Cardiac contractility modulation by electric currents applied during the refractory period

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Am J Physiol Heart Circ Physiol 282: H1642–H1647, 2002. First published January 17, 2002; 10.1152/ajpheart.00959.2001.—Inotropic effects of electric currents applied during the refractory period have been reported in cardiac muscle in vitro using voltage-clamp techniques. We investigated how electric currents modulate cardiac contractility in normal canine hearts in vivo. Six dogs were instrumented to measure regional segment length, ventricular volume (sonomicrometry), and ventricular pressure. Cardiac contractility modulating (CCM) electric currents (biphasic square pulses, amplitude ±20 mA, total duration 30 ms) were delivered during the refractory period between pairs of electrodes placed on anterior and posterior walls. CCM significantly increased index of global contractility ($E_{os}$) from 5.9 ± 2.9 to 8.3 ± 4.6 mmHg/ml with anterior CCM, from 5.3 ± 1.8 to 8.9 ± 4.0 mmHg/ml with posterior CCM, and from 6.1 ± 2.6 to 11.0 ± 7.0 mmHg/ml with combined CCM ($P < 0.01$, no significant change in volume axis intercept). End-systolic pressure-segment length relations showed contractility enhancement near CCM delivery sites, but not remotely. Relaxation was not influenced. CCM increased mean aortic pressure, but did not change peripheral resistance. Locally applied electrical currents enhanced global cardiac contractility via regional changes in myocardial contractility without impairing relaxation in situ.

might have application as a therapy for heart failure. It has recently been demonstrated (3) that extracellularly applied electric signals have a similar effect as voltage clamping in muscles isolated from normal animals and failing human hearts. In addition, when applied regionally, electrical currents can enhance contractility of normal and failing hearts in situ (3, 14). Preliminary evidence suggests that the such cardiac contractility modulating (CCM) signals can also increase contractility in patients with heart failure (13).

One major question arising regarding the mechanism by which electric currents enhance myocardial contractility in vivo is whether increased contractility of the whole heart is a consequence of regional effects on contractility or do these signals have more global effects on remote portions of the heart.

To gain understanding of their effects on ventricular contractile performance, the main purpose of the present study was to test the hypothesis that regionally applied CCM signals exert their inotropic effects in normal dog hearts only in the region of application. This was accomplished by indexing global and regional function through the use of load-independent indexes of contractility derived from global pressure-volume and regional pressure-segment length analyses.

METHODS

The animals involved in this study received humane care in compliance with the Guide for the Care and Use of Laboratory Animals published by the National Institutes of Health (NIH Publication No. 85-23, Revised 1985). This study was approved by the Institutional Animal Care and Use Committee of Columbia University.

Surgical preparation. The main part of this study was conducted in six mongrel dogs of either sex weighing between 26 and 31 kg. A thoracotomy was performed in the left fifth intercostal space with the dogs anesthetized with pentobarbital sodium (30 mg/kg iv) and under artificial ventilation. Left ventricular (LV) pressure was measured by a

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catheter tip transducer (Millar; Houston, TX) placed inside the LV from the right carotid artery. A transit time ultrasonic flow probe (Transonic Systems; Ithaca, NY) was placed on the ascending aorta to measure aortic flow. A piece of umbilical tape was placed loosely around the inferior vena cava for temporary occlusion (IVCO). Temporary pacing wires (Medical Corp.; Farmingdale, NJ) were placed on the right atrium for pacing. Two additional sets of four temporary pacing wires were inserted intramyocardially. As illustrated in Fig. 1, one set was placed on the anterior wall and the other on the posterior wall. These electrodes were used for delivering cardiac CCM signals (outer 2 electrodes, ~3 cm apart) and for detecting local bipolar electrograms (inner 2 electrodes, ~1 cm apart). Twenty-eight ultrasound crystals positioned in the midmyocardium (Fig. 1) were used to sense local electrical activity. Twenty-eight sonomicrometer crystal (numbered circles) placement. Two pairs of these crystals, one pair in the anterior wall and one pair in the posterior wall, each oriented approximately in the in-fiber direction, were selected to assess regional contraction near the sites where CCM signals were delivered. All data were recorded by a digital sonomicrometer system that digitized recorded pressure signals and also measured and stored the distances between every possible pair of crystals every 10 ms (Sonometrics; London, Ontario, Canada).

**CCM signals.** All experiments were performed with right atrial pacing at a fixed rate between 120 and 150 beats/min, which was chosen to be ~10 beats/min greater than the spontaneous rate. CCM signals (Fig. 2) were biphasic square-wave current pulses with peak-to-peak amplitudes of ±20 mA and total duration of 30 ms (15 ms per phase). Signals were delivered 30 ms after the detection of local electrical activation (from the sensing leads) to ensure that they were delivered during the absolute refractory period.

