Effects of Damaging the Endocardial Surface on the Mechanical Performance of Isolated Cardiac Muscle

Dirk L. Brutsaert, Ann L. Meulemans, Karin R. Sipido, and Stanislas U. Sys

The mechanical properties of mammalian ventricular cardiac muscle have been studied in the presence and in the absence of an intact endocardial surface. Isotonic and isometric twitch contractions were obtained from papillary muscles of the right ventricle of cat at 29° and 37° C, at different extracellular calcium concentrations ([Ca\(^{2+}\)], and at different initial muscle lengths. The endocardial surface was damaged by gentle abrasion of the muscle surface with a plastic blade or by brief immersion for 1 second with 1% Triton X-100. Although there was no evidence of damage to myocardial cells, damaging the endocardial surface resulted in an immediate and irreversible abbreviation of the twitch contractions with, except at the highest [Ca\(^{2+}\)], a decrease in peak isometric twitch tension. These changes induced 1) an asymmetrical shift of the tension-[Ca\(^{2+}\)] relation towards increasing [Ca\(^{2+}\)], but with no effect at the highest [Ca\(^{2+}\)], and 2) a rightward and downward shift of the length-tension relation. Both shifts were significantly more pronounced at 37° C than at 29° C; they were not accompanied by significant changes in V\(_{\text{max}}\). The asymmetrical shift of the tension-[Ca\(^{2+}\)] relation suggests that the endocardium-mediated chain of events may be mediated by changes in the sensitivity of the contractile proteins to Ca\(^{2+}\). This hypothesis is also supported by the similar pattern of changes (i.e., modulation of the onset of early tension decline) induced by decreasing length at each [Ca\(^{2+}\)], and by the removal of a functional endocardium. Accordingly, the endocardium may help to control the performance of the heart by modulating peak contractile performance and relaxation of the underlying myocardium. (Circulation Research 1988;62:358-366)

Materials and Methods

Preparations and Solution

Papillary muscles (n = 32) were isolated from the right ventricle of the cat. The tendinous end of the muscles was attached to an electromagnetic length-tension measuring and controlling device. The lower

Received January 14, 1987; accepted September 2, 1987.

From the Department of Physiology and Medicine, University of Antwerp, Antwerp, Belgium.
Address for correspondence: D.L. Brutsaert, MD, PhD, Professor of Physiology and Medicine, University of Antwerp (RUCA), Department of Physiology and Medicine, Groenenborgerlaan, 171, 2020 Antwerp, Belgium.

The mechanical properties of mammalian ventricular cardiac muscle have been studied in the presence and in the absence of an intact endocardial surface. Isotonic and isometric twitch contractions were obtained from papillary muscles of the right ventricle of cat at 29° and 37° C, at different extracellular calcium concentrations ([Ca\(^{2+}\)], and at different initial muscle lengths. The endocardial surface was damaged by gentle abrasion of the muscle surface with a plastic blade or by brief immersion for 1 second with 1% Triton X-100. Although there was no evidence of damage to myocardial cells, damaging the endocardial surface resulted in an immediate and irreversible abbreviation of the twitch contractions with, except at the highest [Ca\(^{2+}\)], a decrease in peak isometric twitch tension. These changes induced 1) an asymmetrical shift of the tension-[Ca\(^{2+}\)] relation towards increasing [Ca\(^{2+}\)], but with no effect at the highest [Ca\(^{2+}\)], and 2) a rightward and downward shift of the length-tension relation. Both shifts were significantly more pronounced at 37° C than at 29° C; they were not accompanied by significant changes in V\(_{\text{max}}\). The asymmetrical shift of the tension-[Ca\(^{2+}\)] relation suggests that the endocardium-mediated chain of events may be mediated by changes in the sensitivity of the contractile proteins to Ca\(^{2+}\). This hypothesis is also supported by the similar pattern of changes (i.e., modulation of the onset of early tension decline) induced by decreasing length at each [Ca\(^{2+}\)], and by the removal of a functional endocardium. Accordingly, the endocardium may help to control the performance of the heart by modulating peak contractile performance and relaxation of the underlying myocardium. (Circulation Research 1988;62:358-366)

Force and Length Measurement

The electromagnetic length-tension measuring and controlling device was modified after Brutsaert and Claes. It consisted of an aluminum lever, 1 mm thick and 30 mm long, with a tapered end to decrease the moving mass. This lever was firmly attached by epoxy cement to a coil suspended in a strong magnetic field. The equivalent moving mass of the whole system (lever and coil) was 225 mg. The torque on the lever and, hence, the loading on the preparation was proportional to the current through the coil. This current was generated by a current source calibrated for step changes in load of 0.1, 1, 10, and 100 mN to a total of 150 mN.

