The Repeatability of Left Ventricular Volume Assessment by a New Ambulatory Radionuclide Monitoring System During Head-up Tilt

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SUMMARY

The precise measurement of changes in left ventricular volume is important to elucidate the mechanisms of neurally mediated syncope. This study was conducted to determine whether or not a brand-new ambulatory radionuclide monitoring system (C-VEST system) can be clinically used to easily and precisely measure left ventricular volume and function in tilt testing. To assess the repeatability of the C-VEST system, 12 healthy volunteers (mean age 24 ± 4 years old) underwent 20 minute head-up tilt testing and we measured the temporal changes in left ventricular volume and ejection fraction twice a day (first and second studies). To investigate the changes in the C-VEST measurements and the detector position in the first and second studies, tilt testing was performed with an 80-degree passive tilt, which is the same as the standard procedure used in diagnosing neurally mediated syncope. The coefficient of repeatability for both the C-VEST and detector position was well within the clinical range (coefficient of repeatability in left ventricular volume ranged from 1.7 to 2.8; coefficient of repeatability in the detector position ranged from 2.3 to 3.1). Precise evaluation of the left ventricular volume can be achieved by an ambulatory radionuclide monitoring system in tilt testing. (*Jpn Heart J* 2001; 42: 749-758)

Key words: Ambulatory radionuclide monitoring system, Head-up tilt, Left ventricular volume

HEAD-up tilt tests are a widely used diagnostic modality for neurally mediated syncope.¹⁾ The mechanisms of syncope induced by tilt are still not well understood. However, in general, the pooling of blood in the lower limbs and a subsequent decline in the left ventricular volume play an important role in triggering hypotension and bradycardia in patients with neurally mediated syncope. Precise

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Received for publication May 17, 2001.

Revised and accepted June 29, 2001.

measurements of left ventricular volume and ejection fraction during tilt are important to investigate the mechanisms of neurally mediated syncope.^{2,3)}

Several studies have reported that a prototype ambulatory radionuclide monitoring system (C-VEST system, Capintec Inc., Ramsey, NJ) is good enough to be used clinically in the monitoring of left ventricular volume and ventricular function.⁴⁻⁶⁾ Quite recently, a brand-new model of the C-VEST system, which is more accurate and easier to use than the prototype equipment, has become available. However, the usefulness and repeatability of this new system has yet to be validated precisely in a clinical setting. Thus, the purpose of this study was to determine whether or not the new C-VEST system is appropriate for measuring left ventricular volume and function in tilt testing in a clinical setting.

SUBJECTS AND METHODS

Study subjects: The study population consisted of 12 healthy male volunteers (mean age 24 ± 4 years old) who participated in an assessment of the repeatability of the C-VEST system. All subjects had no significant past history and a normal comprehensive physical examination, including a neurological examination, a normal 12-lead electrocardiogram (ECG), normal 24-hour ambulatory ECG monitoring, normal 2-dimensional echocardiography, and normal exercise treadmill testing. In addition, all subjects showed a sinus rhythm. Informed consent was obtained from all subjects.

Head-up tilt test: The test was performed using a standard head-up tilt test protocol in a quiet temperature-controlled environment (21°C to 23°C) with subdued lighting. All subjects were in a fasting condition (>8 hours) at the time of the tilt test. A motor-driven tilt table with a foot board for weight support was used for an 80-degree passive tilt. The head-up tilt test protocol consisted of at least 15 minutes in a supine position under stable and quiet conditions, followed by a 20 minute period of tilt. Testing was immediately discontinued in the event of syncope or presyncope with a drop in blood pressure or heart rate. Blood pressure (mmHg) was measured by an automatic cuff sphygmomanometer (BP203, Nihon Colin Inc., Tokyo, Japan) before and every minute after initiation of the tilt test. The heart rate (bpm) was monitored using ECG lead II throughout the study.

Radionuclide ventriculography: All patients underwent ECG gated blood-pool scintigraphy. After the injection of 740 MBq (20 mCi) of $^{99\text{m}}\text{Tc}$ -labeled human serum albumin, this equilibrium radionuclide angiography was performed in a supine position in a 45 degree left anterior oblique projection, which separated both ventricles optimally. The images were obtained using a GE Medical system gamma camera (GE Yokokawa, Hachioji, Tokyo), with a low-energy, all-purpose collimator. The imaging data were obtained in a 64×64 matrix with a 2.0 zoom

and were acquired for an average of 300 counts per pixel in the cardiac region of interest, with 24 frames per cardiac cycle. The left ventricular ejection fraction was computed from the global time-activity curve using the single semi-automated method.

