Noninvasive Quantitation of Valvular Regurgitation by Gated Equilibrium Radionuclide Angiography

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SUMMARY  R-wave synchronous equilibrium radionuclide angiography (RNA) is a noninvasive method that provides time-activity curve count information proportional to ventricular volumes and is used for relative volume comparisons within the left or right ventricle to derive the ejection fraction. Comparison of the ventricular count output between both ventricles may permit quantitation of the relative amount of valvular regurgitation, i.e., the regurgitant fraction. We performed resting gated RNA in 30 consecutive patients undergoing cardiac catheterization and quantitative ventriculography for aortic or mitral valvular regurgitation. RNA regurgitant fraction correlated well with cardiac catheterization regurgitant fraction ($r = 0.85$). In 11 patients imaged before and 1–4 months after successful valve replacement, the regurgitant fraction declined from $0.68 \pm 0.11$ to $-0.09 \pm 0.13$ ($p < 0.001$). In 20 control patients without valvular regurgitation, the calculated regurgitant fraction did not exceed 0.20. We conclude that valvular regurgitation may be accurately detected, quantitated and followed serially after therapeutic intervention using gated RNA.

MODERATE-TO-SEVERE volume overload of the left ventricle due to mitral or aortic regurgitation may be well tolerated symptomatically by many patients for years. However, chronic valvular regurgitation often results in ventricular dysfunction clinically manifest as angina, arrhythmia or congestive heart failure. Left ventricular dysfunction due to valvular regurgitation may not improve despite successful valve replacement in some patients.\(^1\)\(^-\)\(^7\) A method for serially quantitating the severity of valvular regurgitation, ventricular volumes, and ejection fraction would be highly desirable because selecting the appropriate timing for valvular replacement in asymptomatic or mildly symptomatic patients with aortic or mitral regurgitation is a major problem. Gated equilibrium radionuclide angiography, which provides time-activity curve count information proportional to ventricular volumes, is a safe, noninvasive, easily repeatable method of evaluating left and right ventricular function. In this report we describe the application of gated equilibrium radionuclide angiography for the serial noninvasive quantitation of valvular regurgitant fraction, ventricular ejection fraction and relative ventricular end-diastolic enlargement in patients with chronic mitral or aortic valvular regurgitation.

Methods

Patient Selection

Regurgitant Group

Thirty consecutive patients with mitral or aortic regurgitation who underwent diagnostic cardiac catheterization and quantitative single-plane right anterior oblique contrast angiography were studied. Two other patients with inadequate contrast ventriculograms because of arrhythmia or inadequate opacification were excluded. Twenty-three of these 30 patients were catheterized for a primary clinical diagnosis of valvular regurgitation. Three patients were evaluated for valvular stenosis with associated regurgitation and four patients were evaluated for a primary clinical diagnosis of coronary artery disease with associated mitral regurgitation. Of the 30 patients, 16 had aortic regurgitation and 14 had mitral regurgitation. None of these patients had right-sided regurgitation or cardiac shunt. Significant right-sided regurgitation was excluded on the basis of physical examination and right-heart catheterization. None of these patients had large “v” waves in the jugular venous pulse, systolic or diastolic murmurs that increased with inspiration, systolic hepatic pulsations or right ventricular enlargement and paradoxic septal motion by M-mode echocardiography. Intracardiac shunting was excluded by oximetry or dye-curve analysis. Eleven of these patients were imaged 1–4 months after successful valve replacement.

Control Group (No Valvular Regurgitation)

To obtain control information in subjects without valvular regurgitation, rest radionuclide angiography was performed in 20 patients. Ten of these 20 patients were normal by history, physical examination, ECG and chest x-ray. Three of these normal patients had undergone cardiac catheterization for atypical chest pain. The remaining 10 patients had cardiac disease but no evidence of valvular regurgitation or shunt: Eight had coronary artery disease with significant wall motion abnormality, one had aortic stenosis and one had primary cardiomyopathy. Nine of these 10 patients were studied by cardiac catheterization. The noncatheterized patient had coronary artery disease but no murmur and a normal right ventricle and septal motion by echocardiography. This study was approved by the Human Research Committee, and all patients gave informed consent.

