Noninvasive Quantitation of Right-Ventricular Volume Overload in Adults by Gated Equilibrium Radionuclide Angiography

Sherman G. Sorensen, Mark R. Starling, Tuhin K. Chaudhuri, and Robert A. O'Rourke

Audie Murphy Veterans Administration Hospital, and The University of Texas Health Science Center, San Antonio, Texas

R-wave-synchronized equilibrium radionuclide angiography (RNA) is a noninvasive method whose time-activity curves provide count information that is proportional to ventricular volume. We have performed resting gated RNA in nine consecutive adult patients undergoing cardiac catheterization for evaluation of left-to-right shunting. Pulmonary/systemic flow ratios (Qp/Qs) calculated from RNA correlated well with Qp/Qs defined by oximetry (r = 0.87, y = 0.85x + 0.11, sy-x = 0.46). In five patients imaged before, and within 1 mo after, successful surgical repair, RNA Qp/Qs declined from a mean (±s.d.) of 2.9 ± 1.0 to 1.1 ± 0.2. Right/left ventricular end-diastolic volume ratios declined from 3.1 ± 1.3 to 1.7 ± 0.2. Although left-ventricular ejection fraction did not change, right-ventricular ejection fraction declined in these patients. Imaging in nine patients with right-ventricular dysfunction, but without shunt or regurgitation, yielded a mean Qp/Qs of 0.94 ± 0.27. We conclude that Qp/Qs, right-ventricular ejection fraction, and relative ventricular enlargement may be accurately quantitated and followed serially after therapeutic intervention using gated RNA.


Often the presence of an atrial septal defect is not detected during childhood and may not be diagnosed until late adulthood, when patients develop progressive, nonspecific symptoms due to atrial dysrhythmia, congestive failure, or low cardiac output (1–3). While confirmation of diagnosis and definition of associated disorders usually requires cardiac catheterization in adults with atrial septal defect, new noninvasive methods are helpful in identifying and quantifying right-ventricular volume overload. Echocardiography has proven useful in detecting right-ventricular enlargement and abnormal septal motion due to moderate-to-large atrial septal defects, but it is not quantitative (4–6). First-pass radionuclide angiography using indicator-dilution principles allows quantitation of the extent of left-to-right shunting (7–11). Recently a number of studies have used right- and left-ventricular count data derived from gated equilibrium radionuclide angiography for the quantitation of left-ventricular volume overload (12–18). In the current report, we describe the application of equilibrium radionuclide cineangiography to the serial noninvasive quantitation of shunt ratio and right-ventricular ejection fraction in adult patients with atrial septal defect.

METHODS

Patient selection. Nine consecutive patients undergoing cardiac catheterization for suspected left-to-right shunt were evaluated. All nine had secundum atrial defects. Nine patients with documented right-ventricular infarction but without shunt or valvular regurgitation were also studied. The study was approved by the
Human Subjects Research Committee, and informed consent obtained in all patients.

**Cardiac catheterization.** Invasive evaluation was performed in the fasting state by either the brachial or percutaneous transfemoral approach. The presence of left-to-right shunting was confirmed by oximetry and early recirculation on green-dye curves. Catheter passage through the atrial septal defect was demonstrated by fluoroscopy and oximetry in all patients.

Sampling of blood from the brachial artery or aorta, pulmonary artery, right ventricle, right atrium, superior vena cava, and inferior vena cava was performed and oxygen content determined for each sample using an oximeter. Oxygen consumption was calculated with a paramagnetic analyzer, and spirometry-determined volumes were corrected to dry, standard temperature and pressure. Pulmonary blood flow was calculated as:

\[
\frac{\text{oxygen consumption}}{\text{arterial minus pulmonary oxygen content}}
\]

Systemic blood flow was calculated as:

\[
\frac{\text{oxygen consumption}}{\text{arterial minus mixed-venous oxygen content}},
\]

where mixed venous content was calculated by the formula:

\[
\text{Mixed venous } O_2 = \frac{3 \text{ SVC} + 1 \text{ IVC}}{4},
\]

where SVC and IVC are oxygen contents of the superior and inferior vena cava (19,20).