C-VEST system: To measure the changes in left ventricular volume and ejection fraction during tilt, we used the newly developed Capintec Ambulatory Ventricular Function Study System (C-VEST system, Capintec Inc.). At the end of equilibrium radionuclide angiography, electrodes were placed to monitor NASA and CM5 ECGs, and then all subjects put on the VEST garment. This new VEST instrument consists of two radiation detectors and an ambulatory ECG recording system. This system is made up of a conventional ambulatory ECG (Holter ECG system, Meadset Inc., Hamburg, Germany) with a newly devised ambulatory radionuclide system. This new C-VEST system makes the analysis of left ventricular function much easier than the previous version of the C-VEST system. One detector is placed over the left ventricle while another is placed over the right lung field attached to the VEST garment. The ventricular detector utilizes a 5.0 cm diameter sodium-iodide crystal with a parallel hole collimator to maximize the sensitivity. The lung detector uses a cadmium telluride crystal with a flat field collimator to minimize the weight. A second detector assesses the changes in background radioactivity. The patient was seated in front of the gamma camera and the detector of the C-VEST system was positioned over the left ventricle. For this positioning, the VEST detector over the left ventricle was modified under a gamma camera control. In most patients, the sensitive area of the detector occupied the left ventricular inferior two-thirds portion verified by a 20 second static acquisition with the gamma camera. Since the C-VEST system is a position sensitive modality,⁴⁾ we confirmed the position of the detector not only while sitting but also in a supine position, and also ensured that the detector was placed over the left ventricle. As described above, the ECG data and the global time-activity curve were recorded into a specially adapted Holter ambulatory ECG recording system (Meadset, Inc.). These apparatuses were placed in a small bag. This entire set is similar to a conventional Holter ambulatory ECG recording system, and it weighs about 3.0 kg, including the garment. All data over 30 seconds were averaged and gated to reduce the effect of statistical noise and respiratory induced changes in left ventricular function. In the same manner as in previous reports using a prototype C-VEST, the background for the calculation of ejection fraction, stroke volume, end-diastolic volume and end-systolic volume was estimated by equalizing the left ventricular ejection fraction by the initial VEST to that of the resting equilibrium radionuclide angiography by the gamma camera. After completing the study protocol, additional static imaging acquisition was repeated both while sitting and in a supine position to confirm that the detector had not

moved during the tilt. The radionuclide data were analyzed by a microprocessor within a few hours using a modified Holter ambulatory ECG analyzing system (GateWay 2000, Capintec Software, Capintec Inc.). Graphical and numerical data of left ventricular volume and ECG were automatically analyzed with manual editing. The entire analyzing time was about 15 minutes. All clinical information was blinded to the person who analyzed the measurements.

Repeatability of left ventricular volume measured by C-VEST system and the effects of body position during tilt:

In order to assess the repeatability of the C-VEST system, 12 healthy volunteers underwent a 20 minute tilt with the C-VEST system twice a day, and the values of the left ventricular volume in the first tilt were compared with those in the second one. The effect of body position during tilting was evaluated by measuring the changes in the detector position between the start and end of the first tilt. The patient was seated in front of a gamma camera and the detector of the C-VEST system was positioned over the left ventricle using the gamma camera before the first tilt. Generally, blood-pool scintigraphy can show clear images of the aorta, right and left ventricles, and the detector over the left ventricle.⁷⁾ The detector position was determined by measuring the distance from the upper margin of the aortic root to the upper edge of the detector and the distance from the right margin of the cardiac imaging to the right edge of the detector. After the first tilt, the patient was seated in front of the gamma camera again and then the same measurements were performed.

Study protocol: All study subjects wore the C-VEST system about one minute after undergoing ECG gated blood-pool scintigraphy and the ventricular detector was positioned over the left ventricle in front of the gamma camera. The data acquisition of the C-VEST system was begun after sitting for 5 minutes. After stable recording waves were obtained, the study subjects lay down on the table in a supine position. Thereafter, the subject was tilted up while the C-VEST system continued to run (Figure 1). After completing the tilt protocol, they returned in front of the gamma camera and 20 second static images were repeated to confirm that the C-VEST detector had not moved during the recording interval.

Data analysis: Beat to beat data of the C-VEST recordings were taken over 30 second intervals, from which the relative end-diastolic volume, relative end-systolic volume, relative stroke volume, and left ventricular ejection fraction were calculated. The system does not permit absolute measurements. The data are considered to be 100% at the beginning of the study and subsequently are expressed relative to this initial value.

