteries or less severe CAD. The theoretical basis of the ΔR criterion resides in Brodie's hypothesis[19)] that assumes QRS voltages to be related to intracavitary blood volume. In normals, the reduction of cardiac volumes during stress should be associated with R wave voltage reduction, while in coronary patients the absence of this reduction or the increase in cardiac volumes during effort should be associated with values of $\Delta R \geq 0$.[1),9)] The direct correlation between QRS voltage and intracavitary blood volume, although confirmed by other reports,[20)–22)] is however still controversial.[23)–26)]

The interpretation of the ΔR phenomenon is further complicated by the controversies surrounding the variations in cardiac volumes during exercise in normals and CAD patients.[10),17),27)–29)] More recently it has been reported that stress-induced left ventricular dilatation is not a specific marker for CAD because it may also be seen in normals.[30)] Alternative hypotheses such as a shift in cardiac electric axis,[31),32)] variations in intramyocardial conduction,[33),34)] red blood cell number or kalemia[35),36)] and development of myocardial ischemia[37),38)] have been advanced to explain stress-induced R wave changes.

Influence of exercise tolerance on stress-induced R wave changes: Previous authors have suggested that the increase in R wave voltage in patients with CAD is caused by the fact that the majority of these patients very frequently perform submaximally on stress testing;[18)] in agreement with this opinion, we showed that sensitivity and specificity of the ΔR criterion were influenced by the level of HR achieved;[8)] the sensitivity was significantly lower at submaximal and maximal HRs, while the specificity showed the opposite behavior. These data suggest that the correlation between the severity of CAD and R wave changes could be at least in part artefactual.

Present study: The elevation of ΔR at the end of stress testing seems to confirm that the sensitivity of this criterion is higher in patients with multivessel disease than in those with less severe CAD.[9),12)]

In contrast, similar incidences of $\Delta R \geq 0$ were found during effort among patients with different degrees of severity of CAD. The sensitivity of the ΔR criterion was very low at the highest HRs in patients with single, double, and triple vessel disease. These data were confirmed by a quantitative evaluation of ΔR wave during exercise. In fact, for wide ranges of HRs similar values of ΔR were found in the OV group compared to patients with CAD. The only significant differences between patients with and without CAD were found at HRs higher than 150 b/m; the small number of patients in CAD subgroups at the highest HR level prevented meaningful statistical analysis. The stress test in our patients was interrupted for reasons other than the R wave changes, therefore; we have not enough data to perform reliable statistical analysis at very high HR steps. These limitations also apply to a prospective study, since it is unethical to prolong the stress test to the highest HR steps when we can achieve without additional risks a correct diagnosis using ST segment criterion. Both OV and CAD patients show decreasing incidence of $\Delta R \geq 0$ at HRs higher than 140 b/m. Beyond this level of HR, ΔR values are progressively more frequently less than zero. Therefore, the step between 131 and 140 b/m could be considered a boundary line to differentiate ΔR changes.

However, an important role is played by the values of HR reached by individual patients at the peak of exercise. While 50% of SVD patients continued their exercise over 140 b/m and 19% stopped the test at rates over 161 b/m, only 3 patients (6.9%) with DVD and none of the TVD group were able to reach similar HRs. This difference in exercise tolerance could explain the lower frequency of $\Delta R \geq 0$ in patients with SVD than in DVD and TVD groups. In contrast, the higher percentages of OV patients with $\Delta R < 0$ at the end of exercise is a consequence of the majority of them reaching high levels of HR. In fact, all patients reaching a HR of 171 b/m had a ΔR lower than zero.

Furthermore, the higher incidence of false negative responses in patients with SVD, compared to those in the DVD and TVD groups, contributed to the lower percentages of $\Delta R \geq 0$ in the former subgroup; more patients with less severe CAD achieved higher values of HR because of the absence of significant ST segment depression. On the other hand, all false negative patients were able to reach higher HRs and showed a lower incidence of $\Delta R \geq 0$ than did true positive patients.

