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Significance of gated equilibrium radionuclide ventriculography in quantification and follow up of valvular regurgitation

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Abstract. In order to evaluate the significance of gated equilibrium radionuclide ventriculography (RNV) for non invasive quantification of valvular regurgitation and follow up, various approaches were tested concerning accuracy and reproducibility.

By using in vitro labeling of red blood cells and extending the acquisition time, a clear reduction of dispersion was obtained in patients without valvular insufficiency. Quantification of regurgitation directly from functional images (ventricular amplitude or stroke volume image) was clearly superior compared to the variable region of interest method. Employing functional images, reproducibility between two observers and between two independent measurements was excellent. Correlation to regurgitation values determined by cardiac catheterization was only moderate with all RNV approaches tested.

RNV is limited in the absolute quantification of valvular regurgitation due to the variable overlap of right atrium and right ventricle. However, because of its high reproducibility, RNV is a non invasive technique suitable for intraindividual follow up of patients with valvular insufficiency.

Key words: Radionuclide ventriculography – Aortic regurgitation – Mitral regurgitation

Selection of the appropriate time for valve replacement is a major problem in patients with valvular regurgitation (O'Rourke and Crawford 1980; Levine and Gaasch 1983). Long term evaluation of hemodynamic parameters is often necessary (Alderson 1982). Severity of regurgitation is an important hemodynamic factor in valvular insufficiency and should be included in the follow up (Kress et al. 1981). The ratio of regurgitant volume to end diastolic volume was supposed to be a major determinant of ventricular response to surgical correction (Levine and Gaasch 1983). Regurgitation can be quantified by cardiac catheterization using a comparison of total (angiographic) and forward (thermodilution) cardiac output (Sandler et al. 1963). However, because of its invasive nature, this technique is not suitable for repeated measurements (O'Rouke and Crawford 1980). Therefore, a non invasive technique for serial, quantitative analysis of valvular regurgitation is highly desirable (Kress et al. 1984; Sorensen et al. 1980).

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Gated equilibrium radionuclide ventriculography was introduced by Rigo et al. (1979) for non invasive quantification of valvular regurgitation by comparing left and right ventricular stroke counts. Due to some limitations based mainly in the overlap of right atrium and right ventricle, the significance of this technique is not yet clearly defined (Kress et al. 1981; Lam et al. 1981; Sorensen et al. 1980; Thompson et al. 1981; Urquhart et al. 1981). In order to overcome these difficulties, some authors introduced modifications by using a slant hole collimator (Gandsman et al. 1981), calculating left to right ventricular stroke count ratios directly from functional images (Gerson et al. 1984; Makler et al. 1983; Nicod et al. 1982), correcting for right atrial overlap (Berthout et al. 1984; Henze et al. 1982) or combining first pass and equilibrium radionuclide ventriculography (Klepzig et al. 1985a).

It was the aim of the present study to evaluate and compare some of the various radionuclide techniques, more specifically to test their accuracy and reproducibility for follow up of patients with valvular insufficiency.

Materials and methods

Patients. Eighty-four men and 20 women (age 33–74 years, mean age 55 years) were included in the study. Patient groups 1 and 2 consisted of 64 and 15 subjects, respectively, with various cardiac diseases but without evidence of valvular regurgitation or intracardiac shunts.

Group 3 included 25 individuals, who underwent cardiac catheterization for the evaluation of valvular heart disease. Eighteen had aortic, five mitral and two combined aortic and mitral valve regurgitation. There was no evidence of right heart regurgitation in any of the subjects.

Patient group one was only used in order to evaluate different techniques of labeling red blood cells and data acquisition (compare radionuclide ventriculography).

Cardiac Catherization. All patients of groups two and three had left heart catheterization and coronary angiography mostly be using the technique of Sones et al. (1962). Left ventricular angiography was performed biplanely in 30° right and 60° left anterior projections. Ventricular volumes were determined by employing the biplane area length method with corrections for magnification (grid filming) and overestimation of ventricular volumes (Dodge et al. 1960). Total left ventricular output was calculated by the difference of end diastolic minus end systolic volume multiplied by registered heart rate.

