Postextrasystolic Potentiation

Do We Really Know What It Means and How to Use It?

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Postextrasystolic potentiation (PESP), the increase in contractility that follows an extrasystole, is an interesting phenomenon that has been known for almost 100 years. The literature on this effect is reviewed. It is found that there is significant evidence that the phenomenon is independent of muscle loading and represents a distinct property of the myocardium. Examination of the literature pertaining to the cause of the effect suggests that calcium shifts within the sarcoplasmic reticulum are responsible, although there are some conflicts with this conclusion. Regarding the utility of PESP as a diagnostic test of latent viability of ischemic myocardium, the literature review reveals contradictions and conflicts with several methodological problems of the experiments. Finally, concerning the utility of continuous PESP (paired-pacing) to augment ventricular function in the failing ventricle, the studies again are inconclusive and methodologically suspect. Conditions for the proper analysis of the PESP response are reported, and suggestions for future studies are introduced. (Circulation. 1993;88:2962-2971.)

Key Words • potentiation • force-frequency • contractility

The phenomenon of potentiation of contractility of the systole following a premature extrasystole (postextrasystolic potentiation [PESP]) has been known in physiology for about 100 years1 and has been the subject of hundreds of reports. Yet, the results of many of these reports conflict, and it is still unclear what are the meaning and utility, if any, of PESP. The purpose of this article is to review the literature on PESP, with special reference to these two issues, and to suggest the direction for further investigation.

The Phenomenon

There is considerable evidence supporting the existence of the phenomenon.2-28 There has been some debate concerning the question of whether the PESP response was independent of ventricular loading.4,5,12,14,22,29-49 That is, since there is usually a compensatory pause following an extrasystole due to the failure to reset the sinoatrial node, there is a following "compensatory pause"; this results in the diastolic interval of the following systole being longer than the basic beat. As a consequence, there is a longer period for diastolic filling, so "potentiation" might putatively be due merely to this augmented filling.51,33,40,43-46,50-55 Or, conceivably, the potentiation might be due to changes in afterload leading up to the following systole.30,40 Additionally, several studies have suggested that the phenomenon is an artifact.16,56,57 However, there have been numerous studies addressing these issues, with particular attention to controlling the loading conditions of the heart muscle being tested, and it has been shown that there clearly is potentiation of contractility in the following systole irrespective of the loading conditions.5,12,22,40,47-49,57 Although the phenomenon is usually recorded following a ventricular extrasystole, it appears to be equally manifest following an atrial extrasystole.22,27,58,59

Coupling Phenomenon

A fundamental feature of the phenomenon is the increasing degree of potentiation as the interval between the normal systole and the extrasystole becomes shorter.4,9-12,16,24,34,36,60-71,134 This feature has been noted since earliest reports and is so consistent that it may be used to determine if PESP is occurring, i.e., a stimulation sequence may be repeated with a shorter coupling interval to determine if the expected increase in potentiation is present, thus confirming that the original sequence was actually manifesting the phenomenon. To take advantage of this feature, one must, however, be certain that all other intervals are equivalent.12,73

Cause

There have been numerous investigations to determine the cause for the PESP.

Autonomic nervous system. There is conflict in the literature regarding the question of whether changes in the autonomic nervous system are responsible for PESP. Blocking doses of β-blocker failed to block the response,69,74 as well as postextrasystolic relaxation75 and the more general force-frequency response of increasing heart rate.56,76 Yet, rapid pacing did increase norepinephrine levels in the coronary sinus,77 and there is enhancement of sympathetic nerve activity by single premature beats; in addition, the latter response was found to be related to ventricular extrasystole coupling interval,78 perhaps mediated by alteration in baroreceptors.64 Further support for an association is the finding that coupled pacing, which is thought to be a form of continuous PESP, acutely lowered mean aortic pres-
sure, leading to baroreflex sympathetic activity.79 Thus, the available evidence points toward an associated increase in sympathetic activity with premature extrasystoles but away from the association being causal of the potentiation. A plausible hypothesis would seem to be that baroreceptor-mediated sympathetic simulation might have a modulating effect on the PESP, without being responsible for the fundamental response. In support of this hypothesis is the finding that a given vagal stimulation causes a greater depression of atrial contractile force at lower heart rates.80