Force was measured by a unidirectional force-sensing feedback circuit. The unfiltered displacement signal was compared with a preset reference level, representing the position of an “electronic stop.” If the signal was smaller than this level, no feedback occurred and the preparation had to carry the imposed load. When the preparation was lengthened beyond the reference position, the lever was held in that position by feedback action and the current through the coil was proportionally decreased and represented the load.
carried by the preparation. By adjusting this reference level, resting length and preload could be set. In the course of an isometric contraction, the lever did move a very small amount, proportional to the developed force. The static compliance amounted to 0.25 μm/mN, and the dynamic compliance was negligible. The force signal was filtered with a low-pass, third-order filter (cut-off frequency, 150 Hz; rise time, 3 msec) and differentiated with an active differentiator (RC = 0.05–0.1 second). This low cut-off frequency minimized noise on the derivative signal.

The displacement of the lever was measured by an optico-electronic system. The light beam of a miniature infrared light–emitting diode (Texas Instruments TIL 32) was modulated by the lever acting as shutter, and captured by a photodiode (Philips BPW 41). The resulting signal was amplified by operational amplifier circuits. The linear range was 2.5 mm with an error of 1%. The displacement signal was filtered and differentiated with the same kind of circuits as the force signal to minimize relative phase errors.

**Experimental Protocol**

After a stabilization period of at least 2 hours at 29°C, at [Ca²⁺] 2.5 mM, and at lmax (i.e., the initial muscle length at which the greatest peak twitch tension was developed), experiments were performed at 29°C or at 37°C. The characteristics of the muscles at 29°C (n = 20; Figures 2, 3, 5, and 6) were (mean±SEM) length 7 ± 0.3 mm, mean cross-sectional area (assuming cylindrical uniformity and a specific gravity of 1.00) 0.8 ± 0.05 mm², resting tension (RT) 7 ± 0.7 mN/mm², and ratio of RT to total peak isometric twitch tension (TT) 10 ± 0.5%. The characteristics of the muscles at 37°C (n = 5; Figures 3 and 5) were length 8 ± 1.0 mm, mean cross-sectional area 0.6 ± 0.08 mm², RT 6 ± 0.6 mN/mm², and RT:TT 10 ± 1.6%. For the experiments in Figure 4, a separate group of muscles (n = 7) was used at 29°C. The characteristics of these latter muscles were (mean±SEM) length 8.5 ± 0.3 mm, mean cross-sectional area 0.9 ± 0.07 mm², RT 5 ± 0.6 mN/mm², RT:TT 8 ± 0.5%.

The contractile properties were derived from 1) a preload isometric contraction at lmax and 2) isometric contractions at lmax and at various lengths below lmax. Maximal velocity of shortening (Vmax) was obtained by abruptly unloading the stimulated muscle to zero load after the latency period. To eliminate the effect of the muscle’s memory for length and load during the preceding contractions, all test contractions were separated by a series of at least 8 preload isometric contractions at lmax; that is, any isometric or isometric contraction at any given initial length was always the first contraction following the length step to that length.

**Damaging the Endocardial Surface**

After the baseline observations, the possible role of the endocardium was assessed by repeating the observations after either gentle abrasion of the muscle surface with a sharp plastic blade (n = 8) or immersion for 1 second with 1% Triton X-100 dissolved in a Krebs-Ringer solution at 29°C or 37°C followed by rapid abundant wash (n = 25; Figure 1). An exposure time of 1 second is only a minimal fraction of the time needed for detergent treatment to damage myocardial cellular membranes. Abrasion or immersion was carried out in the working position of the muscles; that is, the muscles were kept under tension, as it was possible to move the organ chamber independently of the fixed preparation and measuring device.

