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Review Article

The Meaning, Measurement and Function of Post Extrasystolic Potentiation (Pesp)

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Abstract

Since the earlier complete review [1], there has been considerable research directly on the PESP phenomenon (the augmentation of contractility which occurs after an extrasystole in the mammalian heart. These studies have both contributed to and benefited from broader research in excitation-contraction coupling, the mechanism by which the myocardium converts electrical impulses into mechanical work. The general mechanism of PESP has come to be reasonably well known. At the same time, and occasionally as a consequence of the studies on mechanism, other studies have demonstrated that there are different methods of measure of the phenomenon. These have been characterized as qualitative, and quantitative (ratio-potentiation (RP) and recirculation fraction (RF). It is shown that the first two are more amenable to use in clinical studies while the third is more appropriate for research. Further research in other areas, particularly in evolutionary studies, have the result of suggesting that PESP has no specific function for the organism. Accordingly, it is considered to be a "spandrel," a character trait which is essentially a side-effect of other, functional, traits of the organism.

S1----------S1----S2----------S3----------Sn

500 200 800

The PESP phenomenon is made up of the following intervals:

S1-S1 interval = basic drive rate, for example, 500 msec.

S1-S2 interval = extrasystolic coupling interval (ESI), for example, 200 msec.

S2-S3 interval = postextrasystolic interval (PESI), for example, with a full "compensatory pause," 800 msec (twice S1-S1).

S3-Sn interval = decay interval.

Keywords: *Post Extrasystolic Potentiation (Pesp); Ratio-Potentiation (RP); Recirculation Fraction (RF)*

Abbreviations

PESP: Postextrasystolic Potentiation; S1: First Stimulus of a Train of Stimuli; S1-S1: Basic Drive Interval; Msec.: Millisecond; S1-S2: Extrasystolic Coupling Interval; CI: Extrasystolic Coupling Interval (ESI); S2-S3: Postextrasystolic Interval; PESI: Postextrasystolic Interval; RP: Ratio Potentiation; RF: Recirculation Fraction; CP: Coupled Pacing; AF: Atrial Fibrillation; DDD: Dual Chamber Synchronous Pacing; AV: Atrioventricular; PVC: Premature Ventricular Contraction; NES: Non-excitatory Stimulation; EC: Excitation Contraction; CCM: Cardiac Contractility Modulation; NCX: Sodium/calcium Exchange; HFpEF: Heart Failure with Preserved Ejection Fraction; Abn: Abnormal; Incr: Increased; NS: Nervous System; Microvasc: Microvascular; Decr: Decreased; Mito: Mitochondria; SR: Sarcoplasmic Reticulum; MRC: Mechanical Restitution of Contractility; HCM: Hypertrophic Cardiomyopathy; HOCM: Hypertrophic Obstructive Cardiomyopathy

The current general understanding of the meaning of PESP

The fundamental mechanism of PESP is the time-related recovery of uptake and release of activator calcium from the intracellular storage site, the sarcoplasmic reticulum (SR) [5]. With an extrasystole (S2), there is relatively more calcium taken up by the SR than is released, making it such that the contractility of the following beat, (postextrasystolic beat) (S3) is increased relative to the basic beat (S1).

In order to understand the phenomenon more clearly, we must go more deeply into the basic mechanism of excitation-contraction coupling (EC-coupling).

Excitation contraction coupling (EC-coupling)

In general, cardiac inotropic state is governed largely by the amount of Ca^{2+} presented to the contractile proteins. Upon myocyte membrane depolarization, Ca^{2+} enters the cytosol by several routes, mainly down a voltage gradient calcium current (Ica). This Ca^{2+} triggers further Ca^{2+} release from intracellular stores, mainly the sarcoplasmic reticulum (SR) via calcium channels or ryanodine-receptors (RyR), a process termed Calcium-induced Ca release (CICR). During relaxation, all of this added Ca^{2+} must be removed from the cytosol. In order to accomplish this, calcium is actively transported back into the SR by the Ca^{2+}-ATPase pump (SERCA2A), as well as out of the cell via sodium/calcium exchange (NCX). Each of these features of EC-coupling will be examined in greater detail.