**Sodium and potassium.** Increasing the rate of stimulation produces a rate- and time-dependent elevation of intracellular sodium,81 but there is no evidence that this has relevance to PESP. There has, however, been more investigation of the role of potassium in the phenomenon. At a potassium concentration of 5.9 mmol/L, the premature action potential has a longer plateau than the preceding control action potential, lending support to the latter being involved in the response. On the other hand, when extracellular potassium concentration is reduced to 1.2 mmol/L, the PESP response may be obtained without the expected prolongation of the premature action potential.82 However, this result does not necessarily support the concept that potentiation is anything other than indirectly related to potassium concentrations since the increase in contractility with an increase in heart rate is associated with a net potassium loss that approximates that seen with a dose of digitalis.83 thus suggesting instead that the potassium changes might be consequent to changes in concentration of calcium. Indeed, studies of the resting transmembrane potential and the effects of changes in extracellular concentrations of potassium failed to support the concept that potentiation is related solely to changes in fiber potassium content.3

**Calcium.** As would be expected from a current understanding of its role in excitation-contraction coupling, calcium appears to be intimately involved in the PESP response. Direct 45Ca47,84 and indirect calcium measurements85,86 have demonstrated increased intracellular calcium concentrations with paired pacing. Increasing external calcium concentrations increased the inotropic effect of the positive staircase,87,88 but slow channel calcium antagonism failed to alter the inotropic effect of paired pacing in isolated cat cardiac muscle.89 The strength of contraction was found in one study to be linearly correlated with peak internal calcium,86 but another reported that peak systolic position, which is a measure of cell motion, was markedly increased at a time when peak systolic internal calcium concentration was not changed or slightly increased.89 The latter investigators suggested that PESP is not entirely explained by an increase in calcium concentration and that alterations in the sensitivity of the myofilaments are also involved.

**Effects of drugs and source of calcium.** Determination of the effects of various drugs on the PESP response is helpful not only in determining if calcium is responsible for the effect but also in ascertaining the source of calcium and how it affects the response. Traditionally, the sarcoplasmic reticulum (SR) has been considered to be the source of the calcium responsible for the augmented contractility, because agents known to have a direct effect on this calcium storage/release site have been reported to have a marked effect on the PESP response. Caffeine produces SR calcium release, depleting calcium stores and thereby leading to loss of PESP.90-92 Ryanodine, an agent that is believed to inhibit the release of calcium from the SR, was similarly shown to abolish PESP86 and abolishes the inotropic effects of paired electrical stimulation (continuous PESP) in isolated cardiac muscle.93,94 Additionally, histamine, which is thought to increase calcium sequestration by the sarcotubular system, produces a slow loss of PESP.92,95 These studies suggest that PESP is caused by release of calcium from intracellular stores.

Yet, this does not seem to be the entire explanation for PESP. In particular, agents thought to have more effect on transsarcolemmal calcium transport than SR calcium have been found to alter PESP. Administration of epinephrine enhances the effect92 and decreases the rate of decay of potentiation.26 A corollary to the former effect would be abolition of PESP with a β-blocker, and this has indeed been found,96 but this conflicts with other literature74 that found no effect with propranolol. Other agents that affect transsarcolemmal calcium transport, calcium channel blockers, have consistently produced a decrease in the potentiated response.97-99 Speculation seeking to explain this effect centers around transsarcolemmal calcium flux96 or peripheral hemodynamic effects98 and not on dynamics of SR calcium. Perhaps the controversy is resolved by the study of Meir et al in which isoprenaline (20 μmol) abolished PESP but the reduction of extracellular calcium or the addition of verapamil partly restored tension potentiation. These results were interpreted as reflecting changes induced by isoprenaline in the degree of filling of SR stores with calcium and in the rate of calcium recycling between uptake and release sites within the SR network. Additionally, there was a large PESP found in the neonate guinea pig atrium along with a relative insensitivity to isoprenaline. This was interpreted as reflecting a scarcity of SR and implying that tension potentiation may also reflect changes in sarcolemmal calcium currents.96

