Excitation-contraction (E-C) coupling in ventricular myocardium has received exhaustive investigation. Feedback processes in the reverse direction between contraction and excitation are less conspicuous and, not surprisingly, have attracted little notice despite their potential physiological and clinical importance. For the present, contraction-excitation feedback is inferred when changes in mechanical stress or strain cause or precede changes in membrane potential. For example, reduced force development or increased shortening can induce greater depolarization. Contraction-excitation feedback, according to the type and timing of the mechanical change producing it, can appear either as a prolongation of an action potential, or as a transient depolarization. This review will describe the circumstances under which contraction-excitation feedback occurs, discuss possible explanations for the phenomenon, and speculate on its potential importance in selected clinical situations.

The durations of the action potential and of contraction in the heart are of the same order of magnitude. This relationship allows mechanical activation to influence the initiating, concurrent action potential. However, the term “feedback” may be a misnomer, as the process may comprise initiating factors that cause both electrical and mechanical changes. These factors may also be common to excitation-contraction coupling. Accordingly, a precis of the relevant aspects of excitation-contraction coupling is given in Figure 1.

I. Prevalence of Contraction-Excitation Feedback

Electrocardiographic studies by Stauch (1960) provided the first evidence for a feedback between contraction and excitation. He demonstrated shortening of the Q-T interval of the ECG in an isovolumic contracting frog ventricle as compared with the auxotonic beating heart, allowed to empty. Later corroborations used monophasic action potentials in a similar experimental preparation (Stauch, 1966; Lab, 1968). The plateau phase of the action potential was steeper during isovolumic than during auxotonic contraction. Stretch can also induce resting membrane potential changes (Penefsky and Hoffman, 1963; Kaufmann and Theophile, 1967). Because of this, as well as the length-tension relation and length-dependent changes in activation (Jewell, 1977), this review will briefly include the effects of length changes on membrane potentials.

Before proceeding, we should note that the experimental protocols used in the studies produce results which need cautious interpretation because the mechanical maneuvers can disturb the electrical relationships between the biological signal generator and the recording electrode. In addition, isolated preparations can show internal inhomogeneity in contraction, as well as relaxation (Krueger and Strobeck, 1978). This inhomogeneity is exacerbated by damaged and compliant ends associated with anchoring the preparation. Mechanically induced changes in potential may thus vary within and between preparations because of nonrepresentative sampling. However, reasonably...
consistent results have been found using a variety of preparations and recording techniques, some of which sample many if not all the cells. Further, several predictions based on the existence of this “feedback” have been fulfilled.

(i) Mechanical Changes in Resting Muscle

(a) Effect on Resting Potentials. In several different ventricular preparations, a stretch during diastole, to about L_{max} (the length at which maximum tension is produced) can result in an immediate reversible depolarization (Penesky and Hoffman, 1963; Lab, 1978a; Boland and Troquet, 1980). These depolarizations may produce action potentials (Lab, 1978b) or spontaneous activity (Kaufman and Theophile, 1967). Boland and Troquet (1980) attributed their results in the intact rat ventricle to ischemia, but no blood flow measurements were made and their results were in keeping with those from the superfused isolated preparations cited above. In all these cases the depolarization was sufficiently fast to operate on a beat-to-beat basis. Dudel and Trautwein (1954) found depolarization with large stretches in cat papillary muscle but interpreted this as muscle damage. Two studies conflict with the foregoing results by showing no change in resting potential with length change (Spear and Moore, 1972; Allen, 1975).

(b) Effect on Action Potentials. When stretched muscle is stimulated, the action potential shows a reduced spike amplitude (Dudel and Trautwein, 1954; Penesky and Hoffman, 1963; Lab, 1978a), as expected with a partially depolarized membrane (see previous section). Spear and Moore (1972) also found reductions in action potential amplitude, and conduction velocity, recorded from stretched rat ventricle. However, the latter changes were slowly reversible and were unlikely to operate on a beat-to-beat basis. This preparation also showed graded and asynchronous electromechanical behavior, which was absent in guinea pig, cat, and frog.

