Electrophysiological Alterations After Mechanical Circulatory Support in Patients With Advanced Cardiac Failure

John D. Harding, BA; Valentino Piacentino III, BA; John P. Gaughan, PhD; Steven R. Houser, PhD; Kenneth B. Margulies, MD

Background—Recognizing that mechanical circulatory support with a left ventricular assist device (LVAD) induces changes in myocardial structure and contractile function, we examined whether there are changes in ventricular conduction and/or repolarization among failing human hearts after LVAD implantation.

Methods and Results—We examined 12-lead electrocardiograms before surgery, immediately after LVAD placement, and at a delayed (>1 week) postoperative time point in 23 patients who were receiving LVAD support for refractory heart failure. The immediate effects of hemodynamic unloading via LVAD placement included a decrease in QRS duration from 117±6 to 103±6 ms (P<0.01), an increase in absolute QT duration from 359±6 to 378±8 ms (P<0.05), and an increase in the heart rate–corrected QT interval (QTc) from 379±10 to 504±11 ms (P<0.01). None of these immediate changes were observed among 22 patients undergoing routine coronary artery bypass grafting. With sustained cardiac unloading via LVAD support, there was a marked decrease in the QTc from 504±11 to 445±9 ms (P<0.001). Studies in isolated cardiac myocytes, obtained at the time of transplantation, confirmed that delayed decreases in heart rate–adjusted QTc were the result of decreases in action potential duration after LVAD support.

Conclusions—Acute electrocardiogram responses to LVAD placement demonstrate the dependence of QRS and QT duration on load in the failing human heart. Delayed decreases in QTc and action potential duration reflect reversal of electrophysiologic remodeling in the failing heart. Shortening of the action potential duration likely contributes to the improved cellular contractile performance observed after sustained LVAD support. (Circulation. 2001;104:1241-1247.)

Key Words: heart failure ■ heart-assist device ■ QT interval ■ action potential ■ calcium

The hallmarks of the pathological phenotype observed in failing human cardiac myocytes include hypertrophy, slowed contraction and relaxation, abnormal calcium homeostasis, impaired responses to adrenergic or frequency stress, and electrophysiological abnormalities. Electrophysiological abnormalities observed in failing myocytes from humans or animal models are manifested by a distortion of myocyte action potential shape and duration. Prolongation of the action potential delays myocyte repolarization and cellular relaxation. Because the QT interval is a direct measure of ventricular repolarization on the surface electrocardiogram (ECG), it is not surprising that many patients who have heart failure exhibit a prolonged QT interval. Moreover, both QT prolongation and conduction abnormalities, reflected by an increased QRS duration, have been associated with increased mortality among patients who have chronic heart failure.

Effective as a means of sustaining medically refractory patients awaiting transplantation, clinical use of left ventricular assist devices (LVADs) also provides a novel opportunity to explore the pathophysiology of chronic heart failure, providing data on the effects of unloading on the myocardium. Highlighted in recent reviews, studies of LVAD-supported hearts have demonstrated striking structural, functional, and biochemical plasticity in human hearts with advanced heart failure. To date, no studies have examined the effect of unloading on the electrophysiological properties of the failing human heart. Therefore, the purpose of our study was to determine whether there were significant early or delayed changes in ventricular conduction and/or repolarization, as reflected by the surface ECG, among failing human hearts after LVAD implantation. We hypothesized that LVAD support would induce significant alterations in the cardiac electrophysiology of failing human hearts.

Methods

Patient Population
We retrospectively examined the medical records of 57 patients who received LVAD support between January 1993 and August 2000 at Temple University Hospital. From this set of patients, we identified 35 patients with archived 12-lead ECGs obtained within 4 days...
before LVAD insertion, immediately (≤6 hours) after LVAD placement, and at a delayed (>1 week) time after LVAD placement. A final set of 23 patients was obtained after excluding patients with atrial fibrillation, paced rhythms, and marked changes in heart rate (>20 bpm) immediately after LVAD placement. In all cases, the delayed ECG was used as the last archived ECG before cardiac transplantation.