Right heart catheterization was performed immediately before contrast angiography. Effective forward cardiac output was determined by thermodilution or by the Fick oxygen method with three measurements in each patient. Thermodilution was performed with injections of 10 ml cold 0.9% sodium chloride solution into the right atrium and the thermistor placed within the pulmonary artery (Ganz and Swan 1972). To calculate effective forward cardiac output by the Fick oxygen method, blood samples were obtained from the aorta and the pulmonary artery. Hemoglobin concentration and oxygen saturation were measured (Franch 1978). Oxygen consumption was estimated on the basis of the patients age, sex, body surface and heart rate (La Farge and Miettinen 1970). The regurgitation index (RI) by catheterization was calculated as total left ventricular output divided by effective forward cardiac output.

Gated equilibrium radionuclide ventriculography (RNV). RNV was performed within three days of cardiac catheterization using an Anger camera with a low energy, all purpose, parallel hole collimator and a dedicated computer system (IMAC 7300). In patients of group 1, red blood cells were labeled in vivo (Callahan et al. 1982), in subjects of groups 2 and 3 in vitro with 740 MBq ^{99m}Tc (Neumann et al. 1983). Data acquisition was performed in the left anterior oblique projection with best septal visualization. Each acquisition consisted of 16 frames (64 × 64 matrices with a 1.5 zoom) spanning 90% of the cardiac cycle. In patients of group one, one acquisition was performed for five min without using a caudal tilt. In subjects of groups two and three the time per acquisition was extended to ten min. Studies were performed with and without using a caudal tilt of 15° starting 5 min after reinjection of the labeled red blood cells. Measurements were repeated three h later.

Left ventricular ejection fraction (LVEF) was calculated by a count based semiautomatic program employing the isocount line concept with end diastolic and end systolic regions of interest (ROI) and a left paracardiac posteroapical ROI for background correction (Neumann et al. 1984; Schicha et al. 1985). Correlation of this procedure with LVEF values determined by biplane angiography showed a strong correlation with a coefficient of 0.93 (Schicha et al. 1985).

RIs by RNV were calculated by three different methods:

1) Stroke count ratio (SCR) (Rigo et al. 1979; Sorensen et al. 1980). End diastolic and end systolic ROIs were defined semiautomatically for the left ventricle using the same program as for LVEF determination described above. In case of the right ventricle, end diastolic and end systolic ROIs were constructed manually because of the more complicated geometry. Information from endless loop movie format images was additionally employed in order to define the exact separation of right atrium and right ventricle (Schicha et al. 1987) (Fig. 1a, b). Background activity was corrected using a left paracardiac ROI (Schicha et al. 1987). End diastolic images were selected separately for both ventricles. Stroke counts were calculated by subtracting end systolic from end diastolic counts, the SCR by dividing left by right ventricular stroke counts.

2) Stroke volume ratio (SVR) (Nicod et al. 1982). Stroke volume images were generated by subtraction of end systolic from end diastolic images. ROIs were constructed manually for both ventricles on the stroke volume image (Fig. 1c). The SVR was obtained directly from the stroke volume image by dividing left by right ventricular counts.

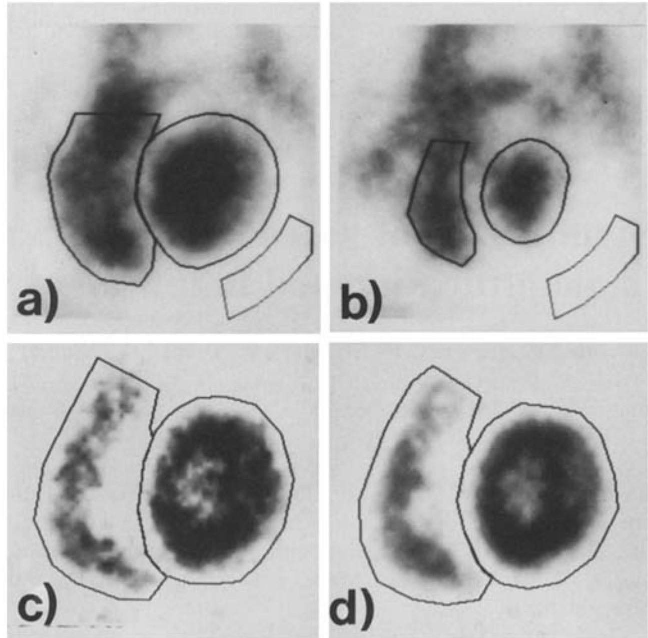

Fig. 1. End diastolic (**a**), end systolic (**b**), stroke volume (**c**) and ventricular amplitude image (**d**) of a patient with aortic regurgitation with respective ROIs

3) Fourier amplitude ratio (FAR) (Makler et al. 1983). Using a first harmonic Fourier analysis program, phase and amplitude images and phase histograms were obtained. From these a ventricular amplitude image was constructed by displaying all pixels having a phase difference of $\leq 90°$ from the ventricular peak in the phase histogram. Left and right ventricular ROIs were defined manually on the ventricular amplitude image (Fig. 1d). The FAR was calculated as the ratio of left to right ventricular amplitudes.