Indeed, Weir and Yue have provided evidence from experiments with the calcium indicator aequorin that an extra quantity of calcium is released on the postextrasystolic beat commensurate with the extra force of the contraction.96 The source of the calcium was not determined, and the SR is as likely a candidate as any.100 But Lab et al,101 again with aequorin, showed that when shortening occurred, myoplasmic calcium was increased and the membrane potential was more positive than in isometric contraction. The change in calcium apparently preceded the depolarization, and they proposed that muscle shortening reduces calcium binding to the contractile proteins and leads to a rise in myoplasmic calcium and that the rise activates an inward current leading to the observed changes in the action potential.101 There is consequent negative feedback control of calcium influx—the amount of calcium released during a beat determines the extent of calcium influx—extra calcium enters the system on the extrasystole because it is a weak beat. In favor of this hypothesis is the well known coupling phenomenon whereby the earlier an extrasystole is introduced, both the weaker it is and the greater is the following potentiation. Alternative explanations were considered and rejected: (1) An increase
in sarcolemmal calcium influx as the mechanism was rejected because an increase in [Ca\textsuperscript{2+}], would be expected to increase mechanical activity, whereas in fact mechanical activity was found to be reduced after shortening. In addition, if sarcolemmal calcium influx were increased, one would expect the effect on the action potential to precede the effect on measured [Ca\textsuperscript{2+}], since it will take some time for calcium to diffuse to the aequorin molecules, which are thought to be distributed throughout the myoplasm. In fact, the changes in [Ca\textsuperscript{2+}] appear to precede the change in membrane potential. (2) An increase in calcium release from intracellular stores or decrease in calcium uptake by intracellular stores also seemed unlikely because these should lead to a prolongation of mechanical activity. Thus, Lab et al concluded that calcium attached to contractile proteins is released into the myoplasm by the process of shortening, and this leads to both prolongation of the calcium transient and a reduced duration of mechanical activity.\textsuperscript{107} This seems a plausible explanation but seemingly equally consistent with the experimental results is the suggestion that shortening might affect the movement of calcium within the SR network.

In conclusion, experiments to date fail to exactly determine either the mechanism of PESP or the source of the augmenting calcium.

Other Associations

Numerous other associations and correlations have been reported with PESP. How these play into a coherent conception of the phenomenon is difficult to judge but warrant discussion.

Other force-frequency effects. The relationship between stimulation pattern and contractile force has been known since the work of Bowditch in 1871\textsuperscript{102} and Woodworth in 1902.\textsuperscript{103} It might be reasoned that the PESP response is nothing more than another manifestation of these responses, whereby the early coupling interval of the extrasystole is simply an instantaneous representation of the Bowditch (positive staircase) effect\textsuperscript{13,38,39,48,83,88,104-116} and the postextrasystolic interval represents the Woodworth effect (rest potentiation).\textsuperscript{117} Investigators have found results that do lend some support to this suggestion\textsuperscript{35,56,73}; however, other results suggest a more complicated relationship.\textsuperscript{34,57,90} So, this issue is unresolved. Mechanical restitution, rest decay, and postrest recovery are other force-frequency effects that may also be related to PESP in some yet-undefined way.

Indeed, mechanical restitution, which is the recovery of contractile strength as a function of the preceding cycle length,\textsuperscript{37,56,63,80,118-130} has been examined with reference to its relationship to PESP. Several studies have found results that suggest that the two are different manifestations of the same force-frequency response,\textsuperscript{63,131,132} whereas other results conflict with this conclusion.\textsuperscript{72,133} The demonstration of the voltage dependence of both the maximal rate of rise of the premature action potential\textsuperscript{134} and restitution\textsuperscript{73} would appear to go along with a similar mechanism. The most carefully performed study is that of Yue et al,\textsuperscript{132} in which a single time constant for a monoexponential function was found to describe both phenomena. This would, of course, suggest that the two are the same response, but with different manifestations. On the other hand, the investigation of Kedem et al\textsuperscript{72} found that the time course of restitution after a single stimulation indicated that restitution of contractility is an exponential function, whereas following paired stimulation it is entirely different. Of course, this leaves open the question as to whether PESP and paired stimulation represent the same phenomena. If this is not the case, then the results of many other studies will be brought into question. Although this has been assumed, it has never been proven. Similarly, Seone et al\textsuperscript{135} found that when additional stimuli are placed after the initial stimulation and before the restitution stimulus, the contraction strength rises gradually until it reaches a higher consistent level. Again, this would suggest a potentiation factor separate from the restitution factor.

