Non-imaging nuclear monitoring of left ventricular function: twenty-five years of technical development and clinical experience

Santo Dellegrottaglie, Pasquale Perrone Filardi, Leonardo Pace*, Maria Paola Ponticelli, Luigi Corrado, Maria Cafiero, Michele Polimeno, Roberta Camerino, Massimo Chiariello

*Department of Clinical Medicine, Cardiovascular and Immunological Sciences, *Institute of Nuclear Medicine, University "Federico II", Naples, Italy*

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Although the first non-imaging nuclear probe for clinical application was already available 25 years ago, this technique is still underused for the assessment of ventricular function. Over the years substantial technological progress rendered nuclear probes more accurate and easier to use, and so far the applicability of these devices has been evaluated in several experimental and clinical contexts. Bedside devices can be used in the evaluation of hemodynamically unstable patients and of drug therapy. In patients with several heart diseases, particularly with ischemic cardiomyopathy, accurate information on the changes in ventricular function occurring during routine activities, as well as during structured activities, can be provided using the ambulatory probes. This review will focus on the development and clinical application of these diagnostic tools.

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Address:

Dr. Pasquale Perrone Filardi

Divisione di Cardiologia
Università degli Studi "Federico II"
Via S. Pansini, 5
80131 Napoli
E-mail:
fpperron@unina.it

Introduction

The concept of a device that provides a continuous measurement of left ventricular function using a non-invasive approach is theoretically attractive for clinical cardiologists. In 1976 Wagner et al.[1] introduced the "nuclear stethoscope", the first non-imaging nuclear probe available for clinical application. The initial instrument was bulky and inaccurate, but during the last 25 years important technical developments have been made and today both devices for bedside (stationary) use and for the ambulatory monitoring of left ventricular function are available for the cardiologist.

The purpose of this review was to analyze current skills and clinical applications of non-imaging nuclear devices.

Bedside nuclear probes

Instrumentation. The nuclear stethoscope (Bios Inc., Valhalla, NY, USA) was a device designed for the repetitive measurement of left ventricular function and consisted of a sodium/iodide detector affixed to a single bore converging collimator with a 6-cm field of view[1,2]. In this technology an excellent temporal resolution (10 ms) replaced the high spatial resolution which is required to produce images in the gamma camera studies.

The instrument, as initially manufactured, showed important practical limitations and was not designed for continuous use since the relatively heavy and cumbersome probe must be manually held in position on the patient's chest (the probe is arranged on a free-swinging mechanical arm), clearly an impractical proposition for a routine clinical study lasting several hours[3-5].

In the '80s intense efforts were made to develop more manageable devices, and an initial trend of research has been directed towards solid state devices (such as cadmium/telluride and mercury/iodide detectors), able to resolve important technical problems, i.e. low energy resolution, brittleness and high cost of production[6-8].

In 1991 Broadhurst et al.[9] presented the "Cardioscint" (Oakfield Instruments Ltd., Oxford, UK), a miniaturized probe consisting of a cesium/iodide scintillation crystal optically coupled to a photodiode, fixable to the chest with an elastic belt and equipped with a single-lead ECG for analysis of the ST segment. The elastic belt and low-weight detector (140 g) cause minimal inconvenience to the patient.

The detector is interfaced to a personal computer that allows on-line analysis and

data display of the variables of left ventricular function (ejection fraction, end-diastolic volume and end-systolic volume, peak filling rate) and ST-segment deviation. Data are presented in real time either as gated-summed or as beat-to-beat high temporal resolution (10 ms) time-activity curves. Results can be reviewed as a trend on the screen or stored on disk for later review[9-11].

These devices are manually positioned on the patient's chest wall: initially the probe is placed over the cardiac apex and is then moved slowly away from this position, thus allowing the physician to observe the beat-to-beat time-activity display until maximum stroke counts are achieved. This procedure was facilitated by a computerizing "positioning algorithm", which continuously displayed the stroke count/average count ratio as a dynamic bar graph on the screen[9,10].

Over a wide range of ejection fractions (31 to 76%), Breisblatt[11] reported an excellent correlation between the Cardioscint detector and the gamma camera (r = 0.94) in patients with and without regional wall motion abnormalities. Nevertheless, above all because of the difficult positioning, several investigators reported unsatisfactory results with the bedside probes[3,11-13].

