Significance of Increased Right Ventricular Uptake on ^{99m}Tc-Sestamibi SPECT in Patients with Coronary Artery Disease

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The significance of increased right ventricular (RV) tracer uptake in patients with coronary artery disease (CAD) without pulmonary or valvular heart disease is unclear. **Methods:** Forty consecutive patients with increased RV uptake on SPECT myocardial perfusion imaging and right heart catheterization within 4 wk were studied prospectively. Thirty-five individuals with very low likelihood of CAD served as controls. Rest and stress SPECT myocardial perfusion data were obtained using a standard ^{99m}Tc-sestamibi 1-d imaging protocol. A quick and simple RV-to-left ventricular (LV) myocardial uptake ratio was calculated from the maximum counts per pixel detected in the right and left ventricles using the reconstructed coronal slices. RV end-systolic pressure (RV-ESP), mean pulmonary artery pressure (PAP) and pulmonary capillary wedge pressure were obtained by standard techniques. **Results:** The RV/LV uptake ratio in the controls was 0.31 ± 0.05. Thirty-six of the 40 (90%) CAD patients with increased RV tracer uptake had increased RV-ESP, and 39 (97.5%) had increased PAP. Highly significant positive correlations between the RV/LV uptake ratio and RV-ESP and PAP were found (r = 0.45, P = 0.003; and r = 0.52, $P < 0.001$, respectively). **Conclusion:** Increased RV uptake, assessed from standard myocardial perfusion studies, can identify RV pressure overload among patients with CAD. In the absence of pulmonary or valvular heart disease, increased RV uptake (i.e., RV pressure overload) indicates significant backward failure, a variable with known significant negative prognostic implications.

Key Words: right ventricle; myocardial perfusion; SPECT; sestamibi

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Increased right ventricular (RV) tracer uptake (Fig. 1) is not an uncommon finding in individuals with suspected or known coronary artery disease (CAD) studied with myocardial perfusion imaging. There are, however, few data in the literature regarding the meaning and significance of this finding in CAD patients. Increased RV tracer uptake is often seen in patients with chronic lung disease (*1–5*), congenital heart disease (*5–11*), valvular heart disease (*6–8,12,13*) and primary pulmonary hypertension (*1,5,7,8*), and positive correlations to RV end-systolic pressure (RV-ESP) and pulmonary artery pressure (PAP) have been demonstrated (*2,4,6–10,12*).

Increased RV tracer uptake in myocardial perfusion studies generally has been seen as a sign of RV hypertrophy. If this is valid in patients with CAD without pulmonary or valvular heart disease, then information about backward failure with significant diagnostic and prognostic implications could be obtained. In one study (*14*), increased RV uptake in acute myocardial infarction was found to be indicative of poor prognosis.

RV uptake generally has been estimated visually, although quantification has been tried (*4,5,8,9,11*), but in only two studies using SPECT (*4,11*). No data are available about RV uptake in healthy volunteers, and without such data it is difficult to define abnormal uptake quantitatively. All previous studies used ^{201}Tl except for one study of children with congenital heart disease (*10*), in which RV uptake of ^{201}Tl and ^{99m}Tc-sestamibi were found to correlate closely. The aims of this study were (a) to establish a reproducible quantitative method for assessing RV uptake using SPECT and ^{99m}Tc-sestamibi, (b) to define the normal range of RV uptake and (c) to test the hypothesis that increased RV uptake reflects RV pressure and PAP in patients with CAD.

MATERIALS AND METHODS

Control Population

Thirty-five individuals (21 men, 14 women; mean age 52 ± 13 y) referred for evaluation of atypical chest discomfort served as control subjects in this study. All reached >85% of predicted maximum heart rate on a standard Bruce treadmill protocol. None had chest pain or electrocardiogram abnormalities during or after the test. No myocardial perfusion abnormalities were detected by qualitative or quantitative analysis. Post-test likelihood of significant CAD was thus very low (<5%). History and physical examination revealed no evidence of pulmonary or valvular heart disease, and none of the volunteers were taking pulmonary-active medications.

