Cellular Uncoupling During Ischemia in Hypertrophied and Failing Rabbit Ventricular Myocardium
Effects of Preconditioning

Lukas R.C. Dekker, MD; Han Rademaker, MD; Jessica T. Vermeulen, MD; Tobias Opthof, PhD; Ruben Coronel, MD; Jos A.E. Spaan, PhD; Michiel J. Janse, MD

Background—Patients with heart failure show a very high incidence of arrhythmias and sudden death that is often preceded by ischemia; however, data on electrophysiological changes during ischemia in failing myocardium are sparse. We studied electrical uncoupling during ischemia in normal and failing myocardium.

Methods and Results—Tissue resistance, intracellular Ca$^{2+}$ concentration (Indo-1 fluorescence ratio), and mechanical activity were simultaneously determined in arterially perfused right ventricular papillary muscles from 11 normal and 15 failing rabbits. Heart failure was induced by combined volume and pressure overload. Before sustained ischemia, muscles were subjected to control perfusion (non-PC) or ischemic preconditioning (PC). The onset of uncoupling during ischemia was equal in non-PC normal (13.6±0.9 minutes of ischemia) and non-PC failing hearts (13.3±0.7 minutes of ischemia). PC postponed uncoupling in normal hearts by 10 minutes. In failing hearts, however, PC caused a large variability in the onset of uncoupling during ischemia (mean, 12.2±2.1; range, 5 to 22 minutes of ischemia). The duration of uncoupling process was prolonged in failing hearts (12.9±0.9 minutes) compared with normal hearts (7.8±0.4 minutes). The degree of heart failure and relative heart weight of the failing hearts significantly correlated with the earlier uncoupling after PC and the duration of uncoupling. In every experiment, the start of Ca$^{2+}$ rise and contracture preceded uncoupling during ischemia.

Conclusions—The duration of the process of ischemia-induced electrical uncoupling in failing hearts is prolonged compared with that in normal hearts. Ischemic PC has detrimental effects in severely failing papillary muscles because it advances the moment of irreversible ischemic damage. (Circulation. 1998;97:1724-1730.)

Key Words: heart failure ■ ischemia ■ arrhythmia ■ calcium

Patients with chronic heart failure have a high incidence of sudden death, which most often is caused by ventricular arrhythmias.$^{1-3}$ Holter monitoring and autopsy studies have shown that myocardial ischemia may be an immediate precursor of sudden death.$^{4-7}$ In addition, in animal models of heart failure, the incidence of ischemia-induced ventricular arrhythmias is significantly increased compared with that in normal hearts.$^{8,9}$ Studies on basic electrophysiology have shown distinct differences in active membrane ionic properties in failing hearts compared with normal hearts.$^{10-13}$ In addition, passive electrical properties may be altered in hypertrophied and failing myocardium because in these hearts, gap junction density is reduced and gap junction genetic expression is altered.$^{14-16}$ However, reports on the electrophysiological changes during ischemia in failing myocardium resulting in arrhythmogenic states are sparse.$^{17,18}$ This is in clear contrast to normal hearts, in which ischemic changes in active and passive electrical properties have been well documented.$^{19}$

A considerable body of evidence indicates that in normal hearts, degeneration of cellular coupling during ischemia produces conduction delay and conduction block and thereby serves as an important facilitator of ventricular fibrillation.$^{19-21}$ However, it is unknown whether the altered gap junctional organization in failing myocardium$^{14,15}$ modifies cell-to-cell uncoupling during ischemia, contributing to the increase in the incidence of ischemia-induced arrhythmias.