In order to assess the decline of the left ventricular volume, the percent changes between the values at the end and those at 2 minutes after the start of tilt were calculated for the left ventricular end-diastolic and end-systolic volume, respectively, as follows; (1) the percent change in left ventricular end-diastolic

Figure 1. A patient undergoing the head-up tilt test using the C-VEST system and real time C-VEST wave recording.

volume (%) = $\frac{[\text{Left ventricular end-diastolic volume at the end of tilt} - \text{Left ventricular end-diastolic volume at 2 minutes after the start of tilt}]}{\text{Left ventricular end-diastolic volume at 2 minutes after the start of tilt}} \times 100$ and, (2) the percent change in left ventricular end-systolic volume (%) = $\frac{[\text{Left ventricular end-systolic volume at the end of tilt} - \text{Left ventricular end-systolic volume at 2 minutes after the start of tilt}]}{\text{Left ventricular end-systolic volume at 2 minutes after the start of tilt}} \times 100$. The differences in the ejection fraction between the values at the end and those at 2 minutes after the start of tilt (%) were also calculated using the same formula as above. We did not measure the changes in left ventricular volume or ejection fraction between the supine and upright positions because the obtained data are likely to be confounded by detector motion even if the gamma camera confirms that the dislocation of the detector to the heart is small.

Statistical analysis: The values are expressed as the mean $\pm$ standard deviation. Differences were considered significant at a value of $P \leq 0.05$. To examine the repeatability of the C-VEST measurements, we used the method proposed by Bland and Altman,⁸⁾ which analyses the plot of the differences in the parameter values between the two C-VEST measurements against their mean. A coefficient of repeatability⁹⁾ was then computed as twice the standard deviation of the differences.

RESULTS

Figure 1 shows a picture of the tilt study with the C-VEST and real time recording waves by the C-VEST. None of the 12 healthy volunteers showed any hypotension or bradycardia response to the head-up tilt. In the first tilt, as defined in the methods section, these percent changes were obtained by comparing each value measured at 2 minutes after the tilt started with the value at the end of the tilt. The value of the percent change in left ventricular end-diastolic volume was $-3.4 \pm 2.2\%$. The value of the percent change in left ventricular end-systolic volume was $1.2 \pm 5.1\%$. As a result, the ejection fraction changed by $-2.4 \pm 6.6\%$. The mean values of the left ventricular end-diastolic volume and left ventricular end-systolic volume at 2 minutes after the start of tilt and at the end of tilt were not statistically different between the first and the second tilt. The mean difference in the values of left ventricular end-diastolic volume and the left ventricular end-systolic volume at 2 minutes after the start of tilt between the first and second tilt were $0.1 \pm 1.4\%$ and $0.3 \pm 1.2\%$. The mean difference in the values of left ventricular end-diastolic volume and left ventricular end-systolic volume at the end of tilt between the first and second tilt were $0.4 \pm 0.8\%$ and $-0.2 \pm 1.1\%$ as shown in Table I. The coefficient of repeatability was well within the clinical range reported by Altman, *et al*; the 95% difference in each parameter was less than two standard deviations.⁸⁻¹⁰ A plot of the differences in the value of the left ventricular end-diastolic volume at the end of tilt between the first and second tilt against their mean is shown in Figure 2 and the plots of the other parameters showed the same pattern. No relationship was found between the differences in the parameter measurements by the two C-VEST studies and their mean. As a result, no relationship was suggested to exist between the measurement error and the estimated true value.

Table I. Repeatability of the C-VEST Measurements

Variable	First tilt	Second tilt	<i>p</i> value	d	CR
LVEDV-2MIN (%)	86±12	86±13	NS	0.1±1.4	2.8
LVEDV-END (%)	86±12	85±12	NS	0.4±0.8	1.7
LVESV-2MIN (%)	40±5	40±4	NS	0.3±1.2	2.4
LVESV-END (%)	39±4	39±3	NS	-0.2±1.1	2.1

Data presented are the mean±standard deviation, CR=coefficient of repeatability; d=difference between the values of first and second tilt; LVEDV-2MIN=left ventricular end-diastolic volume at 2 minutes of head-up tilt; LVEDV-END=left ventricular end-diastolic volume at the end of head-up tilt; LVESV-2MIN=left ventricular end-systolic volume at 2 minutes of head-up tilt; LVESV-END=left ventricular end-systolic volume at the end of head-up tilt; NS= not significant.

Figure 2. Plot of the differences in left ventricular end-diastolic volume at the end of tilt between the first and second tilt against their means.

Table II. The Effect of Body Position on the Detector Position; Repeatability of the Detector Position.

Variable	At the start	At the end	<i>p</i> value	d	CR
Right distance (mm)	68.7±18.5	69.1±18.5	NS	-0.4±1.1	2.3
Upper distance (mm)	84.1±15.8	84.2±15.6	NS	-0.2±1.6	3.1

Data presented are the mean±standard deviation, CR=coefficient of repeatability; d=difference between the values at the start and end of tilt; NS=not significant; Right distance=the distance from the right margin of cardiac imagings to the right edge of the detector; Upper distance=the distance from the upper margin of the aortic root to the upper edge of the detector.

