Right Ventricular Ejection Fraction During Exercise in Normal Subjects and in Coronary Artery Disease Patients: Assessment by Multiple-gated Equilibrium Scintigraphy

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SUMMARY The response of right ventricular ejection fraction (RVEF) during exercise and its relationship to the location and extent of coronary artery disease are not fully understood. We have recently developed and validated a new method for scintigraphic evaluation of RVEF using multiple-gated equilibrium scintigraphy and multiple right ventricular regions of interest. The technique has been applied during upright bicycle exercise in 10 normal subjects and 20 patients with coronary artery disease. Resting RVEF was not significantly different between the groups (0.49 ± 0.04 vs. 0.47 ± 0.09, respectively, mean ± SD). In all 10 normal subjects RVEF rose (0.49 ± 0.04 to 0.66 ± 0.08, p < 0.01) at peak exercise. At peak exercise in coronary artery disease patients, the group RVEF remained unchanged (0.47 ± 0.09 to 0.50 ± 0.11, p = NS), but the individual responses varied. In the coronary artery disease patients, the relationship between RVEF response to exercise and exercise left ventricular function, septal motion and right coronary artery stenosis were studied. Significant statistical association was found only between exercise RVEF and right coronary artery stenosis. RVEF rose during exercise in seven of seven patients without right coronary artery stenosis (0.42 ± 0.06 to 0.58 ± 0.08, p = 0.001) and was unchanged or fell in 12 of 13 patients with right coronary artery stenosis (0.50 ± 0.09 to 0.45 ± 0.10, p = NS). We conclude that (1) in normal subjects RVEF increases during upright exercise and (2) although RVEF at rest is not necessarily affected by coronary artery disease, failure of RVEF to increase during exercise, in the absence of chronic obstructive pulmonary disease or valvular heart disease, may be related to the presence of significant right coronary artery stenosis. The possibility that severe left ventricular dysfunction in the absence of proximal right coronary artery obstruction may cause abnormal RVEF response to stress requires further evaluation in a larger, more varied patient population.

THE MEASUREMENT of left ventricular ejection fraction (LVEF) by equilibrium scintigraphy was recently validated1-3 and applied to the evaluation of left ventricular function during stress.4-6 However, only preliminary reports have been made of right ventricular ejection fraction (RVEF) during exercise and its relationship to coronary anatomy.7-9

We recently developed a new method of analysis using multiple-gated equilibrium cardiac blood pool scintigraphy to measure RVEF, the same scintigrams that are routinely obtained for assessment of left ventricular function.10 This multiple-gated equilibrium scintigraphic technique for determination of RVEF demonstrated a high correlation with estimates of RVEF made by first-pass scintigraphy and was associated with minimal inter- and intraobserver variations.10 These findings, therefore, defined a new, rapid method well-suited to the evaluation of RVEF during multiple stages of graded exercise.

Using the new approach to multiple-gated equilibrium cardiac blood pool scintigraphy for measurement of RVEF, our results10 supported those reported by other investigators11, 12 that RVEF at rest is not a sensitive indicator of the presence of coronary artery disease (CAD) and bears no relationship to the degree of right coronary artery narrowing.

As with the left ventricle, functional abnormalities of the right ventricle may be seen under circumstances of physiologic stress. Therefore, the evaluation of RVEF during stress may provide a sensitive indicator for right ventricular myocardial functional reserve.

In the present study we evaluated (1) the normal response of RVEF to stress, (2) abnormal right ventricular function during exercise as related to the presence of CAD, and (3) the relationship between RVEF response to stress and exercise left ventricular function, septal motion during exercise, and the presence of right coronary artery stenosis.