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Cardiac Catheterization

In the fasting state, all patients underwent right- and left-heart catheterization and coronary arteriography by the brachial or percutaneous transfemoral approach. Pressures were measured through fluid-filled catheters with Statham transducers and recorded on an Electronics for Medicine VR16 recorder. Forward cardiac output was measured by Fick and dye-dilution techniques immediately after pressure recordings and immediately before left ventricular contrast angiography. When indicated, aortography was performed after ventriculography.

Left ventricular contrast angiography was performed in the 30° right anterior oblique position by the injection of 45-60 ml of Renografin at 15-20 ml/sec through a retrograde #8F angiographic catheter during 35-mm cine filming at 60 frames/sec. Coronary arteriography followed ventriculography or aortography in all cases. Ventricular angiograms were analyzed as described by Kennedy et al. by selecting a well-opacified, normally conducted cycle not preceded by a premature ventricular complex. The longest length and area for end-diastole and end-systole were determined and ventricular volumes were calculated using a high-resolution projector and a computer-interfaced digitizing table. Correction for magnification was made by grid filming at the level of the mid-left ventricle as determined from 30° right anterior oblique patient position and 60° left anterior oblique fluoroscopy. Left ventricular ejection fraction, end-diastolic volume, end-systolic volume, stroke volume and angiographic cardiac output were then obtained or derived. Regurgitation was quantitated as the left ventricular regurgitant fraction, which expresses the relationship between regurgitant flow and total ventricular flow. The regurgitant fraction was calculated as

\[
\text{regurgitant fraction} = \frac{\text{angiographic output} - \text{forward output}}{\text{angiographic output}}
\]

Radionuclide Angiography

Within 1-10 days of cardiac catheterization, without change in clinical status or therapy, resting anterior and straight left anterior oblique view, R-wave synchronous equilibrium radionuclide angiography was performed after the i.v. injection of technetium-99m-labeled human serum albumin. Eleven patients were also imaged 1-4 months after successful valve replacement. Supine blood pressure and heart rate were obtained immediately before imaging. Imaging was performed with a gamma scintillation camera using a low-energy, all-purpose, parallel-hole collimator. Using a dedicated computer system (Medical Data Systems), images were acquired under electrocardiographic control such that consecutive corresponding 40-msec segments of each cardiac cycle were summed and stored in the computer core memory until each synchronized 40-msec image contained at least 300,000 counts. Images were processed by nine-point spatial smoothing and background subtraction was determined from a light-pen-defined 90° region-of-interest arc (3 o'clock to 6 o'clock) two to three pixels removed from the left anterior oblique left ventricular end-diastolic edge. Left ventricular time-activity curves were then generated by the Medical Data Systems MUGE program that, in an edge-detection program with operator intervention, defined new left ventricular regions of interest for each frame of the composite cardiac cycle. Figure 1 shows selected end-diastolic, midsystolic and end-systolic images. Computer-defined regions of interest edges demonstrate the varying size of regions of interest throughout the composite cardiac cycle. Computer-assigned increases in background subtraction from an end-systolic region of interest were accepted for left ventricular curves. Because this edge-detection algorithm functioned infrequently when applied to the right ventricle, the multiple region-of-interest method of right ventricular analysis of Maddahi et al. was used. By this method, a right ventricular end-diastolic region of interest was defined by magnetic light pen on

![Figure 1. Gated equilibrium radionuclide angiography. Counts are obtained for end-diastole and end-systole for each ventricle by varying region-of-interest methods that minimize overlap of ventricular and atrial activity.](image-url)
smoothed, background-subtracted images, and a time-activity curve was generated. From this curve, the endsystolic frame was identified as the frame containing the fewest right ventricular counts. End-systolic counts were obtained from this frame by light pen region-of-interest definition of the right ventricle, excluding the right atrium. From these right and left ventricular time-activity curve data, end-diastolic counts, end-systolic counts, stroke counts or ventricular count output (end-diastolic counts minus end-systolic counts), and ejection fraction were obtained or derived for each ventricle.

