Left Ventricular Systolic and Diastolic Function Measurements Using an Ambulatory Radionuclide Monitor: Effects of Different Time Averaging on Accuracy

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The accuracy of an ambulatory radionuclide detector (VEST) for left ventricular systolic (ejection fraction, EF) and diastolic (peak filling rate, PFR) measurements was assessed at different time averaging of the nuclear and electrocardiographic data. Fifty-one patients, in a total of 67 studies, underwent equilibrium radionuclide angiography (RNA) immediately before a VEST study. VEST data were analyzed using single-beat analysis and different time averaging of 5, 10, 15, 30 and 60 sec. Agreement between VEST and RNA in estimating EF and PFR was evaluated by computing limits of agreement (LA). These were computed as 1.96 times the s.d. of the mean differences between the two methods, expressed in the same unit as EF and PFR. Differences between the two methods were plotted against their mean, allowing investigation of any possible relationship between measurement error and the true value (whose best estimate is the mean between the two methods). The entire statistical analysis was repeated at each different time averaging. LAs for EF measurement by VEST were −10.4:8.8 (single-beat analysis), −11.2:9.9 (5-sec averaging), −5.4:4.8 (10-sec averaging), −4.9:4.5 (15-sec averaging), −6.2:5.6 (30-sec averaging), −6.9:4.5 (60-sec averaging). Results indicate good agreement between VEST and RNA in measuring EF, at least for time averaging ≥10 sec. LAs for PFR ranged from −0.6:0.6 (single beat) to −1.0:0.6 (60-sec averaging), which was considered a clinically acceptable agreement between VEST and RNA. No relationship between measurement error and true value was found either for EF and PFR.

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In the past few years new devices have been developed to evaluate left ventricular (LV) function continuously in ambulatory patients using radionuclide techniques (*1–6*). Among the clinical applications proposed for such instruments, one of the most appealing is the detection of silent myocardial ischemia either during ambulatory activities or after intervention (*3,7–11*). In particular, changes in ejection fraction (EF) and in peak filling rate (PFR) have been used as markers of LV function impairment suggestive of ischemia.

Two commercially available devices have been proposed for continuous ambulatory monitoring of LV function: VEST (Capintec Inc., Oakfield Instruments, England) and CARDIOSCINT. Although these devices have some distinguishing differences, the underlying method is substantially the same: acquiring simultaneously nuclear and electrocardiographic data continuously in an ambulatory setting. After the acquisition end data are usually averaged over 15–60-sec periods to obtain time-activity curves suitable for further analysis (i.e., determination of LV function index and electrocardiographic monitoring). Previous studies demonstrate that ambulatory monitoring systems are powerful tools for physiologic research (*2,6,11*). In particular, these devices permit assessment of change in EF over relatively short time periods. Reproducible measurement can be obtained by averaging data over 30-sec intervals. On the other hand, traditional 2-min averaged data may underestimate the magnitude of change in EF response to different stimulations (*12*). This may be important in evaluating EF response to ambulatory stress characterized by sudden onset and transient in nature. The purpose of this study was to evaluate the accuracy of VEST in measuring both EF and PFR, and the influence of different time averaging on these measurements.

METHODS

Patients

Fifty-one consecutive patients (43 men and 8 women, mean age 57 ± 10 yr, range 39–84 yr) underwent both equilibrium radionuclide angiography (RNA) and VEST study. A total of 67 studies were performed (9 patients were studied twice, 2 were studied three times, and one was studied four times). Thirty-eight patients had coronary artery disease, four had dilated cardiomyopathy, five had hypertension and four had orthostatic hypotension.

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Data Acquisition

Radionuclide Angiography. In vivo labeling of red blood cells was performed with 555 MBq of ^{99m}Tc (15 mCi). Radionuclide angiography (RNA) was performed in the 45° left anterior projection at a 15° craniocaudal tilt with the patient in supine position under control conditions immediately before the VEST study. A small field-of-view gamma camera (Starcam 300 A/M, General Electric, Milwaukee WI) equipped with a low-energy all-purpose collimator was used. Data were recorded at a frame rate of 30 frames/cardiac cycle on a dedicated computer system (General Electric, Milwaukee, WI). At least 200,000 counts/frame were acquired.