Materials and Methods

Patients

Multiple-gated cardiac blood pool scintigraphic studies for evaluation of RVEF were performed on 30 subjects. Of 10 subjects (eight males and two females) with mean age of 36 years (range 23–66 years), two had normal coronary arteriograms and the other eight...
were normal volunteers (normal group). These volunteers were considered normal by having all of the following: (1) no symptoms of cardiopulmonary disease; (2) a normal physical examination; (3) a normal exercise ECG; and (4) no smoking history. Twenty patients (19 males and one female) with mean age of 56 years (range 39–75 years) had angiographically proven CAD. The mean interval between coronary angiography and exercise testing was 19 days (range 1–99 days). A diameter luminal narrowing of ≥ 75% of the normal portion of the vessel was considered significant coronary artery stenosis. Of the 20 CAD patients, five had one-vessel disease, eight had two-vessel disease and seven had three-vessel disease. All 20 patients had significant left anterior descending or left circumflex stenosis or both. Thirteen patients had significant right coronary artery stenosis and seven had normal right coronary arteries. The location of narrowing was more pronounced in all patients with right coronary artery stenosis than proximal. The stenosis was proximal to the right ventricular branch in 10 and distal to the right ventricular branch but proximal to the acute marginal branch in the remaining three. The results of coronary arteriography in each subject are included in Table 1. Patients who were receiving propranolol discontinued its use at least 48 hours before exercise testing. Patients with a history and/or clinical findings of pulmonary disease or with a documented prior myocardial infarction were not included in the study. Specifically, no patient had history of more than 10 pack-years of smoking and no patient had a pathologic Q wave on resting ECG. Only one patient had segmental akinesis or dyskinesis on left ventricular contrast ventriculography. This patient, who had apical dyskinesis, unassociated with pathologic Q waves, had normal apical wall motion after subsequent aortocoronary bypass surgery.

Radionuclide Data Acquisition

The multiple-gated equilibrium cardiac blood pool scintigraphic technique involved serial 2-minute

| Table 1. Response of Heart Rate, Right Ventricular Ejection Fraction, Left Ventricular Ejection Fraction, and Septal Motion to Maximum Exercise and Angiographic Findings in Coronary Artery Disease Patients |
|-----------------|---------|---------|---------------|-----------------|-----------------|
| Case | Heart rate (beats/min) | RVEF (%) | Abn ex response | Angiographic CAD (>75% stenosis) |
|      | Rest Max ex | Rest Max ex | LVEF | Septal motion | RCA | LAD | LCX |
| 1    | 98 130 | 0.57 0.46 | (+) | + + + + + + + + + |
| 2    | 66 120 | 0.55 0.46 | (+) | + + + + + + + + + |
| 3    | 69 150 | 0.46 0.27 | (+) | + + + + + + + + + |
| 4    | 60 140 | 0.31 0.42 | (-) | + + + + + + + + + |
| 5*   | 70 140 | 0.64 0.60 | (+) | - + + + + + + + + |
| 6    | 56 120 | 0.55 0.58 | (+) | - + + + + + + + + |
| 7    | 70 120 | 0.36 0.36 | (+) | + + + + + + + + + |
| 8    | 62 130 | 0.53 0.47 | (+) | + + + + + + + + + |
| 9    | 60 120 | 0.56 0.61 | (+) | - + + + + + + + + |
| 10   | 50 80  | 0.51 0.45 | (+) | + + + + + + + + + |
| 11   | 61 120 | 0.47 0.49 | (+) | + + + + + + + + + |
| 12   | 108 160| 0.43 0.34 | (+) | + + + + + + + + + |
| 13   | 48 86  | 0.53 0.35 | (+) | + + + + + + + + + |
| 14   | 59 120 | 0.45 0.63 | (-) | + + + + + + + + + |
| 15   | 68 120 | 0.51 0.58 | (-) | - + + + + + + + + |
| 16   | 59 140 | 0.46 0.60 | (-) | - - - - - - - - + |
| 17   | 63 120 | 0.41 0.49 | (-) | + + - + - + + + + |
| 18   | 61 120 | 0.31 0.46 | (-) | + + - + - + + + + |
| 19   | 72 140 | 0.41 0.64 | (-) | + + - + - + + + + |
| 20   | 77 160 | 0.39 0.67 | (-) | - + - + - + + + + |

*All subjects were male except for case 5.
†Stenosis distal to the first septal perforator branch.

