Mechanoelectric feedback (transduction) in heart: concepts and implications

Max J. Lab *

British Heart Foundation Cardiac Arrhythmia Research Group, Department of Physiology, Charing Cross and Westminster Medical School, London W6 8RF, UK

Received 14 February 1996; accepted 9 April 1996

Keywords: Mechanoelectric feedback; Excitation-contraction coupling; ECG

1. Introduction

Is mechanoelectric feedback an epiphenomenon in normal heart? Colloquially stated: "What is the use of mechanoelectric feedback?" Mechanoelectric feedback, where electrophysiological changes follow mechanical changes is being increasingly scrutinised. Several reviews from our laboratory [1,2,3,4] cover mechanically induced ventricular arrhythmia. Reiter [5] concentrates on congestive heart failure, Franz [6] reviews it more generally, and Taggart [7] describes its existence in man. Mechanoelectric feedback not only expresses in ventricular myocardium. A review by Kohl and Noble [8] shows it in sinoatrial fibroblasts, and one by Nazir and Lab [9] demonstrates it in atrium. The present review attempts to be broad and addresses its physiological role, context or relevance. Fig. 1 may help outline the review's scope, which includes mechanisms, anatomical and physiological expression, prevalence and clinical expression. It also includes some theoretical slants.

Why use the term feedback (mechanoelectric feedback) at all, rather than mechanoelectric coupling or mechanoelectric transduction? One always regarded excitation-contraction coupling as a unidirectional phenomenon. Similarly, we could construe mechanoelectric coupling or transduction as being unidirectional. The heart cyclically and regularly changes its mechanoelectric state. This is largely parallel in time and anatomical 'space'. Moreover, as Fig. 2 will show, common processes are used in excitation coupling and mechanoelectric transduction. These processes provide a matrix for feedback. Interaction between excitation-contraction coupling and mechanoelectric feedback would produce fine tuning of the regulatory processes in myocardium. In this way, any mechanical change would influence membrane electrophysiology and excitation, and hence, in turn, mechanical function. Although the term 'mechanoelectric feedback' lacks rigor, it could partly describe its functional role. It also lends itself to the concept that the feedback loops could provide stability during electrical or mechanical perturbation under normal circumstances, but may destabilise the situation under pathological conditions. That is, disturbances in this tuning by pathological processes that induce mechanical changes in the heart should produce clinical syndromes that have in the past been difficult to explain, or treat, on a purely electrophysiological basis. For example, although heart disease together with ventricular arrhythmia is a potent cause of death in the Western world, the mechanisms are unclear and the treatment unsatisfactory [10].

Fig. 2 describes some of the well-established interactions between membrane potential and myocardial contraction—including some possible paths of mechanoelectric feedback. More comprehensive reviews are available and good starting points would be reviews by Weir [11] and Ebashi [12]. Use the figure legend to follow excitation-contraction coupling down the left-hand side of the diagram.

2. The transduction or feedback instigators (mechanisms, see Fig. 1, 3 o'clock)

The possible link from mechanical events to electrical ones was inferred in the question "Is there mechanoelectric transduction in heart?" in the title of Lab's pilot study.

* Tel.: (+44-181) 846 7282; fax: (+44-181) 846 7338.

0005-6363/96/$15.00 © 1996 Elsevier Science B.V. All rights reserved
PII S0005-6363(96)00088-0
in 1968 [13]. However, the affirmative answer was already implicit in Bozler’s [14] earlier study as well as in that of Von Stauch [15]. A practising physician, Von Stauch demonstrated a QT interval shortening of the ECG in intact frog ventricle while changing the mode of contraction from auxotonic to isovolumic. The answer was also tacit in several other studies before the 1970s: Penefsky and Hoffman [16]; Trautwein who with Dude1 [17] stretched papillary muscle while measuring the microelectrode action potential; Deck [18] stretched purkinje fibres.

Mechano-electric transduction describes the situation in which a mechanical stimulus is transduced into an electrical signal.