Statistical analysis. Data are presented as mean values ± standard deviations. Linear regression techniques, the dual tailed Wilcoxon U-test and a non parametric test of dispersion (Rosenbaum 1953) were used for comparison of the various RNV methods and for correlation of the RI values determined by RNV and cardiac catheterization.

Results

Cardiac catheterization

The mean RI value obtained by catheterization was 1.01 ± 0.08 (range 0.81–1.11) in the 15 subjects of group 2 with no evidence of valvular insufficiency. In the 25 patients with valvular regurgitation (group 3), the RIs ranged from 1.05 to 3.58 (mean 2.00 ± 0.76).

Gated equilibrium radionuclide ventriculography (RNV)

The mean LVEF was 55% ± 12% in group 1, 61% ± 11% in group 2 and 61% ± 11% in group 3, and did not differ significantly between these 3 groups.

The results obtained without caudal tilt in patients with no regurgitation are shown in Table 1. Mean values of

Table 1. Regurgitation indices determined in patients without regurgitation by RNV without caudal tilt

	Group 1 (n=64)		Group 2 (n=15)	
	Mean±SD	Range	Mean±SD	Range
SCR	1.13±0.35	0.52–2.28	1.03±0.16	0.83–1.28
SVR	1.35±0.23	0.91–2.01	1.30±0.14	1.10–1.51
FAR	1.37±0.25	0.83–1.92	1.35±0.18	1.11–1.58

Table 2. Comparison of radionuclide techniques for quantification of valvular regurgitation (n=40)

Caudal tilt	SCR no	SVR no	FAR no	FAR yes
Reproducibility (2 observers)				
r=	0.96	0.997	0.998	0.996
c.v. (%)	11.4	4.0	3.4	4.9
Reproducibility (2 independent measurements)				
r=	0.83	0.97	0.98	0.96
c.v. (%)	29.0	12.0	10.0	17.0
Correlation with RIs by catheterization				
r=	0.58	0.76	0.72	0.71
c.v. (%)	32.0	33.0	33.0	37.0

c.v.: coefficient of variability

SCR, SVR and FAR did not differ significantly between groups one and two. Although the number of patients was considerably smaller in group two, dispersion of the values was smaller with all three methods investigated. A significant reduction of dispersion was observed for SCR and SVR ($P<0.01$ and $P<0.03$, respectively). Relative dispersion was greatest using SCR, especially in group one. In this group a significant reduction of relative dispersion was observed by applying SVR and FAR as compared to SCR (both $P<0.01$).

In the 25 patients with valvular regurgitation (group 3), the mean RI values were 1.45±0.57 (range 0.83–3.31), 2.46±1.06 (range 1.35–5.19) and 2.56±1.00 (range 1.41–4.83) using SCR, SVR and FAR, respectively.

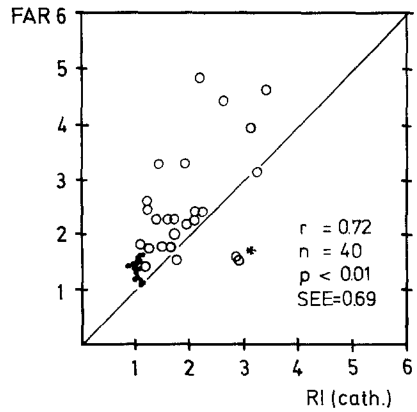

Fig. 3. Correlation between regurgitation indices determined by cardiac catheterization and RNV using the Fourier amplitude approach in subjects with (n=25) and without (n=15) left heart regurgitation. o with regurgitation; • without regurgitation. * 2 patients with LVEF<30%