Entrance of calcium into the myocyte [Ica]

According to the modern theory, there are at least four routes for the entry of calcium into the myocyte: the most important ones are the voltage-dependent Ca^{2+} channels (L-type [Ica] and T-type), the electrochemical Ca^{2+} gradient, the Na^{+}/Ca^{2+} exchange (NCX), which works both ways, but mostly to extrude Ca^{2+} from the cell during diastole, and finally, there is the Tetrodotoxin (TTX)-sensitive Ca^{2+} current [2].

Calcium-induced calcium release [CICR]

Upon the occurrence of the cardiac action potential, Ca^{2+} influx via Ica channels triggers the release of additional Ca^{2+} (Calcium - induced calcium release, CICR) from closely apposed clusters of sarcoplasmic reticulum (SR) Ca^{2+} release channels or ryanodine receptors (RyRs). The resulting net gain of Ca^{2+} released to the sarcomeres is estimated, as a global systolic Ca^{2+} transient, to be from 3 to 16 fold in different mammalian species [2]. This calcium subsequently activates the contractile machinery within the cardiomyocyte [3]. As noted, calcium influx also contributes to the loading of the SR for the next contraction, which will prove to be important for the PESP phenomenon [2].

Calcium-induced Ca release (CICR) is an inherently positive feedback system. SR calcium release normally terminates when [Ca]sr levels are only about 50% depleted [2]. SR calcium release has to stop after each heartbeat in order to allow efficient calcium removal from the cytosol, SR refilling, and relaxation of the myocytes. Ica is activated by depolarization, but Ca^{2+} - dependent inactivation at the cytosolic side limits the amount of Ca^{2+} entry during the action potential [2]. SR Ca^{2+} release also contributes to Ca^{2+}-dependent inactivation of Ica [2]. After SR Ca^{2+} release, time must elapse before a second release event of equal amplitude can occur. So the two fundamental events in this part of EC-coupling are the termination of release and the recovery of the potential for SR Ca^{2+} release. Several mechanisms, which are not always considered to be mutually exclusive, have been put forward to account for the termination of release, including: Ca^{2+}-induced inactivation of the RyRs, RyR adaptation, 'stochastic attrition', Ca^{2+} depletion, or the presence of an SR luminal Ca^{2+} sensor, either on the RyR itself or implemented as a backwards signal from calsequestrin, which is a high capacity Ca^{2+}-binding protein [2]. At the cellular level, recent research has created an interest in what are called "Ca^{2+} sparks," which are local release events caused by the opening of a cluster of SR Ca^{2+} release channels (RyRs) [4]. At present, there has not been significant research into the significance of these events to PESP, but future investigations will likely provide further avenues of research into the phenomenon. Mechanisms underlying recovery of the potential of SR calcium release (recovery from inactivation of ryanodine receptors) remain incompletely understood. Those that have been studied do appear to be closely linked to the factors responsible for calcium spark termination [5-7]. Whatever process shuts off release

in a cluster of RyRs may reduce the probability that the channels will reopen during some subsequent interval [8] and thus would have bearing on force-frequency events.

Ca^{2+} removal and diastolic relaxation [SERCA2A/NCX]

After systole, Ca^{2+} must be removed from the cytosol to lower $[Ca^{2+}]i$ from the myofilaments and allow relaxation. This is achieved by four different routes: 1) The SR Ca^{2+} - ATPase pump (SERCA2A) transports the greatest proportion of the activator calcium back into the SR; 2) Sodium/calcium exchange (NCX) transports the second largest proportion of the calcium out of the cytoplasm; 3) the remainder is removed by the sarcolemmal Ca^{2+}-ATPase and 4) mitochondrial Ca^{2+} - uniporter [2].