Clinical applications. Serial bedside evaluations of left ventricular function can be important in the monitoring and treatment of patients with myocardial ischemia.

In patients with unstable angina Breisblatt et al.[14,15] had demonstrated that non-imaging nuclear detectors can be used to evaluate the effect of intravenous nitroglycerin and thus to optimize therapy. Additionally, monitoring of ventricular function in patients after coronary bypass surgery can be used to assess the frequency and severity of postoperative ventricular dysfunction and the time course of its recovery[16]. Other studies have pointed out the usefulness of non-imaging detector systems in the operating room (during anesthesia induction) and coronary care unit for the non-invasive assessment of ventricular function that can be used to make diagnostic decisions and monitor therapeutic modalities[17].

Particularly, in the evaluation of patients after coronary angioplasty, functional monitoring may identify coronary re-occlusion[18]. In a study performed with the Cardioscint, 12 patients who underwent successful angioplasty were evaluated with the probe for a mean of 280 ± 35 min. Only 4 patients demonstrated substantial changes in the ejection fraction during the monitoring period: in 2 patients there was significant improvement early after angioplasty; one patient had two episodes of a transient reduction in the ejection fraction (ischemia); one patient demonstrated improvement that returned to baseline over the monitoring period (in this patient a re-occlusion was identified at follow-up angiography)[19].

Yet, after the initial enthusiasm, the important technical limitations of bedside probes have determined the disuse of these instruments.

Limitations. Blind positioning (without gamma camera control) of the bedside detectors is an advantage but also a critical step[11]. If the detector is placed at the edge of the ventricle, it moves in and out of the detector's field of view during the cardiac cycle, leading to an overestimation of the ejection fraction. Besides, there are more difficulties in correct probe positioning and measurements in patients with wall motion abnormalities because an akinetic or hypokinetic region of the left ventricle would contribute little to stroke counts and thus easily be excluded from the detector's field of view when the detector is positioned over the left ventricle.

Moreover, it has been indicated that an improper background correction can be the "Achilles' heel" of the bedside nuclear probes which do not monitor the actual changes in background activity during recording[10]. To correct for the activity originating from extracardiac regions, the operator has two options with the Cardioscint: at any time during recording he can push a button on the control panel and thus subtract 75% of the end-diastolic counts (*automatic background correction*); alternatively, the operator can try to make an actual measurement of the background activity by moving the detector to an inferolateral paraventricular region between the left ventricular apex and the spleen and can use the recorded activity as background (*manual background correction*). The modality of background correction has a different impact on the accuracy of measurements. In fact, Lindhardt et al.[10] reported a better agreement between the Cardioscint and gamma camera left ventricular ejection fractions using automatic background correction (r = 0.82) compared with the manual method (r = 0.50).

Ambulatory nuclear probes

Instrumentation. The most relevant applications of non-imaging nuclear monitoring derive from the introduction in 1979 of a new instrument, capable of continuously evaluating, in a Holter-like fashion, the patient's ECG and ventricular functions during his daily activities[20]. This device, of which numerous versions have been developed, consisted of two radionuclide detectors and a Holter ECG recorder that was carried in a vest-like garment, hence its name the "Vest" (Capintec Inc., Ramsey, NJ, USA)[21]. Current instruments generally consist of a low weight apparatus in which a main detector, placed in such a way as to monitor the left ventricular activity, is provided with a single sodium/iodide crystal and a high sensitivity parallel-hole collimator, whereas an auxiliary small cadmium/telluride detector, with a flat-field collimator, monitors the background activity from the right lung (the latter detector is not present in all versions)[22-25]. Moreover, Taki et al.[26] have proposed the "CdTe-Vest" (Aloka Inc., Tokyo, Japan), a light-

weight miniature device in which a left ventricular cadmium/telluride detector is equipped with a straight bore collimator.

A semirigid vest-like plastic garment is used to maintain the detector in a fixed position on the chest wall, and ECG electrodes are positioned in such a way as to record a 1 to 12-lead ECG. The plastic garment consists of the same material used to make masks for radiation oncology, and the detectors are attached to the garment by a series of screws embedded in the plastic[25-27]. In the first version, the weight of the entire apparatus, with the electronic equipment placed in a backpack, was 5.5 kg. Subsequently, technical developments provided lighter devices with a weight of about 3 kg.

