Clinical Validation of a Miniature Nuclear Probe System for Continuous On-line Monitoring of Cardiac Function and ST-Segment

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A new, miniature cesium iodide/photodiode nuclear probe (the "Cardioscint") has been developed for continuous on-line measurement of left ventricular function and the ST-segment. Ejection fraction (EF) measurements in 77 patients were compared with gated equilibrium radionuclide ventriculograms. The probe was positioned over the left ventricle by first using a blind positioning algorithm and then by using the gamma camera. Background was measured both manually and automatically. There was good correlation between probe (positioned blind) and gamma camera EF with both manual ($r = 0.80$, $n = 65$) and automatic ($r = 0.78$, $n = 66$) backgrounds. Use of the gamma camera did not significantly alter the results. Correlation between the probe stroke counts and thermodilution-derived stroke index during atrial pacing in six subjects was also satisfactory ($r = 0.69$, $n = 102$). Thus, the Cardioscint is able to provide a reliable estimate of EF and can track rapid changes in cardiac volumes.

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Several instruments are available for continuous left ventricular function monitoring based on nonimaging nuclear probe technology. Their high sensitivity allows rapid changes in cardiac function to be followed. The Nuclear Stethoscope (Bios Inc., Valhalla, NY) was not designed for continuous bedside use since the relatively heavy probe must be manually held in position on the chest (*1–4*), clearly an impractical proposition for a routine clinical study lasting several hours. The VEST (Capintec Inc., Ramsey, NJ), an ambulatory nonimaging probe, on the other hand, can be fixed to the patient's chest for several hours (*5–7*). Its disadvantages, however, include its weight and the requirement of a gamma camera to position the detector over the left ventricle.

What is required is a miniature lightweight device which can be positioned without the aid of a gamma camera. Previous attempts at this using cadmium telluride (*8,9*) and mercuric iodide crystals (*10*) encountered technical difficulties. A new technique of optically coupling a photodiode to scintillation detectors has now been realized (*11*). We have developed (in conjunction with Oakfield Instruments Ltd, Oxford, UK) a low-cost, miniature nonimaging cesium iodide/photodiode nuclear probe (Cardioscint), capable of continuous on-line monitoring of left ventricular function and the ST segment (*12*). It can be positioned over the left ventricle (using an internal algorithm) and held comfortably in place by an elasticated harness (Fig. 1) for up to 18 hr (depending on the dose of blood-pool labeling agent), thereby conferring the advantages of size and convenience.

Before such a system could be recommended for clinical use, it requires careful validation. We have compared the left ventricular ejection fraction (LVEF) as measured by the probe with that obtained during conventional gamma camera radionuclide ventriculography and also correlated the changes in stroke counts measured by the probe during atrial pacing with the simultaneous changes in stroke index as measured by thermodilution.

PATIENTS AND METHODS

Gamma Camera Group

Seventy-seven patients (55 male, 22 female) undergoing routine gamma camera radionuclide ventriculography were studied. Their mean age was 61 (range 27–86) yr. They were investigated for:

1. Chest pain or dyspnea of unknown origin in 26 cases.
2. Post-myocardial infarction status in 16 cases.
3. Preoperative cardiac status in 16 cases.
4. Cardiac failure status in 6 cases, and for miscellaneous

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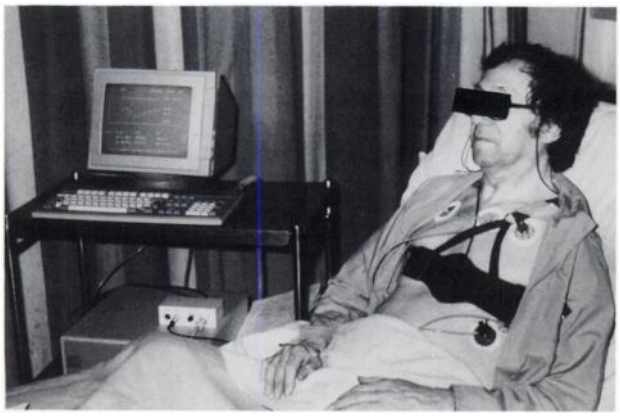

FIGURE 1
A patient wearing the Cardioscint; the probe is kept in place by a harness. The display unit and computer are also shown.

reasons in 13 subjects. One patient was in atrial fibrillation but otherwise all were in sinus rhythm.