Premature ventricular contraction (PVC) - qualitative and quantitative aspects

In the light of the above model, we can see that an extrasystole (S2) which occurs early in diastole has several effects. If Ica recovers (even partially) before the extrasystole, some calcium will enter the cell at the extrasystole. But if SR calcium release is relatively refractory, normal calcium release will not occur, resulting in a weak contraction. And the lower $[Ca^{2+}]i$ will allow more calcium influx via Ica (due to less calcium-induced inactivation) and less calcium efflux via NCX [9]. The net gain in calcium during the extrasystole will enhance SR calcium content. Then, at the next beat, (S3), when the SR calcium release channel has recovered, there is a greater SR calcium release and contraction resulting in PESP [9]. In other words, since the SR loses very little Ca^{2+} at the time of the extrasystole, more is available for the subsequent (S3) (post-extrasystolic) beat. There is also less extrusion of calcium by the NCX pump (because of both the increased $[Na^{+}]i$ [as a consequence of the extrasystole] and the small amount of calcium released from the SR to drive the exchange). The net effect is that there is an increase in calcium for the SERCA2A to pump into the SR. All of these factors contribute to the degree of PESP.

Measurement of PESP

Methods of analysis of PESP

In order to better understand PESP, it is necessary to present and contrast the methods used by investigators to assess the degree of PESP.

Qualitative and semi-quantitative

The literature is replete with studies which have demonstrated the PESP phenomenon. Many of the early studies investigating PESP made qualitative assessments of PESP by reporting the kinetics of myocardial segmental wall motion before and after the extrasystole, for example, on angiogram which was then quantitized globally and segmentally [10].

Quantitative - Ratio Potentiation(RP) - for Clinical Evaluation

The first strictly quantitative method of assessing PESP was developed by Anderson., *et al.* who proposed, based on their investigations in rabbit papillary muscles, in which they were able to control muscle length, that the ratio of two values of the rate of rise of tension obtained by perturbing the rate of stimulation at any given length could be used as a length-independent index of the inotropic state of the muscle [11]. The same investigators followed up with a study in both isolated and intact ventricular preparations and found that the force-frequency ratio reflects frequency-dependent changes in the inotropic state, independent of changes in length [12]. The same investigators followed up these studies with studies in human hearts, both with normal and abnormal contractility. They again found that evaluating the ratio potentiation at the same end-diastolic dimension, as determined by echosound, allowed them to distinguish between normal and abnormal ventricles [13]. Continuing this line of research, Arentzen., *et al. e*valuated the ratio potentiation of the derivative of left ventricular pressure (Pmax) of the postextrasystolic beat to the Pmax of the control beat in chronically instrumented dogs. They found that the degree of potentiation was found to be a direct linear function of the change in contraction frequency induced by the extrasystole. They were able to derive a simple equation: [S2-S3 = ((S1-S1) + (S1-S2) - 100)] [14] whereby the degree of potentiation was programmed to occur when the loading conditions of the ventricle for the control beat and the postextrasystolic beat were the same (the "isolength" interval) [14]. For example, in the series of beats presented earlier, at S1-S1 = 500 msec, S1-S2 = 200 msec, S2-S3 = 600 msec. [(500) + (200) - 100)], which is 200 msec. shorter than a full "compensatory pause", where S1-S3 = 1000 msec, where S2-S3 = 800 msec. These results were extended to studies involving both the "isolength" interval and "complete" (compensatory pause) S2-S3 intervals in both dogs and humans, both before and after myocardial revascularization [15-17].

It should be noted that a disadvantage of using ratio potentiation to determine the degree of potentiation is that if the contractility of the basic interval (S1-S1) is increased for any reason, such as with external adrenergic stimulation, then the heart may be operating at or near its peak capacity, so the denominator of the RP is increased, resulting in little or no PESP, being manifest as a low RP. This shows the need to evaluate the degree of PESP both before and after an intervention by comparing the same intervals (S1-S1; S1-S2; S2-S3) [16].