After a conventional gated blood pool scan with ^{99m}Tc-labeled red blood cells for the baseline definition of left ventricular function, the ventricular detector is settled over the left ventricular blood pool, using the scintillation camera to optimize the detector positioning. The lead shielding around the detector appears as a negative area on the screen of the oscilloscope and the positioning process is repeated by translating or angling the detector until the appropriate position is obtained. Static gamma camera images are acquired before and after the ambulatory protocol to determine if there is any change in the position of the Vest detector during the monitoring period. Compared to the variable region of interest employed with the gamma camera[23,24], a single fixed region of interest is used for data acquisition. The background detector is placed over a right mid-lung field.

During a Vest study the continuous radionuclide and ECG data are recorded on a modified Holter style cassette tape over periods lasting up to 6 hours. As opposed to the real-time on-line assessment which can be obtained with the bedside probes[11,23], data analysis is performed exclusively off-line (the tape is read into a minicomputer). Besides, in the CdTe-Vest all data are transferred directly to a personal computer and may be stored in a 3.5-in floppy disk[26].

The beat by beat radionuclide and ECG data are analyzed for: heart rate; ejection fraction; end-diastolic volume; end-systolic volume (expressed relatively to the initial end-diastolic volume); relative cardiac output; peak filling rate (expressed as end-diastolic volume/s) and ST segment changes[24,25] (Fig. 1).

The background scatter is determined by matching the Vest ejection fraction values to those obtained using the gamma camera (in several studies a fixed scatter correction of 70% of the end-diastolic counts had produced good results)[22,23,27]. Data analysis with the R wave of the ECG facilitates summation of multiple beats to generate an average time-activity curve and ECG during intervals of 10-60 s[28,29] (Fig. 2). The variables are graphically and numerically displayed for analysis. Generally, detector movement or instrument malfunction may be excluded if sudden shifts (> 10% deviation from a straight line) in the average count rate are not observed[21-23].

A number of investigators examined the accuracy and reproducibility of the Vest-derived left ventricular functional parameters. Wilson et al.[21] reported a correlation coefficient (r) between the Vest and gamma camera-acquired left ventricular ejection fraction of 0.95. Tamaki et al.[22] made a similar comparison in normal subjects and in patients with coronary artery disease,

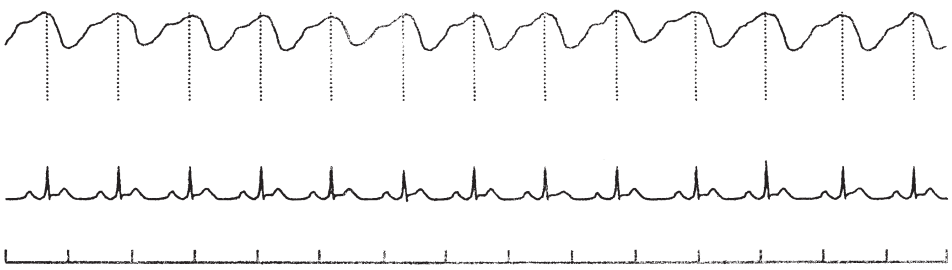

Figure 1. *Representative recording of the beat-to-beat left ventricular time-activity curve and of the 1-lead ECG.*

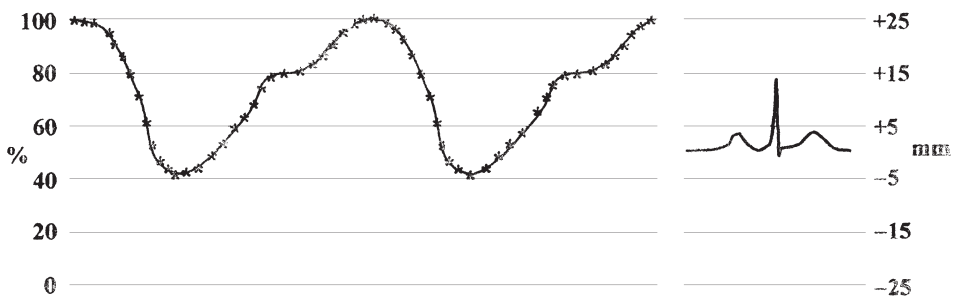

Figure 2. *Representative display of the 30 s averaged volume curve* (dots) *and the fitted curve* (line) (left panel) *and the averaged ECG* (right panel).

