Review Article

Clinical implications of the interval–force relationship of the heart

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Introduction

When the interval between cardiac contractions varies, either on a beat by beat basis such as before an extrasystole or during atrial fibrillation, or in the sustained fashion which can accompany exercise, fever and arrhythmias, a change in the force of contraction of the heart may follow. Since it is recognized that both ventricular filling and aortic end-diastolic pressures are themselves interval dependent, it is to these influences and their modification by neuroendocrine control, that the variations in cardiac function are usually attributed.^{1–4} There is, however, another intrinsic property of cardiac muscle which is a manifestation of interval *per se*.⁵ This interval–force relationship allows the heart to respond to a change in interval with a change in the force of contraction through a mechanism which is independent of changes in ventricular volume and aortic end-diastolic pressure. Why then is this mechanism not invoked more often in clinical thinking? Before this question can be addressed, or the clinical implications of the interval–force relationship explored, an understanding of mechanical restitution and postextrasystolic potentiation is essential.

Underlying physiology: mechanical restitution and postextrasystolic potentiation

If a piece of cardiac muscle is fixed at both ends and stimulated to contract at a fixed rate, then a steady-state force will develop.⁶ If a single short interval is introduced, followed by an immediate return to the basic stimulus interval, the short interval will modify the developed force of a number of subsequent contractions. The contrac-

tion which immediately follows the short stimulus interval, and which has its clinical counterpart in the extrasystole, is weak because of incomplete mechanical restitution of the cardiac muscle.^{7,8} If a slightly longer test pulse interval is introduced, this allows the muscle to reconstitute to a greater extent and there is a corresponding increase in the force of contraction (see lower curve in Figure 1). The time course of mechanical restitution is species dependent,^{6,9} in man restitution is usually complete by 800 milliseconds^{10,11} but may occur later in myocardial disease.^{9,12} The introduction of the short stimulus interval also modifies the subsequent beat which is strengthened or potentiated as compared with the steady-state beats: the inverse relationship between the degree of potentiation and the (now) pre-preceding interval describes postextrasystolic potentiation¹³ (see upper curve in the figure). If an

Figure 1 The relationship between the contractile response of a beat (ES, ■) and its preceding interval (the ESI) described mechanical restitution (lower curve). The influence of the same interval on the subsequent beat (ES + 1, □) is inverse and describes postextrasystolic potentiation (upper curve). Data are from guinea-pig papillary muscle stimulated to contract isometrically in response to the pacing protocol shown (insert).¹¹

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interval is sufficiently long to allow full mechanical restitution of a beat, there is no potentiation of the subsequent beat (for example, this is illustrated in Figure 1 by intervals of 800 milliseconds and beyond). When a short interval provokes post-extrasystolic potentiation, this potentiation can be seen to decay gradually over a number of subsequent beats provided all the potentiated beats are themselves fully restituted.¹³ In other words any single interval variation has the potential to modify the contractile response of several or more beats.

Interval force relationships

Mechanical restitution and postextrasystolic potentiation influence cardiac function on a beat to beat basis, and are mediated through variations in the amount of calcium reaching the contractile proteins. These variations in the calcium transients are determined by the interval between contractions.

Mechanical restitution

- Relationship between the force of contraction of a beat and the preceding interval.
- Independent of ventricular filling or aortic pressure.
- Complete by 800 milliseconds in patients with normal hearts but longer in heart disease.
- Incomplete mechanical restitution following short RR intervals may contribute to the acute cardiac dysfunction of tachyarrhythmias such as atrial fibrillation and ventricular tachycardia.

The central role of calcium

By loading the cytoplasm of isometrically contracting muscles with aequorin (a bioluminescent protein that emits light in the presence of calcium) something of the mechanism that underlies interval–force behaviour can be understood. Using this method it has been shown that changes in stimulus interval are associated with changes in the concentration of calcium ions released to the contractile proteins following depolarization. These fluctuations in intracellular calcium transients, produced in response to both steady-state and transient changes in stimulus interval, are accompanied by parallel changes in developed tension (or force).^{14–17} This ability to modify developed force in response to interval (by varying the intracellular calcium transient) is not peculiar to human cardiac muscle but appears to be an intrinsic property of

cardiac muscle in general.⁶ As such it has been extensively explored in many species and preparations including single myocytes,^{18,19} isolated muscles and hearts^{6,20,21} and *in vivo* in animals and man.^{10,22–25}

