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Monophasic action potentials at discontinuation of cardiopulmonary bypass: evidence for contraction-excitation feedback in man

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ABSTRACT Mechanical dysfunction is the strongest predictor of sudden cardiac death due to arrhythmia. Contraction-excitation feedback whereby changes in myocardial length/tension influence the time course of repolarization and excitability would provide a possible mechanism. Such a relationship has been shown in animals but has yet to be demonstrated in man. A useful model for studying this relationship is provided by the process of weaning off cardiopulmonary bypass after routine coronary artery surgery. During this weaning period of approximately 1 min, the heart is converted from being partially empty and flaccid (i.e., a "nonworking" state) to being filled and stretched to support the circulation (i.e., a "working" state). Monophasic action potentials (MAPs) were recorded from the left ventricular epicardium as a measure of repolarization time in 16 patients at discontinuation of cardiopulmonary bypass. Systolic pressure was recorded from the radial artery line. Measurements were made at three stages that related to different dynamic states of the heart: (1) starting to come off bypass ("minimally working"), defined as the time of first appearance of an inflection on the arterial pressure trace indicating the start of left ventricular ejection and valve opening, when arterial pressures represent left ventricular pressure, (2) half off bypass ("partially working"), and (3) off bypass ("wholly working"). During the process of discontinuing bypass MAP duration shortened, while systolic pressure increased. MAP duration at 90% and 60% repolarization (MAP D90, MAP D60) decreased from 288.0 ± 29.5 msec (mean ± SEM) and 235.0 ± 27.9 msec in the minimally working heart to 274.5 ± 30.2 msec and 224.2 ± 27.3 msec in the partially working heart (p < .001), with a subsequent decrease to 261.0 ± 28.8 and 214.0 ± 28.7 when the heart was wholly working (p < .001). Systolic pressure increased from 54.1 ± 9.3 mm Hg in the minimally working heart to 65.9 ± 13.8 mm Hg in the partially working heart (p < .001) and subsequently increased to 75.5 ± 13.3 mm Hg when the heart was wholly working (p < .001). Mean heart rates did not change significantly. A strong correlation was obtained between absolute MAP duration and systolic pressure. Regression analysis revealed: MAP D90 vs systolic pressure (p < .001) and MAP D60 vs systolic pressure (p < .01). An impressive correlation was also obtained between the change in MAP duration and change in systolic pressure, with p < .001 for ∆MAP D90 vs ∆systolic pressure and p < .02 for ∆MAP D60 vs ∆systolic pressure. When changes in ∆MAP D90 and ∆MAP D60 from the minimally working to the partially working state were analyzed separately both failed to reach significance. However, the change from the partially working to wholly working state for ∆MAP D90 vs ∆systolic pressure was significant (p < .02), although that for ∆MAP D60 just failed to reach significance (p < .1). Our results provide support for contraction-excitation feedback in man whereby changes in myocardial force/tension relations (pressure/volume in our case) influence the time course of repolarization, which is known to influence excitability. Such a feedback mechanism may be relevant to the as yet unexplained association of regional abnormalities of wall motion with arrhythmias.


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ABNORMALITY of left ventricular wall motion is the most important single predictor of sudden cardiac death in patients with coronary artery disease.1-5 Although the cause of death is generally considered to be ventricular arrhythmia the basis of the relationship between left ventricular dysfunction and the development of arrhythmias is not understood.
An association between the dynamics of myocardial contraction and membrane potential has been shown experimentally. Changes in the force of contraction and the extent of muscle shortening have been shown to precede or cause changes in repolarization in isolated muscle. Pressure-volume changes in the intact animal heart may produce similar changes. Changes in mechanical conditions of contractions can also influence the refractory period in intact heart. This phenomenon has been termed “contraction-excitation-feedback.”

Regional asynergic or paradoxical wall motion occurs early during acute myocardial ischemia. A feedback mechanism such as that described may thereby create or enhance inhomogeneity of excitability and repolarization between ischemic and less ischemic areas, conditions known to favor the development of reentrant arrhythmias. There has been one study using the QT interval in normal subjects, but as yet there has been no demonstration of contraction-excitation feedback with the use of direct recordings from the human heart.