reporting a good correlation at rest (r = 0.92) and during bicycle exercise (r = 0.86) in the whole population. A study by Mohiuddin et al.[30] reported a correlation of 0.82 between Vest and left ventriculography, and of 0.91 between Vest and gamma camera in the measurement of the ejection fraction.

The Vest is also able to provide accurate data on the diastolic left ventricular function: the peak filling rate and other diastolic parameters (average filling rate, time to peak filling, percent of early rapid filling and percent of late filling) are obtained from the derivative of the left ventricular time-activity curve[31]. In a recent study by Cuocolo et al.[32] the correlation coefficient between the measurement of the peak filling rate obtained with radionuclide angiography and with the Vest was 0.88; moreover, the Vest assessment of the peak filling rate in the same patients on different days of observation also showed a significant correlation (r = 0.95).

Clinical applications. The nuclear Vest provides accurate information on the changes in left ventricular function during routine activities (such as sitting, walking, climbing the stairs, eating, etc.), as well as during structured activities (such as exercise, mental stress, isometric handgrip, cold pressor test, etc.) performed by the subjects during the monitoring period[21-26,33-36].

Analysis of physiological indices. The non-invasive nature of the nuclear probes renders this instrument ideal for the measurement of physiological parameters in normal subjects.

Flamm et al.[37] used two gamma cameras and the Vest system in 14 healthy volunteers and studied the changes in the regional body distribution of blood volume during upright bicycle exercise, documenting a marked blood volume shift from the legs and abdominal organs to the heart and lungs. Imbriaco et al.[38] evaluated the cardiac responses to exercise in normal subjects using the Vest and a combined analysis of pulmonary gas exchange. During the test, the ejection fraction, end-diastolic volume and stroke volume significantly increased, whereas the end-systolic volume significantly decreased in the period from rest conditions to the attainment of the anaerobic threshold ($p < 0.001$), showing no significant change in the period from the anaerobic threshold to the peak oxygen consumption (p = NS). These data suggest that during exercise the left ventricular performance is limited by the conversion of aerobic to anaerobic metabolism.

These applications of the nuclear Vest are intriguing, but certainly it is in pathological settings that this technology may be more useful (Table I).

Coronary artery disease. Tamaki et al.[23] monitored, with the Vest, for a mean of 2.6 hours 39 patients with coronary artery disease while they performed various daily activities, and documented 36 episodes of a transient decrease in the left ventricular ejection fraction (≥ 6% units lasting ≥ 1 min); 24 (67%) of these episodes were asymptomatic, and 19 (79%) of the asymptomatic episodes were not associated with ST-segment depression. Thus, more than 50% (19/36) of Vest-detected ischemic episodes were clinically and electrocardiographically silent.

The findings of this and other studies using the Vest in the detection of ischemia point out the high sensitivity of this technique in the identification of ischemic episodes during routine activity. In patients with coronary artery disease the Vest may quantify the ischemic burden and may diagnose silent myocardial ischemia more accurately than traditional Holter ECG monitoring[27,35,39].

The presence of residual ischemia in subjects with a recent myocardial infarction identifies a high-risk group[36]. In a study by Breisblatt et al.[40], ambulatory monitoring with Vest was performed during the Bruce exercise test, lunch, the cold pressor test, the mental test and routine activities. It was compared with exercise treadmill testing and stress thallium-201 imaging for the capacity of identifying myocardial ischemia in 35 patients early after an acute myocardial infarction. The results show that Vest monitoring significantly increased the accuracy of the exercise test and provided complementary information to thallium imaging in

Table I. Clinical applications of non-imaging nuclear probes.