In normal hearts, we have previously shown that during ischemia uncoupling is associated with the start of the rise in [Ca$^{2+}$], and contracture. These interrelations are preserved after postponing the moment of uncoupling by ischemic PC.$^{22}$ In the present study, arterially perfused papillary muscles$^{20,22}$ from normal and failing rabbit hearts were used to determine whether (1) uncoupling during ischemia in failing hearts is similarly preceded by a rise in [Ca$^{2+}$], and contracture, (2) the time course of the process of uncoupling in failing hearts is altered compared with normal hearts, and (3) ischemic PC also postpones the moment of uncoupling during sustained ischemia.
ischemia in failing hearts. Heart failure is surgically induced by combined volume and pressure overload. 9

The present results indicate that in failing hearts, as in normal hearts, the onset of cellular uncoupling is closely preceded by an increase of [Ca\textsuperscript{2+}]; however, the process of uncoupling progresses significantly slower in failing hearts compared with normal hearts. In contrast to normal hearts, ischemic PC may advance the onset of ischemia-induced uncoupling in severely failing hearts. These results suggest that alterations in the time course of uncoupling in failing hearts contribute to the higher incidence of ischemia-induced ventricular arrhythmias in heart failure.

Methods

Induction of Volume and Pressure Overload

The method to induce heart failure in rabbits by volume and pressure overload has been described previously. 6,7 Rabbits received care according to institutional guidelines. Rabbits (New Zealand White; 3 to 3.5 kg) were anesthetized with a mixture (0.8 mL/kg of body wt IM) of ketamine (60 mg/mL; Aesculaap) and rompun (2%; Bayer). During the first surgical procedure, a fluid-filled catheter (1.22-mm outer diameter; Bristol) was inserted into the right carotid artery and advanced to the aortic valves. The catheter was propelled repeatedly to damage the aortic valves, which was evident by an increase in the pulse pressure of $50\%$. Three weeks later, animals were anesthetized; after laparotomy, a suprarenal stenosis was made to damage the aortic valves, and the left side of the interventricular septum was secured to a silicon plate. Within 4 minutes after excision of the heart, the septal artery was cannulated, and perfusion was started. The papillary muscle was horizontally connected to a force transducer (Sensonor AE801) with a ligature around the tendon. The resting length of the preparation was stretched to $\approx 115\%$ of slack length.

Papillary muscles were perfused with Tyrode's solution containing (in mmol/L): Na\textsuperscript{+} 155.5, K\textsuperscript{+} 4.7, Ca\textsuperscript{2+} 1.45, Mg\textsuperscript{2+} 0.6, Cl\textsuperscript{-} 136.5, HCO\textsubscript{3} 27.0, HPO\textsubscript{4}\textsuperscript{2-} 0.4, probenecid 0.1, glucose 10, insulin 10 U/L, and FCS 1.0%. Probenecid is an anion transport blocker and has been shown to prevent the loss of tetracarboxylate fluorescent indicators (see below). 24,25 The perfusate was gassed with a mixture of 95% O\textsubscript{2}/5% CO\textsubscript{2} to yield pH 7.4. A flow rate of 1.1 to 1.4 mL/min per gram was maintained with a constant-pressure perfusion system (35 to 45 mm Hg). Ischemia was induced by stopping flow and at the same time replacing the 95% O\textsubscript{2}/5% CO\textsubscript{2} gas mixture in the water-saturated surrounding atmosphere by 95% N\textsubscript{2}/5% CO\textsubscript{2}. During ischemia, oxygen tension in the organ chamber was $<3$ mm Hg. Reperfusion was induced by restarting flow and replacing the anoxic gas mixture with the 95% O\textsubscript{2}/5% CO\textsubscript{2} gas mixture. Myocardial temperature was 37°C.