2.1. Mechanically induced electrical artefact

The conception of mechano-electric feedback has been traumatic. The methodology includes simultaneous impositions or measurements of mechanical variables (force, length, pressure), and electrophysiological variables (probability of channel opening, intracellular action potentials, monophasic action potentials, electrocardiogram). During the electrically oriented recordings, mechanical loading conditions were changed in a variety of preparations. Thus, one of the major reasons for the traumatic conception has been that any mechanical change in the experimental preparation will, physically, alter the relationship between the electrical generator and the recording electrode. This then raises the spectre of mechanically induced electrical artefact. This would apply to all the preparations—from membrane patch, with a change in the seal, to the electrocardiogram with an altered electrical vector. However, the results show a remarkable concordance in the different experimental situations in that mechanically related changes can induce electrically related changes that are generally analogous. This mitigates against artefact, and one can justifiably search for physiological mechanisms.

In the physiological transduction process, force and length changes could link with membrane events (mechano-electric feedback) by processes followed in the right-hand loop in Fig. 2. Indirectly (‘5’ and ‘6’) force and length changes could influence the membrane by altering free sarcoplasmic calcium [Ca]. This may influence ionic flux and hence membrane potential (‘1’ up), by modulation of electrochemical gradients for Ca++, outward potassium currents, ‘leak’ currents and, finally, electrogenic Na/Ca exchange.

Fig. 1. Visual ‘contents’ of review of mechano-electric feedback. The diagram depicts, clockwise starting at 3 O’clock, mechanisms; 6 o’clock, normal expression that includes anatomical divisions of the heart, electrophysiological measures, and prevalence in vertebrates. Its clinical expression (9 o’clock) includes mechanisms of arrhythmia, pathological changes in afterload and preload. Theoretical aspects (12 o’clock) deal with modeling and nonlinear approaches.

Fig. 2. Diagram of interactions between excitation contraction coupling and mechano-electric transduction depicting some of the mechanisms. Ion fluxes (1 ‘up’) determine the membrane potential, which can also provide a driving force for ion movements (1 ‘down’). The changes in membrane potential are a function of the ionic equilibrium potentials and conductances producing a variety of transmembrane currents as reviewed by Noble [146]. Depolarisation (1 ‘down’; and 2) releases calcium from the stores and increases sarcoplasmic concentration (3 ‘down’). This can be an electric effect, but it is probably mostly by calcium-induced calcium release. In mammalian muscle iCa or Na/Ca exchange does not normally immediately raise intracellular calcium ([Ca]) to any significant degree unless the action potential is long, in which case some Ca comes in directly. The calcium combines with troponin-C (tn-C) which causes troponin-I to allow actin and myosin interaction. The process, which needs ATP, produces force (4 ‘down’). As, or probably before, the membrane repolarises, during relaxation, the sarcoplasmic reticulum sequesters Ca (3 ‘up’). Ca can also leave the sarcoplasm by a metabolically dependent Na/Ca exchange (7). Greater binding to troponin C can also lower [Ca], but this produces increased force rather than faster relaxation. Length-dependent force activation is incorporated in 5 and 6. See text for mechano-electric feedback paths.
2.2. Diastolic load changes—related to mechanically (stretch) activated channels (see Fig. 1, 3 o’clock)

In biology, stretch-activated channels, as reviewed by Sachs [19], Morris [20], French [21] and Sackin [22], appear to be a major mechanism for this mechanoelectric transduction. Their participation in, for example, osmoregulation, sensation (tactile, hearing, proprioception) seem obvious, but their role in the heart on initial inspection, is less apparent. Sachs, with Guharay [23] first described these channels in skeletal muscle, with Craclius et al. [24] describing them in cardiac muscle. The transduction is through stretch opening the channels to admit charge carrying ions.

Cyclic AMP, ATP in both membrane and contractile events and could concern mechanosensitivity and mechanoelectric feedback. One may implicate the phosphokinases, various intracellular messengers and the cytoskeleton (Fig. 2, PK) here. The force transmits directly, (Fig. 2, ‘5’ and ‘8’) to stretch-activated channels in the membrane. It also very likely transmits via the cytoskeleton. Mechanical changes thus change ionic flux by affecting permeability via these stretch-activated or mechanosensitive channels to change membrane potential (‘9’). The most convenient explanation for their contribution to the transmembrane currents that influence membrane and action potential is that the ions move towards their relevant equilibrium potentials. In this context, perhaps it is worth illustrating the symbiosis between membrane patch studies and more integrative physiology. Lab’s [25] transient stretches during the voltage excursion in the monophasic action potential recorded from intact frog ventricle first suggested an equilibrium potential for mechanically induced permeability changes. Fig. 3 illustrates these early records. They motioned a stretch equilibrium potential somewhere between −10 and −40 mV. Illustrating a different symbiosis, now with mathematics, Franz’s group, in a preliminary study with Sachs [26], modelled appropriate reversal potentials using their transient stretch observations.