Pathological context	Clinical applications
Coronary artery disease	- detection of ischemic episodes (with or without clinical and ECG signs) in stable patients during exercise or routine activity; - detection of residual ischemia during routine activity in the post-myocardial infarction period; - evaluation of left ventricular performance after coronary revascularization (percutaneous angioplasty or coronary bypass); - detection of ischemia in patients with non-evaluative stress ECG
Hypertrophic cardiomyopathy	- evaluation of the left ventricular performance during exercise
Clinical pharmacology	- evaluation of cardiovascular drug effects on left ventricular function
Electrophysiology	- evaluation of the left ventricular performance in an electrophysiological setting

identifying patients with residual myocardial ischemia. Then, nuclear monitoring of the left ventricular changes during different activities may contribute to the identification of post-infarction subjects with a poor prognosis. Kayden et al.[39] used the Vest to monitor 33 patients with a thrombolysed acute myocardial infarction while they performed routine activities at the time of hospital discharge; adverse cardiac events occurred in 8 of 12 (67%) patients with as opposed to 3 of 21 (14%) patients without episodes of left ventricular dysfunction ($p < 0.01$), underlying the prognostic relevance of the Vest data. Ventricular functional monitoring during routine activity provides accurate prognostic information and it allows one to avoid the exercise test in the post-infarction period. Unfortunately, at present no large-scale study has been performed to confirm these results.

In a study by Ferraro et al.[41] a small group of patients with coronary artery disease underwent a Vest study during daily normal activities 1 week before and 15 days after bypass surgery. During intense physical activity (climbing stairs) the ejection fraction, monitored with the Vest, decreased from 52 ± 8 to 47 ± 11% ($p < 0.05$) in the pre-surgical evaluation, whereas an analogous effort in the post-revascularization period caused an increase in the ejection fraction (47 ± 8 vs 52 ± 11%, $p < 0.05$). Thus, such a non-invasive procedure allows the evaluation of the consequences of coronary revascularization on left ventricular performance.

Finally, although it has not been documented, it is presumable that continuous ventricular monitoring may have an useful application in those circumstances when stress electrocardiograms are difficult to interpret, such as in patients with left bundle branch block, left ventricular hypertrophy, during digitalis administration, or in electrolyte imbalance.

Hypertrophic cardiomyopathy. Several studies have suggested that myocardial ischemia without significant coronary artery stenosis is common in patients with hypertrophic cardiomyopathy[42,43]. Taki et al.[44-46] have obtained interesting data using the CdTe-Vest in subjects with non-obstructive hypertrophic cardiomyopathy and without coronary artery disease. In a preliminary study they demonstrated that the CdTe-Vest was a useful tool for the evaluation of the left ventricular functional reserve to exercise in these patients; one-half of the 41 subjects studied had an abnormal left ventricular functional reserve at Vest evaluation during the exercise stress test[44]. In a subsequent study the patients underwent dobutamine stress echocardiography and CdTe-Vest monitoring during bicycle exercise: the change in ejection fraction during dobutamine echocardiography significantly correlated with the change during Vest ($r = 0.643$, $p < 0.0001$); regional wall motion abnormalities during stress echocardiography were documented more frequently (49%) in patients with a Vest-detected abnormal response to exercise (reduction > 5% of ejection fraction) than in patients with a normal response (16%)[45].

Exercise-induced ST-segment depression in patients with hypertrophic cardiomyopathy is common but its cause is still unclear. Taki's group monitored 53 patients with the CdTe-Vest during bicycle exercise. In the group of patients without post-exercise ST-segment depression, the ejection fraction increased from 65 ± 8 to 71 ± 11% ($p = 0.0002$), whereas in the group with ≥ 1 mm ST-segment depression, the ejection fraction decreased from 70 ± 7 to 59 ± 15% ($p < 0.0001$). These results suggest that the exercise-induced ST-segment depression observed in subjects with hypertrophic cardiomyopathy is associated with systolic ventricular dysfunction[46].

Thus, we can conclude that the nuclear Vest is useful for the assessment of the dynamic changes in left ventricular function during exercise in patients with hypertrophic cardiomyopathy.

Evaluation of drug effects on systolic and diastolic functions. These techniques may be utilized to assess the effects of cardiovascular drugs on left ventricular function.