Several reports show that lengthening can also alter the duration of the action potential, although not all studies are in agreement. Shortening of action potential duration closely follows stretch in several studies (Dudel and Trautwein, 1954; Allen, 1975; Lepeschkin, 1976b, in his Fig. 3; Lab, 1978a; Lab, 1980). Allen showed a small but significant initial shortening during the first few beats after stretch, that was followed by prolongation as steady state was reached many beats later. Two investigators, however, reported no effect on the action potential duration (Gennser and Nilsson, 1968; Hennekens et al., 1977), whereas Nomura (1963), using non-vertebrate cardiac muscle,
found a prolongation of action potential duration with stretch.

A stretch, then release, of turtle ventricle perfused with 40 mM Ca\textsuperscript{2+} solution was reported to cause small mechanical and electrical oscillations (Bozler and Delahayes, 1971). These authors considered the transmembrane potential changes to have been the consequence of the mechanical changes. Stretch of normally perfused resting muscle (normal [Ca\textsuperscript{2+}]) was reported to produce only small changes in membrane potential if the extension was large (see also Lab, 1978a, where large stretches were needed to produce an electrical effect). Bozler and Delahayes also saw oscillations after a twitch in 20 mM Ca\textsuperscript{2+} that occurred with only moderate reliability. The oscillations were absent in some frog ventricles and in all frog atria. Lab (1978a) reported no mechanical induction of a membrane potential change in one intact frog preparation. Possible explanations for these discrepancies already mentioned at the beginning of Section I are outlined in context below.

In general, moderately large passive length changes in ventricular muscle can induce changes in membrane potential. Discrepancies in a few preparations may be species related and/or be due to varying experimental conditions. Changes in sarcomere length with mechanics are inhomogeneous in any one preparation (Krueger and Pollack, 1975), and difficult to control between preparations. This inhomogeneity is enhanced by the variable damage to the ends of the muscle produced in anchoring them at their ends during different experiments. The differing electrical effects of stretch can thus be the result of partially damaged and compliant ends that could take up most of a relatively small length change. In such a situation, electrical recording from a distant area would show no mechanically induced effect, whereas recording sites closer to the stretched region could demonstrate a variable electrical effect or even oscillation due to electrotonic spread. A change in internal milieu might also account for some of the discrepant observations. Isolated and electrolyte superfused cardiac preparations change with time (Reichel, 1976). In keeping with this possibility, Bozler and Delahayes (1971) observed a reduction in amplitude of oscillation after several hours' study, and that storage for an unspecified time and under unspecified conditions prior to experimentation reduced the oscillations.

(ii) Mechanical Changes in Active Muscle

(a) Comparison of Action Potentials in Isometric and Isotonic Contraction. In contrast to the somewhat confused situation regarding the effect of length changes in membrane potential of resting muscle, alteration of the mode of contraction of cat papillary muscle affects the action potential clearly and reproducibly. Kaufmann et al. (1971) found that the action potential duration during an isometric contraction was shorter than that associated with an isotonic contraction. Similar results were found when the action potentials of an isovolumically contracting frog ventricle were compared with those of an isotonic (auxotonic) contraction (Stauch, 1966; Lab, 1978a). These results were not identical to those in the papillary muscle in some aspects, probably because isovolumic contraction of the whole ventricle does not imply isometric contraction of the wall.

(b) Effect of Imposed Perturbations during Action Potentials. A quick stretch of cat papillary muscle at any time does not affect the action potential (Hennekes et al., 1977; Hennekes et al., 1981). A typical example is seen in Figure 2A—(5). Release during the early rising phase of contraction (first perturbation in Figure 2B) also does not affect the action potential. In contrast (Fig. 2, A and B), a quick release near the peak of developed force prolongs the action potential (Kaufmann et al., 1971; Hennekes et al., 1977). Concordant changes are found using microelectrodes, insulation gap, or electrogroms (Lab, 1980). After the onset of delayed repolarization, immediate restretch of the muscle cannot restore control electrical conditions (Fig. 2B). The prolongation of action potential following a late release (Fig. 2C) can be similar in configuration to an early afterdepolarization, as characterized by Cranefield (1977), that can produce a propagated action potential (fig. 2C). This phenomenon may be relevant to some pathological arrhythmias [see Section III (iii)]. In the pig ventricle in situ, a disturbance of segmental wall motion analogous to the foregoing mechanical perturbations, produced by occluding the aorta, can cause both a transient depolarization (Fig. 2D) and an extrasystole (Lab, 1978b).