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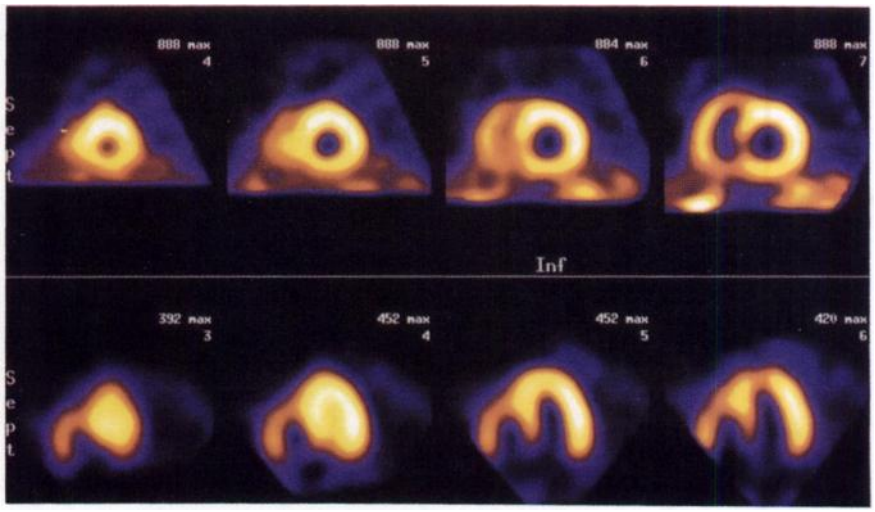

FIGURE 1. Selected coronal (upper) and transaxial (lower) slices from typical patient with CAD and coincidentally detected increased RV tracer uptake. Note typical M sign in transaxial slices and prominent RV wall in coronal slices (RV uptake ratio = 0.56, RV-ESP = 54 mm Hg). Max = maximum; inf = inferior.

Study Population

Forty consecutive patients (28 men, 12 women; mean age 61 ± 9 y) referred for evaluation of known or suspected CAD who were found to have an increased rest RV-to-left ventricular (LV) uptake ratio and who had a right heart catheterization within 4 wk of the myocardial perfusion scan were enrolled in this study. Eighteen had catheterization before the perfusion scan. The right heart catheterization was part of the diagnostic workup and was performed when clinically indicated (e.g., signs of RV failure or other findings suggestive of RV disease). The RV uptake findings were not available for clinical decision making. None of the patients had a history or clinical signs of pulmonary disease, none were taking pulmonary-active medications and none had a history or clinical signs of valvular heart disease.

Myocardial Perfusion Imaging

A rest/stress imaging protocol was used. At rest, 8 mCi ^{99m}Tc-sestamibi were administered. Patients and control subjects ingested a light meal 20–30 min later. Imaging was started 60 min after tracer administration. All patients and control subjects followed a standard symptom-limited Bruce treadmill protocol. At peak workload, defined as maximal possible effort, significant chest pain or severe ST-depression or arrhythmia, 24 mCi ^{99m}Tc-sestamibi were injected. Patients and control subjects ingested a light meal 20–30 min later. Stress imaging began 60 min after tracer administration.

A triple-head camera (Prism; Picker International, Cleveland, OH) equipped with low-energy, high-resolution collimators was used. Data were acquired in a 64 × 64 matrix, over 180° from left posterior oblique 45 to right anterior oblique 45, 32 angles, 25 s per angle for the rest study and 20 s per angle for the stress study.

All studies were reconstructed using filtered backprojection (ramp filter). A low-pass filter was applied (order 0.5 with cutoff 0.25 for rest studies, and order 0.5 with cutoff 0.33 for stress studies). The data were reformatted to sagittal, coronal and transaxial slices (6 mm) according to the individually determined anatomic cardiac long axis. For display and visual assessment purposes, software zoom was applied and coronal slices added, thereby generating perfusion images representing regional myocardial perfusion in the basal, mid and apical thirds of the myocardium. Sagittal and transaxial slices also were created to visualize the apex and walls longitudinally. The stress and rest studies were carefully aligned to ensure that corresponding myocardium in the two studies was compared. The two studies were displayed simultaneously on a high-resolution monitor using a standard color table for visual semiquantitative analysis.

Quantitative analysis of the myocardial perfusion data was performed using the CEqual method (*15*). With this method, the extent (percentage of total myocardium) and severity (sum of SD below lower limit of normal) of fixed and reversible perfusion abnormalities are determined on the basis of normal database measures for men and women.