2.3. Systolic load change—related to calcium (Fig. 1, 3 o’clock)

Although the plethora of investigations implicates stretch-activated channels in the transduction process, contractile myofilament activity [27] in cardiac muscle may be also converted to electrical activity.

We have shown that intracellular calcium changes may relate to mechanoelectric feedback during contraction itself [27]. Increased myocardial shortening reduces the affinity of troponin-C for calcium and deactivates force (see also Housemans et al. [28]). ‘Extra’ calcium comes off the filaments into the sarcoplasm. The calcium changes affect the action potential (Fig. 2, ‘7’) by calcium-dependent currents, notably Ca/Na exchange [29,30], prolonging it, and possibly producing early afterdepolarizations [2,31,32]. Keurs’ group [33] also implicated calcium in their studies. They observed a correlation between triggered propagated contractions and delayed afterdepolarisations, arguing that the electrophysiological event did not trigger the mechanoelectric one: rather that calcium caused both. The calcium ion will need some accent, for not only is it involved in normal electro-mechanoelectrical activity, but it may have a crucial role in arrhythmogenesis. Arrhythmogenesis may also involve cAMP.

3. Some pitfalls in interpretation of the mechanisms

There are some observed mechanically induced electrophysiological changes that do not readily fit into the above mechanisms. The literature reports the existence of stretch-induced arrhythmia in intact ventricle, as fairly extensively reviewed [1,3,34], more often than it reports mechanically induced arrhythmia in isolated superfused preparations [35,36]. Craclius seems to have produced the only study so far showing stretch-induced activation in single cells [37]. The question I raise, if the sample studies are representative, is whether other factors operate in intact ventricle besides direct membrane mechanosensitive mechanisms. Endogenous catecholamines, which are the natural means of producing threshold diastolic depolarisations, constitute one possibility. Our pilot experiments have demonstrated such a possibility. Propranolol inhibits stretch-induced arrhythmia in intact heart [38], and dobutamine exacerbates them. In keeping with this proposal, Monroe et al. [39] showed that raising outflow pressure in
intact isolated hearts produced a catecholamine efflux. Another possibility is that stretch of the whole ventricle produces a different distribution of stresses and strains to stretch in single cells (see Brady [48]).

The division into systolic and diastolic, above, is probably arbitrary. In the intact heart one has to carefully differentiate between a pre- and afterload mechanism (see Hansen [40]) or wall stress or strain (see Halperin et al. [41]). The evidence indicates that systolic events (afterload, contractility) as well as diastolic events (stretch, preload) [42-45] can influence electrophysiology. Moreover, in the intact heart in situ there are confounding changes in baroreceptor reflexes when changing mechanical conditions such as circulatory pressures, but several studies suggest that these reflexes do not play a major role. The mechanism in intact hearts probably also lies in the close interaction between membrane and mechanical events at the cellular level, for mechanoelectric feedback operates in denervated hearts in situ [46]. It also operates in isolated perfused as well as superfused preparations including the single cell [47].

'Strech-activated' channels may be a misnomer. The heart undergoes cyclic length changes and stretch activation implies an importance of increases in length producing a rise in probability of channel opening. It could be of equal functional significance that channels close with length decreases. Viewed from this aspect the state of the channels could contribute directly, not only to diastolic potentials, but also to the action potential due to length reduction during contraction. The contribution throughout the cardiac cycle would depend on the membrane potential. This would be in relation to the reversal potential of the currents passing through the stretch-activated channel. This is easy enough to visualise, for ventricular diastolic filling puts a degree of diastolic stretch on myocardium with a finite open probability. Ejection would then destretch the channels, decreasing the open probability. Given the properties of the extracellular skeleton and the cytoskeleton, micropipette patch studies start with a residual membrane tension that may not be commensurate with that in intact heart. Brady [48] has suggested that cells in isolation develop less force than when interconnected in multicellular preparations, because they are less stretched. Mechanically modulated or length-dependent channels could be alternative nomenclatures to stretch-activated channels, or even to mechanosensitive channels.