Fluorescence Measurements

Adequate loading with Indo-1 (Molecular Probes) was achieved by recirculating 30 mL Tyrode’s solution containing 5 μmol/L Indo-1/AM (initially dissolved in dimethylsulfoxide containing 2% wt/vol pluronic F-127), 5% FCS, and 1 mmol/L probenecid for 25 to 35 minutes. The degree of heart failure in the operated animals was classified at the day of the experiment according to an arbitrary heart failure score calculated as follows: (1) presence of a third heart sound, (2) presence of ascites after laparotomy, (3) LVEDP of $>5$ mm Hg, (4) relative heart weight exceeding the upper 95% confidence interval of the normal hearts ($>3.6$ g/kg), and (5) relative lung weight exceeding the upper 95% confidence interval of the normal hearts ($>3.5$ g/kg). Every item adds 0.2 to the heart failure score. In three failing rabbits, it was not possible to measure LVEDP due to hemodynamic shock during anesthesia. Because these rabbits were positive for the other four parameters of heart failure, we combined them with rabbits that scored 1.0 in the $\geq 0.8$ subgroup.

### TABLE 1. Baseline Characteristics of the Groups With Normal and Failing Myocardium

<table>
<thead>
<tr>
<th></th>
<th>Normal Myocardium</th>
<th>Failing Myocardium</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight, kg</td>
<td>3.58±0.13 (3.26–4.45)</td>
<td>4.04±0.13 (3.23–4.95)</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Relative heart weight, g/kg</td>
<td>3.2±0.14 (2.8–3.5)</td>
<td>5.7±0.4 (3.9–9.3)</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Relative lung weight, g/kg</td>
<td>3.2±0.1 (2.8–3.5) (n=6)</td>
<td>5.3±0.5 (2.7–8.7)</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>LVEDP, mm Hg</td>
<td>3.3±0.8 (0–5) (n=6)</td>
<td>12.5±3.3 (4–28) (n=12)</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Ascites, n</td>
<td>0/11</td>
<td>5/15</td>
<td>NS</td>
</tr>
<tr>
<td>Third heart sound, n</td>
<td>0/11</td>
<td>10/15</td>
<td></td>
</tr>
<tr>
<td>Papillary muscle diameter, mm</td>
<td>1.1±0.1</td>
<td>1.1±0.2</td>
<td>NS</td>
</tr>
<tr>
<td>$R_t$</td>
<td>105±3</td>
<td>107±3</td>
<td>NS</td>
</tr>
<tr>
<td>Peak force, mN/mm\textsuperscript{2}</td>
<td>7.9±1.2</td>
<td>6.2±1.7</td>
<td>NS</td>
</tr>
<tr>
<td>Cell length, μm</td>
<td>125±25</td>
<td>165±34</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Cell diameter, μm</td>
<td>25±8</td>
<td>30±10</td>
<td>&lt;.05</td>
</tr>
</tbody>
</table>

Values are mean±SEM (range in parentheses). For the control group, n=11; for the failing myocardium group, n=15 unless otherwise stated. Cell length and diameter are indicated by mean±SD. Body weight, papillary muscle diameter, $R_t$, peak force, cell length, and cell diameter were compared with an unpaired t test. Relative heart weight, relative lung weight, and LVEDP were compared with a nonparametric Wilcoxon test. Ascites and third heart sound were compared with Fisher’s exact test.
minutes at 30°C. After a 30-minute period of washout at 37°C, fluorescence of the heart had increased by a factor 8–10 compared with fluorescence measured before loading (autofluorescence).

A circular area on the surface of the papillary muscle with a diameter of 1.3 mm was illuminated by 340-nm excitation light from a xenon-arc lamp (75 W) via a 10× objective (NA 0.50; Fluor, Zeiss). Emitted light was measured simultaneously with two separate photomultiplier tubes at 405 and 495 nm. We used the ratio (R) of the 405- and 495-nm signals, after subtracting the autofluorescence at both wavelengths, as an indicator of \( [\text{Ca}^{2+}]_i \). Calibration of fluorescence signals and calculation of actual \( [\text{Ca}^{2+}]_i \) was not feasible because at the conclusion of the experiments, the myocardium was irreversibly damaged by sustained ischemia.