To compare the immediate effects of mechanical unloading on the surface ECG, we selected a group of control patients who underwent cardiac surgery without mechanical unloading. Patients in this non-LVAD control group underwent coronary artery bypass grafting without valve replacement, device implantation, or aneurysmectomy. As in the LVAD group, control patients experienced general anesthesia, a median sternotomy, and cardiopulmonary bypass, and they were free of atrial fibrillation, paced rhythms, or marked changes in heart rate. From 348 patients screened, 22 patients meeting these criteria composed the non-LVAD control group.

Clinical Variables

Patients’ charts and other archived materials were reviewed retrospectively to determine the etiology and duration of heart failure, medications at the time of their ECGs, and other pertinent features of their medical history. Left ventricular ejection fraction, measured by echocardiography within 1 month of LVAD placement, was recorded for each patient. Cardiac hemodynamics, including pulmonary artery systolic and diastolic pressures and right atrial pressure, were measured with a balloon-tipped pulmonary artery catheter immediately before and after LVAD placement.

ECG Analysis

From archived 12-lead surface ECGs, we recorded the computer-derived average QT interval, heart rate, PR interval, and QRS duration. All ECGs included 10 seconds of data digitally recorded at a 250-Hz sampling frequency to a resolution of 5 μV (GE-Marquette Medical Systems). Manual review of all ECGs (K.B.M.) was used to record the presence or absence of atrial fibrillation, right bundle branch block, or left bundle branch block and to assure that ectopic QRS complexes were not used for derivation of QT duration. Accuracy of the computer-based ECG parameters was confirmed by manual analysis of the QT interval with caliper measurements of printed ECGs.

A comparison of the ECG before and immediately after LVAD insertion was used to determine the acute effects of mechanical unloading on cardiac conduction and repolarization. A comparison of each patient’s immediate and delayed post-LVAD ECGs was used to determine the delayed effects of LVAD support on cardiac conduction and repolarization.

Myocyte Action Potential Measurements

In an effort to relate whole-heart repolarization changes to single-cell repolarization, action potentials were recorded in isolated left ventricular myocytes from LVAD-supported and non-LVAD–supported hearts. Myocyte isolation was performed by using a previously described protocol. Briefly, at the time of transplant, the aortic root was perfused in situ with a cold blood–buffered cardioplegic solution. Within 30 minutes of cross clamping, an epicardial artery was cannulated and perfused sequentially with a Krebs-Henseleit Buffer rinse solution, collagenase digestion solution, and a final rinse solution for 20, 30, and 10 minutes respectively. Midmyocardial myocytes were filtered, centrifuged (75g), and resuspended in a Krebs-Henseleit solution containing 1% wt/vol bovine albumin, taurine (10 mmol/L), and CaCl2 (0.2 mmol/L). All solutions were maintained with 95% O2 and 5% CO2 at 37°C.

Myocytes were placed in a chamber on the stage of an inverted microscope. The chamber was superfused with Tyrode solution containing 150 mmol/L NaCl, 10 mmol/L dextrose, 5.4 mmol/L KCl, 1.2 mmol/L MgCl2, 2.0 mmol/L Na pyruvate, 5 mmol/L HEPES, and 1.0 mmol/L CaCl2. By using the whole-cell patch-clamp technique, action potentials were recorded in current-clamp mode (Axoclamp 2, Axon Instruments). To induce action potentials, current was passed through the patch electrode at 10% above threshold. The stimulus artifact was isolated to assure accurate membrane recordings. The pipette-filling solution contained 130 mmol/L K aspartate, 20 mmol/L KCl, 5 mmol/L K2ATP, 1 mmol/L MgCl2, 10 mmol/L NaCl, and 10 mmol/L HEPES. All experiments were performed at a chamber temperature of 37°C. Data were recorded online with pClamp software (Version 7.0, Axon Instruments). For each cell, the action potential duration at 50% repolarization (APD50) was derived from 3 action potentials at 0.2 Hz.