Left-ventricular angiography was performed in seven patients by the injection of 35–50 cc of contrast agent at 15–20 cc per sec, with single-plane 35-mm cine filming in RAO view at 60 frames per sec. Coronary arteriography was performed in these seven patients.

**Radionuclide angiography.** Resting equilibrium radionuclide angiography was performed in anterior and LAO views within one to ten days of cardiac catheterization. Supine blood pressure and heart rate were obtained immediately before imaging. Five patients were also imaged within 1 mo after successful repair of the atrial septal defect.

Since ordinates in a time-activity curve are proportional to ventricular volume, and provide a good estimate of ejection fraction using relative volume comparisons for a single ventricle, comparisons of count information between the right and left ventricles of a given patient should permit the calculation of relative volume overload of either ventricle. We have previously reported the details of our methods of time-activity curve generation and the results of validation of these methods in a control population of 20 patients without regurgitation or shunt (12). Figure 1 demonstrates the method of region-of-interest definition and curve generation for both ventricles. After nine-point spatial smoothing and background subtraction from an end-systolic left paraventricular region of interest, left-ventricular (LV) time-activity curves are generated from the left anterior oblique image using conventional variable-region programs. Left-ventricular count output (LVCO) is obtained by subtracting the counts at the curve's minimum (end-systolic) from those at curve maximum (end-diastolic).

FIG. 1. Count information from time-activity curves: ROI = region of interest, EF = ejection fraction, CO = count output, EDC = end-diastolic counts, ESC = end-systolic counts (see text).
systolic) counts. LVCO has been shown to be proportional to LV cardiac output at different volumes and under different levels of preload, afterload, and contractility (21). In contrast to LV processing, right-ventricular (RV) time-activity information is derived using manual region of interest definition and images corrected for background by an end-diastolic left paraventricular region of interest. The RV time-activity curve shown in the right lower panel of Fig. 1 was generated from an end-diastolic fixed region of interest. In our laboratory, the RV end-diastolic region is defined using the visually apparent edges of the ventricular silhouette. In most patients (85%), the level of the pulmonic valve is taken to be an area of decreased count activity superior to the infundibulum. When such a count-density demarcation is not evident, the level of the pulmonic plane is defined as a horizontal line at the level of the uppermost edge of the LV silhouette. In the right lower panel in Fig. 1, the arrow at the nadir of the curve indicates that the end-systolic frame is identified from the fixed-region RV curve. However, actual end-systolic counts are obtained from a separate RV end-systolic region of interest defined by light pen (bottom center). Pulmonic-valve plane, and infundibular, septal, and apical borders of the region are identified visually as for the end-diastolic image. Since count errors due to atrial activity at ventricular end-diastole (atrial systole) are at their minimum, atrial definition on the end-diastolic region is not attempted unless obvious atrial enlargement is present. However, at ventricular end-systole (atrial diastole), atrial counts are at their maximum and need to be excluded as much as possible from the end-systolic region. In our laboratory, RV end-systolic separation of atrium and ventricle is defined by visual inspection of static images, observation of cine display, and, if necessary, image profiling to define a break point or count falloff at the border between the two chambers (Fig. 2). Reproducibility data for the technique have been reported previously (12,22). Right-ventricular count output (RVCO) is then obtained by subtracting RV end-systolic counts (from the hand-drawn, end-systolic region of interest) from RV end-diastolic counts (maximum counts from the fixed-region curve).

In patients with left-to-right shunting at the atrial level, RV count output should be proportional to pulmonary blood flow, and LV count output should be proportional to systemic blood flow. Thus, calculation of the ratio of pulmonary to systemic flow, Qp/Qs, should be derivable as RVCO/LVCO. This calculation represents a relative comparison of volumes and does not entail conversion of counts to volume, with attendant errors from assumptions regarding attenuation or geometry. Therefore, patients with atrial septal defects (and right-sided regurgitation) should show RVCO exceeding LVCO. Patients with left-sided volume overload demonstrate LVCO exceeding RVCO, and normals show LVCO and RVCO nearly equal (12). Accordingly, for the normal curves illustrated in Fig. 1, LVCO = 6,850 counts, RVCO = 7,385 counts, and thus Qp/Qs = 1.08. Right-ventricular end-diastolic counts (and volume) exceed LV counts (ratio of 1.23) and LVEF exceeds RVEF.