Measurement of Tissue Resistance

The cylindrical shape of the papillary muscle and homogeneous distribution of resistance along the longitudinal axis permit cable analysis.\(^{20,27}\) In this model, longitudinal tissue resistance (\( r_t \)) consists of the intracellular (\( r_i \)) and extracellular (\( r_o \)) longitudinal resistances in parallel, where \( r_i \) is the series resistance of the intracellular space and the gap junctions.\(^{27}\)

Two extracellular Ag/AgCl electrodes were placed on either side of the area of tissue used for fluorescence measurements. Before the excitatory pulse (BCL 450), a 7-ms subthreshold current pulse was applied at the apex of the papillary muscle. Figures 1 and 2 (top) show differential electrograms (\( E_1 - E_2 \)) from normal and failing papillary muscles. With the subthreshold current pulse, the voltage drop (\( V_o \)) and distance between two extracellular electrodes longitudinal electrical resistance (\( r_t \)) were calculated.\(^{20,27}\) To correct for differences in muscle dimensions, \( r_t \) was multiplied by the surface area of transverse section between the extracellular electrodes, resulting in the total specific resistance, \( R_t \). During ischemia, the onset of cellular uncoupling can be appreciated as a sudden increase in \( R_t \) that is caused by an increase in \( r_i \).\(^{20}\)

Data Acquisition and Analysis

Signals from the extracellular electrodes were DC-amplified by high-input impedance amplifiers. Electrograms, current signals, and output of the photomultipliers and force transducer were digitized, stored, and analyzed with a personal computer. The sampling rate was 4 kHz, and the recording interval was 1 minute.
We defined the onset of uncoupling as the moment after the induction of ischemia at which R, rises $\geq 10\%$ above its baseline level and subsequently continues to rise. The duration of the phase of uncoupling was set as the interval between the moment of uncoupling (above) and the moment at which R, surpasses the 95% value of complete uncoupling. We defined the start of the rise in [Ca$^{2+}$], and the start of contracture in individual experiments as the moment after the induction of ischemia at which the diastolic ratio or resting tension increases by $\geq 10\%$ above baseline and subsequently continues to rise.

All data for the control and failing groups were first compared with respect to variance for all measured parameters with use of the F test. When the variance in the two groups was not significantly different (F test), ANOVA or Student’s $t$ test for unpaired observations was used. Otherwise, the nonparametric Wilcoxon test was applied. Differences in the presence of third heart sound or ascites were analyzed with Fisher’s exact test. In all statistical tests, the significance level was set at .05.

Results

Baseline Characteristics

Table 1 summarizes the baseline characteristics of the normal and failing groups. Relative heart and lung weights in the failing hearts are significantly higher compared with those of normal hearts. In addition, LVEDP in the failing group is significantly higher compared with that of normal hearts. Muscle diameter and R, did not differ between the normal and failing hearts, as shown previously.$^{17}$ Peak force in the failing preparations is not significantly different compared with normal preparations, despite a clear trend (Table 1). The preparations is not significantly different compared with normal preparations, despite a clear trend (Table 1). The frequencies of <133/min (cycle length, 450 ms) could not be tested due to spontaneous activity of the preparations.

In failing hearts, cell length increased significantly compared with normal hearts. Cell diameter measurements also show a small, yet significant, increase in failing myocytes compared with normal myocytes (Table 1).

Onset of Uncoupling in Normal and Failing Hearts and Effects of Preconditioning

Figure 1 shows typical registrations from a non-PC normal and a failing papillary muscle. At 20 minutes of ischemia induction of ischemia at which R, rises $\geq 10\%$ above its baseline level and subsequently continues to rise.