**Protocol.** After completion of the surgical preparation, global and regional contractile properties were assessed by recording hemodynamic signals during temporary IVCO with the ventilator off. CCM signals were then delivered to the anterior wall, and IVCO was repeated after ~10 min to allow for steady-state conditions. The CCM signal was stopped for 15 min before performing the next control run. This sequence was repeated two more times for CCM signal delivery to the posterior wall and then to both anterior and posterior walls simultaneously.

**Data analysis.** Recorded signals were analyzed to provide global pressure-volume relations as well as anterior and posterior pressure-segment length relations. From the 28 crystals, 756 (~28–27) distances were measured in real time and stored for each run at 10-ms intervals. Signal with excessive noise as detected by an automated routine were excluded from analysis. The Cartesian coordinates (x,y,z) for each of the 28 crystals were determined for each time point using the included signals (typically >90% of 756 possible signals) by a least-squared, iterative, multivariate curve-fitting technique. Once the crystal locations were defined, the epicardial surface was defined using a surface triangulation method. Ventricular volume was then determined by summing the volumes of all individual tetrahedra formed by the surface triangles connected to a common arbitrary point internal to the ventricular surface. Pressure-volume loops were constructed by plotting instantaneous LVP versus LVV. Stroke volumes (SV) determined from the resulting loops obtained during each vena caval occlusion were plotted as a function of the beat-by-beat SV (true SV) measured directly from the aortic flow probe. This relationship was used to calibrate the gain of the sonomicrometer-derived volumes. Since the sonomicrometers were placed subepicardially, the estimated ventricular volume included the volume of a fraction of the myocardial wall. Because this fraction was fixed, but unknown in each experiment, no attempt was made to subtract the myocardial volume.

The end-systolic pressure-volume relationships (ESPVRs) were constructed in the usual fashion (15) and analyzed by linear regression to obtain the slope ($E_w$) and volume axis intercept ($V_o$). We also measured preload recruitable stroke work (PRSW) (5) as another index of global contractility by determining the slopes ($M_w$) and volume axis intercepts ($V_o$).
of the linear relationships between EDV and stroke work during IVCO. End-diastolic pressure-volume relationships (EDPVR) were also constructed and fit to a cubic equation (EDP = a + bV^3) with the parameter b providing an index of chamber compliance and a is intercept of pressure axis and V is end-diastolic volume. Contractile properties were also quantified by determining maximum (dP/dt_max) and minimum rate of pressure change (dP/dt_min) and the time constant of pressure decay during relaxation as indexed by the logistic time constant (τ_L) (8). For calculation of τ_L, we analyzed the time constant of isovolumic relaxation from the time of peak –dP/dt to the time when LVP fell to 5 mmHg above the EDP using a least-squares method performed in Delta Graph (Delta Point; Monterey, CA).

Regional contractile properties were assessed by the end-systolic pressure-segment length relationships (ESP,SLR) determined during the IVCOs. As in earlier studies (6, 7), linear regression analysis applied to these relations yielded a slope and segment length axis-intercept, which were used to index regional contractility. In addition, fractional regional shortening was calculated as 100 (EDSSL – ESSL)/EDSSL, where EDSL and ESSL are the end-diastolic and end-systolic segment lengths, respectively.

Finally, to test whether the CCM effects were limited to the heart or whether there were any associated systemic hemodynamic effects, we examined mean arterial pressure (MAP), cardiac output (CO), and total peripheral resistance (TPR) defined as MAP divided by CO.

Data are expressed as means ± SD. Linear regression lines (ESPVR, PRSW) were compared by analysis of covariance. Other parameters, such as dP/dt_max, dP/dt_min, and τ_L were compared by Student’s paired t-tests.

RESULTS

CCM signals effects on global contractility are due to effects on regional contractility. Representative pressure-volume loops and pressure-segment loops during IVCO are shown in Fig. 3. With either anterior, posterior, or combined CCM signal application, there is a leftward shift of the global ESPVR (increased global contractility). There were no detectable changes in either the global EDPVR or the local EDPSLRs under any circumstance.