Atrial Pacing Group

Six male subjects with a mean age of 53 (range 45–62) yr and a history of chronic stable angina were studied. Five patients had inducible myocardial ischemia on graded treadmill exercise ECG testing. At coronary angiography, three patients had triple vessel disease and three had single-vessel disease. None of the patients had clinically apparent tricuspid regurgitation. All anti-anginal medication (except short acting nitrates) was stopped at least 48 hr prior to the study. Informed consent was obtained in each case.

Instrumentation

The Cardioscint is a miniature (diameter 48 mm, height 39 mm, weight 140 g), nonimaging precordial nuclear probe which consists of a cesium iodide scintillation crystal (14 × 14 × 8 mm) with a 1-cm long-converging collimator optically coupled to a photodiode. This is interfaced with an Olivetti M240 personal computer with 640 Kbyte main memory, 8086 processor (8 MHz), 8087 co-processor, 20 Mbyte disk, and 360 Kbyte 5.25-in. diskette. Programs were written in Turbo Pascal V3.0 for speed and readability. Special purpose modules inside the computer consist of a low-noise pulse amplifier feeding a simple discriminator, a 12-bit 10-msec scaler interfaced to the Olivetti bus and ECG trigger hardware to provide a gating pulse resistant to signal interference. The detector resolution is <30% full width at half maximum (FWHM) for technetium-99m (^{99m}Tc) in water, using a 1-msec pulse shaping time. The valley between the noise and the ^{99m}Tc peak is <20% of the peak height. For Cardioscint use, the discriminator lower threshold is set at this valley point. Under these conditions, the system saturates at 80,000 cps, with a count loss of 9.5% at 20,000 cps. The field of view at 8 cm is 8 cm FWHM. The high sensitivity of the detector enables ECG-gated or beat-to-beat high resolution (10 msec) left ventricular time-activity curves to be continuously displayed. The ST-segment level is obtained from an averaged electrocardiogram. In "gated" mode, the ejection fraction, relative volumes, diastolic filling parameters and ST-segment level are automatically displayed at the end of each acquisition period (selectable from 10–300 sec). Results can be reviewed as a trend on the screen and/or stored on disk for later review. A retrieval program allows off-line listing of all ECG-gated variables: heart-rate, ST segment level, EF, relative volumes, peak ejection rate, ejection time, peak filling rate, time-to-peak filling rate, and a modified first one-third filling fraction. The first four of these can be displayed as a graphic trend plot either in absolute counts or after background subtraction. Correction for physical isotope decay can be optionally applied, allowing estimates of relative cardiac output to be listed. Hard copy printouts can be made of any part of the listed or trend plotted data.

Gamma Camera Studies

All patients underwent in-vivo blood-pool labeling with stannous pyrophosphate and 740 MBq ^{99m}Tc (*13*). The gated radionuclide scans were recorded using a mobile digital gamma camera (Apex 215m, Elscint (GB) Ltd, UK) in the supine position, in both anterior and left anterior oblique (best septal separation) views, the latter with 10–15-degree caudal tilt. The window of the gamma camera was set at 15% around a 140-keV ^{99m}Tc photopeak. A low-energy, general-purpose collimator was used to acquire 3 million counts in each view. The data were collected in 24 frame format and stored in a 64 × 64 matrix. The radionuclide cine ventriculograms were later assessed for wall motion abnormalities by an independent observer. Wall motion was scored as: normal or exhibiting only minor abnormalities (hypokinesia) or exhibiting major abnormalities (akinesia or dyskinesia). The LVEF was calculated using a semi-automatic edge-detection technique (*13*).