VEST. The VEST consists of two radionuclide detectors: one (sodium iodide crystal and parallel-hole collimator) was used to monitor the left ventricle and the other (cadmium telluride and a flat field collimator) to monitor activity in the lung. Other components of the VEST are an electrocardiographic (ECG) recorder (2-leads), a gating device, a cassette recorder and a microcomputer. A vest-like garment was used to hold the two detectors in place. Optimal placement of VEST was determined by using the gamma camera, as previously reported (*6,9*). The VEST detector was positioned while the patient was standing in front of the gamma camera, and VEST's position was checked before starting acquisition of VEST data by using the gamma camera while the patient was supine. Patients wore VEST for at least 3 hr. During this time patients were allowed to move freely in the department, except for the first 10 min when they were in the supine position under controlled conditions.

Data Analysis

Radionuclide Angiography. RNA studies were analyzed using a standard commercial software (General Electric, Milwaukee, WI), as previously described (*6,9*). LV regions of interest (ROIs) were automatically drawn for each frame. A background ROI was also computer-delineated on the end systolic frame. After background correction, a LV time activity curve was generated. EF was computed on the raw time activity curve, while PFR was calculated after a Fourier expansion with four harmonics. PFR was computed as the maximum positive peak after end systole on the first derivative of the LV time activity curve and normalized by the end diastolic counts.

VEST. Vest studies were analyzed as previously described (*6,9*). At the end of the VEST study, data were reviewed for technical adequacy. Briefly, the average count rate (decay corrected) of the entire study was displayed: if this curve had a <10% deviation from a straight line, the VEST study was considered adequate. The first 2 min of data acquisition were discarded, and the following 8 min of data were considered for analysis. The heart rate (HR) in this part of the VEST data was displayed graphically using a 60-sec time averaging to individuate a period of stable HR comparable to that recorded during RNA. The radionuclide and electrocardiographic (ECG) data were analyzed beat-per-beat and summed for 5, 10, 15, 30 and 60-sec intervals. EF and PFR were computed only in this limited part of the VEST study. EF was computed as the stroke counts divided by the background-corrected end diastolic counts. Background was determined by matching the initial resting VEST EF value to that obtained by the gamma camera. PFR was obtained from the Fourier curve and computed as the inflection point after end systole where the second derivative changes from positive to negative.

TABLE 1
Ejection Fraction (%)

Method	Mean	Range
RNA	47 ± 16	16–72
VEST-1 beat	46 ± 17	13–76
VEST-5 sec	46 ± 16	16–72
VEST-10 sec	46 ± 16	15–73
VEST-15 sec	46 ± 17	15–72
VEST-30 sec	46 ± 16	17–73
VEST-60 sec	45 ± 17	13–73

RNA = Radionuclide angiography.

Statistical Analysis

Data are expressed as mean ± 1 s.d. Correlation analysis was used as a first approach to test the accuracy of VEST in comparison to RNA at each time averaging period. However, it has been pointed out that correlation analysis is not well suited for accuracy studies (*13,14*). A different approach, based on analysis of a plot of the difference between the methods against their mean, has been proposed (*13,14*). The mean difference between the two methods represents the bias, while the s.d. of the differences is related to the difference likely to arise between the two methods (*13,14*). The differences between the two methods would follow a normal distribution, and 95% will thus lie between ± 1.96 s.d. If differences within the mean ± 1.96 s.d. are not clinically relevant, the two methods could be used interchangeably. It has been proposed to refer to these as "limits of agreement" (*13,14*). In particular, the lower LA is computed as the mean difference between the two methods minus 1.96 s.d. of the differences, and the upper limit of agreement as the mean difference between the two methods plus 1.96 s.d. of the differences. The LAs are used to estimate whether VEST is accurate in computing EF and PFR (i.e., the closer they are the higher the accuracy of VEST). Since LAs are only estimates of values that apply to the whole population, 95% confidence intervals should be computed to determine how precise are estimates of LAs. The LAs as well as their confidence intervals are expressed in the same units of parameters evaluated (i.e., percent for EF and end diastolic counts/second for PFR). The plot of differences between the two methods against their mean allows investigation of any possible relationship between measurement error and true value (in this case, the mean of the two methods is the best estimate of true value). If differences diverge as the mean increases, the measurement error increases with the size of measurement, and vice versa.

