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# Cardiac contractility modulation by electric currents applied during the refractory period

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Cardiac contractility modulation by electric currents applied during the refractory period. *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  $\pm 20$  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 ( $E_{es}$ ) from  $5.9 \pm 2.9$  to  $8.3 \pm 4.6$  mmHg/ml with anterior CCM, from  $5.3 \pm 1.8$  to  $8.9 \pm 4.0$  mmHg/ml with posterior CCM, and from  $6.1 \pm 2.6$  to  $11.0 \pm 7.0$  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.

canine heart; calcium; in situ heart failure; voltage clamping

PROLONGATION OF MEMBRANE depolarization by voltage-clamp techniques applied to isolated superfused cardiac muscle have long been known to increase transsarcolemmal calcium entry and thus enhance contractility (2, 17). Because voltage-clamp techniques are not applicable in situ, this approach has not been explored as a means of enhancing contractility of the intact heart, although, if possible, such an approach

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 (LVP) 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 estimate LV volume (LVV, as detailed in *Data analysis*). In addition, 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 sonomicrometry 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  $\pm 20$  mA and total duration of 30 ms (15 ms per phase). Signals

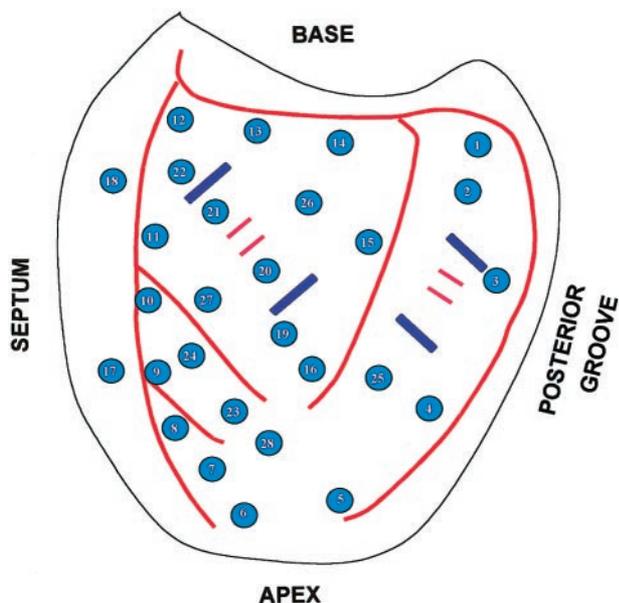


Fig. 1. Schematic diagram of the stitch electrode (red lines) and sonomicrometry crystal (numbered circles) placement. Two pairs of electrodes were placed to deliver cardiac contractility modulating (CCM) signals to the anterior and posterior walls (blue bars, inter-electrode distance ~3 cm for each pair). Two additional stitch electrode pairs (pink bars) placed at center of each CCM electrode pair were used to sense local electrical activity. Twenty-eight sonomicrometry crystals were placed subepicardially for measurement of left ventricular (LV) volume as detailed in the text. Two pairs of the crystals located in the vicinity of the CCM electrodes and oriented in the fiber direction (for example, *electrodes 11–27 and 3–25*) were used to measure regional segment length and the anterior and posterior walls.

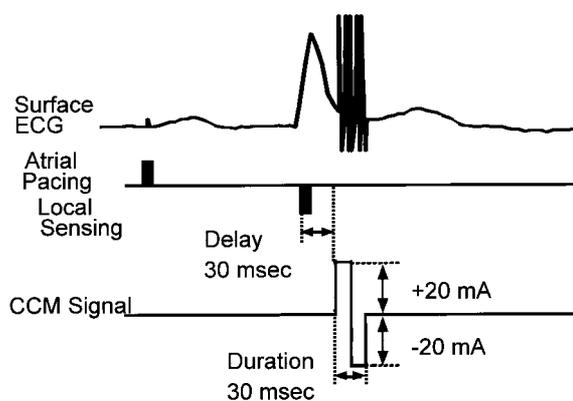


Fig. 2. Timing and characteristics of CCM signal. Experiments were performed with right atrial pacing. CCM signal (biphasic current pulse,  $\pm 20$  mA, 15 ms/phase) was delivered 30 ms after detection of myocardial activation near the CCM site (local sensing).