The precise relationship between the mechanical intervention and the depolarization is unclear. There is no simple correlation between the change in potential and the extent of the mechanical alteration measured as tension, velocity of shortening, and length (Lab, 1980; Hennekes et al., 1981). Further, for any given length change, the change in potential is crucially dependent on time: both early and late release can produce a small depolarization, whereas release of an intermediate timing yields a large depolarization (Fig. 2B). Mechanically induced "uncoupling of the active state" is also a time-dependent process (Brady, 1965; Kaufmann et al., 1972). In this process, a release of the muscle to a short length during contraction is incapable of producing an active tension appropriate for the new length; this phenomenon is called "tension deactivation" (Julian and Moss, 1976). That the release-induced depolarization is related to the release-induced deactivation (Lab, 1980) is supported by some experiments using caffeine, which is known to prolong contraction while leaving the action potential relatively unaffected. In caffeine-treated muscles, release did not produce a voltage change until significant deactivation occurred after repolarization of the action potential (Hennekes et al., 1981): i.e., a very late release produced both a significant deactivation and membrane depolarization. Extrasystoles followed more frequently under these conditions than during normal perfusion.

Notwithstanding some inconsistencies and difficul-
II. Explanatory Mechanisms

When we consider explanations for contraction-excitation feedback, three important properties need to be borne in mind: the phenomenon operates mainly when the muscle is activated, it occurs rapidly, with a time lag of only 10-20 msec (Kaufman et al., 1971), and it can be unidirectional.

(i) Passive, Physical Mechanism [Fig. 1 (7)]

An architectural change could passively affect the relationship between the electrical signal and monitoring electrodes; for example, some studies show changes in the cable properties and electrical constants of muscle with mechanical change (Deck, 1964; Potapova and Challakian, 1965; Dulhunty and Franzini-Armstrong, 1977; Dominguez and Fozzard, 1979). A permeability change that depends on membrane stress or strain could also move the membrane potential closer to the relevant equilibrium potentials. Finally, mechanical changes could distort intercellular spaces, which might alter K⁺ movement or accumulation (Weidman, 1956; Kline and Morad, 1976) to influence membrane potential.

It is difficult to invoke these passive changes to explain all of the experimental observations. A release and a stretch at a given time should produce the appropriate distortions to depolarize and repolarize, respectively, the membrane of cat papillary muscle, whereas stretch—in fact—has no effect on the action potential. Further, a release-restretch maneuver returns the muscle to the passive mechanical state preceding the intervention, but the electrical change is not aborted. These arguments therefore weaken the credibility of a purely passive mechanism.

(ii) Active Indirect Mechanism

Mechanically induced deactivation of tension (Brady, 1965; Kaufmann et al., 1972; Julian and Moss, 1976) has properties similar to those outlined in Section II above: it occurs during muscle activity, is rapid, and directional. Further, Gordon and Ridgeway (1976) found a Ca++ mediated length-dependent change in membrane potential in skeletal muscle. Also, the mechanical-electric effects in cardiac muscle are most prominent at a time when internal calcium [Ca++]ᵢ is changing, i.e., just before peak developed tension (Allen and Blinks, 1978). It seems reasonable to implicate the calcium ion in contraction-excitation feedback, because this ion influences transmembrane currents as well as developed tension. The crucial questions are whether a mechanically dependent [Ca++]ᵢ change occurs in mammalian cardiac muscle under these circumstances, and whether it does so in a directional manner. Allen and Kurihara (1981) clearly showed an increase in light output of aequorin, [Ca++]ᵢ, with release, but no change with stretch. How release enhances [Ca++]ᵢ,
while reducing developed tension remains speculative. Allen and Kurihara suggested a tension-mediated change in the \(Ca^{++}\) binding constant of troponin (Fig. 1 [5±]) possibly related to the number of attached cross-bridges (Bremel and Weber, 1972). However, because stretch has no effect on \([Ca^{++}]_s\) and action potential, this suggestion probably is not the whole explanation, suggesting that cross-bridge interaction during tension deactivation, in particular, may also be important. Although they may prove related, the load-dependent changes in relaxation observed by Brutsaert et al. (1978a, 1978b) remain enigmatic.