Action potential duration changes. It seems intuitively plausible that if calcium influx is increased on the extrasystole, this might be manifest as an increase in the duration and/or amplitude of the action potential since this is known to influence the force of the subsequent and not the concomitant beat.\textsuperscript{136} The action potential duration of a premature beat has been observed to be prolonged,\textsuperscript{34,105,135,136} supporting this speculation. However, this explanation cannot apply universally since many species, including humans, show shortening of the action potential when the preceding interval shortens.\textsuperscript{41,121,122,137-139} Further complications of this hypothesis involve the demonstration that PESP was obtained without prolongation of the premature action potential when extracellular potassium was reduced to 1.2 mmol/L and PESP under the effect of isoproterenol or verapamil was not accompanied by prolongation of the premature action potential. On the other hand, it has been shown that the slow inward current seen during depolarization has a higher peak on premature than steady-state contractions.\textsuperscript{140}

Previous beat contraction history. Several studies have shown that the performance of the left ventricle is influenced by the mechanical events of the previous beat,\textsuperscript{42,141,142} particularly previous beat ejection but not previous beat pressure load.\textsuperscript{143} Although PESP has not been specifically studied in this experimental arrangement, the results are suggestive. It appears that ejection (ie, muscle shortening) causes loss of calcium from the myofilaments (and higher intracellular calcium). This leads to increased early calcium uptake by the SR and, with the postextrasystolic pause, more time for calcium transfer to the release store. The net result is increased calcium transfer to the release store between beats. Thus, ejection on the extrasystole influences activation and contraction in the next beat.\textsuperscript{143} These results are consistent with known phenomena of PESP and with models of calcium movements but lend little further information regarding the causal mechanisms of the events.

PIEA and NIEA. Another way in which PESP has been characterized is the relationship between what is called "positive inotropic effect of activation" (PIEA) and "negative inotropic effect of activation" (NIEA).\textsuperscript{110,144} These are two interval-dependent processes that influence myocardial contractility in opposite directions. The process tending to decrease the strength of contraction as the interval between contractions is shortened is first seen at long intervals and exerts an increasing effect as the
intervals decrease. The cost of contraction produces in the muscle a change that is unfavorable for the development of tension in subsequent beats, which disappears with time, and is capable of accumulation if successive beats follow one another closely enough. This is the NIEA. The opposing process tends to increase contractility as the interval between contractions is decreased. The effect is reversible, but after a change in interval, it approaches a new steady state much more slowly than does the NIEA. This indicates that a change favoring the development of tension is produced in the muscle by the act of contraction and that this change, like that responsible for the NIEA, disappears with time and is able to accumulate. This effect is the PIESA.144 Koch-Weser and Blinks believed that the effects of all changes in rhythm as well as rate can be understood in terms of the general rules governing the production and decay of the NIEA and PIESA: A premature beat encounters more of the NIEA and of the PIESA than the regular beats. Since more of the NIEA than the PIESA is produced by each beat, the effect of the additional NIEA predominates and to an extent that is greater the more premature the beat, i.e., the well-known coupling phenomenon. The increase in strength of the following beat (PESP) reflects the additional PIESA produced by the premature beat.110

While these findings are illuminating and interesting, they are actually merely descriptive of the coupling phenomenon associated with PESP and do not give any more insight into the underlying causes of these effects.

**Length-dependent activation.** Additionally,43 the changes in shape of the end-systolic pressure–volume relationships with PESP were found to be similar to the diastrially induced changes in shape of the force–length relation found in isolated cardiac muscle, which have been attributed to length-dependent activation.50,54 While interesting, these findings lend little information into the underlying causes of these effects.