Positioning the Probe Without Gamma Camera Supervision. Immediately after the camera acquisition the probe was used to assess LVEF, the operator (PB) being unaware of the radionuclide ventriculographic result. The probe was placed initially over the cardiac apex, in a left anterior oblique plane with ~10-degree caudal tilt. The probe was then moved slowly away from this position, observing the "beat-to-beat" time-activity display, until maximum stroke counts were achieved consistent with minimum average counts. This procedure was followed in order to avoid right ventricular activity and was facilitated by a positioning algorithm in the computer which continuously displayed the stroke count/average count ratio as a dynamic bar graph on the screen. Care was taken not to move the detector inferiorly so far as to cause a falloff in counts, which would represent a move off the left ventricle. When the operator was satisfied with the position, the skin was marked. Background counts were obtained using an automatic estimate equivalent to 74% of end-diastolic counts. The probe then monitored left ventricular function for ~2 min in the "gated" mode, utilizing six acquisitions of 20 sec. The mean EF over this period was noted.

Following this, a manual background (MBkg) was estimated by gradually moving the probe away from the left ventricle inferolaterally, so as to sample background counts from a paraventricular region. This was deemed to be the position in which cardiac activity could just be detected, stroke counts being at a minimum. The average counts at this position were then stored to represent "MBkg", the probe returned to its original left ventricular position and EF estimated as before.

Positioning the Probe Under Gamma Camera Supervision. The gamma camera was then positioned over the precordium

in the left anterior oblique position (in order to best separate the ventricles) and the left ventricle was identified on the persistence image. The probe was placed over the silhouette of the left ventricle, taking care to minimize parallax, and the EF measurements were repeated, using first automatic and then manually selected background counts.

Twenty patients underwent an identical assessment by a second operator (PC), who was unaware of the results obtained either by the first operator or from the gamma camera radionuclide ventriculogram. Care was taken to keep the patient still throughout the study to minimize hemodynamic changes.

Atrial Pacing Studies

The atrial pacing studies were all performed mid-morning in the fasted state. A temporary pacing catheter (size 6FG) was passed to the right atrium using the percutaneous Seldinger technique. A triple lumen, thermistor-tipped Swan-Ganz (size 7FG) catheter was then introduced into the pulmonary artery using the same technique. Where possible, identical ECG lead positions were used to those showing maximal ST changes during the exercise test. After 60 min rest to achieve hemodynamic stability, blood-pool labeling with 740 MBq ^{99m}Tc was performed as described above. The nuclear probe was positioned over the left ventricle as in the earlier validation study (but this time without the aid of the camera), and a manually selected background was used to measure EF. A 20-sec acquisition time was used in all cases and the data were recorded in "gated" mode.

Cardiac output was then measured by thermodilution (Marquette Series 7000 monitor) and stability was considered to be achieved when three consecutive measurements agreed within 15%.

The patients then underwent a continuous pacing protocol, starting at 20 bpm above the resting heart rate and increasing by 10 bpm every 2 min until moderate angina or age-related maximum heart rate was reached. Heart rate, cardiac output, and ST-segment changes were measured every minute, as well as simultaneous probe measurements of EF and cardiac volumes. Blood pressure was measured every 2 min. Measurements were continued every minute for 5 min during recovery and at 10 min post-pacing.

Data Analysis

Gamma Camera Validation. Linear regression and/or difference analysis was performed on the following groups of measurements:

1. Gamma camera versus probe-derived EF measurements.
2. The "error" (i.e., the difference between the probe and gamma camera EF) versus the numerical order in which the studies were performed. The operator's experience in the use of the probe system obviously increased during the study, so this analysis was intended to highlight any 'learning curve' associated with the technique.
3. The EF as obtained by the first operator versus the second operator in order to estimate the reproducibility of the probe measurements between observers.

Atrial Pacing Validation. Background corrected probe-derived stroke counts and a thermodilution-derived stroke index were calculated immediately prior to pacing. Percentage changes were calculated relative to baseline (stroke counts being decay-corrected) and regression analysis was performed, both for individuals and for the group.

RESULTS

Gamma Camera Studies

The mean EF of the group, as measured by gamma camera radionuclide ventriculography was 47% (range 16%–76%). In three subjects, later found to have EFs of 17%, 22%, and 23% an adequate time-activity curve could not be distinguished using the probe. The mean (s.d.) EF of the remaining 52 males was 47% (16) and for females 50% (14), the difference between the sexes not being statistically significant. In five subjects, with a mean EF of 37% (range 17%–59%), an adequate time-activity curve could only be detected after the gamma-camera had been used to place the probe. In three patients, the manually derived background counts were greater than end-systolic counts (but a satisfactory automatic background was obtainable), and in a further two patients the automatically derived background counts were greater than end-systolic counts (but a satisfactory manual background was obtainable). In an additional eight patients, one or more of the probe EF measurements was not made for logistical reasons.

