Radionuclide Evaluation of Postextrasystolic Potentiation of Left Ventricular Function Induced by Atrial and Ventricular Stimulation

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Postextrasystolic potentiation of left ventricular function induced by ventricular and atrial stimulation was compared in 10 patients using radionuclide ventriculography. After insertion of pacing wires, a preliminary radionuclide ventriculogram was obtained and then ventricular and atrial trigeminy was induced in random order, each with identical R-R coupling intervals, each for 6 to 10 minutes. During the stimulation studies, radionuclide data were acquired in electrocardiographic gated list mode format. Left ventricular ejection fraction and relative end-diastolic and end-systolic volume changes were measured for each reformatted composite sinus, atrial and ventricular premature beat and potentiated beat. The volume changes were normalized to the count-based values obtained for the sinus beat of the appropriate study. Postextrasystolic potentiation induced by either ventricular or atrial stimulation was characterized by similar significant increases in left ventricular ejection fraction (mean ± standard deviation 7 ± 3 percent, p < 0.01 versus 7 ± 5 percent, p < 0.01; difference not significant [NS]) and decreases in relative end-systolic volume (−12 ± 12 percent, p < 0.01 versus −12 ± 8 percent, p < 0.01; NS) but little change in relative end-diastolic volume (+5 ± 10 percent, NS versus +4 ± 7 percent, NS; NS). This was despite a longer compensatory pause (1,120 ± 220 versus 1,050 ± 190 ms, p < 0.01) after the ventricular premature beat. It is concluded that there is no difference in the postextrasystolic potentiation induced by atrial or ventricular premature stimulation.

In patients with angina pectoris, myocardial asynergy may be due to myocardial scarring or ischemia, or both. Those with myocardial ischemia may have improved global left ventricular function and regional myocardial wall motion after successful myocardial revascularization, whereas little if any improvement can be expected in those with myocardial scarring. Several methods to identify preoperatively those with potentially salvageable myocardial segments have been investigated, including pharmacologic intervention with norepinephrine or nitroglycerin. However, the most useful predictor of myocardial viability appears to be the change in ventricular function evoked by postextrasystolic potentiation.

Postextrasystolic potentiation after induction of ventricular premature beats has been shown to be an excellent predictor of myocardial viability, inotropic reserve and morbidity and mortality after coronary bypass graft surgery. A limitation has been the need to induce ventricular premature beats, which have the potential for provoking sustained ventricular arrhythmias, especially in the group of patients with ischemic heart disease and impaired left ventricular function. Recently, in animal studies, atrial premature beats were shown to demonstrate some potentiation in the following cardiac cycle, thereby potentially reducing the risk of premature stimulation. The purpose of this study...
was to compare in human subjects the postextrasystolic potentiation elicited by atrial premature beats with that evoked by ventricular premature beats using radionuclide ventriculography.

**Methods**

**Study patients:** Informed consent was obtained from 10 patients—5 women and 5 men (mean age 54, range 36 to 68 years)—about to undergo diagnostic cardiac catheterization. Six were found to have significant coronary artery disease, one cardiomyopathy and three normal left ventricular function and normal coronary arteries; all had normal sinus rhythm and none had a history of tachycardia or bradyarrhythmias (Table I). Each patient underwent an uncomplicated standard cardiac catheterization including measurement of left and right heart hemodynamics, contrast ventriculography and selective coronary angiography using either the Sones or Judkins technique. All cardioactive drugs were continued until the time of the study and each patient was appropriately fasted.

**Cardiac pacing:** At the end of cardiac catheterization, arterial hemostasis was obtained and then two 4F pacing catheters were inserted into the vein used for the right heart study. One catheter was positioned in the apex of the right ventricle and the other placed in a variable location in the right atrium, the only criterion for positioning being stable capture. A brief period of cardiac pacing was carried out using a Laboratory Savita model GSO orthorhythmic cardiac pacemaker while the patient was still in the catheter laboratory. With use of a programmable option, continuous ventricular and then atrial trigeminy was induced to screen for the development of sustained cardiac arrhythmias and to confirm adequate placement of pacing wires.