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 ( $E_{es}$ ) 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 ( $V_w$ )

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 ( $\tau_L$ ) (8). For calculation of  $\tau_L$ , 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 (ESPSSLR) 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  $100 \cdot (EDSL - ESSL) / EDSL$ , 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  $\pm$  SD. Linear regression lines (ESPVR, PRSW) were compared by analysis of covariance. Other parameters, such as  $dP/dt_{max}$ ,  $dP/dt_{min}$ , and  $\tau_L$  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-

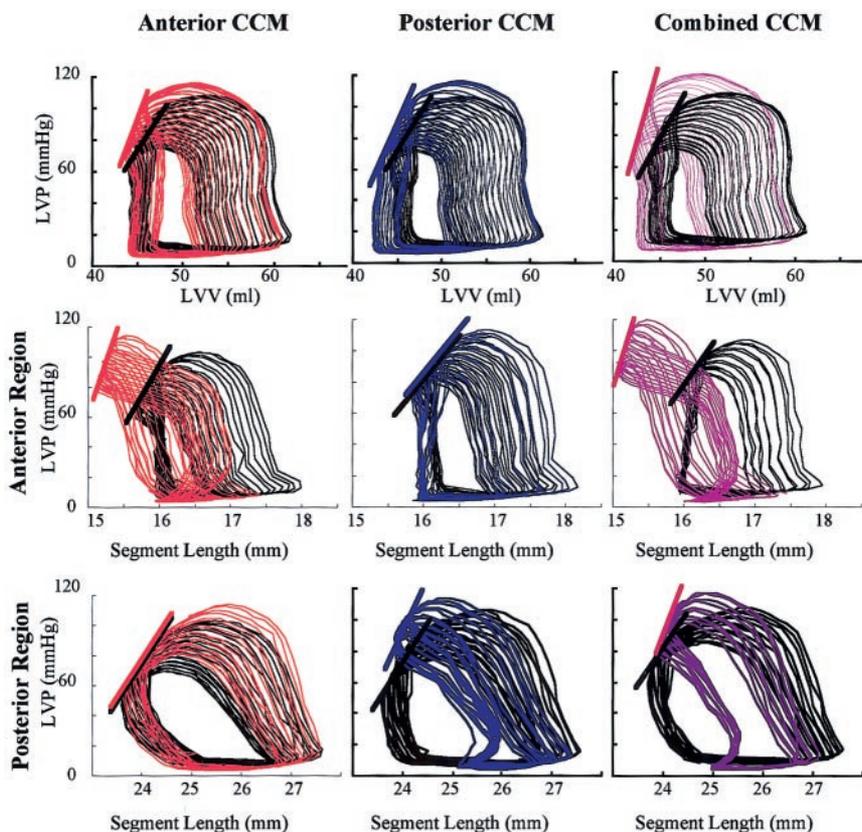


Fig. 3. Representative left ventricular pressure (LVP)-left ventricular volume (LVV) loops (*top*) and pressure-segment length loops from the anterior (*middle*), and posterior (*bottom*) segments. Baseline loops just before the respective CCM delivery are shown in black. Loops during anterior CCM signal delivery shown in red, posterior CCM delivery in blue, and combined (simultaneous 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.

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

Condition	Anterior Wall			Posterior Wall		
	Slope, mmHg/mm	$S_o$ , mm	FS, %	Slope, mmHg/mm	$S_o$ , mm	FS, %
Control	43.1 ± 16.6	23.7 ± 6.26	9.26 ± 1.41	38.5 ± 9.52	26.7 ± 8.27	8.80 ± 3.57
Anterior CCM	76.5 ± 26.9*	23.8 ± 6.41	8.95 ± 2.34	38.2 ± 6.18	28.6 ± 8.73	9.08 ± 4.10
Control	47.9 ± 18.2	24.0 ± 6.47	8.47 ± 1.18	42.6 ± 19.9	26.6 ± 8.19	8.57 ± 3.66
Posterior CCM	44.1 ± 19.4	23.7 ± 6.58	10.1 ± 1.61	76.0 ± 31.6*	27.1 ± 8.04	8.37 ± 3.69
Control	47.4 ± 14.7	24.0 ± 6.42	9.28 ± 2.04	45.3 ± 26.5	26.8 ± 8.17	8.91 ± 3.44
Combined CCM	104 ± 27.3*	24.3 ± 6.89	8.77 ± 2.09	90.0 ± 41.6*	27.1 ± 7.91	8.70 ± 3.46

Values are means ± SD;  $n = 6$  hearts. CCM, cardiac contractility modulating;  $S_o$ , segment length intercept; FS, fractional shortening. \*Statistically different ( $P < 0.01$ ) from respective control condition by ANCOVA.