The gating properties of many stretch-activated channels are different from other previously described channels, suggesting that the channels are different. However, voltage, time, biochemical and ligand dependence of the latter channels presumably involves protein conformational dynamics, and again presumably so do the mechanically activated channels. The transmembrane potential, for example, must somehow couple to a conformational equilibrium of a particular membrane protein: its chemistry is different depending on the electric field. Transduction processes at this level could be complex [49]. Any thermodynamic force could have similar effects on the protein system provided the system had a set of dynamic properties capable of responding. Voltage changes can affect intramolecular charge translocation or separation, and rotation or creation of alpha helical segments. Conversely, it is not difficult to visualise the possibility that mechanical forces on the molecule could similarly affect these structures. There is already some evidence for the possibility that some 'conventional' electrophysiological channels are mechanosensitive [50-58].

Electrochemical coupling could also play a role once the electrophysiological change has occurred, for membrane protein conformation can be remarkably sensitive to voltage changes [49]. That is, the open probability could change during the action potential. Although this concept is attractive, there is no hard evidence that open probability of any stretch-activated channel is voltage-sensitive.

4. Normal expression, and prevalence (membrane to man, SA node to ventricle; see Fig. 1, 6 o'clock)

Fig. 4 diagrammatically describes the general changes in the membrane and action potential with intra- or inter-beat mechanical alterations. It indicates the ubiquity and rough concordance of the results. The diagram is still a simplification, for some studies do not come under any one heading, and others span several headings. For example, Speare and Moore [59] used several types of preparation and measured several electrophysiological expressions.

Fig. 4. Diagram showing the general electrophysiological changes produced by mechanical changes. The left-hand side represents single cells, multicellular preparations and intact hearts. An increase (dashed line) in force, length or pressure of a cell or intact heart (F/L/P) produces depolarisation, a reduction in action potential (AP) duration or shortening of QT interval (QT to QT2) of the ECG (dashed lines). The change in the T-wave of the ECG (T to T2) is a reflection of the inhomogeneity of the phenomenon in the thick-walled ventricle. The right-hand side represents mechanical stretch of stretch-activated channels (SAC) with single channel opening depicted as downward voltage deflections.
Virtually all the anatomical subdivisions of the heart show mechanoelectric transduction or feedback.

1. Sinoatrial node. Bainbridge [60], and later Blinks [61], showed that raising left atrial pressure raised heart rate. The most likely mechanism in intact heart in situ is neuronal via external reflexes. However, one could easily explain their observations by the direct operation of stretch-activated channels in the sinoatrial node influencing the pacemaker potential. Recently, our laboratory [62] has shown that prevention of cyclic sinoatrial stretch produced by the cyclic pressure changes in the atrium accompanying lung inflation reduced sinus arrhythmia—even with B blockade and the vagi cut. Although one could implicate stretch-activated channels in our preliminary studies, reflexes still need careful exclusion.

2. Sinoatrial fibroblasts. An intriguing aspect of mechanosensitivity is emerging as Kohl, Kamkin and colleagues [8,63] demonstrate that non-excitable cells, very likely fibroblasts, in atrium and the sinoatrial node, show mechanoelectric transduction.

3. Purkinje fibres. Kaufmann and Theophile [35] and Rosen et al. [64] have all demonstrated mechanically induced electrophysiological changes in isolated superfused preparations of Purkinje fibres.

4. Ventricle. Several workers in several preparations of ventricle show mechanically induced changes in action potential. These include superfused, perfused, or intact preparations in situ. I describe the changes below.

In similar vein, virtually all the preparations studied show concordant electrophysiological expression of mechanically induced electrical changes (diagrammed in Fig. 4).

1. Membrane-channel opening. Briefly reiterated, membrane distortion (i.e., micropipette suction, osmotic swelling, cell inflation) increases channel opening probability (diagrammed in Fig. 4 on the right). The recorded signal from an undistorted membrane shows simple noise. The stretched membrane produces step changes in the record as the channel opens.