RESULTS

Ejection Fraction. Table 1 shows mean values and the range of EF computed by RNA and VEST. The mean differences between EF measured by VEST and by RNA at each time averaging as well as the limits of agreement and their 95% confidence intervals are shown in Table 2. The values of LAs and their upper and lower 95% confidence intervals show agreement between VEST and RNA for time averaging ≥10 sec. Figure 1 shows plots of EF with the two methods. Standard error of the estimate (SEE) for EF varied from 4.9 (single-beat analysis) to 2.9 (60-sec averaging). To gain more information on agreement, the differences (VEST minus RNA) in the EF mea-

TABLE 2
Ejection Fraction (%)

Time	d	LA	95% CI LLA	95% CI ULA
1 beat	−0.8 ± 4.9	−10.4:8.8	−12.5:−8.3	6.7:10.9
5 sec	−0.6 ± 5.4	−11.2:9.9	−13.4:−8.9	7.6:12.2
10 sec	−0.3 ± 2.6	−5.4:4.8	−6.5:−4.3	3.7:5.9
15 sec	−0.2 ± 2.4	−4.9:4.5	−5.8:−4.0	3.6:5.4
30 sec	−0.3 ± 3.0	−6.2:5.6	−7.3:−5.1	4.5:6.7
60 sec	−1.2 ± 2.9	−6.9:4.5	−8.0:−5.8	3.4:5.6

d = mean difference; LA = limits of agreement (lower and upper); 95% CI LLA = 95% confidence interval of the lower limit of agreement; 95% CI ULA = 95% confidence interval of the upper limit of agreement.

surement were plotted against their mean (Fig. 2). No relationship between the difference and the mean was found, suggesting lack of any relationship between measurement error and the estimate of true value.

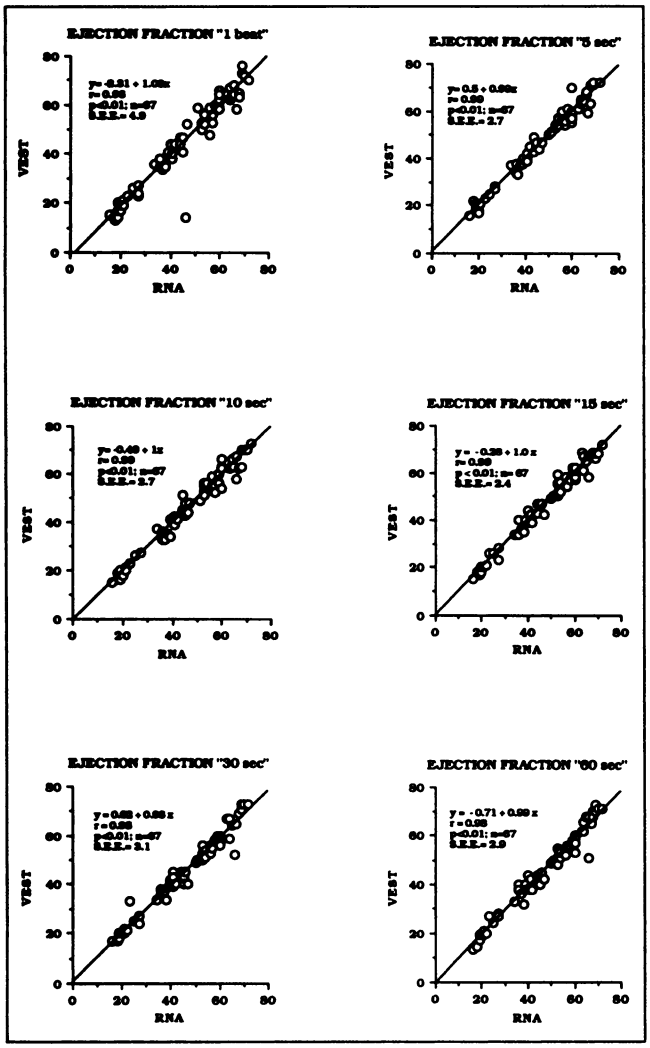

FIGURE 1. Comparison of equilibrium radionuclide angiography (RNA) and VEST measurements of ejection fraction (%) with single beat analysis, and different time averaging (5-10-15-30-60 sec) of VEST data.