Figure 2 shows the correlation between EF as measured by the probe positioned "blind" and by gamma

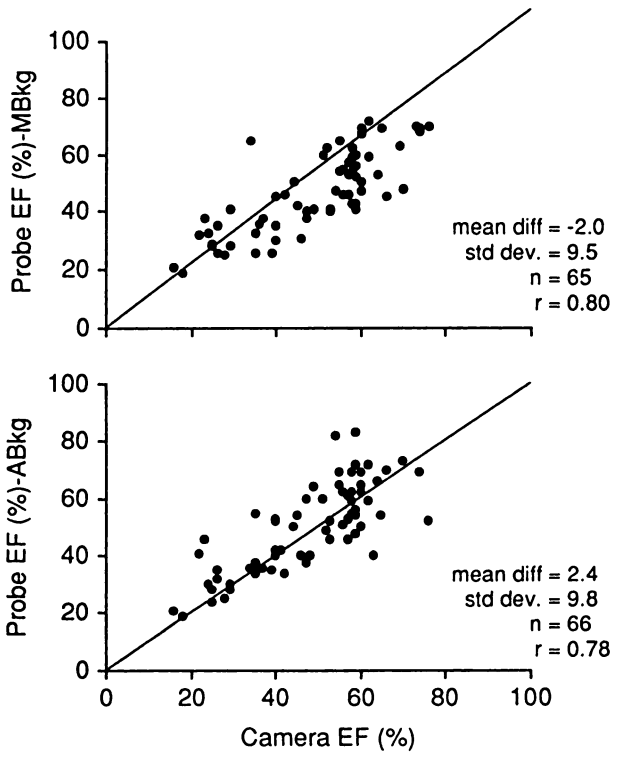

FIGURE 2
Gamma camera ejection fraction (X-axis) plotted against Cardioscint ejection fraction (Y-axis). The latter is positioned without camera supervision and utilizes automatic (ABkg) and manual (MBkg) backgrounds.

camera radionuclide ventriculography. The mean difference between the two methods was 2.4% (9.8) using an automatic background (ABkg) and −2.0% (9.5) using a manual background, i.e., the probe tended to overestimate ejection fraction using an automatic and underestimate it using a manual background. When the gamma camera was used to aid placement of the probe, the results were broadly comparable (mean difference 2.8% (8.6) (automatic), −3.2% (9.3) (manual); p = ns with respect to "blind" positioning). The probe measured the EF as accurately in individuals with wall motion abnormalities as in those with normal wall motion (e.g., for camera positioning of the probe, Figures 3 and 4). Despite the difficulty in moving the detector over the female precordium (because of breast tissue), the probe proved as accurate in women as in men. This was not because of any difference in the degree of left ventricular dysfunction between the sexes (mean EF in males was 47% and in females, 50%). However, the women had a mean (s.d.) antero-posterior ribcage diameter of 19.9 (2.4) cm compared with 23.3 (2.3) cm in the men ($p < 0.001$).

The difference between the measurements obtained by the probe and the gamma camera could be regarded as the "probe error." There was, however, no relationship between this error and the order in which the studies were performed ($y = 0.07x + 0.76$, $r = -0.17$, p = ns; where y = error in percent and x = patient number), suggesting that there was no significant "learning curve" to overcome.