In contrast to untreated muscles, muscles subjected to either mechanical or to chemical manipulation of the endocardial surface of the endocardium could consistently be stained with Evans blue following superfusion of the muscle surface with this dye and followed by rapid wash with Krebs-Ringer solution. Evans blue is a highly charged compound that stains the muscle surface wherever there is loss of endothelium. Hence, following the experiments, this simple procedure provided an elegant check for desquamation and/or irreversibly increased permeability of the endocardial surface.

On light microscopy, transsections of cat papillary muscles after Triton X-100 immersion or after mechanical abrasion could not be distinguished from untreated muscles for mean thickness and apparent continuity of the endocardium. Also, no histological damage of the underlying myocardium could be detected on light microscopy and transmission electron-microscopy. Since the differences between resting and contractile properties of both the mechanically and chemically treated muscles were statistically insignificant before as well as after damaging the endocardial surface, all data were pooled for both groups.

**Results**

**Effects on Twitch Contractions**

In all muscles, a characteristic, immediate, and irreversible phenomenon became fully apparent in the first contraction after damaging the endocardial surface (Figure 2): the onset of isometric relaxation occurred sooner with, except at the highest [Ca²⁺], a decrease in peak isometric tension and, to a lesser extent, velocity of tension development. The mean percent changes of the characteristic phenomenon at 29°C (n = 20) and 37°C (n = 5) are plotted in Figure 3. Similarly, isometric relaxation occurred sooner with some decrease in extent of shortening and in velocity of shortening. However, maximal unloaded velocity of shortening (Vmax) was not significantly different before and after damaging at both temperatures and at all [Ca²⁺] studied. In the rat, a similar immediate phenomenon was also observed after Triton X-100 immersion (n = 11) or after abrasion (n = 2) of papillary muscles from the left ventricle (n = 13). However, these rat cardiac muscles were not further studied here.

The characteristic contractile phenomenon was not correlated with muscle thickness, was similar after both mechanical and chemical procedures of endocardial impairment, was not affected by slightly prolonging the duration of immersion to 5 seconds (always followed by rapid abundant wash), was significantly more
FIGURE 1. Scanning electronmicrographs of the endocardial surface of cat papillary muscles. Upper left: Untreated muscle (× 1,700) showing an undulating continuous sheet of endothelial cells with rounded centrally placed nuclear bulges, a few marginal folds, and scattered plasmalemmal microappendages. Upper right: Triton X-100 immersed muscle (×3,655). The plasmalemma of most endothelial cells is perforated with numerous small pores typical for Triton X-100 treatment (cell to the left), whereas in other portions the endothelial surface is denuded (right) showing the basement membrane and underlying collagen fibers. Lower left: Endocardial surface after gentle mechanical abrasion (×1,700). The continuous sheet of endothelial cells is largely desquamated over major portions, leaving behind denuded collagen fibers. Lower right: Endocardial surface following mechanical abrasion (×850) showing an area where the surface is entirely deendothelialized, leaving only a network of underlying collagen fibers. This area lies adjacent to a remaining small zone of more or less normal endothelial cell sheet with somewhat contracted endothelial cells and marked longitudinal ridging and foldings of the cell membranes with some rare microappendages.
FIGURE 2. The typical phenomenon induced by damaging (dashed lines) the endocardial surface in a representative cat papillary muscle at 29° C by Triton X-100 immersion. Traces of length (l), tension (T), and first derivatives (dl/dt and dT/dt) were derived from isotonic and isometric contractions initiated at l_min at different [Ca^2+]. The marked abbreviation of the contraction was not accompanied by changes in velocity or peak contractile performance at 7.5 mM Ca^2+, indicating an undamaged underlying myocardium. In many muscles, velocity of tension development and of isotonic shortening subsequently decreased after the removal of a functional endocardium, in particular at low [Ca^2+], high temperature, and short length. However, maximal unloaded velocity of shortening (V_max) was not significantly different before and after damaging and was therefore not depicted in this figure. Muscle characteristics were length 8 mm, mean cross-sectional area 0.83 mm², resting tension 10.2 mN/mm², ratio of resting to total peak isometric tension (at 2.5 mM [Ca^2+]) 9.4%.