Right Ventricular-to-Left Ventricular Ratio Assessment

The RV/LV uptake ratio was assessed using two different techniques. First, the coronal slices were displayed. A color table with 10% increments was applied (Fig. 2). The area of the LV myocardium with the highest uptake was thus highlighted. A region of interest (ROI) was then placed over this area, giving the maximum counts per pixel. The upper threshold was then gradually lowered until the area of the RV myocardium with the highest uptake was identified (Fig. 2).The ROI was positioned over this area, giving the maximum counts per pixel. Next, a 3 × 3 pixel-square ROI was placed so it encompassed the myocardial area with the highest tracer uptake on the left and right sides, giving the mean LV and RV counts per pixel around the area with the highest uptake. The RV/LV maximum counts per pixel and RV/LV mean counts per pixel ratios were calculated using the following equation: RV/LV ratio = (RV counts/LV counts) × 100%.

Right Heart Catheterization

Right heart catheterization was performed in all patients in the study group. Systolic, diastolic and mean RV, PAP and pulmonary capillary wedge (PCW) pressure measurements were obtained using standard techniques. An RV-ESP of ≥30 mm Hg and a mean PAP of ≥20 mm Hg was considered abnormally high (*16*).

Statistical Methods

All values are given as mean ± SD. The relationship between variables was analyzed using simple linear regression analysis. Student unpaired *t* test was used for between-groups comparison. $P < 0.05$ was considered significant. Reproducibility was analyzed using the Bland-Altman method (*17*).