2. Diastolic depolarisation. Continuous or transient stretch of healthy heart muscle can depolarise the myocardium (Fig. 4 on the left). This generates spontaneous activity or depolarisation, and there are several example studies [16–18,25,35,65]. The opening of mechanosensitive channels probably produces this diastolic depolarisation.

3. Action potential. A beat with a large load has a short action potential (Fig. 3, dashed traces) compared with a contraction having a reduced load (solid lines). An intra-beat mechanical decrease of load lengthens the action potential duration of the same beat in cat papillary muscle. This can be associated with an ‘early afterdepolarisation’ [1,25,32,36,66]. We see the combination of increased load and action potential shortening in a variety of preparations. We have seen it in isolated papillary muscle [36] and frog ventricular strip [67], as well as the intact perfused ventricles of frog [25] and rabbit [68]. Several laboratories have also seen it in intact ventricle. These include Lerman et al. [44], Franz et al. [32], Benditt et al. [69], and Tobler et al. [70]. We have seen it in pig [42], Taggart et al. [71] and Levine et al. [72] observed similar changes during cardiac surgery in man. Taggart et al. [73] has also seen it during clinical catheter investigations. Fairly recently the phenomenon has been again demonstrated at two ends of a spectrum. White et al. [47] saw mechanically induced action potential changes in isolated ventricular cells. Our laboratory has shown, in intact hearts in situ, that an increase in load affects the electrical restitution curve [74,75]. It steepens the initial rising phase, and accentuates the so-called supernormal phase.

The electrocardiogram (ECG) is the recording of surface potentials and is the manifestation through a volume conductor of electrical vectors derived from the inhomogeneous spread of cellular action potentials through the heart. As intramyocardial contraction is also inhomogeneous, the ECG should express mechanoelectric feedback.

4. QT interval of ECG. The action potential duration is equivalent to the QT interval of the ECG. Analogous with action potential duration changes, the QT interval prolongs with reduced load (Fig. 4 on the left). We found this under various experimental conditions [1,67]. Ford and Campbell [76] found it in man when they reduced blood pressure by amyl nitrite inhalation. Yamashita et al. [77] found that pulmonary or aortic valvuloplasty prolonged the QT interval in an afterload dependent (rather than preload dependent) manner.

5. T-wave of ECG. The T-wave of the electrocardiogram is, more directly than is the QT interval, some function of electrophysiological inhomogeneity of repolarisation. The repolarisation gradient is roughly epi to endocardium and base to apex—opposite in route to depolarisation. This produces similar general directions of the resulting vectors, creating the anomalous 'upright' T-wave of the ECG as discussed by Noble and Cohen [78]. Antzelevitch's group [79] have demonstrated cellular heterogeneity in the ventricular wall. Notwithstanding, it is possible that mechanoelectric feedback can play a modulatory role. Our laboratory [1,42] has shown that mechanical loading does change the T-wave (diagrammed in Fig. 4). This may be the result of the volume change modulating regional mechanical inhomogeneity (see Fig. 5). There are, however, alternative, purely physical, explanations for T-wave changes with volume changes [80].

6. U-wave of ECG. Lab [1], Lepeschkin [81], and Gibson [82], with indirect evidence, have suggested that mechanical changes generate U-waves. Franz has reported U-wave changes in the epicardial ECG during load manipulation in vivo [32] and they may be related to early afterdepolarisations.

7. Excitability. The changes in action potential described above are reflected in changes in myocardial refractoriness and excitability [40,41,43,44,83], although
that 1.5 times control length) decreased velocity. In keeping with this, Sideris [88] found that raised blood pressure could lengthen. Franz showed shortening at early phases of repolarisation, but lengthening when measured later in the action potential. The likely explanation is that an early afterdepolarisation [1,32] which occurs at the tail end of the action potential, prolongs the action potential. An associated U-wave (see below) slurring the QT interval could produce apparent QT prolongation. The inconsistencies are thus, probably, apparent rather than real.

