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Mechanoelectrical Feedback

Role of β -Adrenergic Receptor Activation in Mediating Load-Dependent Shortening of Ventricular Action Potential and Refractoriness

Bruce B. Lerman, MD; Erica D. Engelstein, MD; Daniel Burkhoff, MD

Background—Augmented preload increases myocardial excitability by shortening action potential duration (APD). The mechanism governing this phenomenon is unknown. Because myocardial stretch increases intracellular cAMP, we hypothesized that load-dependent changes in myocardial excitability are mediated by β -adrenergic stimulation of a cAMP-sensitive K^+ current.

Methods and Results—The effects of propranolol on load-induced changes in electrical excitability were studied in 7 isolated ejecting canine hearts. LV monophasic APD at 50% and 90% repolarization (MAPD₅₀ and MAPD₉₀) and refractoriness were determined at low (9 ± 3 mL) and high (39 ± 4 mL) load before and after β -adrenergic blockade. During control, the MAPD₅₀ decreased from 193 ± 26 to 184 ± 26 ms with increased load, as did the MAPD₉₀ (238 ± 28 to 233 ± 28 ms), $P \leq 0.04$. Similar changes were observed in ventricular refractoriness. Treatment with propranolol completely abolished these load-induced effects. Myocardial catecholamine depletion with reserpine in 2 hearts also abolished changes in MAPD and excitability in response to increased preload.

Conclusions—Increases in ventricular load mediate a decrease in ventricular APD and refractoriness through activation of the β -adrenergic receptor. An increase in a cAMP-mediated K^+ current, possibly the slowly activating delayed rectifier I_{Ks} , may account in part for this form of mechanoelectrical coupling. (*Circulation*. 2001;104:486-490.)

Key Words: arrhythmias ■ electrophysiology ■ tachyarrhythmias ■ tachycardia

Mechanoelectrical feedback is the phenomenon whereby changes in myocardial loading conditions modulate cardiac electrophysiological properties and is thought to contribute to arrhythmogenesis in patients with impaired ventricular function and elevated filling pressures. The electrophysiological effects of augmented load have been primarily studied under 2 disparate conditions, ie, during transient stretch (typically ≤ 50 ms)¹ or steady-state increases in stretch (volume).^{2,3} The mechanism underlying the electrophysiological phenomena associated with transient stretch is thought to be related to cardiac mechanosensitive or stretch-activated channels.^{4,5} Activation of these channels during diastole results in an inward or depolarizing current, either prolonging action potential duration (APD) or giving rise to an afterdepolarization. Alternatively, stretch during phase 2 of the action potential, at membrane potentials positive to the reversal potential of these channels ($\geq \approx 0$ mV), can result in an outward current that polarizes and shortens the action potential.

A second form of mechanoelectrical feedback is observed under conditions of steady-state changes in preload. Increments in ventricular load that occur gradually and are sustained over time are associated with an increase in

electrical excitability and shortening of refractoriness due to a parallel decrease in APD.^{2,3,6} The cellular mechanism responsible for this form of mechanoelectrical coupling is generally unknown but has also been attributed to stretch-activated channels.^{7,8} We hypothesized that an alternative mechanism was responsible for this phenomenon and was related to load-mediated activation of the β -adrenergic receptor (β -AR), which in turn activates a catecholamine-sensitive K^+ repolarization current. The purpose of this study was to investigate whether load-induced changes in ventricular excitability and APD can be abolished either by pretreatment with β -AR blockade or by myocardial catecholamine depletion.