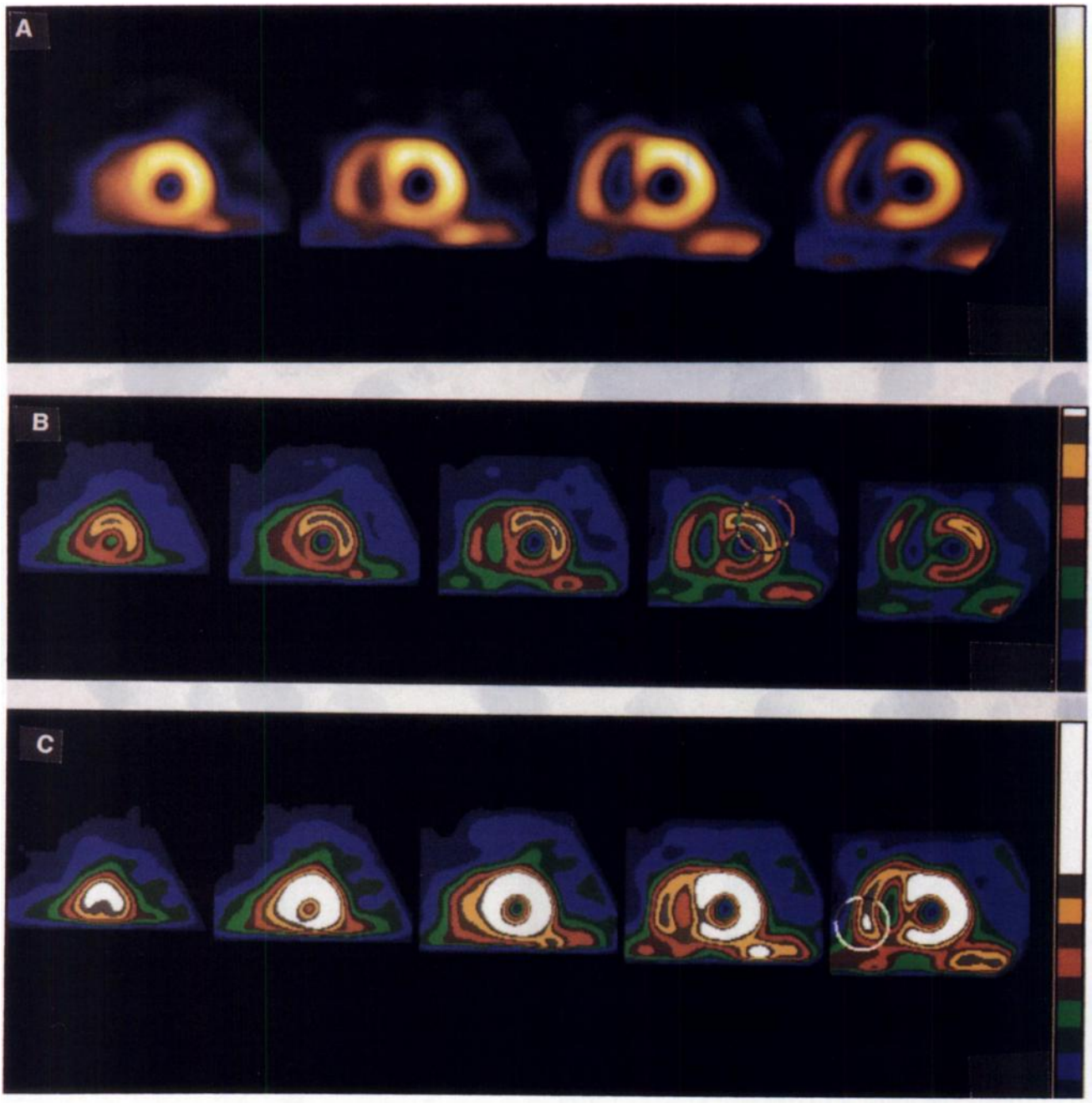

FIGURE 2. RV/LV uptake ratio assessment. (A) Color-coded short-axis slices of typical patient with CAD. (B) Same data with 10% incremental color table applied. Area with highest uptake in LV myocardium is easily identified (white = 90%–100%). Standard circular ROI is positioned around this area, giving maximum LV counts per pixel. (C) Using same color table, upper threshold is lowered until area in RV myocardium with highest uptake is disclosed. This area is then circled with an ROI, giving maximum RV counts per pixel.

RESULTS

Two different methods of calculating an RV/LV uptake ratio were tested. The correlation between the uptake ratios obtained with the two methods was very close (n = 50, r = 0.97, $P < 0.001$, SEE = 0.016; Fig. 3), and no significant difference between the mean values (0.421 ± 0.09 versus 0.426 ± 0.10, $P = 0.97$) was found. Reproducibility (*17*) of the maximum counts per pixel and the 3 × 3 pixel mean counts per pixel methods, determined by reprocessing 20 randomly selected studies twice, was found to be ±2.5% and ±2.7% for the two methods, respectively (i.e., >95% of repeated measurements were within these percentage limits).

The maximum counts per pixel method was much faster than the 3 × 3 pixel mean counts per pixel method (performed in less than one third of the time) and was therefore, given the close correlation and similar reproducibility, the preferred and applied method in this study.

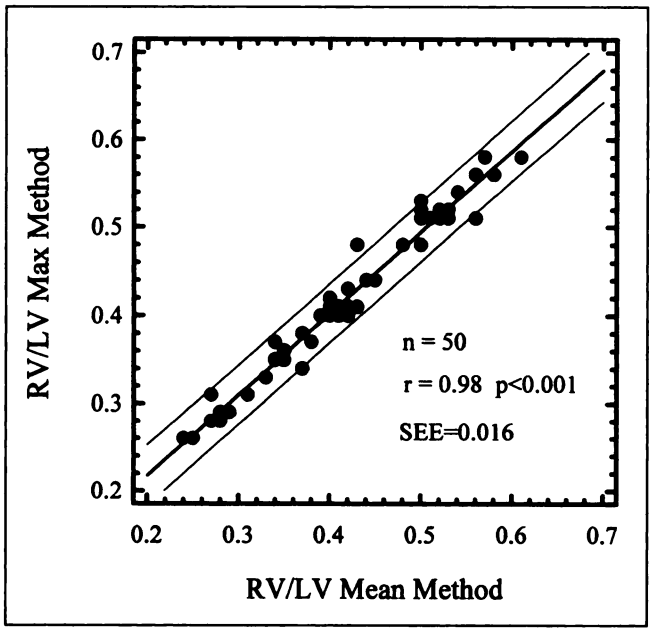

FIGURE 3. Correlation between RV/LV uptake ratio obtained with two methods tested. Max = maximum.