Quantitative: Recirculated fraction (RF) - for research purposes

The other quantitative method of assessing PESP is that of calculating "recirculated fraction" (RF) (or in some publications, "recirculation fraction". The calculation is based on the concept of a two-compartment model for the source of activator calcium. The first compartment here is that calcium which passes across the sarcolemmal membrane during the action potential - the Ica. The second compartment of activator calcium is that which is recirculated from beat to beat from the myofibrils into the SR by SERCA2A then released as activator calcium at the next beat. This RF is calculated from the decay of contractility from S3 to the following beats (S4, out to, in some studies, S6). It is reasoned that the slope of this curve is a function of the proportion of activator calcium which is not extruded from the myocyte by NCX, but recovered by the SR via SERCA2A, to be released by the CICR trigger of the following beat. The potentiated contractility decays exponentially and the time constant of decay (the natural logarithm of the fraction of recirculated activator) was found to be independent of the preceding heart rate and the degree of potentiation [18-22]. The decay of potentiation is thought to be exponential because a constant fraction of the activator calcium released on one depolarization is extruded from the system and a *constant fraction* is recirculated within it, so that it contributes to the calcium released on the subsequent depolarization - the recirculated fraction [25,26].

The RF is a dimensionless term and has been found to vary according to experimental preparation [18-49]. Early determinations of the RF were calculated from the slope of the curve from S3 to S4 [28,30]. A representative RF might be 0.60, which means that 60% of the calcium utilized in the contraction has recirculated from the previous beat. Over time and multiple investigations the calculation has been carried out to S6 [31-34] and thus thought to more precisely represent RF [40,41,43]. In some of these studies the decay curve was found to conform to a simple monoexponential curve [24,26]. Some investigators have reported a biphasic curve [33] or even a decay curve showing mechanical alternans [31,34,36,38,44,45]. These results clearly have some bearing on the ultimate calculation of RF, which could be relevant in the use of the parameter in the research setting, but seem to have little relevance to the clinical use of PESP.

An example of representative RFs in a pathological situation is that from the study of Asgrimsson., *et al.* in which the RF was calculated to be 0.61 in human atria before the production of cardiomyopathy, thereafter decreasing to 0.39 [48].

The mechanisms of ratio potentiation and recirculated fraction

The mechanism of potentiation which becomes manifest in Ratio Potentiation is the combination of the elements of EC-coupling. The mechanism of Recirculated Fraction (RF) is, however, thought to be limited to those features of EC-coupling which serve to recharge the SR with activator calcium after the systole - that is, SERCA2A and NCX [18]. It has been shown that neither the basic driving rate (S1-S1) nor muscle length influence RF [28,42]. There is some conflict as to whether RF is a function of the S1-S2 interval (coupling interval phenomenon) [42,43]. Unfortunately, at the present stage of research it cannot be unequivocally stated that RF is not influenced by other elements of EC-coupling, simply because the permutation of these elements have not been investigated in the setting where RF is calculated.

Comparing and contrasting ratio potentiation and recirculated fraction

It should be noted that the determinations of Ratio Potentiation (RP) and Recirculated Fraction (RF) are taken from fundamentally different parts of the curves of restitution of mechanical contractility (MRC), potentiation and decay of contractility brought about by varying the relevant intervals. RP is taken from the ratio of the potentiated contractility on the *upstroke* of the potentiation curve, that is, the ratio of the measure of contractility of S3 to that measure of S1 (e.g. dp/dt max of S3 divided by dp/dt max of S1). In contrast, RF is derived from the downslope of the *decay* of this potentiation, that is, the relationship of the contractility of S3 to S4, or later). As a consequence of

this difference, it is difficult to make direct comparisons of the two methods of assessing PESP. Another problem with comparing RP to RF is that the studies which have calculated and reported RF the S2-S3 interval has not been consistently applied. Some have calculated RF after S3 occurs with a full "compensatory pause" [32,34,36,44-46]; others have programmed S3 at some other interval [31,39-41,47].

Ratio Potentiation is particularly useful for the assessment of PESP in the clinical setting where one is investigating the presence of "contractile reserve," or "latent contractility." This conclusion is based on the assumption that the potentiated contractility in S3 represents a "reserve" of contractility which is not manifest in S1. Being a ratio, one can predict the degree of potential reserve, typically from 1.2 to 1.5, or, equivalently, 120% or 150% potentiation over the contractility manifest in the basic beat (S1-S1).