**Change in oxygen consumption and coronary blood flow.** A close coupling exists between coronary blood flow and myocardial energy demand due to the dependence of the heart on aerobic metabolism and the near-maximal extraction of oxygen from coronary arterial blood under basal conditions.145 Accordingly, it has been shown that in the diastole immediately following the first potentiated systole, the coronary vascular resistance falls.146 This indicates that a transient increase in cardiac metabolic demand is followed immediately by a compensatory coronary vasodilation. This effect could be important in persistent PESP (paired-pulse stimulation), but it is unlikely that it has any effect on the single PESP. Similarly, it has been shown that absent an overall increase in heart rate, there is no increase in oxygen consumption merely with changes in rhythm,145 again making a physiologically important association with single PESP unlikely.

**Compartment models.** The most widely understood compartment model used to explain phases of tension decline and mechanical restitution following a pause is that of a two-compartment model.36,56,106,128,147-149 The hypothesis suggests the movement of calcium from a functional “uptake” to a functional “release” compartment. PESP may also be explained by such a model: If the inward calcium current recovers (even partially) before the extrasystole, then some calcium will enter the cell at the extrasystole. If the release compartment is refractory, normal calcium release will not occur, resulting in a weak contraction of the extrasystole. The calcium that entered during the extrasystole will, however, contribute to a larger calcium accumulation in the uptake compartment, which will be presented to the release compartment. The latter, on recovering at the next contraction, will release a greater amount of calcium, resulting in PESP. It is unclear if the “compartments” are physical entities or merely a functional construct. Both compartments are sensitive to ryanodine, which suggests that they both involve the SR, favoring an objective entity.128 At any rate, the compartmental modelling is of more benefit to the possible explanation of excitation contraction coupling than it is to PESP. PESP phenomena are consistent with the two-compartment model of excitation contraction coupling, but the model does little to explain PESP.

**Clinical Usefulness**

There have been numerous attempts to use PESP for clinical purposes, both diagnostic and therapeutic.

**Diagnostic**

PESP has been applied extensively in diagnosis of coronary heart disease and valvular heart disease, particularly the former.

**Coronary heart disease.** The differentiation of viable from nonviable myocardium in patients with coronary artery disease and left ventricular dysfunction is a relevant issue in the current era of myocardial revascularization. It is now well established that impaired left ventricular function does not always represent an irreversible process. The development of revascularization techniques has made it imperative to develop methods whereby one can identify myocardium that might benefit from such surgery. Ischemia may depress myocardial contractility, and normal function may return following successful revascularization.150 Regional myocardial contractile function measured at baseline does not reliably distinguish viable myocardium from nonviable myocardium.146,151-154 Under certain conditions, when viable myocytes are subjected to ischemia, prolonged alterations in myocyte function leading to regional left ventricular dysfunction may occur, and this dysfunction can be completely reversible.155,156 Viable myocardium may be difficult to distinguish from scarred or necrotic myocardium because of either chronic hypoperfusion (termed “hibernating myocardium”)155) or a recent acute coronary syndrome with reperfusion (termed “stunned myocardium”).156

PESP during contrast ventriculography has been reported to identify certain asynergic regions that are capable of improvement after revascularization.159 However, this result has been disputed.160,161 It would seem that to demonstrate that PESP is a useful clinical tool in the evaluation of ischemic heart disease, at least five conditions must be met:

**The degree of PESP responsiveness reflects the degree of ischemia.** Several studies in both experimental animals and humans have suggested that normal myocardium is more PESP responsive than ischemic myocardium.13,80,162-179 Further, hypokinetic or “border zone” myocardial segments are more PESP responsive than central zone infarcted, akinetic, or dyskinetic regions.2,13,42,160,162,164,167,179,180 The degree of myocardial blood flow impairment bears a direct correlation with
PESP responsiveness, 13, 158, 167, 168, 171, 172, 176, 181-183 whereas duration of ischemia correlates inversely, as expected, 158, 167, 184-186 However, in some studies, akinetic and dyskinetic regions were more or equally PESP responsive, 4, 34, 160, 161, 178, 187-191 and non-PESP responsiveness did not always predict nonviability, 90, 166, 171, 176, 187 Additionally, the decrease in bulging with PESP in the central infarcted zone was shown to be due to changes in loading conditions and not contractile reserve. 192

Histologically alive myocardium is responsive and histologically dead myocardium nonresponsive. Two studies could be found that fulfilled this condition. 158, 193 One report, however, described loss of PESP responsiveness in zones that were found to be pathologically normal. 187 A recent study reported a greater percentage necrosis in central (less PESP responsive) zones than in border (more PESP responsive) zones. 167