Because time-activity curve information is proportional to volume and provides a good estimate of ejection fraction using relative volume comparisons of a single ventricle, we reasoned that regurgitant fraction could be calculated by relative volume comparisons between the right and left ventricles. The method of calculating the radionuclide regurgitant fraction (analogous to catheterization methods) and a representative left ventricular time-activity curve derived from the MUGE program are shown in figure 2. Left ventricular count output was obtained by subtracting minimum curve counts (end-systolic counts) from maximum curve counts (end-diastolic counts). A right ventricular time-activity curve for the same patients is also shown in figure 2. In contrast to the left ventricular time-activity curve, which was generated by a variable region-of-interest method, the time-activity curve for the right ventricle shown here was generated from a right ventricular, end-diastolic, fixed region of interest and displayed using a computer fixed region program (Medical Data Systems, MGCV). The arrow at the nadir of the curve indicates that the end-systolic frame was identified from the fixed region right ventricular curve. However, actual end-systolic counts were obtained from a separate right ventricular end-systolic region of interest, defined using a light pen. Right ventricular count output was then obtained by subtracting right ventricular end-systolic counts (from the end-systolic region of interest) from right ventricular end-diastolic counts (maximum counts from the fixed region curve). Accordingly, for the curves in figure 2, the left ventricular count output was 25,000 counts (34,000 minus 9000), the right ventricular count output was 8000 counts (16,000 minus 8000), and regurgitant fraction was 0.68 ( [25,000 - 8000] / 25,000).

To determine the reproducibility of the method, gated equilibrium studies from the 10 normal control

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**Regurgitant Fraction (RF) Calculation**

\[ \text{Cath RF} = \frac{\text{Angio Output} - \text{Forward Output}}{\text{Angio Output}} \]

\[ \text{RNA RF} = \frac{\text{LV Count Output} - \text{RV Count Output}}{\text{LV Count Output}} \]

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**Figure 2.** Regurgitant fraction (RF) calculation. Cath = cardiac catheterization RNA = gated radionuclide angiography. Right and left ventricular time-activity curves from which count outputs (end-diastolic counts minus end-systolic counts) are derived are shown. Left ventricular output exceeded right ventricular output resulting in a regurgitant fraction of 0.68.
patients and the first 10 consecutive patients with valvular regurgitation were analyzed by having an experienced technician repeat each analysis on different days without knowledge of patient identity or previously determined results.

Statistical Analysis
A paired t test was used for statistical comparison of variables before and after a single intervention, where each patient served as his own control. An unpaired t test was used to compare different groups of patients or variables. For tests of relationships, least-squares linear regression analysis and Pearson’s coefficient of correlation were used. All values in the text are given as mean ± SD.

Results
Reproducibility
Correlation coefficients for right and left ventricular ejection fraction analyses performed on separate days by an experienced technician were 0.90 and 0.94, respectively. Right ventricular count output (r = 0.90), left ventricular count output (r = 0.92) and regurgitant fraction (r = 0.89) were also highly reproducible.

Control Subjects
The reliability of any method of quantitating the regurgitant fraction is dependent on accurate definition of forward and regurgitant flow. The count outputs of the left and right ventricles were compared for normal controls and controls with cardiac disease but without regurgitation or shunt (fig. 3). Agreement between outputs of both ventricles was excellent (r = 0.97) and the regression equation approached the line of identity. This agreement is apparent for both normal subjects and patients with left ventricular dysfunction, despite marked differences between normal and abnormal nonregurgitant controls. Table 1 shows radionuclide ejection fraction data for patients with valvular regurgitation and controls. For the 10 normal subjects, the mean left ventricular ejection fraction was 0.62 ± 0.07 (range 0.53–0.70), whereas for the 10 cardiac patients without valvular regurgitation, the mean left ventricular ejection fraction was 0.38 ± 0.14 (range 0.23–0.63) (p < 0.01). The mean normal and abnormal control right ventricular ejection fractions were 0.51 ± 0.07 (range 0.42–0.60) and 0.43 ± 0.10 (range 0.22–0.62) (p < 0.05), respectively. The calculated mean regurgitant fraction for the 20 control subjects was 0.01 ± 0.11 (range −0.19–0.19).

Of the 20 control patients, 12 had undergone cardiac catheterization. Calculation of a regurgitant fraction in these patients without regurgitation or shunt was possible in 10 of these 12 patients. One patient was excluded because only right-heart catheterization was performed (and therefore no angiographic cardiac output was performed) and one was excluded due to ventricular tachycardia during contrast ventriculography. Six of the 10 patients had forward cardiac output determined by both dye-dilution and Fick techniques, two had Fick outputs only, and two had dye-dilution outputs only. The calculated regurgitant fraction by the angiographic/dye-dilution method was 0.07 ± 0.17 and by the angiographic/Fick output method 0.07 ± 0.18.