pronounced at 37° C than at 29° C, and was irreversible in all experiments, i.e., once the phenomenon was established, the contractions remained unchanged for the entire duration of the experiments (up to 4–5 hours). No changes in the passive length-tension properties of the muscles were observed despite a rare and transient rise in resting tension in a few muscles. This transient rise in resting tension was always over within 3 to 4 contractions and could be avoided by prewarming the Triton solution to the corresponding bath temperature and by using a plastic, instead of a metal, blade. In muscles where initially only a small area of the endocardial surface had been injured (by a single, gentle longitudinal rub), the characteristic phenomenon was also immediately and fully apparent but disappeared again after about 5–10 minutes. Because this time is too short for true regeneration of endothelial cells, the endothelial monolayer would appear in some way to be capable of rapid resealing or spreading of cells over restricted areas of the denuded endocardium. The characteristic phenomenon was always irreversibly present after a third or fourth single rub over different portions of the endocardial surface.

We also found that the use of an inert phosphor-bronze clip to hold the nontendinous cut end of the muscles was essential in these experiments because it probably allowed for similar resealing of the endothelial monolayer over the edge of the clip during the 2–3 hour stabilization period. This would, in addition, explain why stabilized muscles, when transferred to another phosphor-bronze clip but carefully clipped on the same previously clamped region of the muscle, always necessitated a new stabilization period.

Effects on Tension-[Ca^2+]_o Relation

These results are manifested as an asymmetrical shift of the tension-[Ca^2+]_o relation, significantly more pronounced at 37° C than at 29° C (p<0.01), in the direction of increasing [Ca^2+]_o, but with no effect on the maximum amount of peak developed tension at the highest [Ca^2+]_o of 7.5 mM (Figures 3 and 4).

In all muscles at high [Ca^2+]_o and in many muscles at lower [Ca^2+]_o, changes in velocity of tension development and of shortening could hardly be seen when peak velocity values were considered (Figure 2). Here, changes in velocity occurred after the time of peak velocity concomitant with the early onset of tension decline. In several muscles, a decrease in peak velocity of tension development and of shortening became more apparent after damaging the endocardial surface, especially at low [Ca^2+]_o, high temperature, and short lengths (see representative example at 29° C in Figure 4 and at 37° C in Figure 5). The decreased velocity of tension development after endocardial damage corresponded to the velocity of a contraction with the same peak tension at a lower [Ca^2+]_o on the baseline tension-[Ca^2+]_o curve. For example, in Figure 4, peak tension and rate of tension development of
FiguRe 3. Effect of damaging (dashed lines) the endocardial surface on the relation between [Ca\(^2+\)]\(_i\), and peak isometric tension (TT) of contractions initiated at \(l_m\) at 29° C and 37° C. Notice the asymmetrical shift of the TT-[Ca\(^2+\)]\(_i\) relation towards higher [Ca\(^2+\)]\(_i\). This shift was secondary mainly to an important earlier tension decline during relaxation as manifested by shortening of time from stimulus to TT (fTT) and even more so of time from stimulus to half isometric relaxation (RT\(_{1/2}\)). These effects were more marked at the lower [Ca\(^2+\)]\(_o\), and at the higher temperature. The data are mean ±SEM percent of the baseline values obtained at 2.5 mM Ca\(^2+\) since at 7.5 mM Ca\(^2+\) (especially at 37° C) the indicated [Ca\(^2+\)]\(_i\), might be an overestimate due to some Ca\(^2+\) precipitation.

Effects on Length-Tension Relation

In Figure 5 (right panel), length-peak tension (TT) curves were obtained from isometric contractions at different [Ca\(^2+\)]\(_o\). At 29° C, the decrease in TT was not significant at 7.5 mM Ca\(^2+\) but amounted to 40% of the control at 0.6 mM Ca\(^2+\); alternatively, the presence of a functional endocardium increased TT by approximately 67% at 0.6 mM Ca\(^2+\). At 2.5 mM Ca\(^2+\), the increase in TT by the presence of a functional endocardium was enhanced from 12% at 29° C to 100% or doubling TT at 37° C. Thus, except at the highest [Ca\(^2+\)]\(_o\), damaging the endocardial surface resulted in a significant parallel rightward and downward shift of all length-tension relations, again being much more marked at 37° C than at 29° C (p<0.01). At 37° C and 2.5 mM Ca\(^2+\), the downward shift was asymmetrical (p<0.01).