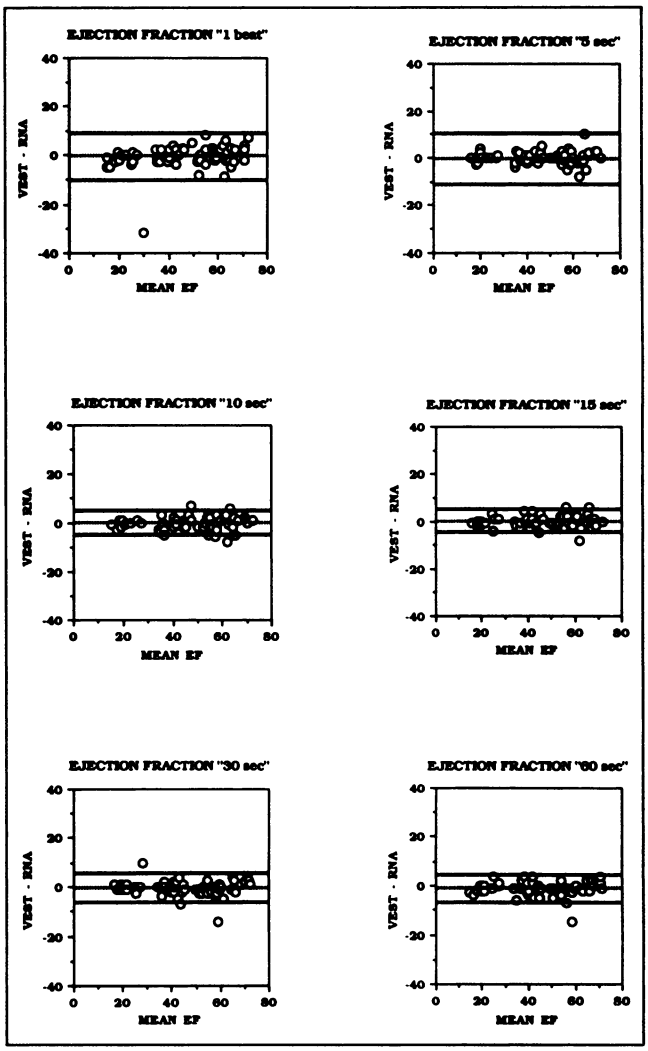

FIGURE 2. Plot of differences between two methods (RNA and VEST) against mean. Results obtained for ejection fraction (%) with single-beat analysis, and different time averaging (5-10-15-30-60 sec) are shown. There are no relations between differences and mean in each instance. Dotted line indicates mean; solid line indicates 2 s.d.

Peak Filling Rate. The mean values and range of PFR computed by RNA and by VEST are shown in Table 3. Table 4 reports the mean differences between PFR measured by VEST and by RNA at each time averaging as well as LAs and their 95% confidence intervals. The LAs were

TABLE 3
Peak Filling Rate (end diastolic counts/sec)

Method	Mean	Range
RNA	1.8 ± 0.7	0.5–3.7
VEST-1 beat	1.9 ± 0.7	0.6–3.5
VEST-5 sec	1.8 ± 0.7	0.5–3.8
VEST-10 sec	1.8 ± 0.7	0.5–3.6
VEST-15 sec	1.8 ± 0.7	0.5–3.9
VEST-30 sec	1.7 ± 0.7	0.5–3.6
VEST-60 sec	1.7 ± 0.7	0.1–3.7

RNA = Radionuclide angiography.

TABLE 4
Peak Filling Rate (end diastolic counts/sec)

Time	d	LA	95% CI LLA	95% CI ULA
1 beat	−0.01 ± 0.3	−0.6:0.6	−0.7:−0.5	0.5:0.7
5 sec	−0.02 ± 0.2	−0.4:0.4	−0.5:−0.3	0.3:0.5
10 sec	−0.05 ± 0.3	−0.6:0.6	−0.7:−0.5	0.5:0.7
15 sec	−0.1 ± 0.4	−0.9:+0.7	−1.1:−0.8	0.6:0.9
30 sec	−0.1 ± 0.4	−0.9:+0.7	−1.1:−0.8	0.6:0.9
60 sec	−0.2 ± 0.4	−1.0:+0.6	−1.2:−0.9	0.5:0.8

d = mean difference; LA = limits of agreement (lower and upper); 95% CI LLA = 95% confidence interval of the lower limit of agreement; 95% CI ULA = 95% confidence interval of the upper limit of agreement.