Historical perspectives

In spite of such observations, interval-related changes in cardiac function continue to be ascribed to the Frank–Starling mechanism.^{26–27} Why is this so? This tradition seems to reflect the difficulties of trying to measure either contractile function or ventricular filling in man combined with the forceful belief of early investigators that the Frank–Starling mechanism was all important, for example, references 1–3. Starling, in an attempt to explain the effects of exercise on the heart, maintained that the heart had to enlarge at the beginning of exercise and, in spite of evidence to the contrary, this provoked a prolonged and heated debate about the relative importance of Starling's Law and neuroendocrine control.²⁸ Lewis appears to have been strongly influenced by Starling and invoked Starling's Law as the mechanism underlying the beat to beat variation of the pulse in atrial fibrillation (AF). Thus beats which followed short RR intervals were said to be weak because of incomplete ventricular filling and the strengthening of subsequent beats was seen as an expression of volume carried over from the weak beats.¹ This view subsequently dominated clinical thinking on the subject, although the idea that the beat to beat variations of the pulse in atrial fibrillation might represent an intrinsic inotropic mechanism of the heart had been suggested by Wenckebach as early as 1903.²⁹ This hypothesis was dismissed by Einthoven and Korteweg² and was then largely ignored until the 1960s when renewed interest in the influence of interval itself followed animal work on either simulated or induced AF. From these studies, where contractile indices could be more easily quantified, it was clear that both preceding and pre-preceding intervals were important determinants of cardiac function.^{30–32}

Confirmation that postextrasystolic potentiation in man was a manifestation of interval, rather than of interval-dependent ventricular filling, came with a series of studies in: patients with atrial fibrillation;^{24,33–36} patients with spontaneous ectopics;³⁷ and patients where postextrasystolic potentiation was produced by pacing.^{23,38,39} These conclusions followed the use of measured variables which were independent of volume,^{23,24,33} the ability to estimate volume changes,^{37,40} or protocols where the timing of the first extrasystolic beat was adjusted to match that of the pre-extrasystolic beat.^{38,39} However, not all investigators have been

this rigorous in their attention to interval or measured variables, and the cumulative clinical literature on postextrasystolic potentiation and its implications for patients is consequently confused.

The extent to which mechanical restitution modifies cardiac function in man has proved a still more elusive issue, though like postextrasystolic potentiation, mechanical restitution is mediated through interval-determined variations in intracellular calcium transients. Mechanical restitution can easily be demonstrated in isolated muscles and isolated hearts where the effects of length and volume can be controlled. The difficulty arising in man is that mechanical restitution and ventricular filling have similar time courses so that their respective influences become difficult to separate. Too often, however, there has been little inherent recognition of this association and it has often been presumed that changes in volume (or aortic end-diastolic pressure) somehow preclude a simultaneous influence of mechanical restitution. This bias appears throughout the literature on atrial fibrillation where much of the data attributed to the effects of volume could, just as plausibly, be explained on the basis of interval.^{1,3,4,34-36} Nonetheless, unequivocal evidence for mechanical restitution in man does exist and comes from studies of spontaneous arrhythmias^{11,41} and from studies in which varying degrees of mechanical restitution were produced by pacing.^{11,20,22,42,43}

Clinical implications

Despite all these difficulties some interesting and potentially useful applications do emerge from those studies in which intervals before and after the extrasystole were carefully controlled.^{22,23,44} One area which merits further investigation is the possibility of deriving an index of cardiac function from interval-force behaviour. There is a tendency for the degree of potentiation, following an extrasystole, to be increased in the diseased heart when compared with the response of the more normal left ventricle. When this is expressed as a ratio of the potentiated beat to that of a preceding steady-state beat,²² comparisons of contractile function between patients appear to be clinically discriminating.²³ This is potentially applicable to a wide range of clinical situations. For example, when does an individual patient with aortic regurgitation require surgical intervention? Many patients can tolerate aortic regurgitation for years with little apparent left ventricular decompensation: cardiac dilatation then heralds rapidly deteriorating cardiac function. The clinician advocates intervention before this point is reached but currently has no means of detecting the early stages of this progressive myocyte dysfunction.⁴⁵

Similarly, whilst it is well recognised that angiotensin converting enzyme inhibitors improve the prognosis of a group of patients with congestive cardiac failure,⁴⁶ there are distinct limitations to the way the response to such therapy in individual patients can be monitored and so optimized. How should we best monitor cardiac function in AF, demonstrate functional improvement following angioplasty or explore preconditioning in patients?⁴⁷ In all of these situations a measure of deteriorating or improving contractile health would prove invaluable.