Methods

Surgical Preparation

All studies were performed in accordance with the guidelines of the American Physiological Society in a protocol approved by the Institutional Animal Care and Use Committee. Experiments were performed in 9 pairs of adult mongrel dogs. The methods used to isolate and support the canine hearts were similar to those previously described.⁹

In brief, 2 mongrel dogs were anesthetized with pentobarbital sodium (30 mg/kg IV). The femoral arteries and veins of the support

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dog were cannulated and connected to a perfusion system used to supply oxygenated blood to the isolated heart. Heparin (15 000 U IV bolus) was given after the arteries and veins were cannulated with tubing from the perfusion system. The second dog (donor dog) was mechanically ventilated, a midline sternotomy was performed, and the heart was removed. The left atrium was then opened, and the chordae tendineae were excised from the mitral valve leaflets. A metal adapter that held the isolated heart to the ventricular volume servopump system was sutured to the mitral ring. The right ventricular apex was vented to permit drainage of coronary venous blood. A water-filled balloon connected to the servopump system was inserted into the left ventricle (LV). A micromanometer (Millar PC 380) placed inside the balloon measured LV pressure. Pacing electrodes were sutured to the apex of the LV, and the heart was paced at a cycle length of 350 to 450 ms.

The coronary arterial pressure was controlled by a 2-pump servo system that maintained constant total flow from the support dog. The temperature of the perfusate was maintained at regular intervals, and sodium bicarbonate and oxygen were supplemented as needed.

Ejecting beats were produced by an impedance loading system that imposed a simulated arterial hydraulic impedance on the LV as described previously.¹⁰ A computer was programmed with the differential equations of the 3-element Windkessel model of aortic impedance. The 3 variables that determine the impedance are a proximal series resistance, peripheral arterial resistance, and arterial compliance. The computer digitizes the instantaneous LV pressure and calculates the appropriate instantaneous flow of the ventricle for a given aortic impedance. The flow signal is integrated digitally and converted to an analog signal, which is used as the command signal for the volume servo system.

Recorded parameters included LV pressure, LV volume, coronary perfusion pressure, LV end-systolic and end-diastolic volumes, epicardial monophasic APD (MAPD), and a surface ECG lead recorded between 2 electrodes sutured to the epicardium.

Experimental Protocol

MAPs were recorded from the epicardial surface of the LV with a contact electrode according to methods described previously.² The electrode provided continuous MAP recordings of stable amplitude, smooth contour, and isopotential diastolic baselines for a >1-hour period, allowing recordings before and after each intervention from the same site. Analysis of MAPD was performed manually at a paper speed of 200 mm/s.

Electrical excitability was quantified by the strength-interval relationship. The hearts were paced by use of bipolar stimulation from an epicardial electrode sutured on the midanterior LV wall, within 5 mm of the MAP electrode. Stimulation was performed with a programmable stimulator and isolated constant-current source.

The stimulation protocol used to determine the stimulus strength-interval relationship consisted of an initial drive cycle of 8 stimuli (S_1) at 350, 400, or 450 ms. Stimuli (S_1) were delivered as rectangular pulses of 2-ms duration at twice diastolic threshold. A premature extrastimulus (S_2) was introduced at a coupling interval (S_1 - S_2) of 250 ms, with a stimulus strength equal to diastolic threshold. The coupling interval was decreased by 2-ms intervals until there was failure to capture. The current of the extrastimulus was then incremented until capture occurred. The above sequence was repeated until the stimulus strength of S_2 reached 10 mA. The longest coupling interval that required a >0.1 mA increase in current for a 2-ms decrement in coupling interval was defined as the relative refractory period (RRP). The longest coupling interval that failed to capture at 10 mA was defined as the absolute refractory period (ARP).

Measurements were made at low and high preloads, 9 ± 3 mL and 39 ± 4 mL, respectively. The protocol was symmetrical in that measurements were made initially at low load, followed by high load, and were repeated again at low load. Results from the sequential low-load experiments were then averaged for purposes of analysis. The protocol was repeated after β -AR blockade with propranolol. Propranolol was infused into the perfusion line circuit

(3 to 5 mg IV) at a dose sufficient to result in an $\approx 20\%$ decrease in LV peak pressure at low preload.