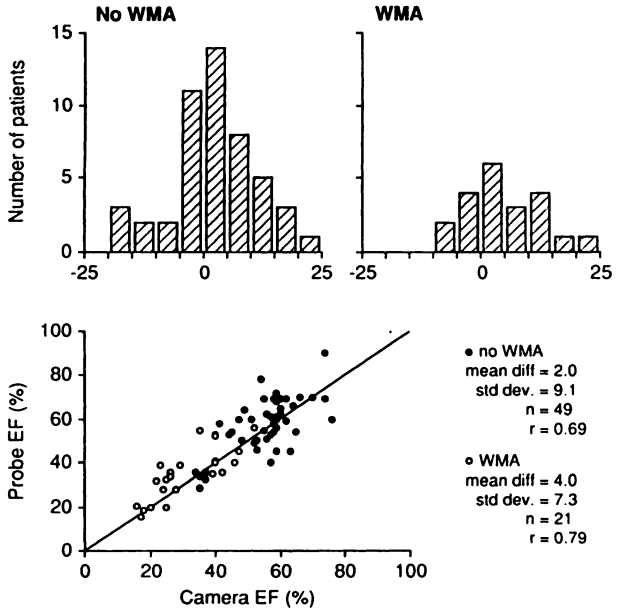

FIGURE 3
Gamma camera ejection fraction plotted against Cardioscint ejection fraction. The latter is positioned under camera supervision and utilizes an automatic background. The effects of wall motion abnormalities (WMA) are demonstrated. Differences in ejection fraction between the two methods are also shown as a frequency histogram.

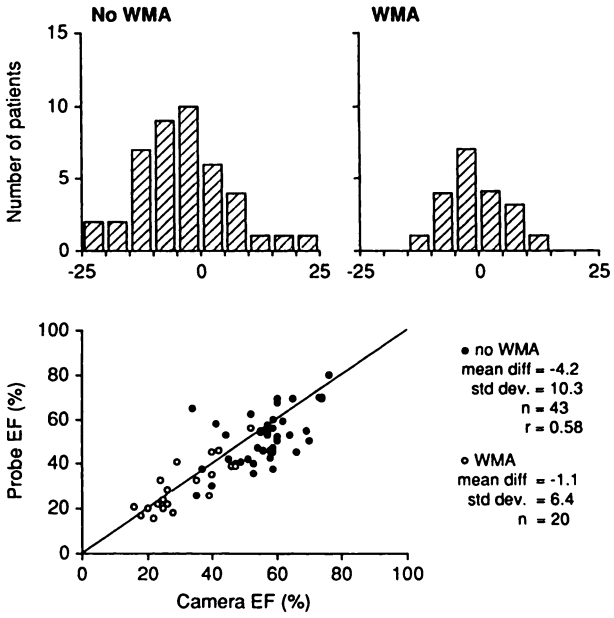

FIGURE 4
Gamma camera ejection fraction plotted against Cardioscint ejection fraction. The latter is positioned under camera supervision and utilizes a manual background. The effects of wall motion abnormalities (WMA) are demonstrated. Differences in ejection fraction between the two methods are also shown as a frequency histogram.

The results of the dual-operator studies are shown in Table 1. One operator estimated a higher EF than the other when positioning the probe "blind." The difference between the two observers was greatly reduced when the gamma camera was used to position the probe.

Atrial Pacing Studies

The details of the atrial pacing tests for individual patients are given in Table 2 along with the correlation coefficients obtained by comparing the change in probe stroke counts with the change in stroke index. The result for the whole group is shown in Figure 5. The patient who gave the poorest results (JB) had a particularly unstable probe position and poor blood-pool labeling. A more representative study is shown in Figure 6.

DISCUSSION

The concept of a device that provides continuous online information on left ventricular function at the bedside using noninvasive means is attractive. We considered that development of the principles underlying probe technology may allow this concept to be realized. We principally concentrated on miniaturization of the detector, using a cesium iodide crystal and a solid-state photodiode. The use of a personal computer containing

TABLE 1
Difference in Measurement of Ejection Fraction Between Two Observers Using the Probe

Positioning	Background	Mean difference (%EF)	s.d.	No. studied
Blind	Manual	−6.6	9.9	17
	Automatic	−0.7	9.0	19
Camera	Manual	−2.8	5.6	19
	Automatic	−0.3	6.2	20

s.d. = standard deviation.