Reproducibility determinations and correlation with catheterization RIs were performed in the 40 patients of groups 2 and 3. Data determined using SCR, SVR and FAR without caudal tilt and the results obtained by FAR with caudal tilt are listed in Table 2. Without caudal tilt comparable results were obtained using FAR and SVR, but employing SCR resulted in clearly inferior data. Variability between 2 observers and 2 independent measurements was significantly greater using SCR as compared to FAR and SVR (all $P<0.01$). Correlation of RIs determined by RNV with values from cardiac catheterization was significant (all $P<0.001$) but only moderate with all 3 RNV methods investigated. As examples, reproducibility of the FAR determination between two observers and between two independent measurements (Fig. 2) and correlation of FAR with RIs determined by cardiac catheterization (Fig. 3) are displayed. In the 2 patients with an LVEF< 30% – labeled in Fig. 3 – regurgitation was clearly underestimated by all 3 radionuclide methods. After eliminating these 2 patients, the correlation coefficients of RIs determined by RNV with those by cardiac catheterization rose to 0.73 (coefficient of variability (c.v.) 26%), 0.88 (c.v. 24%) and 0.83 (c.v. 26%) using SCR, SVR and FAR, respectively.

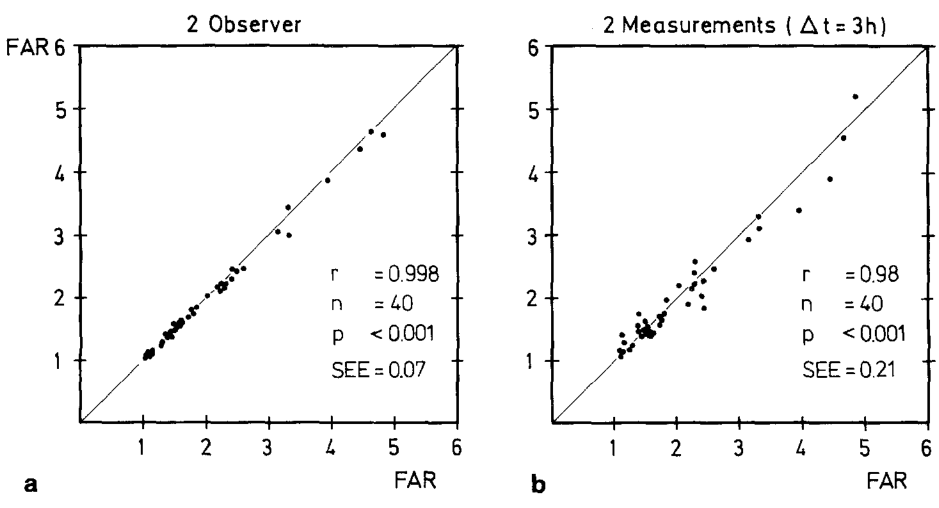

Fig. 2. Correlations between two observers (**a**) and two independent measurements (**b**) using the Fourier amplitude ratio

Comparing acquisition with and without caudal tilt, no significant differences were observed concerning reproducibility and correlation with RIs determined by cardiac catheterization. Overall data obtained without caudal tilt seemed to be slightly superior with all three RNV methods. This is shown for FAR in Table 2. Mean RI values in the 15 patients of group 2 without regurgitation were 0.96 ± 0.20 (range 0.76 – 1.44), 1.25 ± 0.18 (range 1.02–1.61) and 1.33 ± 0.18 (range 1.10–1.72) employing SCR, SVR and FAR, respectively. Compared to data obtained without caudal tilt (Table 1), the mean RI value was significantly smaller ($P < 0.05$) using SCR with caudal tilt and did not differ in SVR and FAR. No significant differences occurred concerning dispersion of the values. Correlation coefficients between RIs determined with and without caudal tilt were 0.89 (c.v. 16%), 0.98 (c.v. 12%) and 0.98 (c.v. 11%) using SCR, SVR and FAR, respectively.

Discussion

In the present study various approaches by RNV (two methods of labeling red blood cells and three methods of RI calculation) to quantify valvular regurgitation were evaluated in order to test their significance for follow up of patients with valvular insufficiency.

For visualization of the cardiac blood pool, in vitro labeling of red blood cells results in a superior delineation of the ventricular cavities due to an increase of ventricular counts combined with a reduction of background activity (Neumann et al. 1983). However, in vitro labeling is rather time consuming and has been used in the evaluation of regurgitation in only two studies (Bertout et al. 1984; Nicoletti et al. 1983) with no comparison to in vivo labeling. Another factor influencing delineation of the ventricles is acquisition time. Prolongation results in a superior delineation because of a reduction of the statistical error. Combining these two factors which increase image quality, a clear reduction of the dispersion of the RI values was obtained in patients with no evidence of valvular insufficiency.