When the heart takes over the circulation after cardiopulmonary bypass surgery it undergoes rapid and substantial changes in the pressure-volume relation. As the pump volume is returned to the patient, over a period of usually less than a minute, the heart is converted from being partially empty and flaccid (i.e., “nonworking” state) to being filled and stretched to support the circulation (i.e., “working” state). Monophasic action potential (MAP) recordings provide a faithful representation of the time course of repolarization and have been used to study feedback mechanisms in animal hearts. We have developed a specially designed hand-held pressure contact electrode for recording the MAP in man during cardiopulmonary bypass surgery. The method is simple, safe, and quick, and allows observations to be made with minimal interference with the normal operative procedure.

We have used this technique to record the MAP from the left ventricular epicardium during the process of discontinuing bypass after the completion of routine coronary artery bypass surgery. Our objective was to document changes in MAP duration (repolarization time) during the period of discontinuation of bypass, relate changes in MAP duration to changes in systolic pressure and, examine the relationship in terms of a possible contraction-excitation feedback mechanism in man, which could possibly be a contributor to the electrophysiologic changes preceding sudden death.

### Methods

Sixteen patients were studied — 15 men and one woman from 41 to 66 years old (mean 55) (table 1). All were undergoing routine coronary artery bypass surgery. The average number of distal anastomoses was 3.6 per patient, including a total of 13 left internal mammary anastomoses (LIMA).

**Anesthesia and surgery.** The patients were anesthetized by use of a standard technique in all cases: drugs included papaverine, scopolamine, pancuronium, lorzepam, and nitrous oxide.

Routine cardiopulmonary bypass was used with a bubble oxygenator (Bently BOS10) primed with 1.5 liters of Hartmann’s solution (131 mM sodium, 5 mM potassium, 2 mM calcium, 111 mM chloride, 29 mM lactate). An ascending aortic cannula and a single right atrial venous cannula were placed and the patient was perfused at 2.4 liters/min/min with a Shiley Stockert or Gambro pump in pulsatile mode. The patient was cooled to 28°C and distal anastomoses were performed during a single period of aortic cross-clamping under protection by cold hyperkalemic cardiac arrest (St. Thomas’s solution [16 mM MgCl2, 16 mM KCl, and 1 mM procaine HCl]); solution was replenished after each distal anastomosis. Cold (4°C) saline was added to the pericardium at the institution of bypass and not thereafter.

Before discontinuation of bypass the heart had been perfused via its own native coronary circulation for a period represented by the difference between bypass time and aortic cross-clamp time (table 1). The time between the last dose of cardioplegia and discontinuing bypass was taken as the difference between bypass time and cross-clamp time plus 10 min. This 10 min period represents the time, before removal of the aortic clamp, during which the surgeon completed the final distal anastomosis in the absence of added cardioplegia. This period is the only estimated time; both aortic cross-clamp and bypass time were measured.

During the cross-clamp period the distal anastomoses are completed and no blood is coursing through the native circulation. At the end of this period the free end of the graft is clipped, the aortic cross-clamp is removed, and perfusion of the native coronary circulation is resumed. The top ends of the grafts are fashioned to the aorta with full coronary flow. In our studies this process took between 35 and 97 min, depending on the number of grafts (see table 1). At no time during this period was there any additional cold cardioplegia injected into the graft.

Blood gases, sodium, and potassium were checked every 20 min, and potassium was corrected if it was lower than 4.0 mM by adding 20% potassium into the pump. Warming restarted during the last distal anastomosis and normal circulation was not restored until the temperature of the blood returning from the patient to the pump was above 36.5°C. In our study the process of discontinuing bypass was performed with use of laminar flow rather than pulsatile flow.

On resumption of normal circulation the entire contents of the pump, except 200 to 300 ml, were returned to the patient and during the period of MAP measurements the lungs were ventilated with 100% oxygen.

Ethical approval was obtained for this study.