In conclusion, our results show that, although many factors can affect

ΔR values, the HR, as an expression of exercise tolerance, plays an important role; the higher frequency of $\Delta R \geq 0$ found at the end of stress testing in the more severe CAD population is influenced to some extent by the lower exercise levels tolerated by these patients, complicating the controversial relationship between R wave voltage variations and severity of CAD.

References

1. Bonoris PE, Greenberg PS, Christinson GW, Castellanet MJ, Ellestad MH: Evaluation of R wave amplitude changes versus ST segment depression in stress testing. Circulation **57**: 904, 1978
2. Yannikas J, Marcomichelakis J, Tappurt P, Kelly BH, Emanuel R: Analysis of exercise-induced changes in R wave amplitude in asymptomatic men with electrocardiographic ST-T changes at rest. Am J Cardiol **47**: 238, 1981
3. deCaprio L, Cuomo S, Bellotti P, Adamo B, Postiglione M, Vigorito C, Rengo F: R wave amplitude changes during stress testing. Comparison with ST segment depression and angiographic correlation. Am Heart J **99**: 413, 1980
4. Gillespie JA, Bodenheimer MM, Fouche CM, Banka VS, Helfant RH: Limitations in the use of changes in R wave amplitude with stress test electrocardiogram to improve detection of coronary heart disease (abstr). Circulation **58** (Suppl II): II-199, 1978
5. Wagner S, Cohn K, Selzer A: Unreliability of exercise-induced R wave changes as index of coronary artery disease. Am J Cardiol **44**: 1241, 1979
6. Rowe DH, Autry A, De Castro CM, Garcia E, Hall RJ: The value of electrocardiographic R wave changes in exercise testing. Pre-exercise versus post-exercise measurements. Cardiovasc Dis **8**: 333, 1981
7. Fox K, England D, Jonathan A, Selwin A: Inability of exercise-induced R wave changes to predict coronary artery disease. Am J Cardiol **49**: 674, 1982
8. deCaprio L, Cuomo S, Vigorito C, Meccariello P, Romano M, Zarra A, Rengo F: Influence of heart rate on exercise-induced R wave amplitude changes. Am Heart J **107**: 61, 1984
9. Bonoris PE, Greenberg PS, Castellanet MJ, Ellestad MH: Significance of changes in R wave amplitude during treadmill stress testing. Angiographic correlation. Am Heart J **99**: 413, 1980
10. Greenberg PS, Ellestad MH, Berge R, Johnson K, Hayes M, Bible M, Morales-Ballejo H: Radionuclide angiographic correlation of the R wave, ejection fraction and volume responses to upright bicycle exercise. Chest **80**: 459, 1981
11. Berman JL, Wynne J, Cohn PF: Multiple-lead QRS changes with exercise testing. Diagnostic value and hemodynamic implications. Circulation **61**: 53, 1980
12. Baron DW, Ilsely C, Shieban I, Poole-Wilson PA, Richards AF: R wave amplitude during exercise; relation to left ventricular function and coronary artery disease. Br Heart J **44**: 512, 1980
13. Bonoris P, Toutouzas P, Papadopoulos P, Zacharoulis A, Augoustakis D: Correlation of R wave amplitude and left ventricular end-diastolic pressure changes during effort (abstr). Abstract Book Vol 1, No 0710, 9th World Congress of Cardiology, Moscow, June 20–26, 1982
14. Sones FM Jr, Shirey EK: Cinecoronary arteriography. Mod Concepts Cardiovasc Dis **31**: 735, 1962
15. Ellestad MH: Stress Test Principles and Practice, FA Davis Co, Philadelphia, p 67–84, 1975
16. Brownlee KA: Statistical Theory and Methodology in Science and Engineering, John Wiley & Sons Inc, New York, 1974
17. Battler A, Froelicher V, Slutsky R, Ashburn W: Relationship of QRS amplitude changes during exercise to left ventricular function and volumes and the diagnosis of coronary artery