With anterior CCM signal administration, there was a clear and significant leftward shift of the anterior ESPSLR, indicating an increase in regional contractility. In the posterior wall, however, although there was a change in the regional pressure-segment length loop shape with an increase of systolic pressure, the ESPSLR was the same before and during anterior CCM signal administration, indicating no change in posterior wall contractility. Conversely, with posterior CCM signal there was increased contractility of the posterior region with changes in the anterior pressure-segment length loop shape due predominantly to changes in loading conditions without change in anterior wall contractility. When CCM signals were applied simultaneously to anterior and posterior walls, contractility was increased in both walls. Fractional shortening, however, was not changed under any condition, which was a result of the changes in regional pre-

Fig. 3. Representative left ventricular pressure (LVP)-left ventricular volume (LVV) loops (top) and pressure-segment length loops from the anterior (middle), and posterior (bottom) segments. Baseline loops just before the respective CCM delivery are shown in black. Loops during anterior CCM signal delivery shown in red, posterior CCM delivery in blue, and combined (simulta-
neous anterior and posterior) CCM delivery in purple. Increases in global contractility were due to local increases in contractility with changes in loading sequence (i.e., change in shape of pressure-segment length loop). See text for further details.
and afterload that occur with CCM stimulation (discussed further below).

On average, regional contractility (Table 1) was increased significantly at the CCM administration site mainly due to an increase in the slope of the local ESPSR with little change in the segment length intercept (S₀). Slope values increased by ~80% from their baseline values, indicating substantial increases in regional contractility due to CCM. On average, anterior and posterior stimulation caused comparable increases in global contractility as indexed by ~30% increase in E₉₀ with little effect on V₀ (Table 2). However, there were individual variations between hearts as to which region provided the greatest increase in global contractility. Combined stimulation generally resulted in the greatest increase in E₉₀. The slope of the PRSW relationship similarly indicated an increase in global contractility with either anterior, posterior, or combined. Finally, dP/dtₘₐₓ was increased comparably by either anterior (23.3 ± 12.0%) or posterior (26.0 ± 9.3%) stimulation and slightly more (31.3 ± 12.5%) by combined stimulation. There was no statistically significant effect on end-diastolic function (indexed by b) or the rate of pressure decay (indexed by dP/dtₘᵢₙ or τₐ). MAP increased comparably with single or combined CCM signal delivery. Once the signal is stopped, all parameters return to baseline conditions within 1 min.

As seen in the example of Fig. 3 and summarized in Table 3, CCM signals also had small but statistically significant influences on regional and global preload. Global preload indexed by end-diastolic volume decreased. Regional preload, indexed by end-diastolic segment length, decreased in the region of signal application, but increased in the remote region (despite the reduction in global volume). Thus, despite no direct effect on contractility, contractile activity can be affected in areas remote to the CCM signal site by alterations in preload.

**DISCUSSION**

Application of electrical currents during the refractory period can enhance contractility regionally in normal anesthetized, open-chest dog hearts in vivo. The effect on regional contractility is substantial, amounting to an ~80% increase in the slope of the local ESPSR with no significant inotropic effect on remote myocardium. This enhancement of regional contractility was not accompanied by significant changes in MAP, CO, or TPR.

### Table 1. Slope and S₀ of regional end-systolic pressure-segment length relationship and as a function of CCM stimulation site

<table>
<thead>
<tr>
<th>Condition</th>
<th>Anterior Wall</th>
<th>Posterior Wall</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Slope, mmHg/mm</td>
<td>S₀, mm</td>
</tr>
<tr>
<td>Control</td>
<td>43.1 ± 16.6</td>
<td>23.7 ± 6.26</td>
</tr>
<tr>
<td>Anterior CCM</td>
<td>76.5 ± 26.9</td>
<td>23.8 ± 6.41</td>
</tr>
<tr>
<td>Control</td>
<td>47.9 ± 18.2</td>
<td>24.0 ± 6.47</td>
</tr>
<tr>
<td>Posterior CCM</td>
<td>44.1 ± 19.4</td>
<td>23.7 ± 6.58</td>
</tr>
<tr>
<td>Control</td>
<td>47.4 ± 14.7</td>
<td>24.0 ± 6.42</td>
</tr>
<tr>
<td>Combined CCM</td>
<td>104 ± 27.3</td>
<td>24.3 ± 6.89</td>
</tr>
</tbody>
</table>

Values are means ± SD; n = 6 hearts. CCM, cardiac contractility modulating; S₀, segment length intercept; FS, fractional shortening.

### Table 2. E₉₀ and V₀ of the global end-systolic pressure-volume relationship, magnitude of b, dP/dt_max, dP/dt min, and τₐ, as a function of CCM stimulation site

