Assessment of Cardiac Function Using Radionuclide Techniques
—Theory, Technical Considerations and Clinical Application—

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Summary: The recent expansion of interventional cardiovascular techniques has stimulated the development of non-invasive cardiac studies, to evaluate the outcome of the interventional therapy. Radionuclide ventriculographic technique provides to quantify global left ventricular systolic/diastolic performance, and evaluate the regional left ventricular wall motion during rest or exercise. This concept was extended from the “bedside” to the ambulatory environment with the description of a battery powered device, the radionuclide ventricular function monitor. To assess the performance of cardiac function using radionuclide ventriculography to that using the ambulatory ventricular function monitor, the systolic and diastolic function were measured at rest in a series of healthy volunteers (n=10) and in patients with cardiovascular disease (n=23). Seventeen patients had coronary artery disease (CAD) with prior myocardial infarction, three patients had coronary artery disease, and three patients had dilated cardiomyopathy. The 23 patients manifested a wide variation in LV systolic function. The relationship between the multiple gated acquisition (MUGA)-ejection fraction and the ambulatory ventricular function monitor-ejection fraction correlated well (r=0.90). As a complement to the radionuclide perfusion studies, cardiac blood pool imaging and radionuclide ventricular function monitoring allow for through non-invasive description of cardiac physiology and function in patients with various cardiac disorders.

Key words: Radionuclide ventriculography — Tc-99m labeled red blood cells — systolic function — diastolic function — continuous radionuclidemonitor

Introduction

Medical imaging studies of the heart and circulation are most often, and appropriately, characterized by the physical process used to sample the phenomena under investigation: x-ray contrast ventriculography, echocardiography, and radionuclide ventriculography (Strauss et al. 1971; Bacharach et al. 1979; Okada et al. 1980; Upton et al. 1980; Bonow et al. 1981; Jones et al. 1981; Papaietro et al. 1981; Reduto et al. 1981; Soufer et al. 1985; Friedman et al. 1986; Grossman, 1988; Yasuda et al. 1990). While this nomenclature defines, in effect, both the procedure and its limits of measurement, these procedure are also accompanied by sets of analytic methods used to extract medically relevant information from the primary image data or non-image data. Although not fully appreciated, these

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analytic methods are inseparably and intimately bound to these procedures and contribute importantly to the success or failure of a procedure in any given clinical application.

The assessment of systolic and diastolic left ventricular function with first pass or equilibrium radionuclide blood pool techniques has become firmly established in the evaluation of patients with both coronary and non-coronary heart disease (Fouad et al. 1983; Bonow et al. 1983, 1985; Brown et al. 1983; Lavbovitz et al. 1987). Measurement of ejection fraction and regional wall motion provides important diagnostic and prognostic information in such patients. Further, the ability to perform serial, non-invasive studies has aided the physician both in defining the natural history of and assessing the response to therapy in a variety of cardiac disorders. For practical purposes, however, performance of cardiac function studies was largely limited to the “in-hospital” setting and frequently was not available for the ICU setting.

Wagner and co-workers (1976) developed the nuclear stethoscope, a non-imaging device for the “bedside” quantitation of ventricular function (Berger et al. 1981; Iskandrian, 1987). In 1979, this concept was extended from the bedside to the ambulatory environment (Strauss et al. 1979) with the description of a battery powered device which incorporated radionuclide detectors and a Holter-ECG recorder carried in a vest-like garment designed to be worn by the patient. Following equilibrium blood pool imaging, the VEST detector was placed over the left ventricular blood pool, the garment was tightened around the patient, and ambulatory monitoring was commenced. Over the past 12 years, the sensitivity of the detectors and the method of recording the ambulatory data have improved, to now permit beat-by-beat recordings of both cardiac function and the electrocardiogram. Given the portable nature of the instrument and its ability to record the electrocardiogram, the VEST can provide quantitative evaluation of left ventricular systolic/diastolic function outside the hospital setting (Strauss et al. 1979; Wilson et al. 1983; Tamaki et al. 1987, 1988; Kayden et al. 1988; Kiess et al. 1988; Ishibashi et al. 1989a, 1989b, 1989c, 1990, 1991). In particular, this device may be well suited for the detection of silent myocardial ischemia, a major clinical issue in the “interventional” cardiology era.

Methods

Patient population

The study population consisted of 23 patients (16 men and 7 women), aged 40 to 74 years (mean 50). Seventeen patients had coronary artery disease (CAD) with a prior myocardial infarction, three patients had coronary artery disease, and three patients had dilated cardiomyopathy. The volunteers, aged 20 to 43 years (mean = 32 years), who were free of clinically apparent cardiopulmonary disease served as controls to establish the normal parameters of LV systolic and diastolic function.