disease. Circulation **60**: 1004, 1979
18. Froelicher VF, Wolthuis RA, Eischer J, Uhl G: Variations in normal electrocardiographic response to treadmill exercise testing. Circulation **60**: 1028, 1979
19. Brody DA: A theoretical analysis of intracavitary blood mass influence on the heart lead relationship. Circulat Res **4**: 731, 1956
20. Vine DL, Finchum RL, Dodge HT, Bancroft WH Jr, Hurst DC: Comparison of the vectorcardiogram with the electrocardiogram in the prediction of left ventricular size. Circulation **43**: 547, 1971
21. Baxley WA, Dodge HT, Sandler H: A quantitative angiocardiographic study of left ventricular hypertrophy and the electrocardiogram. Circulation **37**: 509, 1968
22. Bayley RH, Kalbleisch JM, Berry PM: Changes in the body's surface potentials produced by alterations in certain compartments of the non homogenous conducting model. Am Heart J **77**: 517, 1969
23. Levken J, Chatterjee K, Tyberg J, Stowa DF, Mathey DG, Parmeley WW: Pronounced dependence of ventricular endocardial QRS potentials on ventricular volume. Br Heart J **40**: 891, 1978
24. Talbot S, Kirkpatrik D, Johnathan A, Raphael MJ: QRS voltage of the electrocardiogram and Frank vectorcardiogram in relation to ventricular volume. Br Heart J **39**: 1109, 1977
25. Cuomo S, Vigorito C, deCaprio L, Maione S, Giunta A, Serino C, Romano M, Rengo F: Influenza delle variazioni del volume ventricolare sinistro indotte dalla manovra di Valsalva sull'ampiezza dell'onda R. Giorn It Cardiol **11**: 903, 1981
26. Ishikawa K, Berson AS, Pipberger HV: Electrocardiographic changes due to cardiac enlargement. Am Heart J **81**: 635, 1971
27. Rerych SK, Scholz PM, Newman GE, Sabiston DC, Jones RH: Cardiac function at rest and during exercise in normals and in patients with coronary heart disease. Evaluation by radionuclide angiocardiography. Ann Surg **197**: 443, 1978
28. Stein RA, Nitchelli D, Fox L, Krasnow N: Continuous ventricular dimensions in man during supine exercise and recovery. An echocardiographic study. Am J Cardiol **41**: 655, 1978
29. Slutsky R: Response of the left ventricle to stress. Effects of exercise atrial pacing, afterload stress and drugs. Am J Cardiol **47**: 357, 1981
30. Iskandrian AS, Hakki AH, Kane SA, Segal BL: Quantitative radionuclide angiography in assessment of hemodynamic changes during upright exercise. Observations in normal subjects, patients with coronary artery disease and patients with aortic regurgitation. Am J Cardiol **48**: 239, 1981
31. Bruce RA, Li YB, Dower GE, Nilson K: Polarcardiographic responses to maximal exercise and to changes in posture in healthy middle-aged man. J Electrocardiol **6**: 91, 1973
32. Kentala E, Luurila O: Response of R wave amplitude to postural changes and to exercise. A study on healty subjects and patients surviving acute myocardial infarction. Ann Clin Res **7**: 258, 1975
33. David D, Naito M, Chen C, Morganroth J, Shaffenburg M: R wave amplitude variations during acute myocardial ischemia: an inadequate index for changes in intracardiac volume. Circulation **63**: 1364, 1981
34. David D, Naito M, Michelson E, Watanabe Y, Chen CC, Morganroth J, Shaffenburg M, Blenko T: Intramyocardial conduction: a major determinant of R-wave amplitude during acute myocardial ischemia. Circulation **65**: 161, 1982
35. De Lanne R, Barnes JR, Brohua L: Hematological changes during muscular activity and recovery. J Appl Physiol **15**: 31, 1960
36. Lepeschkin E: Physiological factors influencing the electrocardiographic response to exercise. *in* Measurements in Exercise Electrocardiography, ed by Blackburn H, The Ernest Simonson Conference, CC Thomas, Springfield, ILL, p 363, 1969
37. Holland PR, Brooks H: The QRS complex during myocardial ischemia. An experimental analysis in the porcine heart. J Clin Invest **57**: 541, 1976

38. Carbonin PU, Di Gennaro M, Valle R, Bernabei R, Habed A: Intracellular calcium and electrocardiogram in ischemic isolated rat heart. Am J Physiol **239** (Heart Circulat Physiol): H 380, 1980