**Epicardial MAP recordings.** Several studies have used suction or contact electrodes for recording MAPs in the intact beating heart in situ. The electrodes work by depolarizing the myocardium directly beneath the electrode and measuring the results of change in current flow between this area and surrounding normal myocardium during rest and activation. These phasic electrical differences produce the MAP.

MAPs were recorded with a special bipolar pressure contact silver/silver chloride electrode mounted in an acrylic holder. The sides of the holder are grooved to enable it to be held between the surgeon’s index and middle fingers. The hold-
er is bored out to make a cup of 20 mm diameter and 5 mm in depth that houses the active electrode and a tight-fitting sponge soaked in a 0.9% saline by which contact is made with the reference electrode in the dome of the cup. The support enables the electrode to be manipulated to any desired recording site without the need for direct vision, while ensuring pericardial apposition and eliminating risk of damage to the myocardium. This contact electrode produces an MAP with several characteristics related to intracellular microelectrodes. The fact that the duration of repolarization is comparable to that found in intracellular recordings is particularly relevant to the present study.

A Gould isolated preamplifier (model 11-5407-58) was used to provide patient isolation. The signal was then fed into a Gould universal amplifier (model 13-4615-58-input impedance 108 Ω) set to give an output of 1 V for a 40 mV input with a frequency response of 300 Hz. This was displayed on an oscilloscope monitor (Simonsen and Weel Model MIS 102). Hard copy recordings of the MAPs with radial artery blood pressure were made on a pen recorder (Gould Instruments Brush 220).

The MAP signals were calibrated with a direct-current millivolt source (Time Electronics Limited model 4045) and blood pressure was calibrated with use of known pressures of 50 and 100 mm Hg.

**Study protocol.** After completion of all grafts the heart had been perfused via its own native coronary circulation for some 35 to 97 min and the time since the last dose of cardioplegia was 45 to 107 min (table 1). At the time of recording the temperature of the blood returning from the patient to the pump was at least 36.5°C for 5 to 10 min. The MAP electrode was positioned on the left ventricular epicardial surface between the left anterior descending coronary artery and the first diagonal branch. Recordings were then made as bypass was discontinued in the routine manner with use of laminar flow. The period of discontinuing bypass occupied less than 1 min.

**Analysis of data.** Measurements of MAP duration were made at 90% and 60% repolarization (MAP D90 and MAP D60) together with measurements of peak systolic blood pressure under the following conditions related to the external ejection work done by the heart in supporting the circulation: (1) nonworking heart, in which the bypass system supports the patient’s circulation entirely, (2) minimally working heart, in which ejection is beginning, as judged by the appearance of an inflection on the arterial pressure (i.e., starting to come off bypass), (3) partially working heart, in which there is between a one-half and three-fourths reduction in pump flow (i.e., where the bypass system and the heart share the circulatory workload), and finally (4) wholly working and completely off bypass, in which the heart takes its full share of the support of the circulation.

Our use of the term work is a qualitative assessment of cardiac activity at each stage of recording. The precise external mechanical work (PV, where P = intraventricular pressure; V = stroke volume) was not measured. Such measurements would be inappropriate during a routine surgical procedure.

Data are shown as the mean ± SEM and results of regression analysis are given. The significance of changes was assessed by means of the paired Student’s t test and correlation coefficients, as appropriate.