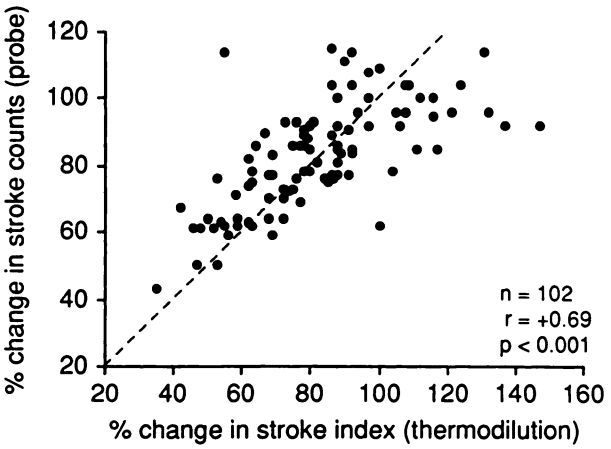

FIGURE 5
Percentage change (relative to baseline) in Cardioscint stroke counts plotted against the corresponding percentage change in thermodilution measured stroke index.

the special purpose modules also facilitated a relatively low cost system.

Such a system may be applied to coronary care, intensive care and anesthetic situations but it may also prove useful in clinical research. It has been demonstrated that changes in left ventricular function and volume precede symptoms and electrocardiographic signs of myocardial ischemia (*14*). On-line monitoring may thus provide early indication of acute myocardial ischemia. A further advantage may lie in the observation that not all patients with myocardial ischemia display electrocardiographic manifestations (*15–17*). This poses a diagnostic problem for the clinician, but if chest pain is shown to be accompanied by reversible changes in left ventricular function, then the diagnosis of angina may be made with more confidence. Conversely, not all ST-segment changes are due to myocardial ischemia (*18*). The potential to optimize cardiac function and volumes using inotropes or vasodilators in patients with serious cardiac disease may be realized. In this era of thrombolysis, invasive information on cardiac function is only obtainable at considerable risk (*19*) so a noninvasive approach is particularly attractive. Finally, the low cost of the system may make it affordable in developing countries.

The results from this study demonstrate that the Cardioscint is able to measure LVEF with a reasonable degree of accuracy, and over a wide range of ventricular function. Our results also agree with those of Berger (*2*) and others who found no loss of accuracy when using the Nuclear Stethoscope to measure EF in females and in patients with wall motion abnormalities (*20*). However, some authors (*21*) have found relatively poor correlation between the Nuclear Stethoscope and gamma camera in patients with regional asynergy, but the explanation may be related to the degree of operator experience in performing studies. In fact, our results suggest that low EFs are measured more accurately than higher values. This observation however is not surprising when one considers the mathematical consequences of a small error in numerator or denominator (i.e., stroke counts or end-diastolic minus background counts) on their ratio (i.e., EF). Thus, measurement errors with the probe are likely to have a more pronounced effect on the EF when the value is high rather than low. In patients with wall motion abnormalities

TABLE 2
Details of Individual Atrial Pacing Tests

Patient	Basal HR	Peak HR	Pacing time (mins)	Basal EF%	Peak EF%	Basal SI	Basal SCts	Peak SI	Peak Scts	'r'
MD	79	171	28	65	34	32	22	15	11	0.88
KT	107	171	22	57	46	38	25	26	16	0.79
JB	87	150	25	34	32	35	13	27	9	0.32*
JG	85	160	24	62	66	50	27	27	17	0.76
JC	66	150	25	55	53	52	28	18	12	0.92
AL	69	160	29	74	79	58	29	31	22	0.65
mean	82	160	25.5	58	52	44	24	24	14	

Pt = patient, HR = heart rate, EF = ejection fraction, SI = thermodilution stroke index (ml/m^2), SCts = probe stroke counts per 10 msec, 'r' = correlation coefficient, all of which are significant ($p < 0.02$) except *. [Each 'r' value is based on a mean of 17 (range 13–22) data points.]

