Parasympathetic effects on cardiac electrophysiology during exercise and recovery in patients with left ventricular dysfunction

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Am J Physiol Heart Circ Physiol 297: H743–H749, 2009. First published June 12, 2009; doi:10.1152/ajpheart.00193.2009.—Depressed parasympathetic activity has been proposed to be associated with an increased risk of sudden death. Parasympathetic effects (PE) on cardiac electrophysiology during exercise and recovery have not been studied in patients with left ventricular dysfunction. We performed noninvasive electrophysiological studies (NI-EPS) and characterized the electrophysiological properties of the sinus node, atrioventricular (AV) node, and ventricle in subjects with depressed left ventricular ejection fraction and dual-chamber defibrillators. NI-EPS were performed during rest, exercise, and recovery at baseline and after parasympathetic blockade with atropine to assess PE (the difference between parameter values in exercise, and recovery at baseline and after parasympathetic blockade with atropine to assess PE (the difference between parameter values in 2 conditions). Ten subjects (9 men; age, 60 ± 9 yr; and left ventricular ejection fraction, 29 ± 8%) completed the study. All NI-EPS parameters decreased during exercise and trended toward rest values during recovery. PE at rest, during exercise, and during recovery, respectively, were on sinus cycle length, 320 ± 71 (P = 0.0001), 105 ± 60 (P = 0.0003), and 155 ± 82 ms (P = 0.0002); on AV block cycle length, 137 ± 136 (P = 0.09), 37 ± 19 (P = 0.002), and 61 ± 39 ms (P = 0.006); on AV interval, 58 ± 32 (P = 0.035), 22 ± 13 (P = 0.002), and 36 ± 20 ms (P = 0.001); on ventricular effective refractory period, 15.8 ± 11.3 (P = 0.02), 4.7 ± 15.2 (P = 0.38), and 6.8 ± 15.5 ms (P = 0.20); and on QT interval, 13 ± 12 (P = 0.13), 3 ± 17 (P = 0.6), and 20 ± 23 (P = 0.04). In conclusion, we describe for the first time the changes in cardiac electrophysiology and PE during rest, exercise, and recovery in subjects with left ventricular dysfunction. PEs are preserved in these patients. Thus the role of autonomic changes in the pathophysiology of sudden death requires further exploration.

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SYMPTOMATIC ARRHYTHMOGENESIS. The role of autonomic changes associated with life-threatening arrhythmias remains unclear. Although increased sympathetic and/or decreased parasympathetic activity at rest and during exercise is associated with arrhythmogenesis, the role of autonomic changes associated with life-threatening arrhythmias remains unclear. Exercise is a physiological condition associated with sympathetic activation and parasympathetic withdrawal, precisely the autonomic changes associated with life-threatening arrhythmias in susceptible patients. Interestingly, the risk of sudden death has been shown to be increased during exercise and in the recovery period following exercise (1, 27, 38). The pathophysiological link between these autonomic changes and ventricular arrhythmogenesis remains unclear. Several studies (12, 29, 34) have assessed the sympathetic and parasympathetic effects on ventricular refractoriness in humans using agonist infusions or autonomic blockade, but not under true physiological conditions. These studies have shown variable effects of parasympathetic activity on ventricular refractory periods through direct and indirect mechanisms.

An evaluation of the changes in ventricular refractoriness during exercise and the postexercise recovery period is a challenging endeavor. However, with the advent of implantable devices capable of noninvasive programmed stimulation, it has become possible to evaluate changes in cardiac electrophysiological properties using programmed stimulation during exercise. Kannankeril and Goldberger (17) studied 10 subjects with normal ventricular function and implantable devices and found that ventricular refractoriness shortened during exercise and trended toward normal in recovery. They studied the parasympathetic effects on cardiac electrophysiology using parasympathetic blockade with atropine and noted significant rest effects on the sinus node, atrioventricular (AV) node, and ventricular refractoriness. These effects became small during exercise and returned to baseline values in recovery. Because patients with depressed left ventricular function are at increased risk of sudden death (3, 16, 24, 35, 40, 42) and have also been demonstrated to have altered autonomic activity (5, 14, 30, 32, 33), we postulated that these patients would have less parasympathetic effects on cardiac electrophysiology, particularly at rest and during recovery. This would be consistent with the notion that normal parasympathetic activity at these times provides a natural antiarrhythmic effect and that the suppression of this normal activity, as observed in patients with depressed left ventricular function, could therefore promote ventricular arrhythmias. This hypothesis was tested in patients with depressed left ventricular function and implantable devices, using the protocol previously performed in patients with normal left ventricular function (17).