### Table 1

**Patient data**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>LAD/DIAG</th>
<th>CX</th>
<th>RCA</th>
<th>LIMA</th>
<th>Bypass time (min)</th>
<th>Cross clamp time (min)</th>
<th>Reperfusion time (min)</th>
<th>Cardioplegia time (min)</th>
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<td>M</td>
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<td>1</td>
<td>LAD</td>
<td>LAD</td>
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<td>55</td>
<td>36</td>
<td>46</td>
<td>AF, DC shock × 1 → SR</td>
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<tr>
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<td>44</td>
<td>M</td>
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<td>1</td>
<td>LAD</td>
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<td>47</td>
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<td>2</td>
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<td>58</td>
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<td>67</td>
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<td>LAD</td>
<td>CX</td>
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<td>42</td>
<td>35</td>
<td>45</td>
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<tr>
<td>5</td>
<td>57</td>
<td>M</td>
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<td>1</td>
<td>CX</td>
<td>LAD</td>
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<td>80</td>
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<td>VF, DC shock no effect initially, then → SR → PAT</td>
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<td>1</td>
<td></td>
<td>DIAG</td>
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<td>47</td>
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<td>48</td>
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<tr>
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<td>2</td>
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<tr>
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<td>50</td>
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<td>107</td>
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<td>1</td>
<td>LAD</td>
<td>LAD</td>
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<td>58</td>
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<tr>
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<td>1</td>
<td>LAD</td>
<td>LAD</td>
<td>91</td>
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<td>40</td>
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<td>SR</td>
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<tr>
<td>16</td>
<td>66</td>
<td>M</td>
<td>1</td>
<td>2</td>
<td>LAD</td>
<td>LAD</td>
<td>115</td>
<td>52</td>
<td>63</td>
<td>73</td>
<td>Sinus tachycardia (110/min)</td>
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</tbody>
</table>

LAD = left anterior descending coronary artery; DIAG = diagonal; CX = circumflex coronary artery; RCA = right coronary artery; LIMA = left internal mammary artery; AF = atrial fibrillation; SR = sinus rhythm; PAT = paroxysmal atrial tachycardia; VF = ventricular fibrillation; DC = direct current; RV = right ventricular.
Results

Discontinuing bypass was associated with a shortening of MAP D90 and MAP D60, with an increase in systolic pressure. Examples of changes in MAP and arterial pressure are shown in figure 1. In the first record (top panel) the patient is on bypass and the arterial pressure trace shows the slow sinusoidal waveform (about 1 Hz) created by the pump. The bottom panel shows a recording with the heart partially working at the start of the discontinuation of bypass, with an inflection on the pressure trace due to the start of left ventricular ejection (A). Records B, C, and D show progressive shortening of MAP duration and an increase in systolic pressure, i.e., the heart progressively increases its share of the workload of the circulation.

Figure 2 shows that as bypass is discontinued there was a significant change in both MAP duration (D60 and D90) and systolic pressure. There was no significant change in cycle length: in the minimally working heart it was 733 ± 132 msec; in the partially working heart, 718 ± 125 msec; and in the wholly working heart, 726 ± 112 msec.

Regression analysis showed a strong correlation between changes in MAP duration and changes in systolic pressure (figure 3). These correlations were more impressive for MAP duration at D90 than at D60. Although for the group as a whole the process of discontinuing bypass was associated with a rise in arterial pressure and shortening of MAP duration, the timing and extent of each of these variables varied considerably between patients, and sometimes within a patient. Two examples are shown in figures 4 and 5. The superimposed records of the MAPs in figure 4 show that most MAP shortening occurred in the period before ejection was first detected; as illustrated in figure 5, in another case substantial MAP shortening occurred after the onset of ejection and during the latter part of coming off bypass. If the changes in action potential duration are mechanically related it may be of interest to see whether any differences in the correlation exists between the early phase of increasing work and the later part, i.e., whether the MAP duration changes and external work done specifically correlate. In general, the changes are more noticeable during the latter part of discontinuation of bypass when external work is noticeable (figure 6).

**FIGURE 1.** MAPs from the left ventricular epicardium and radial artery pressures. Top, MAPs (upper trace) and MAP D90 together with the slow sine wave of the pump pressure (lower trace) on bypass. The slow playout of the MAP trace illustrates stability and zero calibration of the signal (right). Bottom, MAPs at the start of coming off bypass (A). As bypass is discontinued MAPs show progressive shortening (B, C, D) as systolic pressure rises and external cardiac work increases.
Despite the variation between patients, all showed a decrease in action potential duration on increasing work. There was a strong correlation between the absolute values of MAP duration and systolic pressure at all stages. The scattergram (figure 7) incorporates measurements at the start of ejection (minimally working condition) during the partially working and wholly working conditions.