These observations suggest that any explanation for contraction-excitation feedback has to account for a rise in \([Ca^{++}]_s\), together with a reduction in tension and prolongation of action potential, in addition to the three properties listed above. Modulation of \([Ca^{++}]_s\), can affect transmembrane movement of ions in several ways (Fig. 1 [4±]). Whereas it can alter \(I_{Ca}\) (Reuter, 1979), there is no release-induced change in a calcium-mediated action potential (Hennekes et al., 1981). Modulation of \([Ca^{++}]_s\) also can influence outward currents (Isenberg, 1975; Bassingthwaighte et al., 1976; Di Francesco and McNaughten, 1979). On first inspection, neither of these hypotheses explains the observed phenomena because the hypothesis requires that a rise in \([Ca^{++}]_s\), should shorten the action potential and reduce force. More evidence is needed to exclude these explanations because \(Ca^{++}\) compartmentalization is not fully understood. The \([Ca^{++}]_s\), variation could also modulate an electrogenic \(Na^+\)/\(Ca^{++}\) exchange in the appropriate direction (Mullins, 1979). Kass et al. (1978) considered this mechanism for their transient inward current. A mechanically induced alteration in \(Na^+/K^+\) exchange may also be involved, because this ion exchange is also electrogenic (Thomas, 1972; Isenberg and Trautwein, 1974; Schwarz et al., 1975). Calcium could also act as an internal "transmitter substance" and modify a non-specific leak current (Kass et al., 1978; Eisner and Lederer, 1979).

Finally, \([Ca^{++}]_s\), may affect ionic currents by \(Ca^{++}\)-dependent phosphorylation of sarclemmal sites (Kakuchi and Yamazaki, 1970; Harary et al., 1976). In the context of phosphorylation processes, it should be noted that cAMP can also modulate \(I_{Na}\) (Schneider and Sperelakis, 1975; Reuter and Scholz, 1977), and increases in \([Ca^{++}]_s\) can reduce cAMP levels (see also Tsien, 1977; Chapman, 1979; Katz, 1979, for reviews). Furthermore, there is evidence that concentrations or activities of cyclic nucleotides may vary in the heart, on a beat-to-beat basis (Brooker, 1973; Wollenberger et al., 1973) and with length (Flitney and Singh, 1981).

These findings introduce the intriguing possibility that mechanically dependent changes in phosphorylation of membrane sites could mediate in contraction-excitation feedback. This mechanism bears some resemblance to the one proposed by Pollack (1977) for accelerated diastolic depolarizations produced by stretch, and can also account for the changes described in Section I (ii) (a).

III. Role and Context

Few investigators have specifically studied contraction-excitation feedback, but any electrophysiological study that entails some primary mechanical change should show elements of the feedback. A number of experiments that provide circumstantial evidence relating to the existence and importance of contraction-excitation feedback were selected from the literature during the period beginning in 1969 to date, and the mechanical analogues to those producing contraction-excitation feedback extracted. The characteristics shown in Figure 2 were used to predict the electrophysiological and other consequences of the mechanical changes: viz mechanically induced changes in repolarization phase, transient, and/or threshold depolarizations. Finally, the expected observations and interpretations were compared with the ones actually obtained.

(i) Possible Effects of Feedback at a Cellular Level

Relation between Mechanically Induced Action Potential Change and Ensuing Mechanical Change. Electrically induced changes in action potential duration (Antoni et al., 1969; Wood et al., 1969) initiate transient changes in tension over several beats—presumably by changing \([Ca^{++}]_s\). Similar tension transients may also follow a mechanical change (Parmley et al., 1968; Jewell and Rovell, 1973) and subsequently alter direction with a slower time course (Parmley and Chuck, 1973; Maisch et al., 1975; Suga and Sagawa, 1978). It is probable that mechanically induced changes in action potential contribute to the initial tension transients (Kaufmann et al., 1971). Hennekes et al. (1977) later presented evidence to show that there may be additional contributions, an interpretation endorsed by Suga and Sagawa (1978).