METHODS

Study design. Cardiac electrophysiological parameters were measured by performing noninvasive electrophysiological studies (NI-EPS) in subjects with depressed left ventricular function and dual
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chamber defibrillators implanted for primary or secondary prevention of sudden cardiac death. Sinus node effects were measured by the R-R interval. AV nodal effects were measured by determining the AV block cycle length and the AV interval at fixed paced cycle lengths. Ventricular effects were evaluated by measuring the ventricular effective refractory period (VERP) and the QT interval at fixed paced cycle lengths. To assess the parasympathetic effects, we performed NI-EPS during rest, exercise, and the postexercise recovery period in baseline conditions and after atropine administration, as previously described (17). Studies were performed at the same time of day to avoid differences due to circadian variations (19, 37). A parasympathetic effect on any parameter in any stage was defined as the difference between the value of the parameter in the absence of atropine and its value in the presence of atropine.

Subjects. The study group included 10 subjects (9 men and 1 woman; age, 60 ± 9 yr) with depressed left ventricular function (left ventricular ejection fraction, 29 ± 8%; all subjects had an ejection fraction < 40%) and dual (n = 9) or single (n = 1) chamber defibrillators. Table 1 describes the subjects’ clinical characteristics. One patient with AV block and one with a single-chamber device were excluded from the analysis of AV node function.

Subjects were on a stable medical regimen throughout the study period. No subjects had evidence of diabetes mellitus, unstable coronary artery disease, or heart failure within the preceding 3 mo. The study was approved by the Northwestern University Institutional Review Board, and written informed consent was obtained before participation.

Exercise tests. Subjects were studied in four separate sessions: the first three sessions were separated by at least 24 h, and the fourth session was separated by at least 48 h from the third. At each visit, the subjects were attached to an electrocardiogram machine (Marquette MAC VU, Milwaukee, WI; Quest Burdick, Bothell, WA), and the device programming wand was secured over their device. All measurements were taken with subjects seated on a mechanically braked bicycle ergometer (Monark 818E, Vansbro, Sweden; Scifit Pro II, Tulsa, OK). Baseline heart rate and blood pressure were recorded, and

Table 1. Clinical characteristics of the study population

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects</td>
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</tr>
<tr>
<td>Age, yr</td>
<td>60±9</td>
</tr>
<tr>
<td>Men</td>
<td>9</td>
</tr>
<tr>
<td>Left ventricular ejection fraction, %</td>
<td>29±8</td>
</tr>
<tr>
<td>New York Heart Association class</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>1</td>
</tr>
<tr>
<td>II</td>
<td>9</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>7</td>
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<tr>
<td>Myocardial infarction</td>
<td>7</td>
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<tr>
<td>Hypertension</td>
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<tr>
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<td>Primary prevention</td>
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<td>2</td>
</tr>
<tr>
<td>History of VT or VF</td>
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</tr>
<tr>
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<td>5</td>
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<tr>
<td>Inducible VT at EP study</td>
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<td>Underlying rhythm</td>
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<tr>
<td>Sinus with AV block</td>
<td>1</td>
</tr>
<tr>
<td>Medications</td>
<td></td>
</tr>
<tr>
<td>β-Blockers</td>
<td>9</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>9</td>
</tr>
<tr>
<td>Digoxin</td>
<td>6</td>
</tr>
<tr>
<td>Diuretics</td>
<td>6</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>0</td>
</tr>
<tr>
<td>Antiarrhythmic agent</td>
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</tbody>
</table>

Age and left ventricular ejection fraction values are means ± SD. VT, ventricular tachycardia; VF, ventricular fibrillation; EP, electrophysiological; AV, atrioventricular; ACE, angiotensin-converting enzyme.
RESULTS