Changes in MAP duration or systolic pressure did not correlate with any of the following: (1) bypass

**FIGURE 2.** Mean values with standard errors for MAP D90, MAP D60, and systolic pressure (radial cannula) under three conditions (1) in the minimally working heart (left on each graph), (2) in the partially working heart (center point of each graph), and (3) in the wholly working heart (right on each graph). The statistical significance of the changes is shown below each graph.

**FIGURE 3.** Regression analysis showing correlation between change in MAP D90 ($\Delta$MAP D90) and in MAP D60 ($\Delta$MAP D60) and change in systolic pressure from the minimally working to the wholly working condition.
time, (2) cross-clamp times, or (3) the length of time between discontinuing bypass and the last dose of cardioplegic solution.

Once off bypass five patients received controlled infusions of about 150 ml within 10 to 15 sec to rectify the hypodynamic appearance of the heart in these particular patients. During the infusion systolic pressure increased and action potential duration shortened. One example is shown in figure 8. The infusion was administered during the last 16 to 21 sec of the slow playout illustrated in the figure. A progressive increase in systolic pressure was evident, coupled with stabilization of MAP amplitude and diastolic potential. After restarting the fast recording a shortened action potential repolarization associated with the then higher pressure was illustrated.

**Discussion**

In the majority of patients the process of discontinuing (or weaning off) bypass was associated with an increase in systolic pressure, i.e., an increase in external ejection work. This was associated with shortening of MAP duration; these changes were highly significant for the group as a whole. An impressive correlation was observed between absolute MAP duration and absolute systolic pressure such that the longer MAPs were associated with lower systolic pressures and vice versa (figure 7). A strong correlation was also obtained between changes in MAP duration and changes in systolic pressure (figures 3 and 6). This association was more impressive during the latter part of the rising workload: the changes in the transition from a partially working heart to a wholly working heart were greater than those from a minimally working heart to a partially working heart.

These findings are in keeping with contraction-excitation feedback whereby changes in myocardial length/tension influence membrane potential. This phenomenon is the reverse of the extensively investigated excitation-contraction coupling whereby electrical events initiate and modify muscle contraction. Feedback mechanisms, however, have received relatively little attention, despite their potential clinical importance. Experimental studies have shown both stretch and tension to influence membrane potential in isolated tissue and in the intact animal. We have now demonstrated this phenomenon in man.

There were clear limitations to the present study that were dictated by the operative procedure and clinical needs of the patient. There was no direct left ventricular pressure monitoring. In some patients there was a delay between commencing the weaning off process and the appearance of a small inflection on the pressure trace indicating ejection and valve opening when radial artery systolic pressure may be taken as representative of intracavity pressure. For the purposes of the present analysis the control and/or minimally working heart measurement was taken at the first appearance of the inflection, which may have slightly overestimated intracavity pressure in some instances. In the patients in whom there was a delay before the appearance of the inflection the initial phase was associated with MAP shortening presumably coinciding with left ventricular pressure rising from below aortic pressure to equal aortic pressure. Under these circumstances it is likely

**FIGURE 4.** MAPs from the left ventricular epicardium and radial artery pressure. A = minimally working; B = partially working; C = wholly working. In the bottom half of the figure the MAPs and blood pressure have been drawn such that A/B and B/C are superimposed.

**FIGURE 5.** Monophasic action potentials from the left ventricular epicardium and radial artery pressure. A = minimally working; B = partially working; C = wholly working. In the bottom half of the figure the MAPs and blood pressure have been drawn such that A/B and B/C are superimposed.
that, although no systolic ejection work was done, there was nonetheless intramural systolic work due to changing length-tension relations of different segments of myocardium. It is not surprising that although there was a correlation between changes in duration and changes in systolic pressure these changes did not occur in unison. Further analysis of our data showed that the correlation during the early stages of weaning off bypass was poor but improved substantially as bypass was progressively discontinued. This suggests the important influence of volume changes in the initial period of conversion from a flaccid nonworking heart to a fully working heart as the "slack" is taken up by the initially relaxed muscle. Such a contribution would interfere with the significance of the early correlation between changes in duration and changes in systolic pressure.