At present it is not easy to reconcile the feedback with the force changes in homeometric autoregulation ("Anrep phenomenon") in the intact heart. Anrep (1912) showed that an increase in developed pressure accompanies an increase in afterload in the 2 minutes following the change. However, the feedback requires an increased afterload to be accompanied by immediate reductions in force transients (and action potential duration), ostensibly the wrong direction for the Anrep phenomenon. Regional variation in myocardial blood flow has been suggested to explain the latter (Monroe et al., 1972), but it could also be related to the slow action potential changes described by Allen (1975).

(ii) Intact Normal Ventricle

Action Potential Duration and Ventricular Repolarization (Q-T) Interval of ECG and Left Ventricular Shortening. One study in ventricle as a whole is a direct corroboration of the initial experiments in excitation-contraction feedback. Isolated myocardium that shortens substantially and rapidly against a small afterload prolongs the action potential duration (Fig. 2 A and B). An analogous situation exists in intact
human hearts. Ford and Campbell (1980) used amyl nitrite to produce a reduction in afterload, and this speeded wall shortening, reduced systolic time intervals, and prolonged the Q-T interval of the ECG. The second heart sound (S₂) occurred earlier and the T-wave later: i.e. S₂ and T times moved in opposite directions and the S₂-T interval lengthened. Other interventions that changed heart rate only, moved S₂ and T times in the same directions.

Other studies relate to differential intramural shortening during contraction in intact ventricle (Fischer et al., 1966; Dieudonne and Jean, 1968; Rushmer, 1970; Streeter, 1979), and relaxation (Krueger and Strobeck, 1978). These mechanical inhomogeneities should provide a background for intramural feedback interactions. Further, the ECG is generated by electrical inhomogeneities (Schlant and Hurst, 1976); therefore the mechano-electric interactions should cause predictable alterations in the ECG. Three examples will be considered in relation to the T-wave (repolarization changes—Fig. 2, A and B), the U-wave (transient depolarization—Fig. 2, C and D), and extrasyistoles (Fig. 2C).

Action Potential Duration and Ventricular Repolarization Gradient (T-wave of the ECG). During normal ventricular contraction, the epicardial circumference shortens proportionately less than the endocardial circumference (Rushmer, 1970), and the tension distributions are also different (Law of Laplace). According to contraction-excitation feedback, this length/tension distribution implies that epicardial repolarization (short action potential) will precede endocardial recovery (long action potential). Such a repolarization gradient, curiously opposite in direction to the flattening of the T-wave during contraction-excitation feedback, this length/tension distribution implies that epicardial repolarization (short action potential) will precede endocardial recovery (long action potential). Such a repolarization gradient, curiously opposite in direction to depolarization, is and in fact normally found. The vector contributes to the concordancy of QRS and T-waves and the tension distributions are different (Law of Laplace). According to contraction-excitation feedback, this length/tension distribution implies that epicardial repolarization (short action potential) will precede endocardial recovery (long action potential). Such a repolarization gradient, curiously opposite in direction to depolarization, is and in fact normally found. The vector contributes to the concordancy of QRS and T-waves.

FIGURE 3. Monophasic action potentials and ECG from the surface of intact ventricles. A: Action potentials (top trace) and electrocardiogram (bottom trace) from frog. After aortic occlusion (arrow) the T-wave becomes inverted within 6-7 beats, whereas QRS complex changes are small by comparison. The action potential duration (at 50% repolarization) shows a reduction in Q-T interval and a smaller T-wave. The QRS amplitudes superimpose. (In other records, the QRS with the isovolumic beat is smaller than with the auxotonic beat.) Data obtained from 28 kg pig, that had a constant heart rate of 75 beats/min. All records except pressure were from the antero-lateral surface of left ventricle. (Unpublished record. Experimental preparation and recording techniques described in Lab and Woollard, 1978).