Resting heart rate was 65 ± 13 beats/min; resting systolic and diastolic blood pressures were 115 ± 6 and 72 ± 7 mmHg. Subjects exercised for 12 ± 2 (range 9–14) min at workloads of 74 ± 18 (range 50–100) W. NI-EPS were performed at 5.9 ± 1.8 min into exercise when the heart rate was 99 ± 11 beats/min. At peak exercise, systolic and diastolic blood pressures were 151 ± 12 and 83 ± 8 mmHg. During recovery, NI-EPS were started 1 min after the end of exercise when the heart rate was 89 ± 8 beats/min and was completed by 6.5 ± 1.3 min when the heart rate was 81 ± 20 beats/min. Systolic and diastolic blood pressures were 112 ± 9 and 74 ± 9 mmHg after NI-EPS were completed in recovery.

After atropine was given at rest (visit 4, n = 6), the heart rate was 100 ± 29 beats/min (vs. 63 ± 12 beats/min at rest without atropine in these subjects; P = 0.005) and systolic and diastolic blood pressures were 112 ± 19 and 73 ± 8 mmHg. After atropine was administered during exercise, NI-EPS were performed when the heart rate was 125 ± 23 beats/min. At peak exercise after atropine, systolic and diastolic blood pressures were 148 ± 13 and 81 ± 7 mmHg. During recovery after atropine, NI-EPS were also started at 1 min after the end of exercise, at which time the heart rate was 117 ± 24 beats/min and was completed by 6.1 ± 1.6 min, when heart rate was 102 ± 24 beats/min. Systolic and diastolic blood pressures were 118 ± 15 and 73 ± 9 mmHg after NI-EPS were completed in recovery.

Electrophysiological changes with exercise and recovery. Changes in electrophysiological parameters among baseline, exercise, and recovery stages are shown in Figs. 1, 2, and 3. Sinus cycle length shortened from 957 ± 193 ms at rest to 601 ± 85 ms during exercise and increased to 692 ± 121 ms at 1 min in recovery (P < 0.0001 by ANOVA; P < 0.001 for all pairwise comparisons).

AV block cycle length (n = 8) was 416 ± 151 ms at rest, shortened to 298 ± 36 ms during exercise, and increased to 341 ± 62 ms in recovery (P = 0.018 for ANOVA; pairwise comparisons: rest vs. exercise, P = 0.049; exercise vs. recovery, P = 0.031; and rest vs. recovery, P = 0.071). The AV interval at a paced cycle length of 500 ms (n = 7) was 270 ± 65 ms at rest, shortened to 224 ± 44 ms during exercise, and increased to 241 ± 47 ms in recovery (P = 0.002 by ANOVA; pairwise comparisons: rest vs. exercise, P = 0.012; exercise vs. recovery, P = 0.005; and rest vs. recovery, P = 0.032) (Fig. 2). For the six patients with data for paced cycle lengths of 500 and 400 ms, there were cycle length-dependent increases in the AV interval for all conditions (rest, 253 ± 51 and 298 ± 87 ms, P = 0.053; exercise, 218 ± 44 and 240 ± 47 ms, P = 0.001; and recovery, 233 ± 46 and 260 ± 59 ms, P = 0.029 at paced cycle lengths of 500 and 400 ms, respectively).

The QT interval measured at a fixed cycle length of 500 ms (n = 7) was 417 ± 39 ms at rest, shortened to 371 ± 37 ms during exercise, and increased to 387 ± 38 ms in recovery (P < 0.0001 by ANOVA; pairwise comparisons: rest vs. exercise, P = 0.0007; exercise vs. recovery, P = 0.0025; and rest vs. recovery, P = 0.0016), and the QT interval measured at a cycle length of 400 ms (n = 6) was 398 ± 38 ms at rest, shortened to 351 ± 44 ms during exercise, and increased to 379 ± 41 ms in recovery (P = 0.0007 by ANOVA; pairwise comparisons: rest vs. exercise, P = 0.007; exercise vs. recovery, P = 0.013; and rest vs. recovery, P = 0.024) (Fig. 3).