The time traces of isometric twitch contractions obtained in two representative muscles at 29° C and 37° C are also shown (Figure 5, left). For each twitch, peak isometric twitch tension is determined by the rate of rise and by the duration of tension development. In Figure 5, at any given length, changes in [Ca\(^2+\)]\(_o\) markedly

FiguRe 4. Effect of damaging (dashed lines) the endocardial surface of cat papillary muscle (n = 7) on the relation between [Ca\(^2+\)]\(_i\), and peak isometric tension (TT) of contractions initiated at \(l_m\) at 29° C and obtained at 0.625, 1.25, 2.5, and 4.0 mM [Ca\(^2+\)]\(_i\). At each [Ca\(^2+\)]\(_i\), after endocardial damage, [Ca\(^2+\)]\(_i\) was appropriately increased until peak twitch tension and rate of tension development corresponded to the baseline twitch with intact endocardium. A representative example at 1.25 mM [Ca\(^2+\)]\(_i\), (contractions 1, 2, and 3) is illustrated in the insert. Notice that time to peak tension and to half relaxation typically and irreversibly remained shorter after endocardial damage despite the appropriate adjustment of [Ca\(^2+\)]\(_i\). (compare contractions 3 and 1). Similar observations were made at the four different [Ca\(^2+\)]\(_i\). With: with intact endocardium; without: with damaged endocardial surface.
These characteristic patterns of modulation of twitch contractions induced by changes either in [Ca\(^{2+}\)], or in initial muscle length became more manifest still, when the isometric twitch contractions of the muscle at 29° C in Figure 5 were arranged in a different format (Figure 6). In contrast to changes in [Ca\(^{2+}\)], the effect of length on the duration of tension development at any given [Ca\(^{2+}\)] became manifest as a modulation of the onset of early tension decline during relaxation. More striking still is the fact that the presence of a functional endocardium reinforces this same type of modulation even further, at any length.

**Discussion**

Impairment of the endocardial surface influences the mechanical performance of the underlying undamaged myocardium. It immediately and irreversibly shortens the duration of twitch tension development, particularly at a physiological [Ca\(^{2+}\)], and temperature, thereby markedly affecting the relation of peak isometric twitch tension development to both [Ca\(^{2+}\)], and length.

Myocardial tissue was structurally not damaged by the procedure for endocardial impairment because 1) on light microscopy both treated and untreated muscles were covered with a continuous endocardial structure, and regardless of the staining method, differences in endocardial structure could not be detected between muscles with impaired and those with intact endocardial surface; and 2) the histology of the underlying myocardium was intact both on light microscopy and on transmission electronmicroscopy. Functional integrity of the myocardium was confirmed because 1) maximal mechanical performance of the muscles (i.e., peak isometric tension at the highest [Ca\(^{2+}\)], at \(l_{\text{max}}\)) was unaltered in the presence of an impaired endocardium; 2) \(V_{\text{max}}\) was not significantly affected at all [Ca\(^{2+}\)] and temperatures; 3) there was no correlation between the characteristic phenomenon induced by damaging the endocardial surface and muscle thickness; and 4) once fully established, this phenomenon never, not even partly, recovered to baseline levels for the entire duration of the experiment. Moreover, when true myocardial depression is induced (e.g., by too long an exposure time [more than 10–15 seconds], by a second short exposure time to Triton, by too intensive abrasion, or by other means [such as manipulation, overstretching, or adding depressive agents]) twitch contractions are affected differently. In contrast to the characteristic phenomenon after damaging the endocardial surface, true myocardial depression is in general characterized by a fall in peak twitch-force performance with a concomitant decrease in both velocity of rise and velocity of decline in tension. These latter changes are strongly correlated to muscle thickness, are often progressive, and may in some conditions either partly or completely recover. True myocardial depression is also manifested by a diminished peak twitch tension at the highest [Ca\(^{2+}\)], at \(l_{\text{max}}\), and by a fall in \(V_{\text{max}}\) at all [Ca\(^{2+}\)].
The similar pattern of changes—modulation of the onset of early twitch tension decline during relaxation—by decreasing length at each [Ca\(^{2+}\)], and by damaging the endocardial surface could suggest a common underlying mechanism. In addition, the asymmetrical shift of the tension-[Ca\(^{2+}\)]\(_0\) curve induced by damaging the endocardial surface raises the possibility that, as for the ascending limb of the length-tension relation\(^{15,16}\) and in the absence of more direct evidence, the endocardium-mediated chain of events too may eventually be mediated by changes in the sensitivity of the contractile proteins to Ca\(^{2+}\).\(^{17,18}\)