5. Mechanoelectric modulation of normal heart rate and rhythm

The sinoatrial node controls normal heart rate, and, as long established, change in left atrial pressure is one modulator [60,61]. Although, in intact heart in situ, external and central reflexes are major mediators (see Spyer’s review [91]), stretch-activated channels could play a direct role. Our laboratory [62] has shown that splinting the sinoatrial node, thus preventing dynamic changes with respiration, reduced sinus arrhythmia. This seemed unrelated to external reflexes. Kohl, Kamkin [8,63] and colleagues show that mechanosensitive sinoatrial fibroblasts may also affect electrophysiology of the sinoatrial node.

6. Mechanoelectric modulation of mechanical function

Many studies in intact hearts have used fairly heroic load changes to induce clear electrophysiological changes. However, one study indicates that as little as a 10–20% change in systemic blood pressure can induce electrophysiological changes [42]. Mechanoelectric feedback could have a role in fine regulation of electromechanical interaction (Fig. 6). Electrical prolongation of the action potential initiates increases in tension [92] presumably by increasing intracellular calcium. The prolongation of action potential duration with reduced force or deactivation during shortening may do the same. This would ultimately raise intracellular calcium to counter such force reductions or deactivations. One study is in keeping with this possibility [36], the force regulation taking some 8 beats. Slinker [93,94] has also proposed the type of modulation described at the cell level as part of the interbeat interval regulation in the intact heart in situ. Homeometric autoregulation or the Anrep phenomenon [95] in the intact heart describes the situation where a slow rise in developed pressure accompanies an abrupt increase in afterload. Monroe et al. [96] explained this by variations in regional ventricular blood flow, with a slow recovery of an initial subendocardial ischaemia. However, mechanically induced changes in action potential and/or intracellular calcium may offer an alternative explanation. Allen [97] observed action potential duration changes in superfused papillary muscle subjected to mechanical changes analogous to the foregoing. Later he [98,99] showed a slow increase in the calcium transient that could account for the mechanical changes.

![Diagrammatic representation of electro-mechanoelectric interactions of three myocardial segments in series.](https://example.com/diagram.png)
The mechanically induced intracellular calcium changes includes conduction velocity, refractory periods, and current flow. The feedback processes initiated by the perturbation modulate these measures, (right-hand arrow) we have gross as well as patchy dysfunction. Contracdestabilising myocardial function. A chaotic attractor now makes for chaotic attractor maintains a rough status quo. With myocardial disease instability, and possible arrhythmia. With myocardial disease-involvement of Ca comes from LeGuennec et al. [103] and Sigurdson et al. [104] who show increases in intracellular Ca with membrane distortion and stretch. Myocardial stretch could thus increase force by a mechanism complementary to those usually proposed for the Frank Starling phenomenon, such as length-dependent calcium sensitivity of the myofilaments.

7. Mechanoelectric modulation of electrical function—the electrocardiogram (ECG)

The functional significance of the direction of normal repolarisation reflected in the ECG is not clear. We could speculate that the normal gradient is antiarrhythmic. The feedback at the cell level operates in regional electromechanical interaction throughout the ventricular wall to maintain this gradient or normal dispersion of action potential duration. Consider, for example, enhanced normal heterogeneity of segment motion. Segments shorten at the expense of an adjacent stretched one (Fig. 5). The long segment would have a short action potential duration compared with the others. This would augment electrical dispersion which can be arrhythmic if the dispersion is large enough. Under normal circumstances length-dependent force activation (including the operation of stretch activated channels) would increase the force developed by this segment. Its shortening ability increases, and the action potential duration prolongs to re-establish normal electrical dispersion of repolarisation. The homeostatic mechanism operates poorly in myocardial pathology, and regional electrophysiological heterogeneity would persist. This scenario is not as speculative as it seems. Regional electromechanical inhomogeneity in myocardial disease is legion. Nonetheless, further speculation is hazardous.