VERPs were measured in all subjects for all conditions at a drive cycle length of 450 ms (n = 10). It was 261 ± 16 ms at rest, shortened to 233 ± 19 ms during exercise, and lengthened to 251 ± 20 ms in recovery (P < 0.0001 by ANOVA; pairwise comparisons: rest vs. exercise, P < 0.0001; exercise vs. recovery, P = 0.0003; and rest vs. recovery, P = 0.0012) (Fig. 3). VERP was measured at three drive cycle lengths of 500, 450, and 400 ms in all subjects at rest, in 7 subjects during exercise, and in 8 subjects during recovery. For each condition, the VERPs were averaged for all three drive cycle lengths (when 1 measurement was missing, only the value at a drive cycle length of 450 ms was used). The average VERPs were 261 ± 17 ms at rest, 235 ± 20 ms during exercise, and 250 ± 19 ms in recovery (P < 0.0001 by ANOVA; pairwise comparisons: rest vs. exercise, P < 0.0001; exercise vs. recovery, P = 0.0003; and rest vs. recovery, P = 0.0002). The cycle length-dependent effects at each condition are shown in Table 2.

Exercise resulted in an average 36% decrease in sinus cycle length, 24% decrease in AV block cycle length, 16% decrease in AV intervals, 11% decrease in VERP, and 11% decrease in QT interval. Values in recovery were intermediate between rest and exercise.

Parasympathetic effects. The parasympathetic effects on all parameters during rest, exercise, and recovery are shown in Fig. 4. For all parameters, the parasympathetic effect diminished during exercise and recovered toward the resting value during recovery. The individual changes for each condition with the number of available subjects are described here.

At rest (n = 6, except where noted otherwise), the parasympathetic effect on the sinus cycle length was 320 ± 71 ms (P = 0.0001). The parasympathetic effect on the AV block cycle length was 137 ± 136 ms (P = 0.09, n = 5). The parasympathetic effect on the AV interval was 58 ± 32 ms (P = 0.035, n = 4). The parasympathetic effect on the QT interval was 13 ± 12 ms (P = 0.13, n = 4). The parasympathetic effect on the VERP was 15.8 ± 11.3 ms (P = 0.019). The parasympa-
thetic effects were ~34% on the sinus cycle length, 27% on the AV block cycle length, 19% on the AV interval, and 6% on the VERP.

During exercise (n = 10, except where noted otherwise), the parasympathetic effect on the sinus cycle length was 105 ± 60 ms (P = 0.0003). The parasympathetic effect on the AV block cycle length was 37 ± 19 ms (P = 0.002, n = 7). The parasympathetic effect on the AV interval was 22 ± 13 ms (P = 0.002, n = 8). The parasympathetic effect on the QT interval was 3 ± 17 ms (P = 0.6, n = 7). The parasympathetic effect on the VERP was 4.7 ± 15.2 ms (P = 0.4, n = 9).

In recovery (n = 10, except where noted otherwise), the parasympathetic effect on the sinus cycle length was 155 ± 82 ms (P = 0.0002). The parasympathetic effect on the AV block cycle length was 61 ± 39 ms (P = 0.006, n = 7). The parasympathetic effect on the AV interval was 36 ± 20 ms (P = 0.001, n = 8). The parasympathetic effect on the QT interval was 20 ± 23 ms (P = 0.04, n = 8). The parasympathetic effect on the VERP was 6.8 ± 15.5 ms (P = 0.20).

**DISCUSSION**

To our knowledge, this is the first study that has characterized changes in cardiac electrophysiology related to exercise in subjects with left ventricular dysfunction and also evaluated the parasympathetic effects on these parameters. Sinus cycle length, AV conduction, QT interval, and VERP all shortened with exercise and trended toward the resting values during recovery, as was previously noted in subjects with normal left ventricular function. The parasympathetic effects were noted on sinus and AV nodal function at rest, during exercise, and during recovery. The parasympathetic effects on ventricular refractoriness and repolarization were noted at rest, but were absent during exercise, and were more limited during recovery. Surprisingly, the parasympathetic effects on sinus cycle length, AV conduction, and VERP were quantitatively and qualitatively similar to those reported for patients with normal left ventricular function (17). These data show that parasympathetic effects are not markedly diminished in patients with...
depressed left ventricular function. The link between the autonomic changes and the accompanying electrophysiological effects observed during exercise and recovery and the increased risk for sudden cardiac death observed in relation to exercise and recovery (1, 27, 38) requires further exploration.