One investigation was unique in determining PESP responsiveness after reperfusion following occlusion of coronary arteries. It reported the most closely related association between necrosis following reperfusion and loss of PESP-determined contractile reserve. 158

Revascularization of PESP-responsive segments results in return of function, and revascularization of nonresponsive segments fails to return function. Revascularization and reperfusion of PESP-responsive ischemic segments has, in several studies, been found to restore function. 159, 164, 167, 169, 178, 185-187, 194, 195 However, postrevascularization PESP-responsive segments were not always predicted prior to revascularization. 171, 178, 187, 195

The degree of PESP responsiveness is related to surgical risk, relief of ischemia and heart failure, and ultimate survival. In terms of the ultimate hope for PESP, ie, as a predictor of the results and survival of coronary artery revascularization, only four studies were found. 169, 174, 194, 196 In the first, PESP responsiveness indicated mean ejection fraction of ultimate survivors. 196 and in the second, lack of PESP responsiveness was highly predictive of postoperative mortality despite not being predictive of postoperative ejection fraction. 169

The techniques of studying postextrasystolic potentiation conform to standard techniques for the study of latent contractility as well as the study of the force-frequency relationship. 73 In terms of the techniques used to study PESP, several observations arose from review of the studies. First, no one method of analysis of segmental contractility was used. In animal experiments, epicardial length–tension gauges and ultrasonic transducers were most commonly used. 14, 82, 131, 158, 161, 166, 167, 170-172, 174, 178, 179-181, 183-186, 192, 193, 197 In human studies, ventriculography was usually used, but the methods varied considerably. Both biplane 4, 13, 168, 173, 196 and single-plane 74, 90, 104, 162, 164, 169, 173, 181, 185, 187, 188, 194-196, 198, 199 techniques were used with qualitative and quantitative analyses of segment motion. Several studies corrected for rotation 90, 160, 173, 187, 195, 198 during systole, whereas several did not. 2, 4, 6, 74, 159, 162, 164, 171, 173, 181, 185, 188, 196, 198, 199 It would seem that postextrasystolic cardiac rotation might spuriously increase PESP.

Second, in terms of the force–frequency relationships of PESP, the available clinical studies are most vulnerable to criticism. Only a few studies controlled all intervals involved in the PESP relationship, 4, 165, 177, 195, 200 as would be considered appropriate. 70, 73 A few experiments controlled basic heart rate interval and coupling interval of the premature beat. 160, 161, 163, 167, 172, 175, 177, 181, 185, 186, 190, 193, 194, 201 Most of the experiments used spontaneous or catheter-induced premature ventricular contractions at random coupling intervals without control of basic heart rate or postextrasystolic interval. 2, 13, 14, 57, 82, 90, 97, 131, 135, 139, 162, 164, 166, 168-171, 173, 176, 178-180, 182, 184, 187, 189-192, 197, 199, 202, 203 The control of these intervals is admittedly difficult in the clinical situation, but to reliably conclude that ischemic myocardium is responsive and, therefore, potentially salvageable, it is apparent that all intervals must be carefully controlled. Multichannel pacemakers that can be programmed to deliver at least three stimuli at specifically designated intervals are now available and would provide the necessary conditions to reproduce identical intervals.

Of the studies that controlled all intervals, 4, 165, 177, 200, 203 only two studies 177, 223 demonstrated that the degree of PESP responsiveness reflects the degree of ischemia (condition 1), and only one study 223 demonstrated that revascularization of PESP-responsive segments results in return of function and revascularization of nonresponsive segments fails to return function (condition 3). Furthermore, this study demonstrated that occluded grafts following revascularization resulted in loss of PESP. Conditions 2 and 4 were not covered in any of these reports, and three studies 4, 165, 200 showed minimal response in "damaged" myocardium.

Thus, the relationship between PESP and ischemic heart disease is a very complex one, and it is apparent that more extensive studies are warranted with careful control of all the intervals (pre-extrasystolic, extrasystolic, and postextrasystolic) of the PESP relationship.