Patients with Aortic or Mitral Regurgitation
Table 1 shows the cardiac catheterization hemodynamic data and radionuclide data for the 30 patients with regurgitation studies. At catheterization, the mean systolic blood pressure was 140 mm Hg and averaged 10 mm Hg greater than mean blood pressure before radionuclide angiography (p < 0.05). The mean heart rate at catheterization was 77 beats/min and exceeded the mean rate of 72 beats/min during imaging (p < 0.05). The regurgitant fraction at catheterization was 0.48 ± 0.19, which was less than the mean radionuclide regurgitant fraction of 0.54 ± 0.19 (p < 0.05). The left ventricular ejection fraction was similar by both methods (0.55 vs 0.54). The mean radionuclide right ventricular ejection fraction was 0.39.

End-diastolic Volume Ratio
In figure 4, regression lines for the 10 normal subjects and 30 regurgitant patients compare counted left and right ventricular end-diastolic volumes. The 10 cardiac control patients are not included because they had left ventricular enlargement due to coronary disease. For normal subjects, the mean right ventricular end-diastolic counts exceeded
left ventricular end-diastolic counts (23,450 ± 8750 vs 18,730 ± 7850, p = NS). Regurgitant patients, however, had significantly greater left than right ventricular end-diastolic volumes.

**Regurgitant Fraction**

Regurgitant fractions by cardiac catheterization and by radionuclide regurgitant fraction were compared (fig. 5). Good correlation exists at all levels of volume overload (r = 0.85). Because regurgitant fraction by radionuclide angiography was somewhat greater than regurgitant fraction by cardiac catheterization (0.48 ± 0.19 vs 0.54 ± 0.19, p < 0.05), separate comparisons were made for aortic and mitral regurgitation. In the 14 patients with mitral regurgitation, regurgitant fractions by catheterization (0.50 ± 0.21) and radionuclide angiography (0.54 ± 0.20) did not differ significantly. However, the regurgitant fraction by catheterization (0.46 ± 0.19) and radionuclide (0.54 ± 0.19) methods for patients with aortic regurgitation were significantly different (p = 0.01). Correlation coefficients for catheterization and radionuclide methods did not differ when aortic and mitral patients were analyzed separately. Ten of the 30 patients had a regurgitant fraction less than 0.50, and the radionuclide value slightly exceeded the catheterization value (0.31 ± 0.09 vs 0.26 ± 0.09, p = NS). The radionuclide regurgitant fraction also exceeded the catheterization regurgitant fraction (0.66 ± 0.10 vs 0.59 ± 0.13, p < 0.05) in the 20 patients with a regurgitant fraction greater than 0.50. The correlation coefficient for each subgroup did not differ from the correlation for the entire group. The radionuclide method, therefore, appears to overestimate regurgi-
tant fraction to a mild degree. However, because of differences in blood pressure and heart rate between these nonsimultaneous studies, such a conclusion may only be inferred.

Preoperative vs Postoperative Regurgitant Fraction

Figure 6 shows the results of successful valvular replacement in 11 patients with moderate-to-severe valvular regurgitation studied by gated radionuclide angiography before and 1-4 months after surgery. Preoperatively, the regurgitant fraction was 0.68 ± 0.11. After surgery, the regurgitant fraction of −0.09 ± 0.13 (p = 0.001) was well within the nonregurgitant range established by the control population. No patient had postoperative regurgitation. Postoperatively, left ventricular ejection fraction declined (0.57 ± 0.09 to 0.37 ± 0.19; p < 0.01), whereas right ventricular ejection fraction was unchanged (0.36 ± 0.14 to 0.39 ± 0.15, p = NS). In four patients imaged within 3 weeks of surgery and more than 4 months after surgery, left ventricular ejection fraction decreased precipitously early after operation (mean 0.53 ± 0.04 to 0.18 ± 0.06; p < 0.01); individually, ejection fraction declines were 0.57 to 0.28, 0.47 to 0.17, 0.55 to 0.15 and 0.54 to 0.14. The mean ejection fraction improved by 4-6 months (0.37 ± 0.13, p < 0.05); individual values were 0.60, 0.29, 0.20 and 0.31, respectively. In all 11 patients studied before and after operation, left ventricular end-diastolic volume enlargement assessed by left/right end-diastolic count ratios decreased. The ratio fell from 1.63 ± 0.28 preoperatively to 1.08 ± 0.19 postoperatively (p = 0.001).