Changes in autonomic nervous balance have been noted in patients with heart failure (2, 6, 11, 13, 25). There is extensive evidence that heart failure is associated with sympathetic activation. In addition, data from studies on heart rate variability and baroreceptor sensitivity have been interpreted to suggest that there is a diminished parasympathetic “tone” in these patients. Most importantly, the markers of diminished parasympathetic “tone” evaluated at the level of the sinus node—heart rate variability (5, 14, 32, 33), baroreflex sensitivity (9, 10, 15, 20, 30), and heart rate recovery after exercise (7, 8, 31, 43)—have been shown to provide important prognostic information. Thus it is important to understand the contribution of these changes to alterations in ventricular electrophysiology.

In a prior study, a similar evaluation of electrophysiological changes with exercise and recovery, as well as an evaluation of the parasympathetic effects, were performed in subjects with normal left ventricular function (17). Because patients with depressed left ventricular function are thought to have diminished “parasympathetic tone,” we had hypothesized that this evaluation would reveal the diminished parasympathetic effects during rest, exercise, and recovery. Despite the presence of significant left ventricular dysfunction and a high usage rate of β-blockers and angiotensin-converting enzyme inhibitors in the current population, the study results are quantitatively very similar to those noted previously in subjects with normal left ventricular function, with two possible exceptions. The dynamic changes in VERP and QT interval with exercise and recovery were similar, but the actual values were higher in the current subject population with left ventricular dysfunction. In addition, in the current population, the parasympathetic effect on VERP remained small in recovery, whereas it had normalized to the resting values in patients with normal left ventricular function.

Several previous studies (12, 29, 34, 36) have examined the effects of parasympathetic activity on ventricular refractoriness periods in humans. Only Guss et al. (12) found essentially no overall change in VERP in five patients after parasympathetic blockade with 1 mg of atropine. Prystowsky et al. (34) investigated 13 subjects, most without structural heart disease, and administered atropine and propranolol (with either given first) at rest in the electrophysiology laboratory. In the three subjects given atropine first, there was a mean 18-ms shortening in the VERP with atropine, consistent with the current findings and those of our prior study (17). In the eight subjects who received propranolol first, atropine shortened the VERP by 25 ms. Morady et al. (29) investigated the effects of atropine on ventricular refractoriness after infusions of either propranolol or isoproterenol (low dose or high dose), at rest, and in a clinically heterogeneous group of subjects. The parasympathetic effect on VERP was demonstrable after propranolol and during isoproterenol infusion. Interestingly, the data obtained in the present study during exercise differ from those noted with isoproterenol infusion. Despite the demonstrable parasympathetic effect on the sinus cycle length, there was no demonstrable parasympathetic effect on VERP. This likely reflects the real differences between the autonomic states and

### Table 2. VERPs at drive cycle lengths of 500, 450, and 400 ms during rest, exercise, and recovery

<table>
<thead>
<tr>
<th>Condition</th>
<th>n</th>
<th>VERP at 500 ms</th>
<th>VERP at 450 ms</th>
<th>VERP at 400 ms</th>
</tr>
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<tbody>
<tr>
<td>Rest*</td>
<td>10</td>
<td>271 ± 19</td>
<td>261 ± 16</td>
<td>251 ± 15</td>
</tr>
<tr>
<td>Exercise†</td>
<td>7</td>
<td>243 ± 21</td>
<td>234 ± 20</td>
<td>231 ± 23</td>
</tr>
<tr>
<td>Recovery*</td>
<td>8</td>
<td>258 ± 17</td>
<td>252 ± 18</td>
<td>244 ± 16</td>
</tr>
</tbody>
</table>

Values are means ± SD, n, number of subjects. VERP, ventricular effective refractory period. *P < 0.0001 by ANOVA; †P = 0.0003 by ANOVA.