within an acceptable clinical range. Figure 3 illustrates the plots of PFR with the two methods. SEE varied from 0.3 (single-beat analysis) to 0.4 (60-sec averaging). The differences (VEST minus RNA) in parameters measurement were plotted against their mean (Fig. 4). No relationship

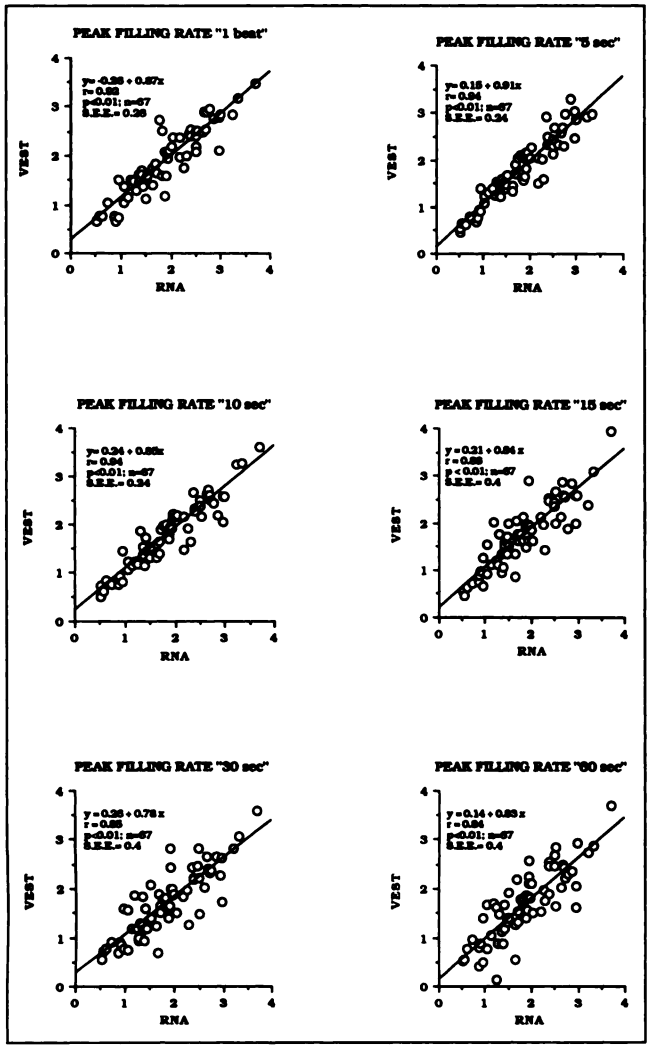

FIGURE 3. Comparison of equilibrium radionuclide angiography (RNA) and VEST (VEST) measurements of peak filling rate (end diastolic counts/sec) with single-beat analysis, and different time averaging (5-10-15-30-60 sec) of VEST data.