Cine Differentiation of Mitral and Aortic Regurgitation

Characteristic appearances of normal, severe aortic regurgitation and severe mitral regurgitation images in the 45° left anterior oblique view are shown in figure 7. In aortic regurgitation, the left ventricle is displaced laterally and downward and is well separated from the right ventricle. In mitral regurgitation, however, the right and left ventricles are not separated and together form a heart-shaped configuration. Cine display of anterior and left anterior oblique gated radionuclide images were viewed in random sequence and without knowledge of diagnosis for all regurgitant and control patients. In all 21 patients with a regurgitant fraction greater than 0.40, mitral and aortic insufficiency were identified and correctly differentiated. Cine display in five of nine patients with a regurgitant fraction less than 0.40 were incorrectly interpreted. Three patients with mild regurgitation were considered normal and two with coronary artery disease and pronounced wall motion abnormality were considered to have coronary disease alone. None of the nonregurgitant control normal or control abnormal patients were considered to have regurgitation.

Discussion

Surgical therapy for aortic or mitral regurgitation is beneficial in many symptomatic patients for relief of symptoms and prolongation of life. However, some symptomatic patients do not improve or die from congestive heart failure despite successful valve replacement. Such observations confirmed by echocardiographic, angiographic, actuarial and pathologic studies have prompted suggestion of extending valvular surgery to asymptomatic patients with moderate or severe valvular regurgitation. Further, recent studies using exercise radionuclide angiography in patients with aortic and mitral regurgitation have shown abnormal exercise ejection fraction reserve in as many as 40% of asymptomatic patients with significant valvular regurgitation. Unfortunately, retrospective information regarding the natural history of aortic and mitral valve disease has lacked hemodynamic verification and is of limited application in this era of potent medical therapy, improved surgical techniques and prostheses, and changing patterns of valvular heart disease. In patients with valvular regurgitation, invasive studies relying upon pressure data alone have shown conflicting results and generally have not been helpful in predicting subsequent course. A number of angiographic and echocardiographic studies have evaluated pre- and postoperative ejection fraction, ventricular volume...
and left ventricular mass in patients undergoing valvular replacement for valvular regurgitation. These investigations have uniformly shown that patients with preoperative myocardial dysfunction tend to show no improvement in ventricular function and have poorer long-term results.

Gated equilibrium radionuclide angiography is a useful addition to these other modalities because it is a safe, noninvasive and reproducible method of evaluating both ventricular volume change and ventricular function. Others have reported on the application of radioisotope methods to valvular insufficiency, but have relied on qualitative assessment of the severity of regurgitation. Using a nonimaging detector, Hildner et al. quantitated the severity of aortic regurgitation from time-activity curve count information after intraventricular isotope injection and found good agreement with qualitative supravalvular angiography. Rigo et al. obtained changes in the ratios of left and right ventricular stroke counts from unprocessed blood pool images and reported good correlation with qualitative angiographic assessment of regurgitation in 20 patients. Janowitz et al. used first-pass radionuclide angiography in 10 patients to quantitate regurgitant fraction from the total count output of each ventricle and reported good correlation with catheterization.

In this study we used the traditional catheterization and angiographic concept of "regurgitant fraction" to quantitate mitral and aortic regurgitation by means of a noninvasive count-based method. Intuitively, symptoms and prognosis in valvular insufficiency should relate to the severity or volume of regurgitation. Hemodynamic studies of quantitatively varied aortic valvular regurgitation in acute open-chest dogs have shown a reduced forward cardiac output, increased end-diastolic pressure and peripheral resistance, and left ventricular myocardial depression with increasing regurgitant flow. Similar experimental studies for mitral regurgitation have shown increased left atrial pressure and reduced forward output with increasing regurgitant flow. In man, the accurate assessment of the severity of regurgitation requires cardiac catheterization and contrast angiography and is dependent on the application of quantitative ventriculography for determining regurgitant volume. Qualitative methods such as cineangiography have been shown to be less sensitive in assessing regurgitant flow, and limitations of noninvasive methods have not permitted quantitation of regurgitation. A number of reports have described the accuracy of quantitating the regurgitant fraction in valvular heart disease.