Statistics

A retrospective analysis of the ECGs from 23 LVAD patients meeting inclusion criteria as defined above was performed to determine if the ECG intervals changed across the 3 time periods measured, ie, pre-LVAD, immediate post-LVAD, and delayed post-LVAD. The following ECG intervals were analyzed: PR interval, QRS duration, absolute QT duration (QTab), and QT duration corrected for heart rate. The heart rate–adjusted QT duration was determined by using 3 separate approaches. The first approach used Bazett’s formula8 (QTc Bazett=QT/RR1/2) which, despite its known shortcomings,7 is used in the great majority of published studies requiring a heart rate–adjusted QT duration. The second approach used Fridericia’s cube-root formula (QTc Fridericia=QT/RR1/3) which has been shown to better model the heart rate dependence of the QT interval.8 Lastly, we used analysis of covariance with QT duration adjusted on the basis of heart rate to determine whether apparent changes in the QT interval could be attributed to changes in heart rate alone. With the exception of QRS, all data were normally distributed. For that reason, a log transformation of QRS was performed before analysis.

The LVAD group’s data were analyzed as a single-factor experiment with repeated measures. An ANOVA was performed followed by pairwise between-time comparisons by using the Dunn–Bonferroni adjustment. Subgroup analyses explored possible differences based on various clinical parameters such as the duration of heart failure, etiology, sex, the presence of a bundle branch block, or the use of antiarrhythmics. Changes in cardiac hemodynamic parameters resulting from LVAD support were analyzed by using a paired Student t test.

Comparisons with the coronary artery bypass graft control group were analyzed by using a two-factor ANOVA with repeated measures on time. For the comparison of APD50 between LVAD-supported and non-LVAD–supported myocytes, unpaired t tests were used.

All data reported in text and tables are expressed as mean±SEM. A P value less than 0.05 was considered statistically significant.

Results

Clinical Characteristics

The demographic data and clinical characteristics of the 23 LVAD-supported patients are presented in Table 1. These individuals had an average age of 48 years (range, 26 to 65), and most were men. The average duration of heart failure before LVAD placement was 30 months (range, 1 to 80). The sample included 6 patients who had heart failure with a duration of less than 3 months. The sample was relatively balanced with respect to heart failure etiology including 13 patients who had nonischemic cardiomyopathy (11 idiopathic, 1 adriamycin-induced, and 1 valvular) and 10 patients who had ischemic cardiomyopathy. Both nonischemic and ischemic subgroups had severely depressed systolic function with an average ejection fraction of 9±1% and 11±1%, respectively. All but 2 patients required both milrinone and dobutamine intravenously before LVAD placement, and 18 of 23 received intra-aortic balloon pump–support before LVAD placement. All patients were receiving vasodilator...
therapy at the time of LVAD placement. The 4 patients who were receiving antiarrhythmic therapy were administered amiodarone before and immediately after LVAD placement. One patient (No. 2) was receiving a β-blocker at the time of LVAD placement.

**Hemodynamic Effects of LVAD Support**

Hemodynamic measurements in the operating room at the time of LVAD placement were available in 21 of 23 patients. LVAD placement was associated with an immediate decrease in pulmonary artery systolic pressure from 54±2 to 36±1 mm Hg (P<0.0001) and a decrease in pulmonary artery diastolic pressure from 31±1 to 17±1 mm Hg (P<0.0001). These marked reductions in pulmonary artery systolic and diastolic pressures reflected immediate left ventricular decompression induced by the LVAD as documented by echocardiography in previous studies.9 In our patients, LVAD placement did not significantly reduce right atrial pressure (18±1 to 16±1 mm Hg), which is also consistent with previous studies.9,10