In order to evaluate further this technique of interventricular count-output comparison in patients with abnormal RV size and performance but no shunt or regurgitation, nine patients with RV infarction were also
studied. Of the first 35 consecutive patients admitted to the coronary intensive care unit with an acute inferior-wall myocardial infarction, RV infarction was diagnosed by imaging and hemodynamic criteria in 13 patients. Four of these 13 were excluded from analysis due to coexistent mitral or tricuspid regurgitation. All patients underwent Swan-Ganz right-heart catheterization and gated blood-pool imaging within 24 hr of hospital admission. Criteria for RV infarction were:

1. Right-ventricular ejection fraction less than 0.40 (12,22).
2. Abnormal RV function as assessed by radionuclide cine display.
3. Two or more of the following hemodynamic findings: (a) right-atrial pressure greater than 10 mm Hg; (b) ratio of mean right-atrial pressure to mean pulmonary wedge pressure greater than 0.8; (c) y descent/x descent ratio > 0.5 in right-atrial pressure tracing; and (d) volume loading causing a change of less than 0.5 in the ratio between right-ventricular stroke/work and right atrial pressure.

Statistical analysis. For statistical analysis of variables before and after a single intervention, where each patient served as his own control, paired t-testing was used. Student's unpaired t-testing was used for comparison between different groups of patients or variables. For tests of relationships, the method of least-squares linear regression analysis and Pearson's coefficient of correlation were used. All values in the text are given as mean ± 1 standard deviation.

RESULTS

Patients with right-ventricular infarction. For these nine patients, radionuclide angiography gave mean LV ejection fraction as 0.51 ± 0.12. Mean RV ejection fraction was 0.29 ± 0.06. Figure 3 compares radionuclide-derived RV and LV count output in these patients. Count outputs between the two ventricles correlated with a coefficient r = 0.85. The calculated R VCO/LVCO ratio in these patients without shunt or regurgitation was 0.94 ± 0.27.

Patients with atrial septal defect. Seven of these nine patients were older than 60 yr of age: range 32–70 yr, mean 61 ± 12. Eight patients had palpatations due to atrial dysrhythmia, shortness of breath, or fatigue. Echocardiography demonstrated findings of RV volume overload characterized by paradoxical septal motion and RV enlargement (> 25 mm) in eight patients. One patient with mild shunting (Qp/Qs = 1.3) had a normal echocardiogram. At catheterization, all nine showed atrial communications. Mitral regurgitation was excluded by angiography in seven and by physical examination in
two. None had evidence of aortic or tricuspid regurgitation by physical examination or echocardiography. Seven had coronary arteriography, and four showed >50% narrowing in at least one major coronary branch. Neither the 32-year-old nor the 70-year-old had clinical, electrocardiographic, or radionuclide wall-motion abnormalities suggestive of coronary artery disease, and coronary arteriography was not performed. Five patients underwent corrective surgery, with surgical confirmation of secundum ASD.

Hemodynamics. Table 1 shows the individual hemodynamic findings derived at catheterization. Functional infundibular/pulmonic gradients >5 mm occurred in four patients. Elevated end-diastolic RV pressures were present in three patients. One of these (Patient 9) also had pericardial constriction. Five patients had pulmonary hypertension. Pulmonary arteriolar resistance was elevated in four patients (normal 20–120 dyne-sec cm⁻⁵).