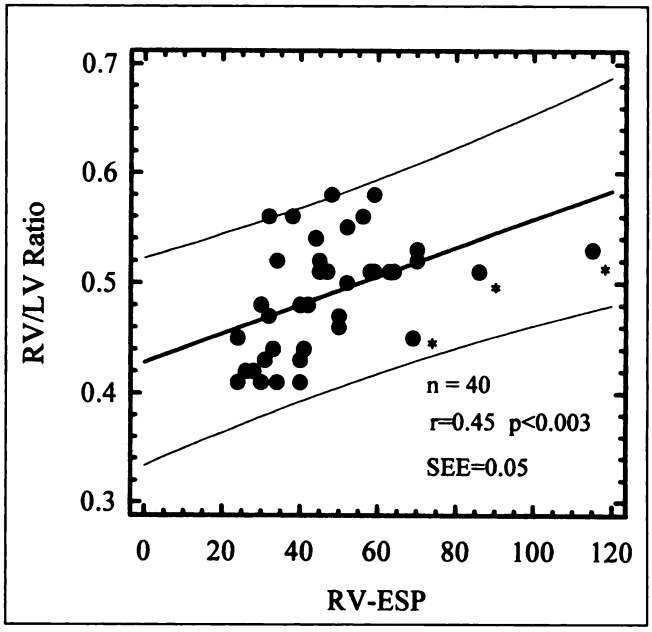

FIGURE 4. Relationship between RV/LV uptake ratio and RV-ESP. Symbols for 3 patients later considered to have dilated cardiomyopathy in addition to CAD are marked with asterisk.

Reference Values

The RV/LV uptake ratio at rest in the 35 control subjects was 0.31 ± 0.05. The 95th percentile was 0.40. Thus, a value of 0.41 or higher was defined as abnormally increased RV uptake at rest.

Patients with Coronary Artery Disease

Thirty-six of the 40 patients (90%) with increased RV uptake had increased RV-ESP, and 39 of the 40 patients (97.5%) had increased mean PAP. Thirty-five of the 40 patients (87.5%) had elevated PCW pressure.

A highly significant positive linear correlation between RV/LV uptake ratio and RV-ESP was found ($r = 0.45$, $P = 0.003$; Fig. 4). A highly significant correlation between RV uptake and mean PAP also was demonstrated ($r = 0.52$, $P = 0.0006$; Fig. 5). It is interesting to note that 3 patients who appeared to be outliers in the correlation plot by having lower than expected RV uptake considering the pressures measured were all eventually considered to have or were suspected of having cardiomyopathy in addition to CAD (2 idiopathic, 1 secondary to hypertension). If these patients, who all had marked dilated and thin-walled RV, are excluded from the analysis, correlation coefficients of 0.66 and 0.63, respectively (both $P < 0.001$), are obtained.

A strong but not statistically significant trend was seen between RV uptake ratios and PCW pressures ($r = 0.32$, $P = 0.07$). Weakly significant positive correlations between RV uptake and extent and severity of LV perfusion abnormalities also were found ($r = 0.34$, $P = 0.05$; and $r = 0.38$, $P < 0.05$, respectively).

DISCUSSION

That increased radionuclide uptake in the right ventricle reflects RV overload in patients with congenital heart disease, valvular heart disease and chronic pulmonary disease has been known for quite some time (*1–13*). Surprisingly, such findings of increased RV uptake in patients with CAD have not been systematically integrated in the interpretation of myocardial perfusion data. In these patients, who account for the large majority of patients undergoing myocardial perfusion imaging, additional information about RV pressure overload has, in the absence of pulmonary and valvular heart disease, obvious clinical

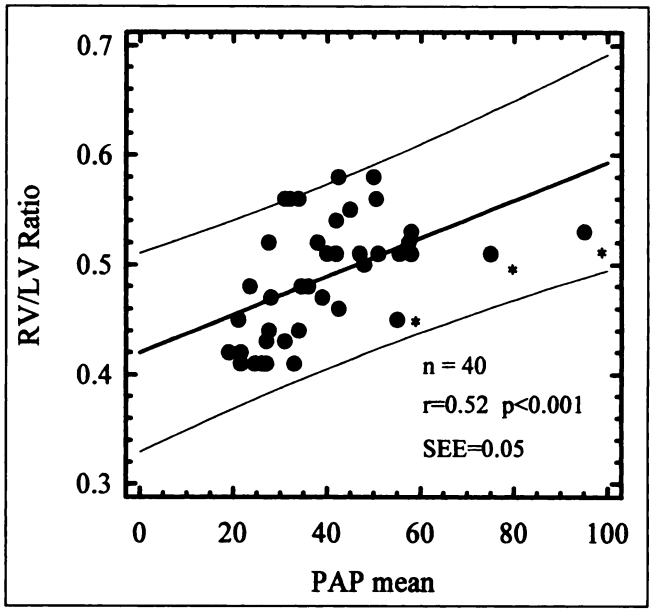

FIGURE 5. Relationship between RV/LV uptake ratio and mean PAP. Symbols for 3 patients later considered to have dilated cardiomyopathy in addition to CAD are marked with asterisk.