Radionuclide ventriculography

Preparation of Radiopharmaceuticals

Blood components were labeled with a radionuclide. First, approximately 1 to 2 μg stannous ion as a pyrophosphate (PYP) kit were injected intravenously to sensitize the RBCs. Approximately 30 minutes after PYP injection, 740 MBq of Tc-99m were injected into the autologus red cells labeled using a modified in-vivo technique (Fig. 1), in which the mixing occurs in the syringe containing heparin while the syringe was still connected to the patient’s vein (Callahan et al. 1982).
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**Data acquisition**

Multigated blood pool scans were recorded approximately 10 minutes after intravenous administration using the modified invivo red cell labeling technique. Gated blood pool images and data were acquired with an all-purpose parallel hole collimator using a 20% window centered on the Tc-99m photopeak. The data was recorded in a dedicated computer system using a 64 x 64 matrix for 16 frames per cardiac cycle in the anterior, modified left anterior oblique, and left posterior oblique views for 10 minutes each.

**Measurement of systolic function**

A background-corrected time activity curve was generated using several hundred beats. End-diastole (ED) was represented by the peak, and end-systole (ES) by the nadir. Thus, the stroke count was equal to peak count minus nadir count, and the ejection fraction was then calculated by the following equation:

\[
\text{EF} (%) = \frac{\text{ED count} - \text{ES count}}{\text{ED count} - \text{Background}} \times 100
\]

The LV ejection fraction was calculated from such theory.

**The VEST**

The ambulatory ventricular function monitor (VEST) was composed of 2 radionuclide detectors, a molded plastic garment to hold the radionuclide detectors in place over the left ventricle and right lung, a modified Holter electrocardiographic (ECG) recorder and associated electronics to store data from two channels of ECG, the pulmonary blood volume, and the left ventricular time-activity curve. In addition, the recorder had an event marker and a real-time clock. The VEST components were carried in a backpack, while the ECG and radionuclide data were acquired (Fig. 2).

The detector placed over the left ventricle consisted of a 5.6-cm-diameter sodium iodide crystal mated to two phototubes. This detector viewed the left ventricle through a parallel hole collimator and iris (Fig. 3). Energy discrimination was achieved with a thresholding circuit set to accept all events above 120 keV. The digital data from the thresholding circuit was averaged for 31.25 milliseconds, converted to an analog signal and recorded in parallel with the ECG. A small cadmium telluride (CdTe) detector was placed over the right lung to monitor changes in pulmonary blood volume. Data from the CdTe was averaged over an 8 second interval prior to re-
cording. To hold the detectors in place over the left ventricle and lung field, a molded plastic garment was fitted securely on the subject (Fig. 4).

In addition to the radionuclide data, the VEST continuously sampled and recorded data from 2 ECG leads in an analog format. The recorded data was subsequently displayed and analyzed on a PDP 11/73 minicomputer (Digital Equipment Corp.).

Prior to the VEST study, subjects had a multigated equilibrium blood pool scan at rest. On completion of the gated scan, electrodes were placed to record a modified CM5 and CC5, and the plastic garment was fit to the subjects thorax, and tightened in place. With the patient upright in the left anterior oblique position that best demonstrates the interventricular septum, thereby optimizing separation of right and left ventricular blood pool, the main detector was positioned over the left ventricle with anger camera guidance. After the ambulatory study, a 10s-20s static image was obtained to confirm that the detector had not moved during the recording intervals (Fig. 5).

**Detector positioning.**

**Fig. 3.** Collimator and iris of VEST.

**Fig. 4.** VEST on volunteer demonstrating thorax geometry and support device.

**Fig. 5.** End-diastolic and end-systolic blood image in left anterior oblique projection and the beginning and after of ambulation positioning image with the VEST detector on in the same projection. The relation of the positioning silhouettes to the left ventricular blood pool remains constant throughout the study.
VEST data analysis.

The radionuclide and ECG data acquired by the VEST were analyzed for heart rate, ejection fraction, filling rate, relative end-diastolic and end-systolic volumes, relative cardiac output and ST segment changes. Data analysis utilized the R wave of the ECG to facilitate summation of multiple beats to generate an average time activity curve and ECG over intervals of 10-30 seconds. The left ventricular ejection fraction was calculated in the standard fashion (end diastolic counts-end systolic counts-background divided by background corrected end-diastolic counts). Peak (PFR) and average (AFR) fast filling rates were calculated from the derivative of the left ventricular time-activity curve; all filling rates were normalized to end-diastolic counts, and expressed in EDV/sec. In addition, the extent of left ventricular filling which occurs during early rapid (%FFF) filling and late filling (%SFF) periods were calculated and expressed as a percentage of stroke counts.