**Immediate ECG Responses**

The electrocardiographic changes observed immediately after LVAD placement are presented in Table 2. After the initiation of LVAD support, there was a significant decrease in average QRS duration (−13±4 ms). As shown in Figure 1, immediate decreases in QRS duration after LVAD support

<table>
<thead>
<tr>
<th>TABLE 1. LVAD Patient Demographics and Clinical Characteristics</th>
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48±3 19 13 30±6 2 2 10±1 4

Male 13 Nonischemic
Female 4 10 Ischemic

CHF indicates congestive heart failure; RBBB, right bundle branch block; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction.

**Immediate and Delayed Changes in ECG Parameters After LVAD Support**

<table>
<thead>
<tr>
<th>ECG Parameter</th>
<th>Pre-LVAD</th>
<th>Immediate Post-LVAD</th>
<th>Delayed Post-LVAD</th>
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<tr>
<td>Heart rate (bpm)</td>
<td>107±3</td>
<td>108±4</td>
<td>91±3†∥</td>
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<td>PR interval (ms)</td>
<td>168±6</td>
<td>158±6</td>
<td>170±5*</td>
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<td>QRS duration (ms)</td>
<td>117±6</td>
<td>103±6†</td>
<td>108±6</td>
</tr>
<tr>
<td>QT interval (ms)</td>
<td>359±6</td>
<td>378±8*</td>
<td>364±9</td>
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<tr>
<td>QTc-Bazett (ms)</td>
<td>479±10</td>
<td>504±11†</td>
<td>445±9‡ §</td>
</tr>
<tr>
<td>QTc-Fridericia (ms)</td>
<td>435±8</td>
<td>458±9†</td>
<td>416±9</td>
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</table>

*P<0.05 vs preceding period; †P<0.01 vs preceding period; ‡P<0.001 vs preceding period; §P<0.05 Pre-LVAD vs Delayed Post-LVAD; ||P<0.001 Pre-LVAD vs Delayed Post-LVAD.
Average changes in surface ECG parameters between preoperative recordings and immediate postoperative recordings among 23 patients undergoing LVAD placement (solid bars) and 22 patients undergoing coronary artery bypass grafting (CABG, open bars). Data are presented as mean ± SEM. *P<0.05 between groups; **P<0.01 between groups; ***P<0.001 between groups.

Figure 2. Average changes in surface ECG parameters between preoperative recordings and immediate postoperative recordings among 23 patients undergoing LVAD placement (solid bars) and 22 patients undergoing coronary artery bypass grafting (CABG, open bars). Data are presented as mean ± SEM. *P<0.05 between groups; **P<0.01 between groups; ***P<0.001 between groups.

Discussion
The major findings of this investigation are that mechanical circulatory support of the failing human heart with a LVAD...
induces both immediate and delayed changes in cardiac electrophysiology. LVAD placement was associated with an immediate decrease in the QRS interval, indicating load-dependent changes in intraventricular conduction. Immediate effects of unloading also included an unexpected increase in the QT interval, reflecting slowed myocardial repolarization. Neither of these changes was observed among patients undergoing coronary artery bypass grafting without myocardial unloading. Over a period of weeks to months after LVAD placement, our findings indicate further electrophysiologic remodeling with a delayed decrease in the heart rate–adjusted QT interval consistent with acceleration of myocardial repolarization. In vitro data from hearts explanted at the time of transplantation suggests that this secondary change in QT duration may reflect a shortening of cardiac myocyte action potential duration compared with failing myocytes without antecedent LVAD support. Shortening of action potential duration during sustained myocardial unloading suggests one mechanism contributing to the increased rate of myocyte relaxation previously observed after sustained LVAD support.5