![Figure 3. Force-frequency relationships of six normal and six failing papillary muscles. Values indicate mean±SEM peak force. *P<.05 vs normal (ANOVA for repeated measurements).](image)

local electrical activation, the Ca$^{2+}$ transient and contraction signals are absent in both preparations. Cellular electrical coupling is decreased (evident by the increase in V_o), and [Ca$^{2+}$], and resting tension are increased (Figure 1, top). Figure 1 (bottom) shows a detailed time course of the changes IN R, during ischemia in the same preparations. The mean onsets of uncoupling during sustained ischemia in non-PC normal and failing hearts are equal (13.6±0.9 and 13.3±0.7 of ischemia, respectively; Table 2). This is in agreement with previous results.$^{17}$

During baseline conditions, electrograms, Ca$^{2+}$ transients, and contraction signals are similar for PC normal and failing preparations (Figure 2, top). However, during sustained ischemia, marked differences occur. At 23 minutes of ischemia in the PC normal preparation, diastolic [Ca$^{2+}$], resting tension, and intercellular coupling have not changed substantially. However, at this time in the PC failing preparation, [Ca$^{2+}$], and resting tension are high, whereas uncoupling is nearly completed. From the time course of the changes in R, during ischemia, it follows that the PC normal heart starts to uncouple after 24 minutes of ischemia, whereas the PC failing heart started to uncouple after 9 minutes of sustained ischemia (Figure 2, bottom).

After ischemic PC in normal hearts, the onset of uncoupling during sustained ischemia is postponed to 23.7±1.8 minutes$^{22,23}$ (Table 2); however, the average onset of uncoupling during sustained ischemia in the PC failing group is 12.2±2.1 minutes, which is not different from that of the non-PC failing group. In failing papillary muscles, the effect of PC on uncoupling ranges from a paradoxical acceleration (5 minutes of ischemia) to a delay (22 minutes of ischemia).

<table>
<thead>
<tr>
<th>TABLE 2. Moments of Ca$^{2+}$ Rise, Uncoupling, and Contracture After Start of Ischemia and Duration of Phase of Uncoupling</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No. of Experiments</strong></td>
</tr>
<tr>
<td>------------------------</td>
</tr>
<tr>
<td>Normal myocardium non-PC</td>
</tr>
<tr>
<td>Failing myocardium non-PC</td>
</tr>
<tr>
<td>Failing myocardium PC</td>
</tr>
<tr>
<td>Normal myocardium PC</td>
</tr>
</tbody>
</table>

Values are mean±SEM (range in parentheses). Due to differences in variances (F test, P<.05), the nonparametric Wilcoxon test (exact version) was used for all parameters. Duration of uncoupling is not dependent on preconditioning.

*P<.05 vs non-PC normal.
†P<.05 vs normal.
‡P<.05 vs non-PC normal.
Ischemia-Induced Uncoupling in Failing Myocardium

Figure 4. Onset of uncoupling during ischemia after PC as a function of heart failure score in normal (C) and failing (○) preparations. Every symbol represents one experiment. In normal preparations, the heart failure score is 0. Because variances are equal between PC normal and PC failing hearts, linear regression analysis was applied to all 15 data points.

Figure 4 shows that the onset of ischemia-induced uncoupling advances in preconditioned preparations as the heart failure score increases. This correlation is statistically significant. In addition, the onset of uncoupling in preconditioned papillary muscles correlates significantly with the relative heart weight (data not shown).

In every experiment in this study, the onset of uncoupling during ischemia is closely associated with the start of the rise in \([\text{Ca}^{2+}]\), and the start of contracture, as shown in a previous study in normal hearts.22 (Table 2).

Duration of Process of Uncoupling

Figures 1 and 2 also demonstrate the typical prolongation of the phase of uncoupling in failing hearts compared with normal hearts. PC has no effect on the duration of the uncoupling process in the normal and failing groups (Table 2). On average, the time window of uncoupling is 7.8 ± 0.4 minutes in normal hearts (n = 11) and 12.9 ± 0.9 minutes in failing hearts (Table 2). Figure 5 shows the significant correlation between the heart failure score and the duration of the uncoupling phase in the failure group. In addition, relative heart weight correlates significantly with the duration of the phase of uncoupling (data not shown).