Recirculated Fraction is a dimensionless term which is meaningless standing alone. One must follow the initial determination of RF with an intervention, such as the infusion of calcium, or agents which are known to affect myocardial contractility, such as a cardiac glycoside, then determine if the intervention significantly changes the previous determination of the RF. Increasing external calcium concentration $[Ca^{2+}]o$ or decreasing external sodium concentration $[Na^{+}]o$ each increase RF [27,28,30,33]. Interventions which have been shown to decrease RF are the infusion of ryanodine (an alkaloid known promote the depletion of calcium from the SR) [27,29,33,34] myocardial stunning [42,49] and an increase in the temperature of the experimental preparation [42,46]. As such, the determination of RF is more useful in the research setting than in the clinical setting.

The comparison of RP with RF will depend on several variables, particularly at what point in time on the potentiation curve the S3 value is determined. If the PESP is programmed to be taken at "isolength," then, by definition, the RP determination will be taken on the upslope of the potentiation curve, before the effects of stretch (Starling forces) are operative [2]. If the S3 contractility value is taken, on the other hand, after a full "compensatory pause," then the calculation of the RP will generate a different value from that taken at "isolength," and, the S3 may actually occur after full potentiation and actually be on the decay portion of the curve [15,16]. In contrast, the RF will be calculated at some time *after* the potentiation of S3, following the decay curve. One might expect, in the case of an intervention, that the degree of RP will move in the same direction (up or down) as the RF. There is one study in the literature which compares RF directly with RP at a fixed coupling interval with varying heart rate. A linear relation with a positive slope of 0.38 was found between the RF and the RP. As expected, as the RP increased so did the RF [50], meaning, presumably, that with increasing potentiation the proportion of calcium recirculated from the prior beat increases. This is consistent with the view that the degree of PESP is directly related to SR calcium recirculation.

The degree of PESP augmentation of contractility is a function of all three intervals

It was asserted in the previous review that the degree of potentiation of contractility following an extrasystole was a function of all three intervals which make up the phenomenon (the basic interval [S1-S1], the extrasystolic coupling interval [S1-S2], and the post-extrasystolic interval [S2-S3] [1]. While this assertion continues to be true, there has been additional research on the phenomenon which allows for greater elaboration of the mechanism.

S1-S1 interval

As the S1-S1 interval shortens there is an increase in contractility, called the "Bowditch phenomenon." This has been known since the 19th century [51] and has been found to occur in response to rapid atrial pacing *in vivo* in healthy patients with normal ventricular function [52]. Multiple mechanisms have been proposed to explain this phenomenon. There is evidence to suggest that under basal conditions this phenomenon is related to increased Ca^{2+} availability for the myofilaments [53]. When stimulation frequency is increased (decreased S1-S1 interval), more calcium enters the cell due to repetitive action potentials, leading to a higher driving force for SR Ca uptake. At the same time, intracellular sodium $[Na^{+}]i$ rises with increasing frequency, which provides a boost to sodium/calcium exchange (NCX) with more calcium entering the cell to be pumped into the SR via SERCA2A. Thus SR Ca^{2+} content and calcium release increase, leading to increased force of contraction (positive force-frequency relation).

In the light of the above, it might seem paradoxical that studies have shown that the degree of potentiation of contractility as measured by ratio potentiation (RP), brought about by a given S1-S2, actually *decreases* as heart rate is increased [15]. There are no empiric studies specifically addressing the cause of this aspect of the PESP phenomenon. However, one must recall the limitations of using RP as the method of assessment of PESP. For a given S1-S2, for there to be the equivalent degree of potentiation as S1-S1 is shortened, the augmentation of contractility at S3 must rise to a relatively equivalent degree to the rise to that which occurs with an increase in heart rate. In other words, since the denominator of the RP rises with an increase in heart rate, the numerator must rise to an equivalent degree. An extrasystole (S2) of a prematurity of, say, 200 msec, is relatively less premature at a higher heart rate than at a lower heart rate, thus giving less potentiation at S3 [15].