One possible criticism of our data may be the influence of temperature and any residual cardioplegia. Even though the time course of discontinuing bypass was very short (i.e., of the order of 40 sec), there may have been temperature fluctuations during this period that might have influenced our results. We therefore performed a formal study using a thermistor probe placed epicardially in the appropriate area of interest. Our data on five patients showed there was a fall from 36.9 ± 0.30°C to 36.5 ± 0.25°C. This would be expected to have minimal, if any, effect on MAP duration. If any change did occur it would have been a lengthening of MAP duration, which would tend to offset the shortening that we observed rather than help to produce it. Similarly, washout of the cold high-potassium cardioplegia would be expected, on the basis of experimental work, to prolong rather than shorten action potential duration over the short term. Finally, one further criticism may be the potential electrophysiologic effects of reperfusion-mediated changes in calcium entry into cardiac myocytes. However, experimental studies have shown that coronary reperfusion after ischemia prolongs the action potential duration and can prolong the refractory period for up to 60 min. An increase in action potential duration has also been shown during short-term recovery from hypoxia in other preparations. Therefore, once again, if there had been any influence as a result of reperfusion it would have been to offset the changes in action potential duration that we found.

The majority of MAP measurements were probably
made in areas that were being bypass grafted to improve perfusion. However, we know that recordings were not made in areas of necrosis or scar tissue since these were easily identifiable in our recordings. Measurements were not knowingly made in areas where abnormal wall motion existed as judged by visual inspection and left ventricular angiographic appearances.

Our results show a clear relationship between MAP duration and systolic pressure that would be consistent with the presence of contraction-excitation feedback in man. Such contraction-excitation feedback may be important clinically in the development of arrhythmias, and could produce these by several mechanisms.\textsuperscript{15, 44}

One of these mechanisms is reentry. Inhomogeneity of repolarization and recovery of excitability is the
basic prerequisite for reentry. Our study suggests that contraction-excitation interactions are not uniform (figures 3 to 6). Segmental dyskinesia characteristic of early ischemia may create local differences in excitability by feedback mechanisms. Conduction block probably produces some localized contraction abnormality and it may not be necessary to reach the stage of conventional clinical asynergy to cause reentry by feedback. Inhomogenous wall stress or strain, particularly marked in the presence of ischemia, could produce electrophysiologic inhomogeneity by contraction-excitation feedback. This could generate current flow and stimulate adjacent cells during their period of enhanced excitability and/or provide the basic prerequisites for reentry, thus leading to ventricular arrhythmia.

Contraction-excitation feedback may also influence the ST-T segment and Q-T interval of the electrocardiogram. The precise electrical gradients that generate the ST-T segment are not clear. However, whatever the mechanism, it is likely that factors that alter the temporal relationship of repolarization between different regions (e.g., endocardium/epicardium, base/apex) are likely to influence the ST-T segment. This may apply not only in ischemia but also in the normal heart, as has been suggested where there is differential intramural and circumference shortening.

In our study the heart was undergoing pressure-volume changes during discontinuance of bypass. At the cellular level this means that membranes and sarcomeres are being stretched by the increasing preload and in consequence force production is increasing. However, the exact relationship between experimentally induced mechanical alterations and the changes in potential is unclear. A mechanical maneuver that increases force is associated with a reduction in intracellular calcium, possibly by an increase in the binding constant of calcium for troponin C. This intracellular calcium change is associated with a shorter action potential duration when compared with that seen with low force development. The action potential change could be explained either by a reduction in a calcium-activated inward current, or a reduction in an electrogenic inward current generated by a calcium/sodium exchange.

Although the exact mechanism at the cellular level remains obscure and requires further evaluation, the demonstration of feedback in man is of potential clinical importance. For example, our results are in keeping with the existence of contraction-excitation feedback in man and encourage further work to define the underlying mechanism. Such a mechanism may provide a partial explanation for the unexplained association of arrhythmia with abnormalities of wall motion and the unfavorable influence on prognosis when these two factors are combined.

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