Discussion

In the present study, we analyzed electrical uncoupling during ischemia in failing ventricular myocardium. The most important findings are (1) as in normal hearts, in failing hearts \([\text{Ca}^{2+}]\), rise and contracture immediately precede the onset of uncoupling during ischemia; (2) electrical uncoupling progresses more slowly in hypertrophied or failing myocardium than in normal myocardium; and (3) in contrast to its protective effect in normal hearts, ischemic PC in failing hearts may advance the onset of uncoupling.

Onset of Uncoupling and Effects of Preconditioning

During ischemia in normal hearts, cellular electrical uncoupling, which coincides with the onset of contracture and the secondary rise in extracellular \([\text{K}^{+}]\) concentration, heralds irreversible damage.22,27,33 We have recently shown in normal hearts that a rise in \([\text{Ca}^{2+}]\), and the start of contracture immediately precede uncoupling during ischemia.22 The present data show that this finding also holds true for failing hearts.

As shown previously by workers at our laboratory, baseline tissue resistance is not different between normal and failing hearts.17 In addition, the moments of uncoupling are similar in non-PC normal and failing hearts.17 However, the normal and failing preparations differ substantially in their response to ischemic PC. In the normal group, PC typically postpones uncoupling22,32 whereas in the failing group, PC may paradoxically advance the onset of uncoupling during ischemia. The heart failure score as well as the relative heart weight correlate with the moment of uncoupling in the PC failing group. These factors are clearly not independent variables because in this model, heart failure is always accompanied by hypertrophy. Therefore, it cannot be resolved whether myocardial changes due to heart failure or hypertrophy reverse the protective effects of ischemic PC.

During the development of hypertrophy, protein kinase C is chronically activated,34,35 which could confine the acute activation of protein kinase C that is supposedly required for cardioprotection in preconditioned myocardium.36–38 However, this seems unlikely because recent studies have shown that protein kinase C activation is not mandatory for cardioprotection.39–41 Therefore, the pathway by which hypertrophy or failure opposes the cardioprotective effects of ischemic PC remains unknown.

Duration of Process of Uncoupling

In failing hearts, the time window of uncoupling is prolonged compared with that of normal hearts. Differences in muscle diameter underlying the increased duration of uncoupling28 can be excluded because we intentionally selected papillary muscles with equal diameters in the normal and failing groups. In addition, the number of myocytes in cross section is about equal in the normal and failing papillary muscles because in this model of heart failure, the compensatory increase in cell diameter is small compared with the increase in cell length.

Because the tissue mass between the recording electrodes contains 5000 to 20 000 myocytes,31 we cannot differentiate between gradual uncoupling of individual myocytes or a high degree of heterogeneous uncoupling between the cells during ischemia. In hypertrophied rat ventricular myocardium, expression of another gap junction molecule, connexin40, is
increased. Connexin40 has different regulatory and conductance properties compared with connexin43, which is the predominant subtype in normal ventricular myocardium. Furthermore, the altered distribution of the gap junctions in hypertrophied and failing myocardium or increased interstitial fibrosis can play a role in the altered time course of uncoupling during ischemia.

Arrhythmogenesis in Heart Failure

On the one hand, degeneration of cell-to-cell coupling contributes to the substrate for reentry by increasing the heterogeneity of conduction through inhomogeneous conduction slowing and blocking. On the other hand, complete uncoupling can be considered a safety mechanism by preventing flow of excitatory injury current between the ischemic and normal zones and by complete conduction block. It was recently shown that the time window of uncoupling during ischemia in normal pig hearts is closely correlated with the incidence of ventricular fibrillation. Therefore, we consider the prolonged phase of ischemia-induced uncoupling an important constituent of the increased incidence of malignant arrhythmias in hypertrophied and failing myocardium. The model of the arterially perfused papillary muscle does not permit reentry due to its small tissue mass.