**Radionuclide ventriculography:** The patients were then injected with stannous pyrophosphate, 25 millicuries (mCi) of technetium-99m pertechnetate and transferred to the nuclear cardiac suite. Radionuclide ventriculography was performed using a General Electric gamma camera with the patient supine under a small field of view (20 cm). Imaging data were collected in a modified left anterior oblique projection to allow optimal separation of the right and left ventricular blood pools. Data were acquired on a Medical Data Systems computer with a 20 megabyte mulitplatter storage disc.

A baseline 16 frame 64 by 64 matrix equilibrium gated blood pool scan was collected followed by two electrocardiographic gated list mode studies. Each of the latter studies was acquired at a frame rate of 1 ms, lasted 6 to 10 minutes and was separated by a 15 minute rest period. For 1 minute before and for the duration of each acquisition, the patient had either ventricular or atrial trigeminy induced by the programmable pacemaker, the order being randomized to eliminate any residual effects of cardiac catheterization on the result of this study. The R-R coupling intervals of the atrial and ventricular premature beats were kept constant for each individual patient to exclude their possible effect on the subsequent potentiation. Each radionuclide study began more than 1 hour after the last contrast injection and took less than 1 hour. At the end, the pacing wires were removed and hemostasis was achieved by compression bandages. No complications were caused by the procedure in any of the 10 patients studied.

**Radionuclide analysis:** Using the $A^2$ software support program, an R-R histogram was generated from the electrocardiographic gated list mode study. From this, it was usually possible to identify three separate clusters of cardiac cycles. The cluster with the shortest R-R interval represented the cardiac cycle of the interrupted sinus beat, that with the next shortest interval represented the cycle during the postextrasystolic potentiated beat and that with the longest interval represented the cycle during the atrial or ventricular premature beat (Fig 1). By separately flagging time windows for

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**TABLE I**

<table>
<thead>
<tr>
<th></th>
<th>Sinus Beat</th>
<th>Coupling Interval</th>
<th>Compensatory Pause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rest study</td>
<td>890 ± 160*</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Atrial trigeminy</td>
<td>900 ± 170*</td>
<td>595 ± 90</td>
<td>1050 ± 190*</td>
</tr>
<tr>
<td>Ventricular trigeminy</td>
<td>850 ± 160</td>
<td>600 ± 60</td>
<td>1120 ± 220</td>
</tr>
</tbody>
</table>

$^*$ p <0.01 when compared with equivalent ventricular trigeminy data

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each of these R-R intervals in turn, radionuclide data were reformatted into a series of 16 to 32 frame 64 by 64 matrix word mode composite cardiac studies representative of each beat in the trigeminal rhythm. The actual time of each acquisition, the number of cardiac cycles accepted and the time/frame of each reformatted cycle were noted for future calculation of relative volume changes.

Three patients had an insufficient compensatory pause after the atrial premature beat to allow its separation from the following potentiated beat. In these studies, the R-R histogram showed only two distinct clusters of cardiac cycles. The first represented the interrupted sinus beat, the second a combination of the premature and potentiated beats. The problem was overcome by using a software option to flag a time window incorporating the second cluster of cardiac cycles. The first of the paired beats that fell within this R-R window was rejected and the second was accepted. Because the potentiated beat always followed the atrial premature beat, this accepted beat always represented the postextrasyostolic potentiated cardiac cycle. The atrial premature beat was separated in a different manner. Because this beat always followed the sinus beat by a fixed coupling interval, it was possible to reformat a study containing both beats by selecting the R-R window of the interrupted sinus beat and then choosing an appropriate time/frame and number of frames to encompass the span of both these beats. Once this study was reformatted, the atrial premature beat could then be isolated for independent assessment.

Identification of all the studies was then removed and the order of the composite cardiac cycles was randomized before the analysis of several indexes of left ventricular function. They were then analyzed by observers unaware of the study number and sequence. Left ventricular ejection fraction was calculated using a previously validated semiautomatic method incorporating a second derivative edge algorithm and variable regions of interest.