Results

With respect to the performance of count rates, each view takes approximately 10 minutes to collect, and each frame within the study usually contains over 200,000 counts. Images were recorded in the anterior, modified left anterior oblique, and left posterior oblique views (Fig. 6). Left ventricular time activity

Fig. 6. Multiple gated cardiac blood-pool images of a normal volunteer. ANT=anterior; LAO=modified left anterior oblique; LPO=left posterior oblique; ED=end-diastole; ES=end-systole. Figure A represents the normal volunteer, and figure B demonstrates a patient with dilated cardiomyopathy.
curves (Fig. 7) were generated after background correction; the left ventricular ejection fraction was calculated automatically using a "gradient" threshold algorithm.

A representative beat-to-beat time activity curve and electrocardiogram using the VEST are shown in Fig. 8. The 30s summed data used to generate the left ventricular volume curve, electrocardiogram, and R-R interval histogram are shown in Fig. 9. Parameters of LV diastolic function were expressed in relation to the LV ejection fraction (EF), as shown in Table 1.

As LVEF decreased, cardiac output and peak ejection rate also decreased. PFR and AFR similarly decreased as the LVEF decreased; the magnitude of the decrement in filling rates was proportional to the fall in LVEF (Fig. 10). The correlation between the VEST-EF and gamma camera acquired left ventricular ejection fraction was $r = 0.90$ (Fig. 11).

**Representative case report**

This 63-year-old was admitted for cardiac catheterization. Approximately 6 month prior to admission he developed classic angina, which gradually increased in severity and occurred with minimal levels of exertion. On 2/18, he developed angina at rest. Cardiac catheterization (3/4) showed: 1. distal LAD graft stenosis; 2. occlusion of his RCA graft; 3. patent LCX graft.

An ambulatory VEST study (Fig. 12) was performed with 30 minutes of continuous recording. While walking from his bed to the bathroom, he had a normal rise in ejection fraction from 50 to 60% (his baseline ejection fraction by gated scan was 50%). On returning to his room, he received a telephone call and, while talking quietly on the telephone, he had a remarkable decrease in ejection fraction, without accompanying chest pain. This study suggested on stability of ventricular function, with bolus of silent ischemia.

**Fig. 7.** Time activity curve from the left ventricular region of interest showing the various phases of cardiac cycle. The left time activity curve is illustrated from frame mode acquisition and right time activity curve is from list mode acquisition.
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Fig. 8. Representative recording of the beat to beat left ventricular time/activity curve and electrocardiogram from a patient with sinus rhythm. Each marker at the bottom represents 1s.

Fig. 9. A representative display of 30s averaged volume curve (dots) and the fitted curve (line) (top), average electrocardiogram (middle) and RR interval histogram (bottom).

TABLE 1

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<th>Relationship and diastolic function parameters to the left ventricular ejection fraction in 23 patients.</th>
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<td>EF</td>
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All values are expressed as mean ±SD. EF, left ventricular ejection fraction; HR, heart rate; CO, cardiac output; PER, peak ejection rate; PFR, peak filling rate; AFR, average filling rate; ASF, average slow filling rate; %FFF, percent fast filling fraction; %SFF, percent slow filling fraction; EDV, end-diastolic volume.

*EF value in normal subjects is 58±14%
Discussion

Radiopharmaceuticals

The radionuclide ventriculography with Tc-99m labeled red blood cells (RBCs) has been used with a modified in-vivo technique. With this technique, labeling efficiency was described to be 90 percent (Pavel et al. 1977).

These radiopharmaceuticals should ideally be maintained at a constant concentration in the blood pool during the interval of measurement.

Another note, Tc-99m RBC had been commonly used before the establishment of procedure, which apply to the red blood cells labeled with Tc-99m. However, Tc-99m RBC has the disadvantage of two injection and waiting times of more than 30 minutes. Tc-99m human serum albumin bound with diethylenetriamine-pentaacetic acid (DTPA-HSA) is a more stable radiopharmaceutical labeled with Tc-99m, and provides the short waiting period after injection (Hnatowich et al. 1982; Shirakami et al. 1987; Nishimura et al. 1989).