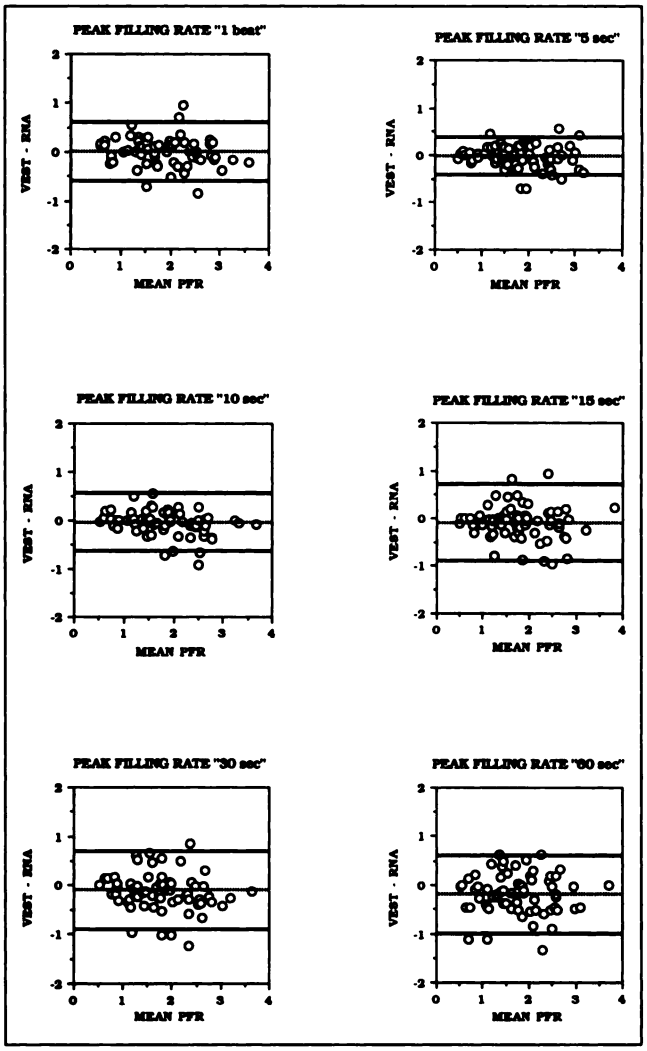

FIGURE 4. Plot of differences between two methods (RNA and VEST) against mean. Results obtained for peak filling rate (end diastolic counts/sec) with single-beat analysis, and different time averaging (5-10-15-30-60 sec) are shown. There are no relations between differences and mean in each instance. Dotted line indicates mean; solid line indicates 2 s.d.

between difference and mean was found, suggesting lack of any relationship between measurement error and the estimate of true value.

DISCUSSION

Ambulatory radionuclide detectors have been shown to be accurate in measuring LV function (*3,5,6,15,16*). However, it is relevant to systematically evaluate accuracy of such devices using different time averaging of nuclear and ECG data. Results of the present study indicate that VEST measurements of both EF and PFR are accurate when compared to RNA and that time-averaging has minimal influence on VEST accuracy.

Other authors report accuracy of both VEST and CARDIOSCINT in measuring EF (*5,15,16*) and PFR (*3*). However, the majority of these studies used linear regression and correlation coefficient to assess accuracy. While the plot of results obtained with one method against those

obtained with another could help in assessing accuracy, the use of correlation coefficient may be misleading (*13,14*). The correlation coefficient measures the strength of the relationship between the two variables and not their agreement. High values of the correlation coefficient will be found when two variables lie along a straight line, not only the line of identity. Use of a different scale of measurement by the two methods does not affect the correlation coefficient, but agreement will be affected. Moreover, authors using linear regression and correlation coefficient use a test of significance to assess accuracy. However, "it would be amazing if two methods designed to measure the same quantity were not related" (*14*), and thus, "the test of significance is irrelevant to the question of agreement" (*14*).

A different approach was used in the present study, based on analysis of differences between the two methods against their mean (*13,14*). Using this approach it is possible to obtain information on both agreement and the relation between error in the new method and value of the parameter. No obvious relation between the difference and the mean for both EF and PFR was found, making it possible to summarize agreement by calculating the mean difference and s.d. for the two parameters at each time averaging. The LAs were computed as 1.96 times the s.d.

The LAs (expressed in units of EF) for EF measurement by VEST were within clinical range and indicate agreement between VEST and RNA, for time averaging ≥10 sec. It should be noted that SEE in the regression analysis suggests the same finding. This was not the case for the single-beat analysis and the 5-sec averaging. In fact, both showed high LAs. The mean difference between VEST and RNA always demonstrated underestimation of EF by VEST when compared to RNA. The fact that VEST slightly underestimates EF is not surprising, since this method is comparable to EF measurement by RNA using a single ROI, while EF measurement by RNA in this study was accomplished by using a multiple ROI method.

The LAs for PFR ranged from −0.6:0.6 (lower and upper LAs) for single-beat analysis to −1.0:0.6 (lower and upper LAs) for 60-sec time averaging. These results suggest a clinically acceptable agreement between VEST and RNA in measuring PFR. It should be noted that the same finding is suggested by the SEE.

The plot of differences between VEST and RNA against their mean value showed no relationship between measurement error and the best estimate of true value of the parameter both for EF and PFR. This finding suggests that the magnitude of the parameter did not affect accuracy of VEST measurement.

Results of this study indicate that VEST is an accurate method to evaluate LV function. Both systolic (EF) and diastolic (PFR) performance of the LV can be assessed. Moreover, no influence of time averaging on results was found for time averaging ≥10 sec, suggesting that short period-of-time summing can be used when transient phenomena should be detected.

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