As for the mechanisms involved in the observed characteristic phenomenon, we can only speculate at present. We might think of at least three possible ways by which the endocardium could affect myocardial performance: by an electrochemical barrier, by the release of a chemical substance or messenger, or by both.

First, as an adjustable physical barrier with variable permeability, the endocardium could control homeostasis of the microenvironment of the interstitial fluid surrounding the cardiac muscle cells, perhaps by establishing a delicate transendothelial electrochemical potential. Although such properties have as yet to be demonstrated, electron-microscopical studies have emphasized the existence of a few specialized junctions, resembling true gap junctions, between the closely apposed endothelial cells.\(^3\) These junctions indirectly support the presence of an electric transcellular potential difference across the endothelial monolayer and would favor the possibility that changes in potential difference may contribute to the functional role of the endocardium. Impairment of this active barrier could then cause a rapid change in concentration of a substance or ion in the interstitial fluid with immediate and dramatic effect on the twitch contraction. This cannot be attributed to a sudden fall in [Ca\(^{2+}\)], as the observed changes in twitch tension profile after damaging the endocardium are not typical for a Ca\(^{2+}\) effect (Figure 6).

In addition, at all [Ca\(^{2+}\)], \(V_{\text{max}}\) was not different before and after damage. Moreover, appropriately rising [Ca\(^{2+}\)], could compensate for the rate of rise and for the peak tension of the twitches but not for the twitch duration, which irreversibly remained shorter (Figure 4). Another plausible candidate is extracellular potassium ([K\(^+\)],), which, through changes in concentration in the interstitial fluid, could contribute to the characteristic contractile phenomenon after damaging the endocardial surface. A sudden increase in [K\(^-\)], would decrease the resting potential, shorten the action potential, and lead to a decreased twitch peak and duration. Experiments are presently in progress to explore further whether potassium may be indirectly involved in helping to establish a transendothelial electrochemical potential.

Second, in analogy with the as yet unidentified endothelium-derived relaxing factor, which mediates vascular smooth muscle relaxation via [cGMP],\(^{19-22}\) it might be tempting to invoke the existence of an endocardially released factor that would induce premature relaxation of the myocardium (myocardium relaxing factor) by decreasing the sensitivity of the contractile proteins to [Ca\(^{2+}\)]. However, the presence of a functional endocardium delays the onset of isometric tension decline, thus shifting the tension-[Ca\(^{2+}\)], and the length-tension curves upward and to the left to lower [Ca\(^{2+}\)], and shorter lengths, respectively. As this effect is irreversibly abolished after removal of a functional endocardium, we may speculate on the release by the endocardium of another factor that would increase the sensitivity of the contractile proteins to Ca\(^{2+}\) (myocardium contracting factor). Recent findings from our laboratory suggest that adenosine 5'-triphosphate (ATP) perhaps participates in this chain of events leading to an increased sensitivity to Ca\(^{2+}\). We found that dibutylryl guanosine 5'-cyclic monophosphate \((10^{-6} \text{ and } 10^{-5} \text{ M})\), sodium nitroprusside \((10^{-5}, 10^{-4}, 10^{-3} \text{ M})\); experiments done in darkened room), and ATP \((4 \times 10^{-7} \text{ and } 4 \times 10^{-6} \text{ M})\) all induced...
a qualitatively similar, but reversible after washing, typical phenomenon on the duration of isometric contractions. Among these substances, ATP was the only one that, in the absence of a functional endocardium, delayed the onset of isometric tension decline of relaxation, thereby reversing the abbreviation induced by the removal of a functional endocardium. This reversal by ATP in the absence of a functional endocardium occurred in general at a lower ATP concentration than its opposite effect in the presence of a functional endocardium. The dual antagonistic effect of ATP, promoting early relaxation in the presence, but promoting further contraction in the absence, of a functional endocardium, resembles the functional role attributed to ATP in the endothelium-mediated control of vascular smooth muscle.23 In the vascular system, intraluminal ATP acts as a vasodilator possibly by the release of a relaxing factor, whereas extraluminal ATP (e.g., in the absence of a functional endothelium or if ATP would be released at the interstitial side of the endothelial cells) acts as a vasoconstrictor by direct effect on purinoreceptors of the smooth muscle cells.23