relevance. RV pressure overload and RV hypertrophy (as reflected by increased RV uptake) imply severe and chronic backward LV failure resulting in pulmonary hypertension. Congestive heart failure (CHF) and pulmonary hypertension are serious complications of CAD and are leading causes of morbidity and mortality among these patients (*18–20*). It is therefore important to identify these patients, preferably with a noninvasive technique. LV cavity size and LV ejection fraction routinely are obtained noninvasively, but these variables have been shown to be unable to differentiate between otherwise similar CAD patients with few signs of CHF versus severe CHF, which has a much more severe prognosis (*18–20*). More specific assessment of PAP or RV pressure, and their consequences, is thus needed for risk stratification and treatment decision making. This study describes a simple and highly reproducible method for obtaining this additional information from standard imaging data at minimal auxiliary processing time and cost. Simple visual qualitative assessment of RV tracer uptake can easily identify patients with moderate or marked increased uptake and can thus be used for screening (Fig. 1), whereas quantification and comparison with normal values are necessary to classify patients with mild to moderate increased uptake. It is presumable that treatment still can affect outcome in this group of patients with mild to moderate pulmonary hypertension. The control subjects included in this study for establishing the normal range of RV uptake were selected from individuals with very low post-test probability of significant CAD; healthy volunteers deliberately were not chosen. This approach was used to ensure that the reference population was compatible with the patient cohort being examined regarding age, gender and prevailing noncardiac conditions.

Regional myocardial uptake of ^{99m}Tc-sestamibi is initially a function of flow (supply) and secondly a function of myocyte membrane integrity (i.e., cellular viability [tracer retention]). Because flow is dependent on demand, increased workload (volume ejected × pressure to overcome) leads to increase in flow and in the long run to increase in muscle mass.

These fundamental pathophysiological principles have been demonstrated for the right ventricle using radionuclide perfusion markers in rats (*21*) and dogs (*22*). In a study by Wackers et al. (*22*) in which well-controlled animal models were used, the pathophysiological correlation between acute volume overload, acute pressure overload, chronic pressure overload and RV myocardial uptake of perfusion tracers was clearly demonstrated by imaging in vivo. Both acute volume overload and, to a higher degree, acute pressure overload led to a marked increase in RV uptake, as did chronic pressure overload. All were detectable with perfusion imaging and confirmed invasively and at autopsy. These findings validate and put in perspective the findings of increased RV uptake in clinical studies of patients with chronic lung disease, congenital heart disease and valvular heart disease (*1–13*). In patients with CAD, an increase in RV uptake correlated with an increase in RV pressure, in all cases secondary to pulmonary hypertension, which in this patient population reflects LV backward failure. The most important clinical determinant of RV tracer uptake is RV hypertrophy, which is unlikely to change significantly in the time between catheterization and myocardial perfusion scan.

Initiated or modified treatment and physiological variations in filling pressures could easily affect the direct relationship between tracer uptake and pressures. However, evidence of the existence of an underlying RV pressure overload situation, sufficient to create RV hypertrophy, is of great prognostic importance (*18–20*).

Prospective studies designed to determine the diagnostic performance (i.e., sensitivity, specificity and predictive values) of this new method for quantitative assessment of RV pressure overload are in progress at Brigham and Women's Hospital, Boston, MA. These studies include patients with both normal and abnormal RV/LV uptake ratios at rest as well as patients with abnormal uptake during stress. Other variables of LV dysfunction are also generated from the myocardial perfusion data for comparison with the RV uptake ratio.

CONCLUSION

This study demonstrated that increased RV uptake, assessed from standard myocardial perfusion data by a simple and quick method, can identify CAD patients with RV pressure overload. In the absence of pulmonary or valvular disease, RV pressure overload indicates backward failure and pulmonary hypertension, which is a major negative prognostic indicator among otherwise compatible patients with CAD. This method should be useful for identifying this subgroup of patients with high morbidity and mortality.

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