Early Decreases in QRS Duration After Unloading

One of the most striking and consistent findings observed immediately after LVAD placement was a decrease in QRS duration. The absence of such immediate decreases in QRS duration among the patients undergoing coronary artery bypass grafting suggests that reduced cardiac distension, rather than other aspects of cardiac surgical intervention (eg, anesthesia, sternotomy, cardiopulmonary bypass) was responsible. Previous studies have conflicted regarding the antecedent LVAD support.5

Early Increases in QT Duration After Unloading

We observed that LVAD placement induced consistent increases in QT and QTc intervals, which suggests prolongation of overall myocardial repolarization caused by altered conduction and/or increased average action potential duration. The absence of similar effects in coronary artery bypass graft patients suggests that reduced cardiac distension, rather than other aspects of cardiac surgical intervention, was responsible for changes in repolarization. The increases in QT and QTc occurred despite significant decreases in QRS duration that would be expected to shorten myocardial repolarization. Thus, QT and QTc prolongation probably reflect acute increases in myocyte action potential duration immediately after cardiac decompression rather than a defect in cardiac conduction. While Pye and Cobbe13 demonstrated shorted action potential duration with increasing load, Zhu et al12 observed a prolonged effective refractory period with reduced preload. Both observations were more pronounced in failing hearts; therefore, in the present study, it seems likely that acute mechanical unloading with LVAD placement acutely increases action potential duration.

Small changes in the ionic currents during the plateau phase of the action potential can either hasten or delay cellular repolarization.14 At least two possible explanations could explain the acute prolongation of action potential by reduced cardiac distension. Inactivation of the swelling-activated chloride channel (Iclswell), that is present in heart failure15 could cause a prolongation of action potential duration. As an outward rectifying current, Iclswell tends to shorten action potential duration when activated by cell swelling or mechanical distension.16 Iclswell has been shown to be present in human myocardium16 and is increased in a canine model of tachycardia-induced heart failure.17 Inactivation of Iclswell in severely failing hearts may induce an immediate increase in action potential duration.

Increased forward-mode Na\(^+\)Ca\(^{2+}\) exchange might also produce an inward current that would prolong QT and QTc with immediate unloading. Acute unloading of the ventricle, reflected by intraoperative hemodynamic measurements, is likely associated with a decrease in overall sarcomere length during the cardiac cycle. Previous studies have demonstrated that shorter sarcomere length decreases myofilament Ca\(^{2+}\) sensitivity.18 Such decreased Ca\(^{2+}\) sensitivity would decrease Ca\(^{2+}\) binding to myofilaments and increase the cytosolic free Ca\(^{2+}\) concentration thereby increasing forward-mode Na\(^+\):Ca\(^{2+}\) exchange (3 Na\(^+\) in:1 Ca\(^{2+}\) out) and increasing action potential duration after cardiac decompression. Of course, such putative mechanisms for immediate changes in QT and QTc after LVAD placement are speculative at this point.

Decreases in QTc and APD During Sustained Unloading

Despite sustained cardiac unloading, the delayed effects of LVAD support on myocardial repolarization were distinct and opposite from the acute effects. We observed significant reductions in the heart rate–corrected QT interval regardless

![Figure 3](http://circ.ahajournals.org/)
of which methodology of heart rate correction was used. Our
in vitro data strongly supports the hypothesis that delayed
decreases in QTc reflected decreases in average action
potential duration among myocytes from LVAD-supported
hearts. Action potential prolongation is one of the signature
abnormalities in failing human hearts.19 Delayed decreases in
QTc and action potential duration, observed during sustained
LVAD support, suggests a reversal of the electrophysiologic
remodeling characteristic of the failing human heart.1 In
previous studies, chronic LVAD support has induced the
regression of left ventricular and myocardial hypertrophy.
LVAD support has been associated with improvements in
contractile performance,5 cellular relaxation,5 Ca++ homeostasis,
and adrenergic responsiveness compared with failing hearts without LVAD support. The present study adds to a growing body of evidence that LVAD support induces recovery of failing hearts and provides a novel model system for identifying pivotal mechanisms of myocardial
plasticity and recovery.