Valvular heart disease. There have been few studies of PESP in valvular heart disease. 2, 5, 204, 205 What has been reported, however, is similar to the results in coronary artery disease in the sense that a positive PESP response is due to increased inotropic state 205 but different from coronary artery disease in the finding that preload contributed to the PESP response in patients with aortic stenosis 5 and potentially reversible myocardial dysfunction was not identified by an increase in ejection fraction with PESP in patients with valvular heart disease. 204 One additional study found PESP to be useful for assessing aortic stenosis severity. 206

Cardiomyopathy. The effects of PESP on global left ventricular function in cardiomyopathy are somewhat paradoxical. Although it might be expected that there would be less PESP response in these vessels, several studies have reported increased potentiation in cardiomyopathic ventricles. 2, 6, 207-209 It might be imagined that this unexpected result might be due to methodologic problems, particularly failure to control all intervals of the PESP relationship, and this was indeed the case in several of the studies. 2, 207-209 But the most carefully controlled study found that abnormal ventricles had greater potentiation. This study, in addition, reported that PESP decayed from the first to the second postextrasystolic beat in a ratio that was fixed in each individual patient. This was thought to represent the "recirculation fraction" of intramyocardial calcium. This fraction was higher in patients with normal than in those with abnormal ventricles. Furthermore, there was an inverse relationship between this ratio and the degree of potentiation of the first PESP beat. 42 This investigation provides evidence for both the intracardiac
site of the PESP response and the inotropic abnormality of cardiomyopathy.

**Therapeutic**

With the discovery that PESP increases myocardial contractility even in the failing ventricle, it is not surprising that it might be considered to be of therapeutic benefit. This is applied by the method of paired pacing, ie, producing an extrasystole every other beat so that there is continuous augmentation of contractility. Numerous studies have demonstrated increased inotropy in the failing ventricle.73 Virtually every result on the spectrum has been paired pacing,213,215,217 which might also compensate for the risk of ventricular arrhythmias,210 and (4) the risk of increasing ventilricular failure.210 To possibly compensate for the increased oxygen consumption, it was found that there was an increase in coronary blood flow with paired pacing,210,211,215,217 which might also compensate for the risk of ventricular arrhythmias, as would introducing the extrasystole in the atrium rather than the ventricle.59

To date, no carefully controlled study of the benefits and risks of paired pacing in the cardiomyopathic ventricle has been reported. With the contemporary possibility of the use of more sophisticated multichannel pacemakers, it would seem that such a study could be more safely undertaken than in the past.

**Effects on Diastolic Properties of the Left Ventricle**

In no area of PESP research are the results more conflicting than in the analysis of the effect of PESP on diastolic properties of the left ventricle. This is probably because of both difficulties in assessing diastolic properties of the ventricle and the failure of recognition of the need to control all intervals of the PESP relationship.73 Virtually every result on the spectrum has been reported, including no change in postextrasystolic diastolic properties,4,12,18 decrease in compliance,219 and increase in compliance.176 It appears that the most carefully controlled studies found "slowed relaxation" following an extrasystole201,220,221 that was thought to be secondary to augmented calcium influx and would be consistent with the finding that resting length at any given resting tension does increase slightly on augmentation of systolic force alone.222

**Conclusions**

Review of the literature on the phenomenon of postextrasystolic potentiation has found that there is still much to learn. It appears to be conclusively shown that the PESP response is an intrinsic property of the myocardium and is independent of loading conditions. The specific cause or causes of the effect, however, is not as conclusively known. The most suggestive studies imply transient intramyocardial shifts in calcium, probably within the SR. Regarding the usefulness of PESP as a diagnostic or therapeutic tool, the studies are even less conclusive. The major liability of most of the studies is the failure to induce PESP by standard reproducible methods where all intervals making up the phenomenon are controlled. It seems inductable that if one is studying the force–frequency response of the ventricle, careful attention to all the details of frequency would be warranted. Unfortunately, this has not always been done; consequently, many of the reported results are dubious. The urgency of determining if PESP predicts myocardium that is potentially salvageable if revascularization is undertaken is still present and recommends larger, more-controlled studies. Concerning the use of continuous PESP (paired pacing) in the therapy of heart failure, the studies are discouraging, although again inconclusive. More carefully designed trials with more carefully controlled pacing intervals also appear to be warranted.

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