Transient Depolarization and U-wave of ECG. If mechanical inhomogeneities in the intact ventricle occur after repolarization is complete, discrete depolarizations (Fig. 2, B and C) could generate current flow after the T-wave, and thus form or influence the U-wave. It has already been proposed that the U-wave may be associated with late afterdepolarizations (Lepeschkin, 1941; Lepeschkin and Surawicz, 1964), and Lepeschkin (1976b) suggested that U-wave amplitude is related to contraction. Variable diastolic intervals and/or extracellular potassium affect con-
traction (Hennekes et al., 1981), afterdepolarizations (Cranefield, 1977), and U-waves (Lepeschkin, 1976b), in accordance with this hypothesis. The electrical vector responsible for the U-wave may thus originate from potential differences between muscle regions with different transient depolarizations that may arise from different degrees of contraction-excitation feedback due to inhomogeneous wall contraction.

Threshold Depolarization and Ventricular Extrasystoles. Mechanical perturbations near or during diastole can induce threshold depolarization (Figure 2C; Kaufmann and Theophile, 1967; Kaufmann et al., 1971; Lab, 1978a, 1978b). Analogous situations should exist if extraneous mechanical perturbations were to be imposed on intact hearts. Mechanically induced depolarizations were found in isolated rabbit hearts, which also demonstrated refractory periods appropriate to the mechanical intervention (Brooks et al., 1964; Kluge and Vincenzi, 1971). Acetylstrophanthidin reduced this “mechanical” refractory period and could precipitate fibrillation. Strophanthidin alone can generate afterpotentials or transient inward currents (Kass et al., 1978), perhaps facilitated by the mechanically induced depolarization. Clinical analogues to the extraneous mechanical perturbations also exist. A blow to the chest (Hurst and Logue, 1966) and cardiac catheterization (McIntosh, 1968) are well known to precipitate extrasystoles, and Zoll et al. (1976) were able to stimulate the heart non-invasively with a “mechanical thumper.”

(iii) Intact Abnormal Ventricle

During ischemia, contractile and electrical performance at the cellular and gross levels deteriorate (Samsen and Scher, 1960; Coraboeuf et al., 1976; Kubler and Katz, 1977; Elharrar and Zipes, 1977; Lazzara et al., 1978) and cause abnormal wall motion (Tennant and Wiggers, 1935; Tyberg et al., 1974; Forrester et al., 1976; Theroux et al., 1976). Thus, as described above in normal hearts (Fig. 2), appropriate timing of ventricular mechanical changes during the action potential could affect corresponding deflections in the ECG of the abnormal heart. Several studies indicate that mechanical changes could initiate electrophysiological variation in this and other pathological settings; examples of three abnormalities will be briefly considered.

Reduced Action Potential Amplitude and QRS Complex during Ventricular Dilation. Stretch reduces the amplitude of cardiac action potentials (Penefsky and Hoffman, 1963; Lab, 1969, 1978a; Boland and Troquet, 1980), so that left ventricular distension should reduce the QRS vector by reducing the potential differences across the depolarizing wave front, and, as with the T-wave (Section ii), reduce the electromechanical differences between epicardium and endocardium. Observed reductions in QRS amplitude with dilation have been explained by increases in blood volume (Brody, 1956), or reduced tissue mass under the electrodes (Lekven et al., 1979). However, an alternative possibility is that a length-induced change reduces the amplitude of the action potential.

Altered Membrane Potentials and S-T Segment Elevation. S-T element elevation in the ECG results from abnormal current flow between different regions of the heart and is attributed to different membrane potentials and action potential durations in normal and abnormal myocardium. Varying mechanical conditions could modulate the action potentials differently in the normal and abnormal areas, and thus alter the extent of S-T segment elevation. Lekven et al. (1980) found that ventricular distension during regional ischemia induced S-T segment changes that depended on whether the distension was produced by volume infusion or aortic constriction. Although their plausible explanation was based on differential changes in blood flow, it is of interest that they noted length changes in ischemic segments that would be predicted by contraction-excitation feedback.