The effect of body position was evaluated by comparing the detector position at the start of the study to that at the end of the entire study. The mean difference in the distance from the aorta to the detector between the start and end of the study was -0.2 ± 1.6 mm. In addition, the mean difference from the right margin of the heart to the detector was -0.4 ± 1.1 mm, as shown in Table II. These values were so small that the coefficient of repeatability was well within the clinical range. A plot of the differences in the distance from the upper margin of the aortic root to the upper edge of the detector against their mean is shown in Figure 3, and a plot of the differences in the distance from the right margin of the cardiac image to the right edge of the detector against their mean showed the same pattern. No relationship was found between the differences in the parameter measurements

by the distance at the start and the end of the entire study and their mean, suggesting no relationship between the measurement error and the estimated true value. These results confirm that the new C-VEST detector had not moved during our study protocol.

DISCUSSION

To determine whether the new model of the C-VEST system is clinically useful for measuring left ventricular volume in tilt testing, we assessed the repeatability of the C-VEST measurements of left ventricular volume under two different conditions; at the beginning and at the end of head-up tilt in 12 healthy volunteers. Our findings demonstrated the new C-VEST system has an acceptable repeatability and that the effect of body position during tilt does not affect the accuracy of the C-VEST measurements.

To clearly demonstrate the repeatability of this new C-VEST system, the coefficient of repeatability should be revealed within the appropriate clinical range.^{5, 8-10)} Prior studies have used a linear regression and correlation analysis to examine the repeatability of the C-VEST.^{4, 6, 11)} Other authors have outlined the drawbacks of these methods (Altman and Bland).^{8,10)} They stressed that the correlation analysis measures the strength of a relation between two variables and not the agreement. Moreover, both a linear regression analysis and a correlation analysis are less useful than determining the 'coefficient of repeatability'.⁸⁻¹⁰⁾ We evaluated the coefficient of repeatability of the left ventricular volume and function during the tilt study and found it to be good enough for clinical use. The coefficient of repeatability for the left ventricular volume and ejection fraction was within the clinical range.

A second finding, which indicates the new C-VEST system is a clinically useful and accurate modality for examining left ventricular volume and function, showed the effects of body position on the measurement to be trivial. It is well known that the most relevant advantage of the C-VEST system is its ability to monitor left ventricular volume continuously over time,^{4,6,12)} but the patient's position changes during tilt and the position of the C-VEST are a critical part of this study. Since the heart changes its position when the patient lies down, the detector of the C-VEST was positioned in the sitting position and the measurement of left ventricular volume was started after the patient was tilted up. In this study, the detector position over the left ventricle was found to be stable throughout the entire study as shown in Figure 3.

The present study has demonstrated that no marked changes in left ventricular volumes are observed in healthy volunteers with a negative response to head-up tilt testing. The value of the percent changes in left ventricular end-diastolic

Figure 3. Plot of the differences in the distance from the upper margin of the aortic root to the upper edge of the detector between the start and end of study against their means.

volumes was relatively stable during the tilt-up position. In addition, the left ventricular ejection fraction values were stable over the entire tilt-up position. This stable behavior of left ventricular volumes during tilt agrees with previous reports^{13,14)} which showed stable left ventricular volume levels during the tilt-up position in patients with a negative response to head-up tilt testing. Stable left ventricular volumes during tilt-up position might be a typical finding for a normal response to orthostatic stress. However, to clarify this matter, further investigation of the C-VEST system in patients with neurally mediated syncope is necessary.

Study limitations: To clearly demonstrate the excellent usefulness of this new model of the C-VEST, we have to compare this new one with the prototype VEST system. However, the prototype is heavy and needed a long time for analysis,⁴⁻⁷⁾ and a prototype VEST system is not now available. In addition, no studies were performed during head-up tilt testing using a prototype VEST. Despite the lack of a direct comparison between the new and prototype VEST systems, we can speculate that the new model is clinically useful. Another limitation of this study is that the short time reproducibility of head-up tilt testing is reported to be excellent, although day-to-day variability does exist.¹⁵⁾ Even if the short time reproducibility is acceptable in the new model, day-to-day repeatability was not evaluated in this study. A study of the day-to-day variability with different supervising physicians might be necessary. However, to apply the C-VEST to head-up tilt testing

in patients with neurally mediated syncope, short time repeatability might be more important because symptoms in patients with neurally mediated syncope have day-to-day fluctuations.

Conclusion: The new model of the C-VEST system has good repeatability and is clinically useful for measuring left ventricular volume and function in the head-up tilt test.

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