**Analysis of volume changes:** The relative end-diastolic and end-systolic volume changes within and between the two stimulation studies and the preliminary study were obtained using the method described by Ritchie et al. Briefly, to compare the volume changes within each stimulation study, the background-corrected counts contained within the end-diastolic and end-systolic regions of interest were obtained from the composite sinus, premature and potentiated beats. They were then corrected for differences in time/frame and the number of cardiac cycles contained in each study and then expressed as a percent of the values obtained from the appropriate sinus beat. No correction for the decay of technetium-99m is required within such a stimulation study because the three composite beats were acquired simultaneously.

The volume changes occurring between the preliminary and the two stimulation studies were obtained in a similar manner. The background-corrected counts contained within the end-diastolic and end-systolic regions of interest of the composite sinus, atrial and ventricular premature and potentiated beats were once more corrected for individual changes in time/frame and number of cardiac cycles for each. However, they were also corrected for the decay of technetium-99m incurred by the temporal separation of the preliminary and stimulation studies, and this time the values were expressed as a percent of the composite sinus beat of the ventricular stimulation study. These volume changes could now be assessed without having to consider the problems of attenuation correction that seem to be necessary for absolute volume measurement.

**Statistical analysis:** Changes in the group data were assessed statistically with use of the two-tailed paired t test.
TABLE III

Left Ventricular Function Variables With Normalized Relative End-Diastolic and End-Systolic Volumes (* = 10 patients)

<table>
<thead>
<tr>
<th></th>
<th>Preliminary Study</th>
<th>VPB Study</th>
<th>PESP Study</th>
<th>APB Study</th>
<th>PESP Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ejection fraction</td>
<td>56 ± 14</td>
<td>54 ± 14</td>
<td>41 ± 15</td>
<td>61 ± 15</td>
<td>56 ± 14</td>
</tr>
<tr>
<td>Rel. ESV % 6</td>
<td>97 ± 12</td>
<td>100</td>
<td>85 ± 16</td>
<td>103 ± 10</td>
<td>96 ± 12</td>
</tr>
<tr>
<td>Rel. ESV % 6</td>
<td>94 ± 10</td>
<td>100</td>
<td>110 ± 18</td>
<td>88 ± 12</td>
<td>93 ± 10</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± 1 standard deviation unless otherwise indicated. For the two paired sets of data, the means ± 1 standard deviation of the signed differences are presented.

Results

Mean heart rate, coupling interval and compensatory pause for atrial and ventricular stimulation (Table I): The intrinsic heart rate for the trigeminal rhythm complex was taken to be the R-R interval of the potentiated beat. As expected, there was no significant difference between the coupling intervals of ventricular (600 ± 91 ms) and atrial premature beats (595 ± 91 ms), and there was a significantly longer compensatory pause after the ventricular premature beat (1.120 ± 220 versus 1.050 ± 190 ms, p < 0.01). However, the intrinsic cycle length of the ventricular trigeminal rhythm (850 ± 160 ms) was significantly shorter than that of the preliminary study (890 ± 160 ms, p < 0.01) and the atrial stimulation study (900 ± 170 ms, p < 0.01); the same trend was evident in all 10 patients. There was no significant difference (p > 0.1) between the intrinsic heart rates of the atrial stimulation and preliminary studies.

Left ventricular ejection fraction and volumes (Table II): Left ventricular function as measured by left ventricular ejection fraction was more seriously compromised during the ventricular premature beat (12 ± 17 percent) than during the atrial premature beat (7 ± 2 percent) in eight of nine patients (p > 0.01). When compared with values of the appropriate sinus beat, the changes in relative end-diastolic volume were almost identical for the ventricular premature (−15 ± 10 percent) and atrial premature (−13 ± 9 percent) beats, but there was a greater residual end-systolic volume for the ventricular (10 ± 18 percent) than for the atrial (3 ± 9 percent) premature beat. However, this difference did not reach statistical significance.

The mean changes in all left ventricular variables for the postextrasystolic potentiation beat were very similar for the ventricular and atrial stimulation studies. The change in left ventricular ejection fraction was 7 ± 3 versus 7 ± 5 percent (NS), in relative end-diastolic volume 5 ± 10 versus 4 ± 7 percent (NS) and in relative end-systolic volume was −12 ± 12 versus −12 ± 8 percent (NS). The mean ± standard deviations of the signed differences between the changes induced by atrial and ventricular premature stimulation were 0.1 ± 2.4 (r = 0.91) for left ventricular ejection fraction, 1.4 ± 10 percent for relative end-diastolic volume changes and −0.1 ± 10 percent for relative end-systolic volume changes.