In patients with mild or moderate essential hypertension and impaired diastolic function Cuocolo et al.[32] demonstrated that valsartan but not enalapril significantly improved left ventricular filling (expressed by Vest-detected peak filling rate) both at rest and during exercise after a 4-week treatment period. Considering that the changes in blood pressure and heart rate induced by the two treatments were strictly comparable, these findings support the hypothesis of an important contribution of the renin-angiotensin system in the control of left ventricular diastolic function in subjects with hypertension.

Using Vest monitoring before and during volume expansion in normal subjects (group 1) and in patients with idiopathic dilated cardiomyopathy and mild heart failure (group 2), Volpe et al.[47] reported that volume expansion increased the ejection fraction and peak filling rate in group 1 ($p < 0.001$), but not in group 2 (p = NS). After 6 to 8 weeks of oral treatment with enalapril the compromised adaptation to acute volume loading in the patients of group 2 was restored to normal. The study does not clarify whether this favorable effect of enalapril on left ventricular function can be specifically attributed to ACE-inhibition or whether it is common to other vasodilator compounds.

In patients with coronary artery disease Mohiuddin et al.[30] using the Vest during exercise documented an increase in the end-diastolic and end-systolic volumes with a reduction in the ejection fraction. Repeating the exercise after nitroglycerin or nifedipine administration, significantly ($p < 0.05$) lower values of end-diastolic volume and end-systolic volume, with increased values of ejection fraction in comparison to exercise without drug administration were ob-

tained. Hence, monitoring by the Vest can demonstrate that nitroglycerin and nifedipine improved cardiac function in an ischemic setting, showing the principal mechanism of action of these drugs in stopping ischemic episodes.

Evaluation of ventricular function during electrophysiological studies. The continuous hemodynamic monitoring by the Vest have demonstrated their applicability even in electrophysiological studies[48,49].

In a study of Mortelmans et al.[50] the ejection fraction, stroke volume and end-diastolic and end-systolic volumes were evaluated with the Vest in patients with a DDD pacemaker, while different atrioventricular delay values from 100 to 200 ms were programmed. A significant ($p < 0.05$) increase in the ejection fraction and stroke volume, with a decrease in the end-systolic volume was found at 200 vs 100 ms. Thus, evaluation of the Vest functional parameters allowed the determination of the optimal atrioventricular delay in patients with programmable dual-chamber pacemakers.

Limitations. The Vest is limited by the necessity of gamma camera positioning and, like all the other non-imaging nuclear probes, by the inability to evaluate segmental ventricular function. These aspects render this technology useless for the detection of regional ischemia in the absence of related changes in the global left ventricular ejection fraction[33].

Changes in the ejection fraction detected during the monitoring period must be interpreted with caution since events other than myocardial ischemia, such as changes in the preload and afterload may affect the ejection fraction values. Moreover, a constant position of the detector relative to the heart does not take the heart/chest wall movements into consideration and, although the relatively isosensitive field of view of the detector allows for some motion, changes in posture and respiratory movements may move the heart out of the detector's field of view[23,34]. Finally, in obese subjects, women, and patients with chronic obstructive pulmonary disease, the distance between the detector and source may increase and the ejection fraction may be overestimated[11,23].

Another important practical question derives from the consideration that currently the National Health System does not refund the cost of the procedure which is comparable to that of a conventional gated blood pool scan with ^{99m}Tc-labeled red blood cells (€ 103.24), considering the trivial additional cost of batteries and of a common tape cassette. Indeed, the cost is substantially higher compared with that of other techniques used for analogous clinical purposes (i.e., Holter ECG € 49.58; stress ECG € 44.62, stress echocardiography € 61.97), but may be justified by the peculiar clinical and prognostic information obtainable in selected clinical contexts (i.e., detection of silent ischemia) from continuous nuclear monitoring.

Conclusions

Non-imaging nuclear probes have been proven to be valuable tools for the repetitive or continuous measurements of left ventricular function. They have been successfully applied in different categories of patients providing important new information about cardiac systolic and diastolic function in several fields of cardiovascular pathophysiology.

However, although the devices for the continuous nuclear monitoring of ventricular function are mature for effective clinical applications, conclusive cost-effectiveness comparative studies with other non-invasive techniques are needed before the routine application of this technique can be advocated.

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