S1-S2 interval

From what was presented earlier concerning the refractoriness of Ca^{2+} release channels it can be appreciated that progressively prolonging the S1-S2 interval of an extrasystole will lead to progressively greater release of calcium from the RyR. In some publications, this is referred to as the "mechanical restitution curve."(MRC)(54) As there is "mechanical restitution" (S1-S2 interval lengthens), which leads to an increase in contractility of S2, there is a decrease in contractility in the following (postextrasystolic) (S3) beat, all other intervals being equal. So, there is a reciprocal relationship between MRC and PESP [55]. This feature of PESP has been referred to as the "coupling interval phenomenon," or "coupling phenomenon" [1]. The specific phenomenon is the observation that the degree of potentiation of contractility at S3 is inversely related to the S1-S2 interval, i.e. the earlier the S2, the greater the degree of potentiation at S3. This phenomenon of PESP was recognized by Hoffman in 1956 [56] but it was assumed to occur because of the occurrence of a "compensatory pause" (i.e. S1-S3 = twice S1-S1, which occurs if a ventricular extrasystole blocks in the AV node and fails to reset the SA node, leading to a prolonged period between the S1 and S3. Such a prolonged pause brings the ventricle into the later phase of diastole so that the loading (Starling) effect occurs, leading to increased stroke volume. If, however, the S3 is programmed to occur at the fixed interval ("isolength") before the recruitment of the Starling effect, then the CI phenomenon still occurs and is more precisely predictable and reproducible [14-16]. For example, if the ratio of contractility of the post-extrasystolic beat to the pre-extrasystolic (basic) beat is calculated (RP), the CI phenomenon becomes manifest. An example of the coupling interval phenomenon is: In the dog (using Fractional shortening (end diastolic dimension - end systolic dimension/ end diastolic dimension) as the measure of contractility, at a basic drive cycle (S1-S1) of 429msec (HR=140), at S1-S2 of 350msec, ratio potentiation = 1.07; at a shorter CI, S1-S2 of 300 msec, ratio potentiation = 1.11; at an even shorter CI, S1-S2 of 250 msec, ratio potentiation = 1.33; at the shortest CI, S1-S2 of 200 msec, ratio potentiation = 1.67. r = 0.95. This is a curvalinear inverse relationship: $y = 0.00404X + 2.406$. X = coupling interval (S1-S2).

In the modern theory of EC-coupling, the standard explanation of the CI phenomenon is that: As the extrasystole is earlier, the SR calcium content will be lower because there has been less time for SERCA2A to pump the calcium into the SR, so less is released from the SR. During the post-extrasystolic interval (S2-S3) SERCA2A has the additional time to load up the SR, leaving more Ca^{2+} for the next (post-extrasystolic - potentiated) beat. There is a sort of "see-saw" effect in that the lower the amount of calcium triggered for release by the S2 (extrasystole), the higher the amount available to be triggered at the S3 (post-extrasystolic) beat. The competition between the SERCA2A and NCX may also change as a function of frequency [57,58]. Bers presents a simple explanation for this effect: As frequency increases, the gradual increase in $[Na^+]i$ [9] limits the ability of the NCX to compete with SERCA2A [9]. In addition, increasing frequency accelerates $[Ca^{2+}]i$ decline due to an increased rate of SR calcium transport, possibly due to the activation of CaM Kinase II which accelerates SERCA2A [9,59]. Thus, the SERCA2A becomes increasingly dominant over the NCX exchanger in transporting calcium from the cytosol at higher frequencies [9]. An additional condition relating to the phenomenon is the temporal nature of the recovery of the potential for SR calcium release [2].

The CI phenomenon can be seen to be an extension of MRC whereby MRC occurs as the S1-S2 interval is prolonged, the contractility of the subsequent S3 will be relatively decreased, which represents the CI phenomenon.