8. A clinical role for mechanoelectric feedback (see Fig. 1, 9 o'clock)

Along with mechanoelectric feedback possibly modulating normal cardiac rhythm and contributing to sinus arrhythmia, there is clear evidence that it can produce pathological types of rhythm disturbances. Several reviews deal with this aspect [1,3,5,6,34]. Further expansion in this area is outside the remit of this review, but it will briefly touch on mechanisms. Essentially stretch can depolarise the myocardium (possibly by opening mechanosensitive channels) to generate spontaneous activity through diastolic depolarisations. 'Early afterdepolarisation' [1,31,32,36,40,105] may also mediate the abnormal rhythm. A rise in intracellular calcium is gaining credence as having a pivotal role in the generation of arrhythmia, and in a variety of pathological disturbances [106–108]. As described above, several investigations demonstrate that mechanical changes can alter [Ca]. Diastolic stretch raises it [103,104], and contraction may mechanically modify the calcium transient per se [27,28]. A sustained rise in [Ca], can produce [Ca], oscillations that are conducive to membrane oscillations and arrhythmia [110]. Invoking a multi-cellular mechanism, reduced refractory periods and/or inhomogeneous expression of mechanoelectric feedback (Fig. 5) could produce re-entrant arrhythmias. An increase in both pre- and afterload 'seen' by the myocardium initiates cascades of events leading in the short term to electrophysiological changes, via mechanoelectric feedback. In the long term an increase in load produces cascades leading to hypertrophy (e.g., following hypertension). Does this process have some cell signalling cascades in common with mechanotransduction or mecha-
Mechano-electric feedback? Intracellular calcium, cell signals and the cytoskeleton would be possible contenders in the cas-
cades. Stretch-activated channels could be one possible
initiator (see also Bustamente [111]). These changes could
switch on early-onset oncogenes. This would then produce
the electromechanical matrix conducive to pathology. Al-
though plausible, there is no clear evidence for a role for
stretch-activated channels in hypertension. Sadoshima et al.
[112] were unable to show an effect of several stretch-
 activated channel blockers on the growth response in
stretched cultured myocytes.

9. Theoretical considerations (see Fig. 1, 12 o’clock)

Mechano-electric feedback, as suggested above, may act
as a fine regulatory system in the heart. The introduction
of feedback pathways and time delays into a system can
increase its range of dynamic behaviour, and possibly
make the ensemble adaptable. This may have bearing on
the stability of the system (Fig. 6), and thus the generation
of ‘chaos’ and/or cardiac arrhythmias. The question is
whether there is mathematical argument that supports the
possibility that mechano-electric feedback plays some nor-
mal regulatory role, as well as a role in arrhythmia.

Feedback processes—and mechano-electric feedback is
one of these processes—generally lend themselves to
non-linear dynamical modelling. Non-linear dynamical
analysis and ‘chaos’ is a relatively new branch of physical
mathematics. Its application to biological rhythms as cov-
ered by Glass and Mackay [113] is generating new ways of
viewing arrhythmia (see right loop of Fig. 6), and interest
is widening in cardiological fields (e.g., Denton [14]).
Although only a few studies have attempted non-linear
dynamical treatment of mechano-electric feedback [115],
there are some interesting if tentative parallels in viewing
chaos, non-linear dynamics, mechano-electric feedback and
arrhythmia.

9.1. Heart rate variability

Chaos has been discussed as a property conferring
physiological adaptability [116]. Normal heart rate variabil-
ity, which includes respiratory sinus arrhythmia, has been
regarded as a chaotic process [116,117]. We have demon-
strated that stretch of the sinoatrial node in the intact pig
heart in situ reduces the normal high-frequency component
of heart rate variability [62]. Can this process disrupt and
be associated with pathology? Ventricular dilatation is a
mechanical change, allied with myocardial failure, and a
reduction of heart rate variability [118]. This particular
association is attracting recent interest [119,120], and au-
nomnic tone appears important [121]. Frequencies are nor-
mally broad band and this can indicate chaotic processes.
The loss of this variability may be significant in pathologi-
cal processes. The power spectrum of the heart rate flattens

in patients before demise. We have proposed a mecha-
on-electric contribution. Near-terminal situations produce di-
lated ventricles with high end-diastolic pressures, and com-
parable mechanical changes in the right atrium. This would
stretch the sinoatrial node and reduce heart rate variability
[62].

9.2. Bigemini and alternans

The evidence and observations presented in several
reviews [1,3–6,38] show that mechano-electric feedback
can produce arrhythmias. Moreover, groups led by Glass
[122] show evidence that some arrhythmias may employ
chaotic processes. Glass and co-workers recently used
non-linear system analysis to model para-systole and bigeminy. [123,124] My as well as Franz's laboratory has
also demonstrated a mechanical induction of these arrhyth-
mas, including bigemini [32,105,125].