Table 2 shows grouped data for the nine patients with atrial septal defect. In the lower panel, control data are presented from previously reported (12) patients with normal function (N = 10), abnormal LV function (N = 10), and the current population of patients with predominant RV dysfunction. Although systolic blood pressure and heart rate appeared lower at the time of imaging for patients with atrial septal defect (123 ± 18 mm Hg vs. 133 ± 21; 71 ± 3 beats per min vs. 80 ± 6), these differences were not statistically significant. Left-ventricular ejection fraction was the same by both methods. For most patients with atrial septal defect, RV ejection fraction was within, or just below, the normal range for this laboratory (0.40–0.60), with RV ejection fraction ranging from 0.37 to 0.50. The two pulmonary-to-systemic flow ratios, Qp/Qs, were equal (2.6 ± 0.9 vs. 2.3 ± 0.9; p = NS). Right-ventricular end-diastolic volume greatly exceeded LV ED volume, with a mean ratio of 2.01 ± 0.31 (determined by dividing RV by LV end-diastolic counts). This ratio is significantly higher than the normal RV/LV ED count ratio (1.26 ± 0.14; p < 0.05).

For the control populations without left-to-right shunt, RV and LV ejection fraction varied as expected for respective abnormalities. Mean Qp/Qs, the ratio of RV/LV count output, did not differ significantly despite differences in RV ejection fraction, LV ejection fraction, and end-diastolic count ratios. Although not statistically significant, Qp/Qs for the RV infarct group showed a wider standard deviation than for control groups with normal or abnormal left ventricles (0.27 vs. 0.12 or 0.09). This tendency to increased variability was due primarily to two patients both of whom demonstrated globular right ventricles and poor atrial and ventricular separation. The exact contribution of geometry, attenuation, or contractility cannot be ascertained from this limited sample.

Pulmonary/systemic flow ratio. Table 3 shows individual data for oximetry-defined Qp/Qs at catheterization (CATH) and count-defined Qp/Qs by radionuclide angiography (RNA). By regression analysis, the two methods correlated (r = 0.87; y = 0.85x + 0.11). Of note is the accurate quantitation of shunt ratio over a wide range of values (1.3 to 4.4).

EFFECT OF SURGERY

Pulmonary-to-systemic flow shunt ratio. Five patients underwent surgical correction of their left-to-right shunts
Table 3. Pulmonary/Systemic Flow Ratio (Qp/Qs)

<table>
<thead>
<tr>
<th></th>
<th>CATH</th>
<th>RNA</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4.4</td>
<td>4.4</td>
</tr>
<tr>
<td>2</td>
<td>2.8</td>
<td>1.7</td>
</tr>
<tr>
<td>3</td>
<td>2.7</td>
<td>2.3</td>
</tr>
<tr>
<td>4</td>
<td>3.0</td>
<td>2.1</td>
</tr>
<tr>
<td>5</td>
<td>2.6</td>
<td>2.4</td>
</tr>
<tr>
<td>6</td>
<td>2.7</td>
<td>2.6</td>
</tr>
<tr>
<td>7</td>
<td>2.3</td>
<td>2.2</td>
</tr>
<tr>
<td>8</td>
<td>1.3</td>
<td>1.4</td>
</tr>
<tr>
<td>9</td>
<td>1.6</td>
<td>1.8</td>
</tr>
<tr>
<td>Mean</td>
<td>2.60</td>
<td>2.32</td>
</tr>
<tr>
<td>1 s.d.</td>
<td>0.88</td>
<td>0.86</td>
</tr>
<tr>
<td>S_y-x</td>
<td>0.29</td>
<td>0.29</td>
</tr>
</tbody>
</table>

CATH = catheterization.
RNA = radionuclide angiography.

determined by contrast angiography, and have shown good agreement at all levels of ventricular function (23–26). Second, LV volumes derived from count information by a variety of methods correlate with ventricular volumes determined by contrast angiography (27–28). Third, information from time-activity curves accurately parallels the timing and magnitude of volume change during ventricular systole. For example, simultaneous electromagnetic flow measurements in an animal model (29) and simultaneous Fick cardiac output determinations in exercising men (21) have correlated well with similar measurements derived from time-activity curves. Fourth, several investigators have recently used analysis of RV time-activity data to estimate LV volume overload. Although using somewhat different methods of RV curve generation, all of these studies have demonstrated good agreement between qualitative and quantitative assessment of the extent of LV volume overload by contrast cineangiography and gated equilibrium scintigraphy (12–18).