Abbreviations: Max ex = maximal exercise; Abn ex = abnormal exercise; LVEF = left ventricular ejection fraction; RCA = right coronary artery; LAD = left anterior descending coronary artery; LCX = left circumflex artery.

\[ p < 0.001 \quad p = 0.38 \]

Mean | 66.85 | 126.80 | 0.47 | 0.50
sd  | 14.33 | 20.17 | 0.09 | 0.11
srm | 3.29  | 4.51  | 0.02 | 0.03
assessments of right ventricular function. Studies were performed with a portable scintillation camera (Searle Low Energy Mobile) equipped with a shielded, parallel-hole, low-energy, all-purpose collimator and a mobile minicomputer (Medical Data Systems, PAD). Images were obtained in the 40–50° left anterior oblique view. In each case, the degree of obliquity used was that which provided the best separation between the right and left ventricles. During each 2-minute acquisition, the computer divided the scintigraphic data from the first two-thirds of each cardiac cycle into 14 frames and added the corresponding frames of the cycles imaged. The average frame contained approximately 100,000 counts. All data were acquired with a hardware zooming device that expanded the data 1.7 times and were recorded in a 64 × 64 BYTE mode matrix.

Radionuclide Data Processing

RVEF determination from multiple-gated equilibrium scintigrams has been described in detail previously. Briefly, the technique of analysis involved light-pen assignment of two regions of interest over the right ventricle, one in the end-systolic and the other in the end-diastolic phase of the cardiac cycle. Assignment of the regions of interest involved conventional nine-point smoothing, determination of the end-diastolic and end-systolic frames and display of the data in an endless-loop movie format. This movie display substantially improved the visual perception of the borders of the right ventricle throughout the cardiac cycle and was particularly important in defining the borders between the right ventricle and the pulmonary artery. With this technique it is important that separate right ventricular regions of interest for end-systole and end-diastole be assigned in order to minimize the contribution of right atrial radioactivity to counts in the right ventricular region of interest. For background, a light pen assigned end-systolic left paraventricular region of interest was selected. This background region was crescent-shaped, separated by one matrix element from the left ventricular activity and was three to five matrix elements wide. We have empirically found that this paraventricular region of interest best represents the contribution of background activity to right ventricular counts. RVEF was determined by dividing the background-corrected stroke counts (end-diastolic counts – end-systolic counts) by the background-corrected end-diastolic counts. LVEF measurement was performed with light-pen assignment of left ventricular end-diastolic and end-systolic regions of interest, using the same background subtraction and ejection fraction calculation as for RVEF. Septal motion was assessed semiquantitatively using a five-point scoring system (−1 = dyskinesis, 0 = akinesis, 1 = severe hypokinesis, 2 = mild hypokinesis, and 3 = normal). Similar to RVEF, LVEF response to exercise was considered normal if the exercise ejection fraction increased by > 10% of the resting ejection fraction value. Septal motion during exercise was considered abnormal when the wall motion score during exercise deteriorated by ≥ 1 point compared with the resting septal motion score.

Exercise Protocol

For this procedure, sitting exercise was the form of stress using an ergometer (Collins) with electrically controlled workload. Before exercise, control 2-minute multiple gated imaging was performed in the sitting position. After control imaging, the patient underwent a warmup pedaling at 0 work load and 70 rpm for 1 minute. Subsequently, beginning at 25 W, the workload was gradually increased until target heart rates of 100, 120, 140, 160 and 170 beats/min were reached. At each stage of exercise, after stabilization of heart rate at the desired level, imaging was performed for 2 minutes. The exercise protocol was continued to the end point of maximal predicted heart rate, severe fatigue or angina pectoris.