S2-S3-the postextrasystolic interval

As has been noted, it can be seen that, using ratio potentiation (RP) as the method of assessing PESP, there is a significant difference between the potentiation seen at "isolength" (in the example, S2-S3 = 600 msec.) versus that observed after a full "compensatory pause", (in the example, S2-S3 = 800 msec.) [14]. This is so because the period following the point in time at which S2-S3 becomes "isolength" there continues to be time for the SERCA2A to pump additional calcium into the SR and time for there to be recovery of the potential for release of calcium (RYR). The additional diastolic filling time also allows the forces of stretch (myofilament sensitivity - Starling) [2] to come into play. Therefore the degree of potentiation after a full "compensatory pause" will show a greater potentiation than at "isolength" [16] (higher RP) but, if the interval goes beyond mechanical restitution of contractility, the RP will show more variability [16].

On the other hand, if the calculation of recirculated fraction (RF) is the method utilized to assess the degree of potentiation, the S2-S3 interval is, theoretically, always allowed (or programmed) to occur after full restitution of contractility. However, as has been noted, in some studies S3 was not always been allowed to go to a full "compensatory pause" making the comparison between RF and RP, and even between different calculations of RF, difficult, if not impossible [31,39,40,41,47].

The functional meaning of PESP

Since its original description 120 years ago [60] the PESP phenomenon has generated many studies in cardiovascular physiology and clinical cardiology. It took almost 100 years before the basic mechanism was tentatively articulated [2]. Since that time, both the understanding of the mechanism of the phenomenon and its application in experimental and clinical studies have widened extensively. This paper has sought to bring up to date the current understanding of that mechanism, the applications of the phenomenon in the clinical setting and hypothesize about possible future routes of more extensive application. Much still needs to be done in both areas of research. In the mechanism of PESP, it is not yet clear what is the basic mechanism which underlies the release and termination of release of the activator calcium from the storage sites. In the area of application, recent extension and elaboration of methods to induce the phenomenon in the clinical setting have opened up new possibilities for future research. Additionally, the activity of generalizing the underlying mechanism of the phenomenon into applications outside of the cardiovascular realm have generated new excitement as to the possibilities for further exploitation this ubiquitous phenomenon of nature.

Remaining questions about PESP

There seem to be three remaining questions about PESP:

1. Is PESP an intrinsic property of the myocardium?
2. Does PESP have a function?
3. Is PESP a spandrel?

Is PESP an intrinsic property of the myocardium?

This rather vague assertion was repeated by other authors [61] without specific description of its meaning. *Prima facie,* the assertion could be taken to mean that the PESP phenomenon is equivalent to "Starling's Law of the Heart," which is known to be an intrinsic property of the myocardium. The PESP response can, however, be distinguished from Starling's Law of the Heart by the fact that, when instigated according to certain criteria, PESP is *independent of the loading conditions* of the myocardium. That is to say that the PESP response is a function of the intrinsic contractility of the myocardium, the central operative function of the heart. Thus, PESP is an intrinsic property of the features which make up EC-coupling in the mammalian myocardium. Viewed in this sense, one would expect that the PESP response should be a phenomenon which could be utilized to identify or diagnose myocardial contractial dysfunction. On the other hand, it would be expected that certain examples of myocardial dysfunction should, on being subjected to the PESP test, demonstrate a certain degree of lower-than expected potentiation of contractility following an extrasystole, again assuming that the test is performed according to certain

criteria. Regarding the first expectation, the utilization of the PESP response to identify or diagnose myocardial dysfunction, indeed PESP has been utilized extensively and has come to be the standard test to identify "stunned" or "hibernating" myocardium. Regarding the second expectation, likewise, there have been several examples of myocardial dysfunction, identified by independent means, which manifest a lower than expected PESP response. All of these features of the PESP response in the mammalian myocardium have been discussed extensively in a separate publication [62].

Does PESP have a function?