The application of equilibrium radionuclide angiography in this context rests upon several previously confirmed features of gated blood pool imaging. First, quantitation of left ventricular ejection fraction using counts defined by radionuclide angiography as relative volume equivalents has correlated well with ejection fraction determined by contrast ventriculography at cardiac catheterization. Second, information derived from the time-activity curve accurately reflects the timing and magnitude of volume change during ventricular systole. Green et al. performed simultaneous gated radionuclide angiography and electromagnetic flow measurements in baboons and found equivalent curve profiles from both methods ($r = 0.95$). Sorensen et al. performed simultaneous gated radionuclide angiography and
Fick cardiac output determination in normal men and showed close agreement in relative cardiac output change throughout exercise. Third, right ventricular count measurements may be accurately defined with conventional blood pool techniques. Right and left ventricular count information may then be compared to obtain volume relationships between the two ventricles. Thus, in the absence of shunt or regurgitation, count outputs (end-diastolic minus end-systolic counts) of both ventricles should be equal. Conversely, in the presence of aortic, mitral or combined aortic and mitral regurgitation, the count output of the left ventricle should be greater than that of the right ventricle and proportional to the left ventricular angiographic stroke volume or cardiac output. The count output of the right ventricle would remain proportional to pulmonary or forward cardiac output. Basic to this radionuclide method of quantitating regurgitant fraction is the assumption that ventricular volume overload is unilateral. Accordingly, if right- and left-sided regurgitation are present, the severity of either lesion cannot be quantitated. The presence of significant right-sided volume overload in our subjects was excluded on the basis of physical examination, echocardiography, analysis of right-heart pressures obtained at catheterization and dye-dilution curves.

In the present study, we performed gated blood pool imaging and cardiac catheterization with quantitative ventriculography in 30 patients with valvular insufficiently of varying severity (regurgitant fraction ranging 0.17–0.83) and found a close correlation between regurgitant fractions determined by catheterization and by radionuclide angiography (r = 0.85) (fig. 5). Agreement was good for all degrees of regurgitation. The method we used compares ventricular time-activity curve count output information using a varying region-of-interest method for each ventricle, which decreases the error due to atriовentricular overlap by more accurately defining ventricular end-systole and thereby more accurately quantitating count output (or stroke counts) and ejection fraction. Caudal angulation of the gamma camera in the 45° left anterior oblique position may also improve separation of atria and ventricles. However, we used an unmodified straight 45° left anterior oblique projection based on experience showing good correlation of radionuclide and contrast ejection fraction and serial increases in left ventricular count output compared with Fick output during exercise using an unmodified left anterior oblique projection. The problem of atrioventricular overlap is illustrated in our series by comparing calculated radionuclide regurgitant fraction for aortic regurgitation and mitral regurgitation with left atrial enlargement. Using our method, the mean radionuclide regurgitant fraction for the 30 patients (0.54 ± 0.19) exceeded catheterization regurgitant fraction (0.48 ± 0.19; p = 0.05). However, when analyzed separately, radionuclide regurgitant fraction significantly exceeded catheterization regurgitant fraction for aortic regurgitation (p < 0.01) but not mitral regurgitation. Although these data suggest that left atrial enlarge-
regurgitant fraction calculation in nonregurgitant subjects by cardiac catheterization and quantitative ventriculography.\textsuperscript{25, 35, 36, 51, 82} For example, in seven patients with isolated mitral regurgitation reported by Kennedy et al.,\textsuperscript{22} the "regurgitant fraction" after successful surgery was 0.17 ± 0.14 (SD).

We conclude that gated equilibrium radionuclide angiography is a useful method of evaluating valvular regurgitation and permits noninvasive, accurate quantitation of ejection fraction, relative ventricular enlargement and regurgitant fraction. Such information is highly reproducible and should provide a means of serially monitoring these patients.

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