Although there was a small increase in end-diastolic volume during the potentiated beat of the atrial trigeminal study (+7.3 ± 4 percent) and ventricular trigeminal study (+5 ± 10 percent), neither increase reached statistical significance. However, the changes in end-systolic volume were highly significant for both atrial trigeminy (−12 ± 8 percent, p < 0.01) and ventricular trigeminy (−12 ± 12 percent, p < 0.01), occurring in 9 of the 10 patients in both stimulation studies.

Relative volume changes for each study: By correcting for the decay of technetium-99m, it was possible to compare the relative volume changes of each study in each individual patient. The values of the normalized volume changes for the study are summarized in Table III and Figure 2. There was a small but insignificant difference in left ventricular ejection fraction and end-diastolic volume of the sinus beat of the ventricular stimulation study when these variables were compared with those obtained from the sinus beats of either the preliminary or the atrial stimulation study. The values for left ventricular ejection fraction and end-diastolic volume of the latter two studies were essentially the same. However, the relative end-systolic volume of the sinus beat of the atrial stimulation study (93 ± 7 percent) and the preliminary study (94 ± 10 percent) appeared to be smaller than the corresponding variable (100 percent) for the ventricular stimulation study, with the former reaching statistical significance (p < 0.05) and the latter just failing to do so (0.1 > p > 0.05). No other statistically significant differences between the two stimulation studies were found.

To determine whether there was any reduction in the postextrasystolic potentiation with time, changes in left ventricular ejection fraction during the first stimulation study (+7.3 ± 4 percent) were compared with the changes during the second stimulation study (+6.5 ± 4 percent). These were the same (NS).

Discussion

Atrial versus ventricular postextrasystolic potentiation: The changes in left ventricular ejection fraction, end-diastolic volume and end-systolic volume during postextrasystolic potentiation were identical.
after either an atrial or a ventricular premature beat when the coupling interval of the premature beat was kept identical. This occurred despite the longer compensatory pause and the greater end-systolic volume at the end of the ventricular premature beat, thus supporting the concept that postextrasystolic potentiation may be an "all or none" phenomenon.16

The small but insignificant increase in end-diastolic volume and highly significant decrease in end-systolic volume induced by the postextrasystolic potentiation in this study are in agreement with findings in most previous contrast ventriculographic studies17-19 and support the contention that the Starling mechanism plays only a small role in the postextrasystolic potentiation response.

Role of radionuclide ventriculography: This study was performed using radionuclide ventriculography in preference to contrast ventriculography because of the ease of controlling the R-R coupling intervals, the lack of spontaneously induced ectopic activity and the lack of myocardial depression that is usually induced by the contrast materials. The ability of postextrasystolic potentiation to differentiate between viable but ischemic from nonviable or scoured regions of the impaired left ventricle12-15 makes the assessment of regional as well as global left ventricular function an important part of the analysis. The technique of quantitative radionuclide ventriculography has been extensively validated against contrast ventriculography for the assessment of both global and regional ventricular function at rest and during various interventions.20,21 However, regional analysis was not performed in this study because our aim was to compare atrial with ventricular stimulation. Furthermore, it is necessary to acquire the radionuclide studies in the right anterior oblique, left anterior oblique and left lateral views to assess regional function adequately.22 The lack of tachyphylaxis between the first and second stimulation studies now makes such acquisition feasible.

Clinical application: The importance of the finding that postextrasystolic potentiation induced by atrial stimulation is the same as that induced by ventricular stimulation lies in the increased ease and safety of performing atrial stimulation in the catheterization laboratory. Atrial postextrasystolic potentiation also may have the potential for allowing noninvasive assessment of postextrasystolic potentiation by combining radionuclide ventriculography with recently introduced esophageal pacing techniques.23 Thus, it may become feasible to screen noninvasively patients with known impaired left ventricular dysfunction by postextrasystolic potentiation to judge whether they are suitable for surgical intervention.

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References