Threshold Depolarizations and Ventricular Arrhythmias. A conduction block probably produces some localized contraction abnormality, and thus provides a setting for contraction-excitation feedback. Regular coupled extrasystoles, alternating with irregular parasystoles, may be related to mechanically induced depolarizations. During parasystole, the focus is “protected” from the normal ventricular action potential by an entrance block which may be mechanically transcended for coupling. Such alternating arrhythmias are difficult to explain using the re-entry theory (Schamroth, 1980), and Figure 4A from a preliminary report suggests that contraction-excitation feedback may also provide an explanation. In this experiment, occlusion of the pulmonary artery in an intact heart in situ produced changes in wall motion, transient depolarizations, and regular coupled extrasystoles often alternating with irregular rhythms (Covell et al., 1981).

Finally, early ischemic arrhythmia may also be viewed in the light of contraction-excitation feedback. An ischemic segment is stretched during systole and shortens late in relaxation, i.e., it is dyskinetic (Tyberg et al., 1974; Forrester et al., 1976). As a result, such regions of the myocardium that are still responsive could generate mechanically induced extrasystoles (Figs. 2C and 4A). Preliminary studies show transient depolarizations on the monophasic action potential accompanying segment dyskinesia. These electrical changes can be associated with threshold depolarizations (Lab, 1978b), and Figure 4B is an example in which ventricular fibrillation was precipitated. Within 1 hour of coronary occlusion, ventricular extrasystoles (and often fibrillation) were regularly found. During this period, transient depolarizations were consistently observed, together with segment dyskinesia. Although an ubiquitous electrical artifact must be excluded before contraction-excitation feedback is added to the other membrane factors as a cause of ventricular extrasystoles (Arnsdorf, 1977; Hauswirth and Singh, 1978; Cranefield, 1977; Cranefield and Wit, 1979; Hoffman and Rosen, 1981), this mechanism warrants further study as fibrillation could occur in situations in which there is depressed conduction, re-entry, and altered automaticity.
Figure 4. Changes in action potential and segment length from the epicardium of intact ventricles in situ. Traces from above down: monophasic action potential, epicardial segment length, intraventricular pressure. A: Records from right ventricle of an anesthetized dog. Pulmonary artery occlusion increases right ventricular pressure and segment length, causes changes in segment contraction, and produces transient depolarizations (TD) on the action potential. Coupled right ventricular extrasystoles follow. (Modified with permission: Covell et al., 1981.) B: Records from a pig left ventricle during regional ischemia. The action potential shows transient depolarizations (TD) which are related to the stretch and rapid late systolic shortening of the segment (upward is shortening). A premature beat arises during the crest of the depolarization (ES), precipitating ventricular tachycardia and eventual fibrillation within 5 minutes of the coronary occlusion (unpublished record, reported in Lab, 1978b).

Figure 5 summarizes contraction-excitation feedback and its possible ramifications. (1) Contraction and mechanical changes influence myocardial electrophysiologic properties (quadrant C to A). In particular, stretch followed by shortening can produce transient depolarizations which prolong action potentials, or produce discrete depolarizations that can precipitate premature beats. (2) The mechanism is undefined. One or more tenable mechanisms, common to both mechanical and membrane events, may arise from changes in calcium kinetics and perhaps in specific phosphorylation of selected intracellular sites, although an altered architecture cannot be excluded. (3) The normally contracting left ventricle provides a suitable microenvironment for the expression of contraction-excitation feedback. Inhomogeneous wall motion can produce electrophysiological inhomogeneity (quadrant D to B) that can influence the T-wave and, conceivably, produce U-waves in the ECG. (4) Regional ischemia exaggerates mechanical inhomogeneities and magnifies the expression of the feed-back. Contraction-excitation feedback can generate “extrasystoles” that may contribute to ventricular arrhythmia in early ischemia.

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Contraction-excitation feedback in myocardium. Physiological basis and clinical relevance.

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Circ Res. 1982;50:757-766
doi: 10.1161/01.RES.50.6.757

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

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