To evaluate whether the effects of ventricular load on MAPD and refractoriness were dependent on the effects catecholamine release from intramyocardial nerve terminals, 2 dogs were given reserpine (1 mg/kg SC) for 7 days before the heart was isolated. This method has been shown to result in catecholamine depletion, as shown by an absence of heart-rate and blood-pressure response to bilateral stellate ganglia stimulation.¹⁰ After 7 days, the heart was isolated, and the protocol outlined above was repeated at low and high preloads.

Statistical Analysis

All values are expressed as mean \pm SD. Comparisons between ARP, RRP, and MAPD at 50% and 90% repolarization (MAPD₅₀ and MAPD₉₀) at low and high load were analyzed with paired *t* tests. A value of $P < 0.05$ was considered statistically significant.

Results

Hemodynamics

The LV end-diastolic pressure at low load was 5.5 ± 9 mm Hg and at high load, 22 ± 5 mm Hg. LV end-systolic pressure was 32 ± 9 mm Hg (low load) and 85 ± 12 mm Hg (high load), whereas peak systolic LV pressure was 37 ± 10 mm Hg at low load and 105 ± 14 mm Hg at high load. After propranolol, LV end-systolic pressure decreased to 26 ± 8 mm Hg at low load and to 69 ± 10 mm Hg at high load ($P < 0.05$ compared with control, respectively). Similarly, LV peak systolic pressure decreased to 29 ± 9 and 77 ± 10 mm Hg at low and high loads, respectively, $P < 0.05$. In the 2 reserpinized dogs, LV peak systolic pressure was 39 and 43 mm Hg at low load and 105 and 106 mm Hg at high load, respectively.

Electrophysiological Data

Consistent with previous studies, during control the ARP shortened from 195 ± 19 ms (low preload) to 190 ± 18 ms (high preload), $P = 0.004$. Similarly, an increase in preload decreased the RRP from 222 ± 26 to 216 ± 26 ms, $P = 0.005$. These findings were paralleled by changes in the MAPD. There was a decrease in MAPD₉₀, from 238 ± 28 to 233 ± 28 ms, $P = 0.04$, as well as a decrease in MAPD₅₀, from 193 ± 26 ms (low preload) to 184 ± 26 ms (high preload), $P = 0.04$.

To determine whether these mechanically related electrophysiological changes were mediated through stimulation of the β -AR, we examined the effects of β -adrenergic blockade with propranolol. This perturbation completely abolished shortening of the ARP, RRP, MAPD₅₀, and MAPD₉₀ in response to increased ventricular load (Table). Normalized refractory period data for each of the 7 dog hearts are shown in Figure 1. As shown in the lower panels, propranolol eliminated the effects of augmented load on the RRP and ARP. MAPD data for each dog are similarly displayed in Figure 2. Note that in the presence of propranolol, the MAPD₅₀ and MAPD₉₀ were not affected by increased preload. Data are displayed for only 6 dogs, because stable MAPD recordings could not be maintained in 1 dog.

A representative strength-interval curve is shown in Figure 3. During control, an increase in electrical excitability in response to augmented load was represented by a leftward shift of the curve. This response was eliminated by β -AR blockade, because the curve associated with high preload

Effect of Ventricular Load on APD and Refractoriness

	Low Preload, ms	High Preload, ms	P
Control			
RRP	222±26	216±26	0.005
ARP	195±19	190±18	0.004
MAPD ₅₀	193±26	184±26	0.04
MAPD ₉₀	238±28	233±28	0.04
β-Blockade			
RRP	229±29	230±29	NS
ARP	200±25	202±25	NS
MAPD ₅₀	202±33	200±32	NS
MAPD ₉₀	240±33	242±34	NS

shifted slightly rightward compared with that derived at low preload.

Additional evidence to support the role of the β-AR signaling cascade in mediating mechano-electrical coupling was provided by the 2 dogs in which we produced myocardial catecholamine depletion by pretreatment with reserpine. This abolished the effects of increased preload on electrical excitability. In the first dog heart, the ARP at low preload was 200 ms, whereas at high preload, it was 206 ms. In the other dog, the ARP was 186 ms (low preload) and 190 ms (high preload). The strength-interval curves from both dog hearts are shown in Figure 4.