How these two possible mechanisms—an electrochemical barrier or the release of a chemical messenger—could either alone or in concert participate in a chain of events eventually leading to changes in the sensitivity of the contractile proteins to [Ca++] is still difficult to conceive at present. To what extent these changes could affect the action potential of the underlying myocardium, and, hence, the endocardium-mediated control of myocardial performance, is presently under investigation. Recent preliminary experiments have demonstrated a shortened action potential duration in the steady-state twitches after damaging the endocardial surface (K.R. Sipido, P.R. Housmans, and D.L. Brutsaert, unpublished observations). A possible link to underlying ionic mechanisms, in particular the potassium ion, is under investigation. Rapid changes in action potential duration could be established by some electrotonic coupling of the transendothelial electrical potential to the myocardial sarcomere membranes. Spread of these electrotonic potentials would allow for a rapid control by the endocardial monolayer over the entire thickness of the ventricular wall. In the present study, all effects were immediate responses inducing instantaneous changes of the onset of isometric tension decline, often, but not always, accompanied by subsequent changes in peak velocity of contraction as outlined above. Voltage clamp experiments in cat papillary muscle have shown that sudden changes in duration of the action potential always affected the contraction phase (including velocity and duration), mainly of subsequent contractions.24 On the other hand, step changes in initial muscle length just prior to the experimental contraction, similar to the length changes in the present study, shortened the twitch contraction without affecting the duration of the first action potential at that new length.11 Progressive shortening of subsequent action potentials occurred over several minutes. Such changes in action potential duration mainly in subsequent contractions could be secondary to changes in [Ca++]., resulting from changes in actin and myosin interaction, e.g., by altered sensitivity of the contractile proteins.23

Similar to vascular smooth muscle control by the vascular endothelial cells, an important role could thus also be attributed to the endocardial endothelial cells. In the intact heart, several substances in the superfusing blood or several conditions may take part in the endocardium-mediated chain of reactions, which could eventually lead to a diminished sensitivity of the contractile proteins to Ca++. For some of these plasma factors, the presence of an intact endocardium seems to be a prerequisite. We have recently observed that atrial natriuretic peptide (ANP) has, in addition to its natriuretic and vasodilating properties, a direct effect on isolated cardiac muscle.28 ANP, similarly as the removal of a functional endocardium, induces an early tension decline with no changes in the rate of rise. This effect is easily reversed after washing but is abolished after damaging the endocardial surface. Specific receptors for ANP have been demonstrated exclusively on the endocardial endothelial cells in the ventricle of the rat.27

Accordingly, the endocardium as the most primitive structure of the heart, may help to control the performance of the underlying myocardium by modulating the onset of early tension decline. These effects will result in important variations of peak contractile performance and of relaxation of the underlying myocardium.

Acknowledgments

The authors appreciate the expert help of Professor Buysens (Department of Pathology) for preparing and interpreting the light micrographs, and of Dr. Andries (Department of Anatomy) for studying the transmission electronmicrographs and for providing the scanning electronmicrographs in Figure 1.

References


KEY WORDS • endocardium • myocardium • calcium • length-tension relation • endothelial cells
Effects of damaging the endocardial surface on the mechanical performance of isolated cardiac muscle.

D L Brutsaert, A L Meulemans, K R Sipido and S U Sys

doi: 10.1161/01.RES.62.2.358

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1988 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/62/2/358