In the current report we describe the extension of this approach of interventricular count comparison to the estimation of RV volume overload in patients with left-to-right shunting. We have previously shown that our method of RV and LV count-output comparisons provides a reliable estimate of LV regurgitant fraction in patients with unilateral left-sided volume overload (12). In patients with regurgitation or shunt, the error of this method is comparable to that occurring with oximetry methods of cardiac-output determination. That is, due to the variability of oxygen-content measurements in cardiac chambers or great vessels, shunts of less than 1.5 at the atrial level, 1.3–1.5 at the ventricular level, and 1.3 at the level of the great vessels are not detectable by oximetry (20,30). In our control patients, the upper
ranges of the Qp/Qs ratios were 1.1, 1.2, and 1.5 respectively for normal subjects, patients with abnormal LV function, and those with RV infarction. In the current report, radionuclide-defined Qp/Qs correlates well with Qp/Qs as determined by oximetry. This agreement is evident from low shunt ratios to ratios as high as 4 to 1. Five patients in this study were evaluated serially before, and soon after, surgical correction of their shunts. On repeat radionuclide angiogram after surgery, the ratio of right-to-left count output (Qp/Qs) decreased and became normal. This occurred despite persistence of RV enlargement, reduction of RV ejection fraction, and no change in LV ejection fraction.

The performance of quantitative RV determinations using equilibrium radionuclide angiography is inherently more complex than similar evaluation of the left ventricle, due to geometric problems with the right heart, including infundibular definition, possible greater chamber attenuation, and greater RA/RV overlap. These problems exert greatest effect upon definition of end-systolic counts. Several different approaches in image processing and region-of-interest selection have been applied in an attempt to minimize these errors, which may contribute to underestimation of stroke counts, RV ejection fraction, and stroke count ratios. These include the manual variable region method, which we have utilized, geometric modeling with partial atrial-count correction (16), and slant-hole collimation with subtraction-image region-of-interest definition (18,31). Future improvements in interpretative image processing and edge-detection algorithms may permit improved accuracy of RV functional assessment. However, our data from patients with RV infarction suggest that differences in anatomy and ventricular performance will continue to influence the reliability of these techniques despite improved processing methods.

First-pass radionuclide angiography has been reported to permit quantitation of very small shunts and localization of the level of shunt (7–10). It remains the noninvasive method of choice for the detection and quantification of left-to-right shunting. As with our method, technical considerations remain important and include ensuring adequate bolus, appropriate algorithm and curve-fitting techniques, and caution in the presence of valvular regurgitation. As with all indicator-dilution methods, severe aortic or mitral regurgitation may result in nonexponential curves and spurious identification as shunting (10). Our technique using gated equilibrium imaging is also limited in valvular regurgitation since tricuspid or pulmonic insufficiency cannot be distinguished from left-to-right shunting at the atrial level. Moreover, the components of bilateral volume overload—e.g. RV and LV regurgitation, mitral regurgitation and ASD, or LV-to-RV shunting—cannot be distinguished by this technique.

Despite these considerations, our report suggests that reliable serial estimation of ejection fraction, Qp/Qs, and relative ventricular volume differences may be obtained. This procedure may, therefore, be useful in evaluating these parameters during hemodynamic interventions such as exercise or afterload augmentation. Subtle physical signs, nonspecific symptoms, and acquired common cardiopulmonary disorders often result in diagnostic confusion in the evaluation of older patients with atrial septal defects. These patients are often studied by radionuclide angiography for other reasons and the detection of an unsuspected atrial shunt and the determination of its magnitude are possible by this technique.

FOOTNOTE
* Renografin-76, Squibb.

ACKNOWLEDGMENT
Supported in part by American Heart Association, Texas Affiliate, Grant-In-Aid and NIH New Investigator Research.

REFERENCES
12. Sorensen SG, O'Rourke RA, Chaudhuri TK: Non-