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 ESPSLR with little change in the segment length intercept ( $S_o$ ). 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  $E_{es}$  with little effect on  $V_o$  (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  $E_{es}$ . The slope of the PRSW relationship similarly indicated an increase in global contractility with either anterior, posterior, or combined. Finally,  $dP/dt_{max}$  was increased comparably by either anterior ( $23.3 \pm 12.0\%$ ) or posterior ( $26.0 \pm 9.3\%$ ) stimulation and slightly more ( $31.3 \pm 12.5\%$ ) by combined stimulation. There was no statistically significant effect on end-diastolic function (indexed by  $b$ ) or the rate of pressure decay (indexed by  $dP/dt_{min}$  or  $\tau_L$ ). 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.

*No effect of CCM on TPR.* To test whether CCM signals are associated with systemic effects, we looked for changes in TPR (Table 2). Such changes could be mediated by norepinephrine release into the blood stream from the heart or by autonomic reflex effects. CCM signal application was associated with slight increases in MAP, no statistically significant increase in CO, and no significant effect on TPR.

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 ESPSLR with no significant inotropic effect on remote myocardium. This enhancement of regional contractil-

Table 2.  $E_{es}$  and  $V_o$  of the global end-systolic pressure-volume relationship, magnitude of  $b$ ,  $dP/dt_{max}$ ,  $dP/dt_{min}$ , and  $\tau_L$  as a function of CCM stimulation site

Condition	$E_{es}$ , mmHg/ml		$M_w$ , mmHg	$V_w$ , ml	$b$ , $\times 10^{-5}$	$dP/dt_{max}$ , mmHg/s	$dP/dt_{min}$ , mmHg/s	$\tau_L$ , ms	MAP, mmHg	CO, l/min	TPR, mmHg·min $^{-1}$
	$V_o$ , ml	$M_w$ , mmHg									
Control	7.75 ± 4.33	52.2 ± 10.3	63.25 ± 21.16	66.93 ± 14.15	5.98 ± 5.12	1,344 ± 265	-1,230 ± 201	31 ± 8	96 ± 8	1.72 ± 0.65	62 ± 18
Anterior CCM	9.97 ± 6.02*	52.6 ± 9.9	68.39 ± 24.93*	65.13 ± 11.82	5.67 ± 4.36	1,775 ± 350*	-1,206 ± 175	31 ± 6	106 ± 12	1.86 ± 0.73	65 ± 22
Control	7.53 ± 3.45	53.7 ± 9.8	61.8 ± 21.13	65.11 ± 12.52	6.21 ± 4.70	1,324 ± 229	-1,207 ± 289	32 ± 7	99 ± 12	1.63 ± 0.44	65 ± 17
Posterior CCM	9.15 ± 4.24*	53.6 ± 11.0	68.40 ± 22.94*	65.88 ± 15.27	6.30 ± 5.25	1,818 ± 421†	-1,161 ± 289	35 ± 8	108 ± 11†	1.67 ± 0.42	68 ± 15
Control	7.33 ± 3.72	52.2 ± 11.4	61.58 ± 24.29	63.82 ± 12.03	5.94 ± 5.20	1,298 ± 269	-1,208 ± 254	32 ± 7	95 ± 8	1.50 ± 0.31	66 ± 20
Combined CCM	12.04 ± 7.20*	55.3 ± 11.9	73.44 ± 27.89*	64.43 ± 12.98	5.38 ± 4.55	1,934 ± 454†	-1,285 ± 260	31 ± 6	105 ± 17	1.58 ± 0.48	71 ± 21

Values are means ± SD;  $n = 6$  hearts.  $E_{es}$ , slope;  $V_o$ , volume axis intercept;  $M_w$ , slope;  $V_w$ , 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;  $\tau_L$ , 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  $V_o$  values and by paired  $t$ -test for other parameters.