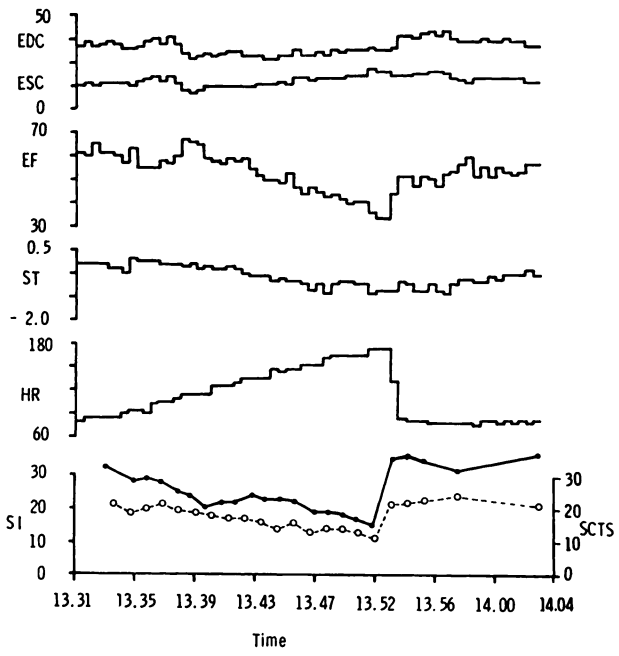

FIGURE 6
Atrial pacing study of patient MD. The horizontal axis represents real time and EDC, ESC and SCTS represent background subtracted end-diastolic, end-systolic, and stroke counts, respectively (as measured by the Cardioscint, /10 msec). EF = ejection fraction (%), HR = heart rate (beats/min), and SI = the stroke index (ml/m^2). Open circles represent absolute stroke counts and closed circles represent stroke index.

(who also have lower EFs), the probe slightly overestimates the EF compared to the gamma camera. This is probably due to the positioning algorithm which relies on identification of maximal stroke counts to locate the left ventricle, thus an akinetic or dyskinetic apex may be incorrectly excluded from the probe's field of view with the operator concentrating on more normally functioning anterior and basal regions instead. The same would be true with severe posterior dysfunction, where the probe is less able to detect cardiac activity probably due to increased attenuation and scattering (*22*). The empirical choice of 74% of end-diastolic counts to represent automatic background appears too high, as overall EF is slightly overestimated thereby.

Further modification of the Cardioscint will utilize a lower percentage of end-diastolic counts as automatic background. However, all of these factors only explain the mean error and their correction is unlikely to affect the standard deviation about this mean. It must also be remembered that gamma camera radionuclide ventriculography itself has limitations. Kaul et al. (*23*) demonstrated considerable variability in the radionuclide EF at rest in the same patient when different methods of measurement were used (first-pass or a gated equilibrium study). Furthermore, quantification of the ventriculogram is generally performed by one of a number of different, commercially available software packages that may produce results differing by up to 10% in absolute values of EF when applied to identical image data (*13*). In this light, the results from the Cardioscint appear satisfactory and clinically useful.

The probe was designed to provide continuous and long-term monitoring of cardiac function and the results of the atrial pacing tests show that it can reliably track changes in left ventricular volumes as measured by thermodilution, the limitations of which are understood (*24*). Although we studied our patients for only 20–30 min, longer periods of monitoring at the bedside are feasible and their validation using thermodilution is part of an ongoing study. In addition, the problems resulting from inaccurate background measurement should be less important, as the device is designed to measure changes in function rather than assume the role of conventional radionuclide ventriculography. We have shown that such changes are reliably monitored.

Many potential limitations in the clinical application of the Cardioscint are common to all probe systems measuring left ventricular function. In individuals where myocardial ischemia is manifest by segmental, and not global, ventricular dysfunction probes are less likely to be of use as the sole means of detecting myocardial ischemia (*25*). A further, practical difficulty lies in the maintenance of a constant geometrical relationship between the probe and left ventricle. This is usually comfortably achieved by an elasticated harness, but difficulties may still occur, especially in female patients. A short, tapered collimator was chosen to be less 'directional' and, consequently, less sensitive to tilting than the longer parallel-hole collimators employed in other probe systems. Although the collimation of both the Nuclear Stethoscope and the VEST produces a narrower field of view than the Cardioscint system (but with increased tilt sensitivity), our results would suggest that there is little effect on overall accuracy.

In summary, the Cardioscint is able to provide an on-line update of left ventricular function and ST segment. The probe is simple to position over the left ventricle using an interactive algorithm that permits a usable estimate of cardiac function, although for "single" estimates of EF use of a gamma camera enhances accuracy. From an operator's viewpoint, the option of both manual and automatic background facilities enables a measurement of the EF to be obtained within 10 min in nearly every case. Although more research needs to be conducted, the instrument clearly merits further clinical assessment.

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