Radionuclide ventriculography

〈Data acquisition and imaging〉

The acquisition and display of the gated and first pass studies are also different. The first pass method may use gated or ungated techniques. The gated method uses a physiologic marker, or trigger, usually the R wave of the electrocardiogram, as the gating device (Papapietro et al. 1981). One cardiac cycle is divided into equal portions (generally 16 to 32). In the clinical application, a framing interval of approximately 40 milliseconds is used at rest, and 25 milliseconds during exercise (Bacharach et al. 1979). Further, the computer algorithm can be set to exclude beats that fall beyond a preset criteria of the predetermined R-R interval. Based
on this technique, our data was cut the last 2 frames. The acquisition can be proposed in one of two forms, either the frame mode or the list mode. In the clinical setting, the list mode acquisition is not commonly used because it requires a large computer storage capacity and accelerative processing of numerous nuclear data points. In the next step, data collections were derived from the forward or backward collection. Under the investigation of systolic function, the frame mode acquisition and forward collection can be allowed with the radionuclide ventriculography. If the investigators try to study the diastolic function, the list mode gated equilibrium is the best method for measuring left ventricular diastolic function. With regard to the gated equilibrium technique, the frame mode acquisition has two major problems; it does not allow rejection of bad beats (e.g., VPC), and it does not allow evaluation of the terminal phase of diastole. In most frame mode acquisitions, there is a rapid fall-off during the terminal part of diastole, which is a function of the alteration in the heart rate. As another note, the list mode acquisition has the advantage of constructing a forward frame curve similar to that of the frame mode, as well as a backward frame curve, to allow completion of the late diastolic characteristics performance.

<Correlation between the VEST and gamma camera-acquired left ventricular ejection fraction.>

Initial studies determined that a background/scatter correction of 70% of the end-diastolic counts produced VEST-EF values that best correlated with those obtained by conventional camera acquisition (Tamaki et al. 1987). Wilson et al. (1983) reported a correlation coefficient between the VEST and gamma camera-acquired left ventricular ejection fraction of \( r = 0.95 \) for supine and standing studies. Further, the present data demonstrates a correlation coefficient between the VEST and gamma camera-acquired left ventricular ejection fraction of \( r = 0.90 \) for supine studies.

The correlation of EF with the VEST and gamma camera calculated methods during each stage of graded bicycle exercises in 10 normal volunteers was \( r = 0.86 \) (Tamaki et al. 1988). Breisblet et al. (1988) reported that the correlation of VEST ejection fraction with radionuclide angiography in 18 patients with post myocardial infarction was 0.975.

<Measurement of systolic/diastolic function>


There are potential pitfalls in the use of radionuclide ventriculographic methods to evaluate left ventricular filling, and prerequisite technical considerations must be borne in mind, including acquisition methods, framing rates, temporal smoothing effects, normalization parameters, and the influence of heart rate, e.g., EDV/sec creates a “diastolic” index that is influenced markedly by the ejection fraction. Such effects must be considered
when comparing patient groups or assessing the effects of intervention.

The peak filling rate (PFR) is the most widely applied parameter of diastolic function, and is often viewed as an index of LV compliance. The time to peak filling rate (TPFR) is the time from end-systole to the time of PFR. This parameter is viewed as an index of relaxation. The average filling rate (AFR) integrates the filling events that occur during the early, rapid filling phase. The atrial contribution of LV filling quantifies the late increment in ventricular count activity attendant to atrial systole.

Left ventricular diastolic function is altered in disease states characterized by left ventricular hypertrophy, and impaired rapid filling has been demonstrated by radionuclide ventriculography in over 70% of patients with hypertrophic cardiomyopathy, despite the common observation of normal or supranormal indices of systolic function (Bonow et al. 1983, 1985). Accordingly, efforts have focused on the development of non-invasive methods to determine the diastolic properties of the left ventricle (Friedman et al. 1986).

Patients with coronary/non-coronary heart disease were confirmed by impairments in rapid filling using the ambulatory ventricular function monitor (Ishibashi et al. 1989b; Ishibashi et al. 1990). Thus, the VEST can provide information related both to the rate and temporal partitioning of the left ventricular filling events (Ishibashi et al. 1989b; Ishibashi et al. 1990).