Statistical Methods

RVEFs and heart rates during control and maximal exercise stages were compared in the CAD patients using the paired t test. RVEFs and heart rates of the normal subjects were each analyzed by analysis of variance for repeated measurements in order to compare the mean values obtained at rest, intermediate and maximal exercise stages. When the analysis of variance indicated a significant result, the Newman–Keuls test was used to ascertain which of the means were significantly different from one another. An unpaired t test was used to compare the RVEFs and heart rates at rest and exercise between the normal subjects (intermediate exercise) and the CAD patients (maximal exercise).

Fisher's exact test was used to assess the significance of the relationship between RVEF response to stress and exercise LVEF, septal motion during exercise, and the presence of right coronary artery stenosis. This statistical procedure is used to provide an exact test of significance when the data are arrayed in a 2 × 2 contingency table and the smallest expected value is less than 5. P values < 0.05 were defined as statistically significant.

Results

Clinical Illustrations

Figures 1, 2 and 3 depict the responses of RVEF and LVEF to exercise in a normal subject, a patient with dominant right CAD and a patient with left coronary artery disease and a normal right coronary arteriogram, respectively.

Figure 1 demonstrates the response of LVEF and RVEF to exercise in a normal subject (case 1, table 2). RVEF increased from 0.45 to 0.68 and LVEF increased from 0.63 to 0.83. This improvement in right and left ventricular function is evident from visual inspection of the ventricular radioactivity in the multiple gated equilibrium scintigrams.

The patient (case 11, table 1) illustrated in figure 2 had a proximal 90% left anterior descending stenosis
and a distal 99% first-diagonal narrowing. The right coronary system had a combination of a proximal 75% and mid 90% stenoses. During the control phase, RVEF was normal at 0.47. During maximal exercise to heart rate 120 beats/min, RVEF remained unchanged (0.49) while LVEF increased from a resting value of 0.54 to 0.66. The unchanged RVEF is evident from inspection of the multiple-gated equilibrium cardiac blood pool scintigraphic images.

The patient illustrated in figure 3 (case 14, table 1)
FIGURE 3. Representative example of normal right ventricular ejection fraction (RVEF) and abnormal left ventricular ejection fraction (LVEF) responses to exercise in a coronary artery disease patient without right coronary stenosis. At rest, the RVEF and LVEF were 0.45 and 0.65 respectively. During maximal exercise (heart rate [HR] of 120 beats/min), the RVEF rose to 0.63 but the LVEF did not change. These findings are evident from inspection of the multiple-gated equilibrium scintigrams.

had a proximal 99% left anterior descending stenosis and distal 90% left circumflex narrowing. The right coronary system was normal. RVEF rose from a resting value of 0.45 to a maximal exercise level of 0.63, while the left ventricle developed apical dyskinesis at maximal exercise and the resting LVEF of 0.65 was unchanged (exercise LVEF = 0.66).

Group Responses

Values for RVEF at rest and during exercise in normal subjects and the coronary artery disease patients are shown in figure 4 and in tables 1 and 2. For the CAD patients, rest and maximal exercise values are shown. Since many of the CAD patients did not

<table>
<thead>
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<th>Case</th>
<th>Age (years)</th>
<th>Heart rate (beats/min)</th>
<th>RVEF (%)</th>
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<td></td>
<td></td>
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<td>76</td>
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</table>

*Analysis of variance for repeated measurements was performed excluding case 4. However, the means and standard deviations for this table are computed including this normal subject.

Abbreviations: Intermed ex = intermediate exercise; Max ex = maximal exercise.
achieve a maximal heart rate as high as the normal subjects, RVEF values at an intermediate level of exercise are included for the normal subjects.

Normal Subjects

The mean RVEF in the normal subjects at rest was 0.49 ± 0.04 (mean ± SD). At the intermediate stage of exercise, RVEF increased significantly to 0.60 ± 0.07 and during peak exercise, further increased to 0.67 ± 0.08. The mean heart rate at rest was 76 ± 10 beats/min, increased to 126 ± 13 beats/min during intermediate stage of exercise and further increased to 162 ± 12 beats/min at peak exercise. (All exercise values were significantly different from resting values at p < 0.01). In each of the normal subjects, the intermediate exercise RVEF rose by at least 10% and the maximal RVEF increased by at least 20% of the resting value (fig. 1).