Discussion

Although the phenomenology related to mechano-electrical feedback has been well characterized, the mechanism governing this process has been more difficult to define. The prevailing hypothesis attributes this process to activation of cardiac mechanosensitive ion channels. The results from the present study provide support for an alternative mechanism. Our principal finding is that an increase in ventricular load mediates a decrease in ventricular APD and refractoriness through activation of the β-AR–cAMP signal transduction cascade. We suggest that cAMP activation of the slowly

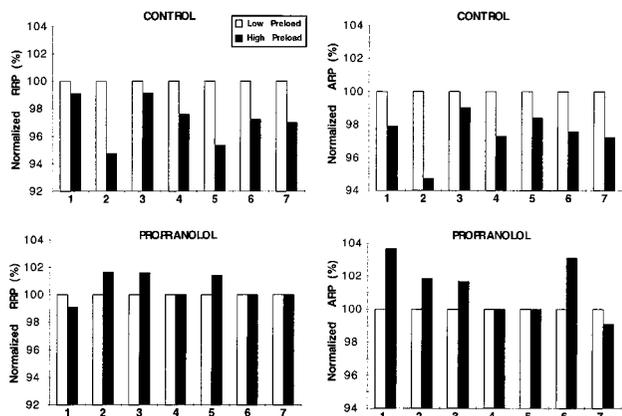


Figure 1. Effect of increased load on RRP and ARP in each of 7 dogs. Data are normalized. Left, Effect of load on RRP before and after propranolol. Right, Effect of load on ARP before and after propranolol.

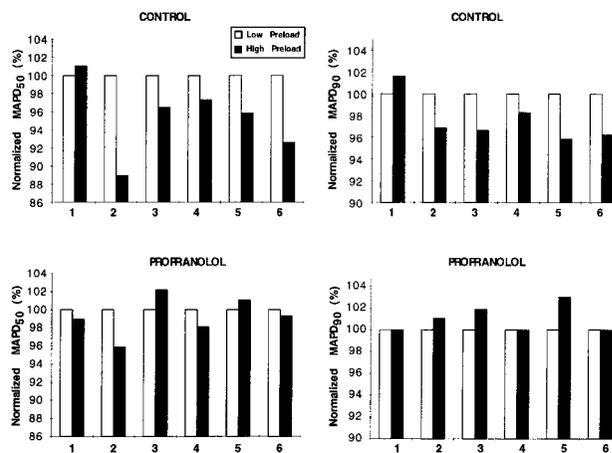


Figure 2. Effect of increased load on MAPD₅₀ and MAPD₉₀ in each of 6 dogs. Data are normalized. Left, Effect of load on MAPD₅₀ before and after propranolol. Right, Effect of load on MAPD₉₀ before and after propranolol.

activating delayed rectifier I_{Ks} is the most likely mechanism responsible for the mechanically induced electrophysiological changes observed in this study.

Lab^{7,11} was the first to postulate that a cAMP-mediated process may underlie the mechanism of mechano-electrical coupling, and β-adrenergic stimulation was subsequently shown to augment load-induced shortening of the ventricular action potential.¹² It has long been appreciated that stretch activates adenylyl cyclase activity and increases cAMP levels in isolated muscle preparations and in intact canine hearts,^{13,14} which in part may be a result of stretch-mediated release of catecholamines from intramyocardial nerve endings. These findings are consistent with the hypothesis that enhanced release of catecholamines and/or increased intracellular cAMP production in response to augmented ventricular load mediates the associated changes in APD and refractoriness observed in our study. To that end, we reasoned that if stretch-induced intramyocardial catecholamine release was contributory to this process, then β-AR antagonism should abolish load-induced electrophysiological effects. Our data confirmed this hypothesis in that propranolol eliminated these effects, resulting in superimposition of the strength-interval curves for high- and low-load conditions (Figure 3).