Another question which arises is whether or not PESP has a function? By this is meant that PESP is adaptive, that is, that it serves a survival function in the evolution of the heart from primitive organisms to the mammalian heart. The question is confounded by the fact that it has been shown that the PESP phenomenon is made up of several features, including each interval of the phenomenon (S1-S1; S1-S2; S2-S3), each of which occurs because of different features of the working myocardium. Accordingly, one must then ask if the ability of the myocardium to shorten the S1-S1 interval (i.e. increase the heart rate) serves a survival advantage, and is so, when and why did this arise in the evolutionary tree? Additionally, one might ask if the main feature of the S1-S2 interval, the "Coupling Interval Phenomenon" serves a survival advantage, if so, what is the evidence and, again if so, when did it arise in the evolution of the mammalian heart? It must be recalled that the Coupling Interval Phenomenon is directly connected to the S2-S3 interval, so one must additionally look at its constitutive features to answer this question. These questions can be specifically focused on the questions.

The evolutionary advantage of increasing the heart rate (shorten S1-S1)

Studies have shown that increasing the heart rate provides an adaptive advantage in reacting to various environment stresses, including variations in ambient temperature, requirements for increase in metabolic rates and hemodynamic demands [63].

The evolution of the features which make up the coupling interval phenomenon

Sarcoplasmic Reticulum: Extensive studies have shown that the sarcoplasmic reticulum, which markedly increases the amount of activator Ca^{2+} available to the contractile apparatus, provides a response to stress, including cold temperature [65,66] and hibernation [67]. Of course, this information does not answer the question of whether or not PESP *per se* has a function. We see that increasing heart rate has a function and the evolution of the SR has an adaptive function. This raises the third question:

Is PESP a spandrel?

A question which arises is: Does PESP have a function in the biological organism? Or to put the question another way: Is there an adaptive advantage to PESP? We have seen that there certainly is such an adaptive advantage *to having an SR*. And it is known that only those hearts which have an SR can generate PESP, but this does not necessarily tell us that PESP itself has an adaptive advantage. Stepehn J Gould and RW Lewontin have made it clear that not all traits of an organism have an adaptive advantage [64]. They give the example of the "spandrels," which are triangular spaces formed by the arches of the dome of St. Mark's Cathedral in Venice. These spaces have no structural utility but are merely a consequence the arches producing the spaces. They suggest that there are numerous traits in biological organisms which arose for reasons other than adaptability. PESP may fit into that category. PESP thus seems to be an *Epiphenomenon*, or something like a "side-effect." Having an SR is both *necessary* and *sufficient* for there to be PESP. Recall that the selective advantage of having an SR is that it provides an intracellular storage site for activator calcium in times of increased environmental demand. We can say that the organism evolved as an integrated package. Other questions which might arise:

- Does having PESP offer any benefit to the organism?
- Does having PESP offer any detriment to the organism?

Based on the current level of research, there does not seem to be any answer to either of the questions than "Not as far as we know." Arguably, there is a disadvantage to having an extrasystole (S2), which will generate PESP, but this does not necessarily apply to PESP. The increase in contractility is so brief that it would not seem to give any significant benefit. Likewise, there is no known detriment to having PESP.

Conclusions

This brief review has covered the topics of the *mechanism* of PESP and the *methods of measurement.* The mechanism of PESP is reasonably well understood but more basic research in cellular and molecular medicine will provide more elaboration of the mechanism. Predictably, some of these developments will contribute to the application of PESP in clinical and research venues. Regarding the measurement of PESP, one of the limitations in coming to understand the measurement of PESP is the varied methods of production and assessment of PESP. Hopefully, this review will provide some insight into the forms of measurement so that further refinement will supervene.

The question of PESP as an intrinsic property of the myocardium as well as the evolutionary significance of PESP have been questioned. It has been reasoned that the phenomenon is merely an epiphenomenon, that is, a side-effect of there being a sarcoplasmic reticulum, which does itself have an adaptive advantage. Despite this conclusion, it has been demonstrated that the PESP phenomenon does have significant utility in both the diagnosis and therapy of cardiac diseases. It is anticipated that there will continue to be research on the phenomenon in the context of EC-coupling with the aim of extending these applications.

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