Regional diastolic dysfunction in coronary artery disease appears to be caused by an incomplete inactivation of the myocardium in underperfused areas. The alteration in diastolic behavior of the left ventricular mass, such as asynchronous diastolic wall motion, prolongation of isovolemic relaxation, reduced peak filling rate, and a shift of the pressure-volume relaxation, are likely to be the direct consequences of an impairment in regional myocardial relaxation. In addition, the alterations in dynamic ventricular compliance that are evident during severe ischemia, and even in the basal state when large myocardial areas are underperfused chronically, appears able to limit the functional capacity of these patients.

〈Assessment of ischemia〉

The fall in EF preceded the angina by 30-90 seconds, confirming data established by echocardiography during PTCA-induced myocardial ischemia (Wohlgelernter et al. 1986). Analysis of the data to determine the subjects' activity at the time of the fall in ejection fraction revealed that most of the patients were sitting quietly. This representative observation in our data suggests that the majority of ischemic episodes were not due to an increase in myocardial oxygen demand, but rather a decrease in supply.

With respect to the Holter electrocardiogram, many reports (Stern et al. 1974; Schang et al. 1977; Deanfield et al. 1983; Stern et al. 1988a; Stern et al. 1988b) have described a "silent" myocardial ischemia. Cohn (1987) reported that there were 1 to 2 million totally asymptomatic middle-aged men, 50,000 new cases of post-infarction silent ischemia per year, and 3 million patients with angina who also have frequent episodes of silent ischemia. In addition, large numbers of people with silent myocardial infarction have been identified in the Framingham Study and other series. Many of these individuals with silent infarctions may also turn out to have active, but painless, myocardial ischemia.

Shang et al. (1977) reported that the episodes of asymptomatic ischemic type ST-T depression occurred more frequently than angina during the usual daily activities and were evident at heart rates
and activity levels well below those expected to evoke ischemia. There may be other factors that cause angina.

Silent myocardial ischemia is frequently observed during exercise testing. ST depression, without accompanying pain, was detected in 50% of 540 patients who had a positive result during the Bruce protocol treadmill test (Weiner et al. 1987b).

Gottlieb et al. (1986) described that silent ischemia occurred in more than half of the patients admitted to the coronary care unit with a diagnosis of unstable angina, despite an intensive medical regimen that was sufficient to control symptoms in most of these patients. Further, the mean LVEF was somewhat lower in the patients with silent ischemia than in those without it (56±13% vs. 64±13%, p<0.05). Although the EF did not contribute additional prognostic information in the presence of the silent ischemia variable, one may speculate that this finding reflects the presence of a “stunned” or “hibernating” myocardium, presumably secondary to subclinical myocardial hypoperfusion (Stern et al. 1974). Although serial measurements of EF to confirm this hypothesis were not available, there were no differences in the other indexes that could easily explain this difference between the two groups.

**Conclusion**

It should be emphasized that for clinical evaluation and management purposes, qualitative assessment of regional wall motion by experienced readers and calculation of ejection fraction, at rest and during exercise, remain the most powerful clinical applications of radionuclide ventriculography.

The major advantage of the nuclear stethoscope is as a nonimaging device for the “bedside” and “in-hospital” quantitation of left ventricular function. To investigate the left ventricular function during daily activity, the ambulatory ventricular function monitor should be used to enhance the value of the nuclear stethoscope. Also, the investigator may analyze the relationship between cardiac function, using radionuclide techniques, and myocardial imaging using the new radiopharmaceuticals (Jain et al. 1988; Kishimoto et al. 1989, 1991).

Several limitations of the VEST technique should be addressed. First, compulsive attention must be made during the fixation of the detector and VEST garment to ensure the integrity of the data acquisition. In most instances, motion artifacts can be detected by reviewing the data for unanticipated changes in global count rate, or displacement of the detector from the left ventricular blood pool on the final static image. Second, the 70% “background” was established empirically, and may not be applicable to all patients. It suggests that the VEST provides the correct ejection fraction in >95% of patients when backgrounds ranging from 65-72% are used. Finally, this non-imaging modality provides no data on regional wall motion. As such, this technique will probably have little role for CAD detection. It is a consensus that exercise/redistribution thallium scintigraphy (Phost et al. 1977) is the preferable technique for this indication. Alternatively, this technique provides information regarding the functional impact of ischemia on left ventricular systolic performance, and thereby important prognostic data.

Despite these caveats, it is our contention that the ambulatory ventricular function monitor is an important addition to the armamentarium of non-invasive techniques available for the quantitative description of cardiac performance. Its application in the “outpatient” setting provides a unique opportunity to expand
our understanding of systolic and diastolic performance in both coronary (e.g., "silent ischemia") and non-coronary artery disease (valvular diseases or hypertrophic cardiomyopathy).

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