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**Fig. 4.** Parasympathetic effects (in ms) on cardiac electrophysiology in patients with depressed left ventricular function during rest (R), exercise (Ex), and recovery (Rec) on sinus cycle length, AV block cycle length, AV interval (at paced cycle length of 500 ms), and VERP (means ± SD, *P < 0.05).
Underlies the importance of evaluations under physiological conditions.

Our hypothesis was that subjects with left ventricular dysfunction will have evidence of diminished parasympathetic ‘tone’ or effect. However, this was not observed at the level of the sinus node, AV node, or VERP compared with the group of patients with normal ejection fraction studied previously (17). This is despite the fact that our group of subjects may be considered a high-risk group for ventricular arrhythmia and sudden death, as all 10 subjects had a low left ventricular ejection fraction and 7 subjects had either spontaneous (n = 5) or inducible (n = 2) ventricular arrhythmia and/or cardiac arrest. It is interesting to note that Vanoli et al. (41) showed that vagus nerve stimulation could prevent ventricular fibrillation in susceptible dogs undergoing ischemia during treadmill testing. However, when pacing was used to prevent the heart rate reduction that accompanies vagus nerve stimulation, the incidence of ventricular fibrillation dramatically increased (though it was still less than without vagus nerve stimulation). Thus further studies are needed to characterize the role of parasympathetic and adrenergic activation in patients with depressed left ventricular function in relation to the risk for sudden death.

Limitations. This study required multiple measurements from multiple patients during multiple physiological conditions. Because of the spontaneous changes in heart rate and conduction parameters, not all measurements could be obtained in all subjects. However, repeated measurements in the same subjects allowed for a comprehensive evaluation, even with the small number of subjects studied. Because we had to select patients who can exercise safely and comfortably during all the testing, this could represent a generally “healthier” group of patients with depressed left ventricular function. Because NI-EPS were performed using implanted defibrillators and all ventricular leads were located in the right ventricular apex, all VERP determinations are from this single site. It is possible that other areas of the myocardium undergo qualitatively or quantitatively different changes, at least in part related to potential heterogeneities in autonomic innervation and scar distribution. Because of the inherent limitations, we could not investigate the effects on myocardial conduction velocity or dispersion and temporal variations of ventricular repolarization. Further studies should investigate the autonomic effects on other parameters, such as dispersion of repolarization and T-wave alternans, which have been linked to an increased risk for sudden cardiac death (26, 39).

Parasympathetic effects undergo dynamic changes during exercise and recovery. In this study, only the specified time points where evaluated. It is possible that the parasympathetic effects and their dynamics may be different in other stages of exercise and recovery.

Finally, the exercise protocol involved a moderate level of exercise for a limited time, rather than maximal efforts. In addition, most of the patients were taking β-blockers and/or digoxin, which may affect the various electrophysiological parameters, as well as the parasympathetic effects. It is possible that, in the absence of β-blocker and digoxin therapy, diminished parasympathetic effects might be observed. If these drugs correct the heart failure-related defect in the parasympathetic effects, this underlies the importance of these therapies. In addition, these are also strengths of the study, in that it addresses patients exercising at levels they most commonly experience in daily life and taking their routine medications.

Conclusions. We describe for the first time the changes in cardiac electrophysiology in subjects with left ventricular dysfunction during rest, exercise, and recovery, as well as the parasympathetic effects on cardiac electrophysiology during these conditions. Surprisingly, the parasympathetic effect at rest is preserved in patients with left ventricular dysfunction, and there are persistent parasympathetic effects on cardiac electrophysiology during moderate exercise and postexercise recovery, though there may be a longer lag to the restoration of parasympathetic effect on the VERP in the recovery period. These data underscore that understanding the pathophysiological role of the parasympathetic effects on the ventricle may not be achieved with surrogate measures of sinus node effects. In this group of patients with left ventricular dysfunction and increased risk of sudden cardiac death, major abnormalities of parasympathetic effect on electrophysiological properties were not identified. Further studies are warranted to address whether regional changes or other parasympathetic effects on the ventricle mediate an increased risk for sudden cardiac death.

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