Postextrasystolic potentiation (PESP)

- Inverse relationship between the force of a beat and the pre-preceding interval.
- Potentiation of a beat is only fully expressed when the beat is completely restitutioned.
- Contributes to the irregular cardiac function of atrial fibrillation.
- Future possibility of manipulating PESP to modify the inotropic state of patients with both therapeutic and diagnostic benefit.

Postextrasystolic potentiation reflects an increase in the amount of calcium released in the vicinity of the contractile proteins upon depolarization.¹⁷ The idea of manipulating this during pacing to strengthen systolic contractions of the diseased or failing heart has obvious clinical appeal and to some extent this application has been explored during paired pacing (where normal pacing intervals alternate with short intervals). When postextrasystolic potentiation occurs spontaneously the 'price' of augmentation of the potentiated beat is the reduced force of the extrasystole (which may reflect a combination of incomplete mechanical restitution, inadequate ventricular filling, a high aortic end-diastolic pressure and an abnormal sequence of ventricular conduction). During pacing a short stimulus interval can be introduced which produces electrical depolarization but no contraction and which strengthens the subsequent beat or beats. The idea of paired pacing is an alternation of interval so that every systole is potentiated in this way but whether this actually represents the optimal arrangement is unclear. Although this area initially attracted widespread interest,^{48,49} it has only been explored to a limited extent in patients^{50,51} and may yet offer intriguing therapeutic options.

Studies in muscles isolated from patients suggest that the time course of mechanical restitution is

delayed by disease.^{9,11,12} This effect can be seen in patients as well¹¹ and may explain why slowing of the heart rate may have beneficial effects even when this is achieved using beta adrenergic receptor blockade in patients with cardiac failure.⁵² Thus by increasing the extent of mechanical restitution, the negative chronotropic influence of the beta blocker could result in a positive inotropic response which far outweighs the negative inotropic effects of the same drug. Beta blockade may also prolong ventricular filling where left ventricular diastolic dysfunction has produced critical shortening of the effective filling time.⁵³ Interestingly, both mechanisms would suggest that chronotropic 'incompetence'⁵⁴ may actually confer a therapeutic advantage. The similar time course of mechanical restitution and ventricular filling, in health and some forms of cardiac disease, underlines the difficulties involved in trying to disentangle the relative influences of the two mechanisms.

The influence of sustained interval changes (which were the focus of Bowditch's early work⁵) on contractile and ejection function of the heart is still more complex and the clinical role is correspondingly less well understood. Some, but not all, patients with a ventricular tachycardia develop signs of acute left ventricular decompensation which occurs despite 'normal' ventricular function and which is abolished with a return to their usual

rhythm. The mechanism which underlies this remains obscure. Similarly, there is no adequate explanation for the cardiomyopathy described in association with prolonged episodes of some of the more 'benign' tachyarrhythmias.⁵⁵ This also appears to be reversible and it is the gradual recovery of function, following a return to sinus rhythm, that offers the most convincing argument for a tachycardia-induced cardiomyopathy, as distinct from the acute dysfunction which may accompany the tachycardia. The extent to which normal or abnormal interval-force relationships contribute to such acute and chronic manifestations of sustained tachyarrhythmias is an intriguing question but one which has barely been considered.

As clinicians we are only just beginning to acknowledge that the interval-force relationship is of fundamental clinical importance. Such tardiness belies the extent to which mechanical restitution and postextrasystolic potentiation have been investigated during the course of this century. If we were to base future clinical studies on this knowledge of the underlying physiology, then we would stand to gain exciting answers to some basic clinical questions.

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