Normal ranges obtained under these conditions were comparable to values in the literature determined with similar techniques (Fridrich and Gassner 1984; Gandsman et al. 1981; Makler et al. 1983; Manyari et al. 1982; Nicod et al. 1982; Rigo et al. 1979; Sorensen et al. 1980). Using the variable ROI method (SCR), the mean value of the RI did not differ significantly from unity. This value is theoretically assumed according to the equal stroke volume of both ventricles. Calculating regurgitation from functional images (SVR and FAR), the mean RI values were significantly greater than unity, 1.30 and 1.35, respectively, because the overlap of right atrium and right ventricle, and the out of phase contraction of both cavities lead to an underestimation of the right ventricular amplitude (Henze et al. 1982; Makler et al. 1983).

Comparing the three radionuclide techniques to quantify regurgitation, SCR was clearly inferior to SVR and FAR, which has also been reported by Nicod et al. (1982) and Makler et al. (1984). Direct comparison of SVR and FAR resulted in no significant differences. FAR was tendentionally superior concerning reproducibility, SVR concerning correlation with data from cardiac catheterization. Using SVR or FAR, a very high reproducibility between two observers and two independent measurements was observed. The former has been reported by several authors (Fridrich and Gassner 1984; Nicod et al. 1982; Ormerod et al. 1986), the latter has only been assessed by Makler et al. (1983) in 5 patients with sequential studies ($r = 0.95$). Our data of reproducibility clearly show the advantage of calculating regurgitation directly from the stroke volume or the ventricular amplitude image as compared to calculation from the blood pool scan (SCR technique). On these functional images only the ventricular cavities have significant amplitudes (Fig. 1). Therefore, the result of RI calculation is much less sensitive to variations of the boundaries of the ROIs.

Even employing the SVR and FAR techniques, correlation between the results of catheterization and radionuclide RI values was only moderate. The correlation coefficients determined in this study were slightly lower for SVR and FAR, and clearly lower for SCR than values previously reported (Makler et al. 1984; Manyari et al. 1982; Rigo et al. 1979). RNV clearly underestimated regurgitation in the 2 patients with severely depressed left ventricular function (LVEF < 30%) just as in the investigation of Nicod et al. (1982). Eliminating these two patients, correlation coefficients between catheterization and radionuclide data in our study increased to values comparable to published ones (Makler et al. 1984; Manyari et al. 1982; Rigo et al. 1979).

Another point, that has to be discussed in radionuclide evaluation of regurgitation, is caudal angulation. Gandsman et al. (1981) obtained, in subjects without regurgitation, significantly better data using a 30° slant hole collimator as compared to employing a parallel hole collimator without caudal angulation. Nicod et al. (1982) found no difference in accuracy for detecting regurgitation in patients, in whom a slant hole collimator was used, as compared to subjects investigated with a parallel hole collimator 5°–10° caudally angulated. No data have yet been published comparing intraindividual results in the evaluation of regurgitation obtained by using a parallel hole collimator with and without caudal tilt. According to the results of the present study, acquisition using a parallel hole collimator caudally angulated by 15° does not improve radionuclide evaluation of regurgitation. Correlation between RI values obtained with and without caudal tilt was comparable to data determined between two independent measurements. Dispersion in subjects without regurgitation and variability between two observers and two measurements was slightly greater using the caudal tilt as compared to acquisition without caudal tilt. Employing the caudal tilt, delineation of the ventricles was inferior in some patients in the apico septal region probably due to the greater distance of this part of the heart from the camera.

In conclusion, absolute quantification of regurgitation by equilibrium RNV is limited due to the variable geometry of the heart, more specifically due to the variable overlap of right atrium and right ventricle. Therefore, RNV is not a technique to replace cardiac catheterization. However, performed under optimal conditions, that means in vitro labeled red blood cells, acquisition time of ten min or more and calculation of regurgitation directly from the stroke volume or the ventricular amplitude image, RNV is a non invasive technique with a very high reproducibility. It is therefore suitable for intraindividual follow up of patients with valvular insufficiency, especially of those with isolated aortic regurgitation (Klepzig et al. 1985b), where atrial volumes do not change much when regurgitation volume increases. Additionally, RNV can be used to follow left ventricular function at rest as well as under exercise, resulting in further information to determine the appropriate time for valve replacement (O'Rouke and Crawford 1980; Levine and Gaasch 1983).

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