Further support for the hypothesis was obtained from the hearts of dogs that were reserpinized. We have previously shown that dogs reserpinized in this manner are depleted of

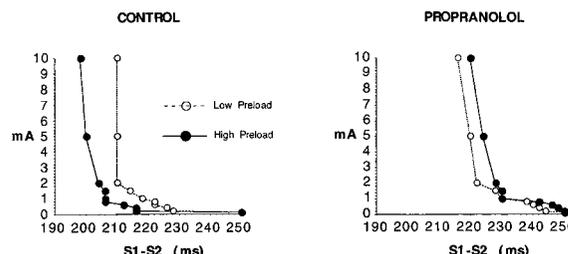


Figure 3. Representative effect of increased load on ventricular excitability, ie, strength-interval (S-I) relationship. Left, Dog 2. Effect of load on S-I relationship during baseline. Right, Effect of load on S-I relationship after propranolol.

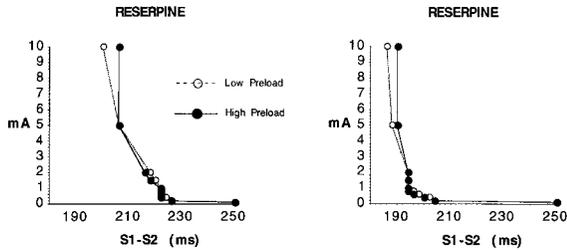


Figure 4. Effect of reserpine on load-induced changes in ventricular excitability in 2 dogs. Note that catecholamine depletion abolishes shortening of ARP and RRP with increased load.

endogenous catecholamines (supported by an absence of response of blood pressure and heart rate to stellate ganglion stimulation).¹⁰ As shown in Figure 4, ventricular refractoriness in hearts from these dogs did not shorten in response to increased load. These data are thus consistent with the concept that load-induced electrophysiological effects are mediated through intramyocardial catecholamine release and activation of the β -AR and also indicate that these effects do not occur independently of β -AR activation. Although the latter phenomenon may account for a secondary rise in developed pressure with increased load,¹⁰ it does not appear relevant to the process of mechanoelectrical feedback, because elimination of the upstream effector (ie, catecholamines) with a β -AR blocker or reserpination abolishes the electrophysiological response to increased load.

By what means does activation of the β -AR–cAMP-signal transduction cascade ultimately govern the cellular processes that couple mechanical (increased load) and electrical (repolarization) events? Because repolarization is primarily dependent on K^+ currents, our data would suggest linkage between stimulation of cAMP and a particular K^+ ion channel responsible for repolarization. The 2 main voltage-gated channels that have a primary role in determining repolarization are the transient outward current, I_{to} (I_{to1} and I_{to2}), and the delayed rectifier current, I_K (I_{Kr} and I_{Ks}). I_{to} is responsible for early repolarization (phase 1) and contributes to the spike-and-dome configuration of epicardial action potentials. Although these currents can be augmented by β -adrenergic stimulation, the net effect of catecholamine stimulation during the plateau phase is to increase the inward current (mainly I_{Ca}) and thus accentuate (prolong) the dome of the action potential, effects that would not account for the findings in our study.

I_K is responsible for repolarization during the plateau and phase 3 of the action potential and therefore is the most likely current to mediate the repolarization changes due to mechanoelectrical coupling.¹⁵ Of particular significance, I_{Ks} (but not I_{Kr}) is activated by intracellular Ca^{2+} and β -adrenergic stimulation.^{16–18}

The effects of β -adrenergic stimulation of I_{Ks} are potent, increasing the current amplitude up to 6-fold,¹⁹ which is independent of its stimulatory effects on $I_{Ca(L)}$.²⁰ I_{Ks} can be enhanced by β -AR agonists, forskolin, and direct intracellular introduction of cAMP,^{17,21–23} suggesting that the open probability of the I_{Ks} channel is increased by protein kinase A phosphorylation of an intracellular protein, which causes a negative shift in voltage activation of the channel.