CAD Patients

In the patients with CAD, mean resting RVEF was not significantly different from the resting RVEF in normals (0.47 ± 0.09 vs 0.49 ± 0.04, p = 0.49). During maximal exercise in the CAD patients as a group, RVEF did not rise significantly (0.47 ± 0.09 vs 0.50 ± 0.11, p = 0.38). Mean maximal RVEF in CAD patients was significantly lower than mean RVEF of normals at intermediate stage of exercise (0.50 ± 0.11 vs 0.60 ± 0.07). The individual responses of RVEF in the CAD patients showed marked variation. RVEF increased by 10% of the resting value in eight and either remained unchanged (± 10%) or decreased (> 10% fall) in 12 of the 20 patients with CAD.

Since right ventricular function during exercise might be affected by exercise left ventricular function, septal motion during exercise and the presence of right coronary artery stenosis, we further analyzed the relationship between normal and abnormal RVEF response to stress and each of these parameters.

Although nine of 12 patients with abnormal RVEF response had abnormal LVEF response to stress, five of eight patients with normal RVEF during exercise had abnormal LVEF response to exercise. The difference between these proportions was not statistically significant.

Abnormal exercise septal motion was observed in 10 of 12 patients with abnormal RVEF response and in seven of eight patients with normal RVEF response to exercise. There was no significant difference between these proportions.

Of 12 patients with abnormal RVEF exercise response, all had right coronary artery stenosis. In contrast, of the eight patients with normal exercise RVEF, one had right coronary artery stenosis. The difference between these proportions was significant (p < 0.001).

In patients subgrouped by the presence of right coronary artery stenosis, mean RVEF values at rest and maximal exercise were compared. In the seven patients without right coronary artery stenosis, RVEF rose during exercise (0.42 ± 0.06 to 0.58 ± 0.08, p = 0.001) similar to the response observed in normal subjects at comparable heart rates (fig. 1). In five of the seven patients, RVEF increased by more than 20% of the resting value and in the remaining two patients the increase was between 10–20%. In contrast, in the subgroup with right coronary stenosis, mean RVEF did not change significantly (0.50 ± 0.09 to 0.45 ± 0.10, p = 0.08).

Discussion

The results have demonstrated that our new technique for evaluating RVEF from standard multiple-gated scintigraphic gated blood pool images

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**Figure 4.** Graphic representation of the relationship between right ventricular ejection fraction (RVEF) at rest and during exercise in the normal subjects (left panel) and the coronary artery disease (CAD) patients (right panel). The solid line is the line of identity; the dashed line represents exercise values 10% greater than the resting RVEF, and the dashed-dotted line represents exercise values 20% greater than the resting LVEF. The dashed and dashed-dotted lines converge to zero intercept. RCA = right coronary artery.
can be applied to the assessment of RVEF during exercise.

The RVEF response in normal subjects was characterized by a significant increase during intermediate exercise and by a marked increase during maximal exercise.

It is well-recognized that resting RVEF or LVEF may be normal in the presence of severe disease of any part of the coronary artery system.\textsuperscript{10, 12, 13} The results of the present study corroborate this finding in that the mean resting RVEF was not statistically different in the patients with CAD from the resting RVEF of the normal subjects.

The present study describes the responses of RVEF to stress in patients with CAD. In the CAD patients, as a group, RVEF did not rise significantly during exercise, in contrast to the normal subjects. However, the wide scatter in the individual responses was not readily explained by the mere absence or presence of CAD.

Since the right and left ventricles function as pumps in series, abnormalities of right ventricular function during stress might be secondary to stress-induced left ventricular dysfunction. Sharma et al.\textsuperscript{14} have demonstrated that during supine bicycle exercise in normals and CAD patients, left ventricular filling pressure increased to a greater extent in CAD patients. This increase left ventricular end-diastolic pressure increased right ventricular afterload. This increase in right ventricular afterload might reduce RVEF; however, this was not measured by these investigators.

