Br Heart J 1992;67:213–5

REVIEW

Interaction between ventricular loading and repolarisation: relevance to arrhythmogenesis

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Abnormality of left ventricular wall motion is a major predictor of sudden cardiac death in patients with coronary disease[1 2] or after myocardial infarction.[3 4] Death is usually caused by arrhythmia.[5] Some patients with chronic heart failure die as a result of profound bradycardia and/or asystole[6] but there is also a high incidence of lethal or potentially lethal ventricular arrhythmia.[7–10] Moreover, the incidence of ventricular arrhythmia is high in patients with hypertension,[11–13] and in patients with aortic stenosis.[14] The mechanism for the association between wall motion or mechanical load abnormality in these patients and arrhythmia is unclear. One possibility is a direct interaction between mechanical and electrical events whereby myocardial load or strain influences the electrophysiology[15]—that is, the excitability and refractoriness of the myocardial cells. Such a mechanism has been shown in isolated tissues and in animal studies[15 16] and is now receiving attention in humans.[17 18] This mechanism if present could well be implicated in the genesis of human arrhythmias[19] particularly if it could be shown that there was a differential response between areas of abnormal wall motion and normal wall motion, as has been shown in studies of dogs with chronically infarcted hearts.[20]

To date three studies in humans provide evidence for a relation between stretch or strain and the electrophysiological behaviour of myocardial cells.[17 18 21] One of these studies also shows that abnormality of wall motion can significantly modify this relation.[21]

Possible arrhythmogenic mechanisms

There are several ways by which mechanically induced electrophysiological effects may be arrhythmogenic in the clinical setting of ischaemia, acute infarction, or in hearts subject to pressure/volume overload.

MECHANICALLY INDUCED REACTIVATION

Regional asynergic or paradoxical wall motion occurs early during myocardial ischaemia.[22–24] Patients who develop an aneurysm within 48 hours—that is, an area of systolic akinesia or dyskinesia with a distinct systolic deformity and preserved adjacent wall motion—are particularly at risk of sudden death.[25] It has been suggested that because activation of injured muscle is slow, it may still be in electrical diastole when the surrounding muscle is in systole.[26] As the ventricle contracts the injured segment would be stretched and this would induce electrical activation in this area.[27] This electrical wavefront would again propagate slowly to the surrounding normal tissue, which by that time would be no longer refractory and so would be reactivated.

MECHANICALLY INDUCED REENTRY

An important arrhythmogenic mechanism is reentry.[26 28 29] The basic principles underlying the development of a reentry circuit may be illustrated by the following model. A propagating impulse may meet an obstacle—for example, infarcted muscle or scar tissue. The impulse would then divide into two and pass round either side. If conduction around the obstacle is impaired, conduction may fail down one limb (decremental conduction) and be blocked. If the impulse travelling down the other limb is slowed it may reach the distal part of the blocked limb after a delay which has allowed time for the blocked limb to become re-excitable. The impulse may then travel backwards up this limb and then continue round the obstacle in a circular fashion following in the wake of the change in muscle from the refractory to the excitable state. This constitutes a reentry circuit which is autonomous and may take over the activation of the ventricle.

An obstacle does not necessarily need to be an anatomical one: it could be created by an inhomogeneous alteration in the refractoriness in neighbouring fibre groups which may induce "functional" unidirectional block. It is apparent therefore from the above model that factors which create regional differences in conduction and excitability would be expected to encourage the development of reentry. In this context it has been shown that conduction block may be induced by local differences in refractory period of the order of 11–16 ms in atrial tissue[30] and of the order of 10–20 ms in ventricular muscle.[31] The path of a reentry circuit is usually in the border zone between scar tissue (or non-conductive muscle) and normal myocardium. Local mechanical stress has been shown to be magnified by up to four times at the junction between normal myocardium and scar tissue by a process known as

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Accepted for publication
15 August 1991

stress amplification.[32] This may exaggerate regional electrical inhomogeneity at border zones and this territory would be particularly susceptible to mechanically induced electrophysiological effects.

ABNORMAL CURRENT FLOW

Another possibility is abnormal current flow. Inhomogeneous wall stress or strain, particularly marked in the presence of ischaemia[22-24] could produce local electrical inhomogeneity by contraction-excitation feedback. For example one area could have wall motion that is out of phase with an adjacent area (dyskinesia). The two areas would then generate current by virtue of the potential differences created by the now out of phase action potentials which would stimulate adjacent cells during the period of enhanced excitability.[28]

AFTERDEPOLARISATIONS

Early afterdepolarisations are seen as inflections of the normal repolarisation phase of the action potential.[16 21 31] If such inflections are large enough they can trigger an early beat and they have been implicated in the genesis of arrhythmias. The interpretation of inflections in the downstroke of the monophasic action potential that is characteristic of early afterdepolarisations, however, is contentious because it is impossible to exclude a mechanically induced artefact caused by passive electrical changes at the tissue/electrode interface.[33 34] Nonetheless, several observations support the possibility that these afterdepolarisations are not an artefact.[35 36] Also the monophasic action potential electrode reliably records early afterdepolarisations in vivo under circumstances known to produce them in vitro, when they are recorded by microelectrodes.[37 38]

CELLULAR MECHANISMS

Cellular mechanisms may involve stretch and fibre excursion.[15] Stretch would invoke a non-specific permeability change perhaps via stretch activated channels[39] and fibre excursion would invoke a change in intracellular calcium.[40] It may be that enhanced excursion deactivates force by reducing the affinity of calcium for troponin C. Calcium comes off the myofilaments and increases sarcoplasmic concentrations to prolong the action potential via electrogenic sodium-calcium exchange[41] or calcium activated currents.[42]

Therapeutic relevance

Electromechanical interactions may be relevant to the high incidence of sudden death caused by ventricular arrhythmia in patients with impaired left ventricular function.[1-5] Such interactions may also be relevant in patients with acute ischaemia, in whom local wall motion abnormality is a usual early feature.[22-24] Several factors may interrelate with electromechanical interaction. For example, arrhythmia may be initiated by an extrasystole or the subsequent beat. Both the extrasystolic and the post extra-systolic impulse have an altered cycle length and are associated with altered force of contraction. In addition these impulses may induce a sudden change in direction of propagation which in turn may alter the orientation of wall stress between areas of normal and ischaemic myocardium or between neighbouring areas of normal and abnormal wall motion.

Therapeutic interventions designed to manipulate preload and afterload are now commonly used, as are drugs that influence the inotropic state of the ventricle. In fact, load reduction, a pure mechanical intervention, may turn out to be an antiarrhythmic intervention in congestive heart failure.[43] An important consideration would be the relative effects of a drug given to alter loading conditions on the adjacent normal and abnormal segment of ventricle. It may be that such a medication would have an antiarrhythmic effect in one area and an arrhythmogenic effect in another area with a different force-tension velocity profile. Understanding of these mechanisms involving electromechanical interaction may be important for the future development of therapeutic strategies.

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