<table>
<thead>
<tr>
<th>Condition</th>
<th>E₉₀, mmHg/ml</th>
<th>V₀, ml</th>
<th>M₀, mmHg</th>
<th>Vₐ, ml</th>
<th>b, ×10⁻⁵</th>
<th>dP/dt_max, mmHg/s</th>
<th>dP/dt_min, mmHg/s</th>
<th>τₐ, ms</th>
<th>MAP, mmHg</th>
<th>CO, l/min</th>
<th>TPR, mmHg/min⁻¹⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>7.75 ± 4.33</td>
<td>52.2 ± 10.3</td>
<td>63.25 ± 21.16</td>
<td>66.95 ± 14.15</td>
<td>5.98 ± 5.12</td>
<td>1.344 ± 265</td>
<td>−1.230 ± 201</td>
<td>31 ± 8</td>
<td>96 ± 8</td>
<td>1.72 ± 0.65</td>
<td>62 ± 18</td>
</tr>
<tr>
<td>Anterior CCM</td>
<td>9.97 ± 6.02*</td>
<td>52.6 ± 9.9</td>
<td>63.89 ± 24.93*</td>
<td>65.13 ± 11.82</td>
<td>5.67 ± 4.36</td>
<td>1.775 ± 350*</td>
<td>−1.206 ± 175</td>
<td>31 ± 6</td>
<td>106 ± 12</td>
<td>1.86 ± 0.73</td>
<td>65 ± 22</td>
</tr>
<tr>
<td>Control</td>
<td>7.53 ± 3.45</td>
<td>53.7 ± 9.8</td>
<td>61.8 ± 21.13</td>
<td>65.11 ± 12.52</td>
<td>6.21 ± 4.70</td>
<td>1.324 ± 229</td>
<td>−1.207 ± 289</td>
<td>32 ± 7</td>
<td>99 ± 12</td>
<td>1.63 ± 0.44</td>
<td>65 ± 17</td>
</tr>
<tr>
<td>Posterior CCM</td>
<td>9.15 ± 4.24*</td>
<td>53.6 ± 11.0</td>
<td>68.40 ± 22.94*</td>
<td>65.88 ± 15.27</td>
<td>6.30 ± 5.25</td>
<td>1.818 ± 421*</td>
<td>−1.161 ± 289</td>
<td>35 ± 8</td>
<td>108 ± 11*</td>
<td>1.67 ± 0.42</td>
<td>68 ± 15</td>
</tr>
<tr>
<td>Control</td>
<td>7.33 ± 3.72</td>
<td>52.2 ± 11.4</td>
<td>61.58 ± 24.29</td>
<td>65.82 ± 12.03</td>
<td>5.94 ± 5.30</td>
<td>1.288 ± 256</td>
<td>−1.208 ± 254</td>
<td>32 ± 7</td>
<td>95 ± 8</td>
<td>1.50 ± 0.31</td>
<td>60 ± 20</td>
</tr>
<tr>
<td>Combined CCM</td>
<td>12.04 ± 7.20*</td>
<td>55.3 ± 11.9</td>
<td>73.44 ± 27.89*</td>
<td>64.43 ± 12.98</td>
<td>5.38 ± 4.55</td>
<td>1.934 ± 454*</td>
<td>−1.285 ± 260</td>
<td>31 ± 6</td>
<td>105 ± 17</td>
<td>1.58 ± 0.48</td>
<td>71 ± 21</td>
</tr>
</tbody>
</table>

Values are means ± SD; n = 6 hearts. E₉₀, slope; V₀, volume axis intercept; M₀, slope; Vₐ, volume axis intercept; b, magnitude of end-diastolic pressure-volume relationship; dP/dt_max and dP/dt_min, maximum and minimum rate of pressure change; τₐ, logistic time constant of relaxation; MAP, mean arterial pressure; CO, cardiac output; TPR, total peripheral resistance. Statistically different (*P < 0.01 or †P < 0.05) from respective control condition by ANCOVA for slope and V₀ values and by paired t-test for other parameters.
creased calcium release to the myo
transsarcolemmal calcium entry. This in turn causes
potential duration by CCM signals, which enhances
shown to fundamentally relate to an increase in action
myocardial contractility (3). The mechanism has been
rated papillary muscles in vitro, CCM signals increase
decay.

indexed by global and regional ESPVR or pressure-
critical change in active or passive diastolic properties as
/H11011
30% with dual-site stimulation. There was no signif-
ificant change in electrode con
fi
ction.

Values are means ± SD; n = 6 hearts. EDSL, end-diastolic segment length. *P < 0.05 vs. control by paired t-test.

Chronic inotropic drug therapies for heart failure have been shown to worsen survival and increase the need for hospitalization (10, 12). This has been postulated to be due to detrimental effects of continual β-adrenergic pathway stimulation (by β-agonists and phosphodiesterase inhibitors), which worsens myocardial contractility, induces arrhythmias, and has potentially unfavorable systemic effects. Intermittent, short-term intravenous inotropic therapy, on the other hand, is commonly employed to treat heart failure exacerbations. It is envisioned that CCM signals could be delivered therapeutically via a pacemaker-like device in a manner akin to intermittent short-term inotropic therapy. They could be delivered for relatively short periods of time (e.g., hours per day). Some of the detri-

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REFERENCES