Interpretation of these data is consistent with the view that the reciprocal relationship between myocardial load and APD is related to the linkage of enhanced catecholamine stimulation and activation of I_{Ks} . According to this paradigm, an increase in ventricular load increases release of catecholamines from intramyocardial nerve endings, which results in stimulation of the β -AR and an increase in intracellular cAMP. In turn, cAMP augments activation of I_{Ks} , abbreviating the plateau phase of the action potential and accelerating phase 3 repolarization, thus shortening APD and ventricular refractoriness.

Alternative Mechanisms

There has been considerable interest in the potential role that cardiac stretch-activated ion channels may have in mediating mechanoelectrical coupling. Several of these ion channels may have potential relevance with respect to the events observed in this study. For example, increasing cell volume by exposing guinea pig ventricular myocytes to hypotonic bathing solutions increases the magnitude of I_{Ks} (as well as decreasing I_{Kr}).²⁴ Similar findings have also been reported in cells inflated by positive pressure. For example, shortening of the APD with cell inflation has been shown to be due to a net increase in I_{Ks} .²⁵

Also of note is a recently described stretch-activated ion channel identified in cultured chick ventricular myocytes, a Ca^{2+} -activated K^+ channel (K_{Ca}).²⁶ This channel has a linear current-voltage relationship and a reversal potential of ≈ 0 mV. Gating of the channel is very sensitive to changes in intracellular Ca^{2+} and is blocked by charybdotoxin. It is unknown whether this channel is also expressed in the canine ventricle.

Myocardial stretch can also have direct effects on $Ca_{i(L)}$,^{27,28} increasing intracellular Ca^{2+} through an increase in the open probability of the channel, which occurs independently of protein kinase A activation. This pathway is of potential significance because elevated intracellular calcium can augment I_{Ks} through a cAMP-independent mechanism.²⁹ Although of interest, this mechanism is probably not operative in our study, because β -AR blockade abolished load-induced changes in refractoriness.

Finally, the mechanism proposed in this study for load-induced changes in ventricular refractoriness has been verified only for the conditions defined in this study. Multiple mechanisms may be responsible for the various forms of mechanoelectrical feedback identified in other preparations, such as membrane patches, single cells, superfused papillary muscle, and superfused frog tissue.⁷

Limitations

This study has several limitations. We did not control for the potential effects of spontaneous variability in catecholamine levels of the support dog on the electrophysiological parameters of the donor heart. We also did not directly measure catecholamine release in response to increased ventricular load. We believe that sufficient data exist, however, to conclude that this indeed occurred. First, previous studies have clearly demonstrated a direct relationship between myocardial stretch and enhanced intracellular cAMP levels,

and second, β -AR blockade with propranolol, as well as myocardial catecholamine depletion with reserpine, completely abolished load-induced electrophysiological effects.

Although it could be argued that the effects of propranolol on ventricular refractoriness were due to the mechanical effect of lowered LV pressure rather than its specific antiadrenergic effects, we believe that this is unlikely. First, similar results were also reproduced in catecholamine-depleted hearts from reserpinized dogs, and second, the magnitude of effect of propranolol on LV pressure was relatively small (<20%). Previous studies have shown that a 100% to 200% increment in LV end-systolic pressure is necessary to produce changes in refractoriness similar to those observed in the control phase of this study.²

We did not directly test for catecholamine depletion in the reserpinized dogs. The standard method used in this study for depleting myocardial catecholamines with reserpine, however, has been reproducibly validated in our laboratory.¹⁰ Furthermore, if the dog hearts in this study had not been catecholamine-depleted, a completely different result would have been expected, ie, an increase in ventricular load should have decreased ventricular refractoriness, which it clearly did not.

Our conclusion that I_{Ks} is the primary cardiac current that mediates mechano-electrical feedback is inferential. Nonetheless, the implication of I_{Ks} would appear reasonable, because I_{Ks} is a predominant repolarization current and is markedly sensitive to β -AR stimulation (unlike I_{Kr}), and studies in isolated myocytes have identified I_{Ks} as the current responsible for linking stretch and APD shortening.

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