Numerous studies in normal hearts on the electrophysiological mechanisms of ventricular arrhythmias have provided insights into the changes of active membrane properties during ischemia (for a review, see Janse and Wit). Under nonischemic conditions, active electrophysiological properties of failing myocardium are altered compared with normal myocardium. \(K^+\) channels are downregulated, corresponding to the prolongation of the action potential duration, whereas the changes in the \(Ca^{2+}\) currents in failing myocytes are controversial. However, only very few studies report on the changes during ischemia of the active membrane properties of failing myocardium. Therefore, further investigations are required to elucidate the mechanisms underlying the malignant arrhythmias in heart failure.

Methodological Aspects of Study

The degree of hypertrophy and heart failure that was caused by inducing aortic regurgitation and stenosis varied considerably within the failing group. Despite the wide range of the parameters of heart failure and hypertrophy in the failing group, differences between the normal and failing group were significant. Rabbits in the failing group showed clinical signs of heart failure, such as tachypnea, ascites, and gallop rhythm. Furthermore, multiple ventricular arrhythmias (registered with the use of Holter monitoring) and sudden death occurred, which were absent in nonfailing rabbits (H. Rademaker, unpublished observations).

Although the volume and pressure overload initially involves the left ventricle, its hemodynamic and humoral consequences exert a graded effect on the right ventricle. We have previously shown that in this model, relative right ventricular heart weight is increased in proportion to relative total heart weight and that ascites occurs only in the severely diseased rabbits. Furthermore, on the level of the right ventricular papillary muscle, it has been shown that in this model, the force-frequency relation is flattened and the action potential duration is increased. Therefore, in this model of chronic congestive heart failure, right ventricular papillary muscles show pathophysiological characteristics of hypertrophy and heart failure.

Substantial controversy exists regarding \(Ca^{2+}\) transients in failing myocardium. Gwathmey et al showed two distinct components of the aequorin signal in dilated cardiomyopathy. However, that study was performed at low temperatures (30°C). Other groups have demonstrated a reduced rate of decline of the \(Ca^{2+}\) transient in failing human myocardium. In the present study, the \(Ca^{2+}\) transients under isometric conditions were similar in normal and failing papillary muscles (Figures 1 and 2). Vahl et al also showed that under comparable experimental conditions (isometric contractions at 37°C), \(Ca^{2+}\) transients are equal in normal and failing human myocardium. We cannot exclude that we missed subtle alterations in the \(Ca^{2+}\) transients in failing muscles compared with normal muscles. Because in the present setup Indo-1 fluorescence was measured with a low magnification objective (10×), propagation in the rather large field of fluorescence measurement could have blunted minor differences of the \(Ca^{2+}\) transient between normal and failing myocardium. Contraction signals were similar between normal and failing preparations, despite a tendency to a lower peak force in the failing group. Corresponding results from various models of heart failure have been reported previously.

As discussed previously, the Indo-1 signals cannot be obtained and actual \([Ca^{2+}]_i\) cannot be calculated in irreversibly damaged ischemic myocardium. It is, therefore, not possible to provide data on the interrelation between the changes of the true \([Ca^{2+}]_i\), and \(R\), during sustained ischemia.

In conclusion, a rise in \([Ca^{2+}]_i\), plays a crucial role in uncoupling in normal as well as failing hearts. In contrast to normal papillary muscles, in papillary muscles from severely failing hearts, ischemic PC induces an advancement of \([Ca^{2+}]_i\), rise, contracture, and electrical uncoupling during sustained ischemia. The duration of the process of cellular electrical coupling during ischemia in failing papillary muscles is prolonged compared with that of normal papillary muscles. This probably contributes to the high incidence of ischemia-induced arrhythmias in failing hearts.

References

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_Circulation_. 1998;97:1724-1730
doi: 10.1161/01.CIR.97.17.1724

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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