Interestingly, electrophysiologic remodeling with sustained
ventricular unloading appears to occur within the first month
after LVAD placement. Specifically, the 7 patients with
LVAD durations of <1 month showed significant reductions
in QTc which were not different from those observed with
longer durations of LVAD support.

Potential Significance of Electrophysiological
Reverse Remodeling
Although changes in the surface ECG clearly reflect changes
in conduction and repolarization at the tissue level, to our
knowledge, this is the first demonstration of parallel shifts in
the QT interval and cellular repolarization in human hearts. In
addition to its role as a marker of pathological hypertrophy
and failure, increasing evidence indicates that increased
action potential duration contributes to abnormal excitation-
contraction coupling in the failing heart.1,10 Through direct
actions on voltage-dependent processes, such as Ca++ entry
through the L-type Ca++ channel and Na+ -Ca++ exchange,
action potential duration has a profound impact on both the
amplitude of cellular contraction and the timing of cellular
relaxation.23,24 Shortening of action potential duration after
LVAD support likely contributes to the faster cellular relaxation
and improved force-frequency relationship.25 Given
that Ca++-dependent processes have been implicated in
pathological gene expression in the failing heart,26 decreases
in action potential duration could also contribute to LVAD-
duced changes in myocardial gene expression.10,21,25,26

Prolonged depolarization, as well as heterogeneous depo-
larization (QT dispersion), contributes to arrhythmogenesis in
failing hearts.27 This is clearly demonstrated by the increased
risk of sudden death associated with both familial long QT
syndromes and drug-induced QT prolongation. Previous stud-
ies have demonstrated that QT prolongation is associated
with increased QT dispersion.28-32 We may therefore speculate
that the LVAD-induced decreases in action potential and
QTc durations could reduce the risk of spontaneous ventricu-
lar arrhythmias. However, changes in medications, chamber
distension, and neurohormonal activation typically associated
with sustained LVAD support will render it difficult to define

a cause-and-effect relationship between faster repolarization
and arrhythmia risk during LVAD support.

To date, most of the physiological and molecular evidence
of reverse remodeling with LVAD support has relied on
tissue-based analyses, particularly applied to heart tissue
obtained at the time of transplantation. Therefore, another
implication of the present studies is that a set of noninvasive
parameters, including those derived from the surface ECG,
could inform assessments of myocardial recovery and guide
therapeutic strategies.

Study Limitations
In most cases, we were limited to a single delayed ECG to
demonstrate the time course of decreases in QTc. Similarly,
although recent studies highlight the prognostic importance
of abnormalities in QT dispersion, our retrospective study did
not permit demonstration of alterations in temporal QT
dispersion that would require prolonged rhythm analysis.
Because conduction velocity was not measured directly, we
could not determine if immediate decreases in QRS duration
were the result of changes in cardiac geometry versus
changes in intraventricular conduction velocity. There is no
ideal method of heart rate adjustment of the absolute QT
interval. However, it is reassuring that all the changes in QTc
were observed regardless the method used. We could not
exclude the possibility that changes in medications or sec-
ondary neurohormonal changes contributed to the delayed
electrophysiological changes we observed. Our findings sup-
port the concept of early and delayed load-dependent changes
in cardiac electrophysiology among patients with medically
refractory end-stage heart failure. These results may not be
applicable to individuals with less advanced heart failure.

Conclusions
Many of the defects associated with advanced heart failure
are modulated and sustained by increased hemodynamic
loading conditions. Abnormalities of ECG and action poten-
tial shape and duration demonstrated consistent and striking
improvements with sustained mechanical circulatory support.
Parallel observations at the cellular and organ level validate
the use of in vitro techniques for discerning the bases of
defects in failing hearts and demonstrate the potential to
translate such insights into clinically relevant diagnostic and
therapeutic strategies.

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