Glass and his co workers [126] regard electrophysi-
ological alternans as a period 2 doubling bifurcation,
which may be a route to chaos (figurative in Fig. 6, right
loop). Electrophysiological alternans can precede ventricu-
lar fibrillation [130–135]. We [136] and Janse's group,
earlier [137,138], have also seen alternans in the action
potential in experimental regional ischaemia. A ventricular
premature beat can either turn the electrical alternans on or
off. In analogous fashion, we have also shown that a
sudden load change can turn a mechanical alternans off or
on [139] Cardiac failure and ischaemia (which also show
load changes) can modulate or produce electromechanical
alternans [140,141].

9.3. Electrical restitution

There are 'arrhythmic' mechanistic links between dy-
namical analyses and mechano-electric feedback. One ex-
ample is a change in electrical restitution. It derives, purely
by analogy, from the analyses of Chialvo, working with
Jalife [142]. Briefly, they describe a model of deterministic
chaos in Purkinje fibres. The non-linear system (electrical
restitution) showed supernormality, and steepening of the
restitution curve. They showed that these changes, theoret-
ically, are arrhythmogenic. They modeled the dynamics by
empirical, experimentally determined curves. We have ex-
perimental observations on restitution curves in keeping
with this concept. An increased load in intact ventricle in
situ can enhance the supernormal period, and steepen the
curve [74,75].

Although it seems plausible that one could link mecha-
on-electric feedback, non-linear dynamics and chaos, elec-
physiological stability and instability, precisely how one
might establish the quantitative significance needs more
detailed mathematical exploration. We also need more
experiments designed specifically to meet these objectives.
Previous experiments may not provide enough direction.
For example, Chialvo et al. [142] measured action poten-
tials and refractory periods in isolated Purkinje fibres. We have to treat their interpretations of the results in relation to arrhythmia with caution. Arrhythmia occurs in reality in a complex 3-dimensional electrical and mechanical matrix, and at much slower heart rates.

There is also some interest in an alternative mathematical approach in modelling different aspects of mechano-electric feedback. This approach uses equations derived rigorously from experiments. Within limits, one can use some of these models to 'test' hypotheses. Sachs [143] used a type of modelling that explored the introduction of equations, representing appropriate stretch-activated channel density and cationic reversal potentials, into his own and existing models of the action potential (e.g., that developed by Noble and others [144]). Winslow's group (personal communication with Hyde – see [145]) also used modifications of these equations but developed a 2-dimensional cellular matrix programmed into the massively parallel connection machine. They showed that a small area of stretch-induced electrophysiological change can disturb the matrix to produce arrhythmia. Pelce's [115] approach was different in that he modelled force (deactivation—in-C, intracellular calcium), and coupled it to the membrane through intracellular calcium changes rather than stretch-activated channels.

9.4. Summary

It seems that one could regard mechano-electric feedback in normal heart as an intrinsic regulatory process that modulates normal electromechanical interactions (Fig. 6, left loop). Any physiological mechano-electro-mechano perturbation is self-adjusting and homeostatic. This preserves the status quo, or the heart adapts to form a new electro-mechano-electric situation. The position in cardiac pathology is different (Fig. 6, right loop), particularly if the disease process produces inhomogeneities. A premature ventricular contraction can be mechanically induced by several of the accepted electrophysiological arrhythmic mechanisms. Thereafter, instantaneous feedback develops within and between regional heterogeneous mechanical conditions. These non-linear recovery processes compound interacting non-linear time courses of recovery of restitution and excitability. Changes in initial loading or mechanical conditions could initiate arrhythmia. Both mechanical and electrical inhomogeneities (also diagrammed in Fig. 5) compound the situation in the intact ventricle. This would enable a milieu of altered excitability, arrhythmogenic current flow and re-entry, to sustain the arrhythmia.

Acknowledgements

Supported by grants from the British Heart Foundation, The Garfield Weston Trust and The Wellcome Trust.

References


Lab MJ, Yost J. Regional differences in electrical restitution of the pig left ventricle. J Physiol (Lond) 1994;483:70P[Abstract].