Since the interventricular septum comprises a major portion of the right ventricular wall, abnormality of septal motion might produce right ventricular dysfunction. Brooks et al.\textsuperscript{15} demonstrated deterioration of right ventricular function after induced anteroseptal infarction in the pig.

Since the vascular supply of the free wall of the right ventricle is largely derived from the right coronary artery,\textsuperscript{16} right ventricular dysfunction during stress might be related to right coronary artery stenosis with exercise-induced right ventricular ischemia. Brooks and co-workers\textsuperscript{17} evaluated performance of the right ventricle in a canine model during graded increase in right ventricular afterload and assessed the relationship between stress right ventricular function and right coronary artery blood flow. They have demonstrated that with right coronary artery occlusion, right ventricular dysfunction occurs at a much lower level of stress.

Therefore, three mechanisms — global left ventricular dysfunction during exercise, abnormal exercise septal motion, or ischemia of the right ventricular free wall — could explain abnormal RVEF response to stress. In our study, no significant association between exercise RVEF response and either left ventricular function during exercise or exercise septal motion was found. However, a significant relationship was observed between exercise RVEF response and right coronary artery stenosis. In 19 of the 20 patients with CAD, concordant results regarding the presence of right coronary artery stenosis and the RVEF response were noted. In contrast, with respect to the relationship between left ventricular function and right ventricular function, discordant results were observed in eight of the 20 patients, including the abnormal subject illustrated in figure 2. With respect to the relationship between septal motion during exercise and RVEF response, discordant responses were observed in nine of the 20 patients.

These findings suggest a major role of right coronary artery stenosis in the production of abnormal RVEF fraction during stress. Further elucidation of the mechanism for abnormal RVEF response in patients with CAD will require assessment of patients with severe left ventricular dysfunction in the absence of proximal right coronary artery stenosis and patients with isolated right coronary artery stenosis. These aspects are currently under investigation in our laboratories. We suspect that all three of the postulated mechanisms might interact to produce an abnormal RVEF response to stress.

None of the CAD patients in this study had prior myocardial infarction. In patients with prior right ventricular myocardial infarction, response of RVEF to exercise is variable and depends on the extent of functional myocardium and residual ischemia.

Additional information provided by determination of RVEF during stress may improve the accuracy of exercise left ventricular wall motion analysis for assessment of the severity and extent of CAD. Although abnormalities of the septal wall motion imply the presence of left anterior descending CAD, and abnormalities of posterolateral wall motion imply the presence of left circumflex CAD, the standard left anterior oblique scintigrams do not provide direct visualization of the portion of the left ventricle supplied by the right coronary artery. Abnormalities of the inferoapical left ventricular region of the left anterior oblique scintigrams may be secondary to obstruction of any of the three major coronary arteries. If assessment of larger numbers of patients with CAD supports the high specificity of abnormal RVEF response to stress for right coronary artery stenosis, this measurement could provide additional information for assessment of the extent of CAD.

Since this new method for evaluation of RVEF during stress provides a technique for assessment of right ventricular functional reserve, the technique may be applicable in a variety of other clinical settings, including the evaluation of patients with pulmonary disease and valvular heart disease.

Acknowledgment

The authors gratefully acknowledge the research assistance of Nancy Pantaleo, R.N., the technical assistance of Autumn Anderson, Debbie Drake, Lance Laforteza, Terry Collett and Tina Orvis, and the statistical support of Jo Ann Prazue and Emily Kushida.

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Right ventricular ejection fraction during exercise in normal subjects and in coronary artery disease patients: assessment by multiple-gated equilibrium scintigraphy.
J Maddahi, D S Berman, D T Matsuoka, A D Waxman, J S Forrester and H J Swan

Circulation. 1980;62:133-140
doi: 10.1161/01.CIR.62.1.133

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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