Table 3. Changes in regional and global preload indexed by EDSL and end-diastolic volume, respectively, in response to CCM signals

CCM Delivery Site	Anterior Wall EDSL, mm		Posterior Wall EDSL, mm		End-Diastolic Volume, ml	
	Control	CCM	Control	CCM	Control	CCM
Anterior CCM	28.4 ± 6.5	27.8 ± 7.1*	31.7 ± 9.0	32.1 ± 9.1	71.9 ± 13.8	70.9 ± 14.0*
Posterior CCM	27.9 ± 6.0	28.2 ± 6.4*	32.0 ± 9.4	31.7 ± 9.1*	71.6 ± 14.5	70.9 ± 14.1*
Combined CCM	28.1 ± 6.1	27.4 ± 6.7*	31.6 ± 9.3	31.3 ± 9.1*	71.2 ± 3.4	69.5 ± 14.7*

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

ity translates to an ~30% increase in global  $E_{es}$  for single-site stimulation and ~70% increase in global  $E_{es}$  with dual-site stimulation. Similarly, increases in  $dP/dt_{max}$  averaged 25% for single-site stimulation and ~30% with dual-site stimulation. There was no significant change in active or passive diastolic properties as indexed by global and regional ESPVR or pressure-segment length relationships, respectively, by time constant of relaxation or by maximum rate of pressure decay.

Prior studies have shown that when applied to isolated papillary muscles in vitro, CCM signals increase myocardial contractility (3). The mechanism has been shown to fundamentally relate to an increase in action potential duration by CCM signals, which enhances transsarcolemmal calcium entry. This in turn causes calcium loading of the sarcoplasmic reticulum and increased calcium release to the myofilaments. In isolated intact ferret hearts, CCM signals have also been shown to have a marked influence on local intracellular calcium release (3). The present study has not examined the mechanism of local contractility enhancement by CCM signals in dog hearts in vivo. In addition to the mechanism discussed above, electrical stimulation of local nerve endings to release norepinephrine could be an additional contributing factor. Furthermore, although signal delays and durations are comparable to those used in earlier in vitro studies, comparison of in vitro and in vivo results is difficult because of the marked differences in electrode configurations, tissue-electrode interfaces, and the different electrical environments present in intact tissue and in a papillary muscle bath. Because of these factors, it is not possible to relate the current densities to which the myocardium is exposed under these two conditions.

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  $\beta$ -adrenergic pathway stimulation (by  $\beta$ -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-

mental effects of continuous intravenous inotropic therapies have also been attributed to systemic side effects (10). CCM signals have local myocardial effects and are devoid of systemic hemodynamic effects as suggested by our findings of the lack of effect on TPR.

The present study has been carried out in normal dogs, and inotropic effects may differ in the heart failure state. When compared with normal hearts, the hearts of patients with chronic heart failure are significantly dilated, the molecular properties of failing hearts is different, and patients take a multitude of drugs. It is therefore pertinent to note that preliminary studies have shown that CCM signals are inotropic in dogs with microembolization-induced chronic heart failure (14) and in patients with chronic heart failure (13) with currents of ~15 mA, which can, on average, enhance  $dP/dt_{max}$  by ~10–20% (13, 14). In addition, the hemodynamic effects of increased contractility may differ in normal and failing hearts. Specifically, the inotropic effects of CCM signals in the present study of normal hearts were associated with increases in blood pressure but no significant increase in CO. Prior studies of ventricular-vascular coupling (16) have indicated that when baseline contractility is decreased, positive inotropic intervention will have a greater impact on CO and less of an effect on blood pressure.

Many device-based therapies are now being investigated for treating the growing number of heart failure patients because despite improved pharmacological therapies, heart failure remains a progressive disorder (1, 11). Effective therapies that can be deployed relatively noninvasively have the potential for relatively wide-spread application. One such investigational therapy is biventricular pacing; preliminary results suggest that this may be effective in improving ventricular contractility and exercise tolerance in heart failure patients having baseline conduction delays (long QRS durations) (4, 9). The technology to deliver CCM therapy can also be implemented in a pacemaker-like device and in principle could be applicable to a significantly larger group of patients because the inotropic effects are not restricted to patients with baseline conduction delays. Future preclinical and clinical research aimed at understanding the mechanisms and effects of chronic CCM signal application in the setting of heart failure will define the potential of this concept as a therapy for heart failure.

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