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Uses of Postextrasystolic Potentiation (PESP): The Actual and Hypothetical

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Abstract

In this paper, the uses of Postextrasystolic potentiation (PESP) are introduced and briefly reviewed. These uses were found to fall into three categories: 1) Actualized applications which are based on empiric studies; 2) Hypothetical applications which are based on empiric data. 3) Hypothetical applications which are based on speculation about the generalization of the know mechanism of PESP. It is clear that the PESP phenomenon continues to provide fertile grounds for application in multiple areas of scientific investigations. Further research into its mechanism and applications seems to clearly be warranted.

Keywords: Cardiac electrophysiology; Force-frequency relationship; Postextrasystolic potentiation

Introduction

The phenomenon of postextrasystolic potentiation (PESP), the increase in contractility of the myocardium of the beat following an extrasystole, has been studied extensively since its first description over a hundred years ago [1]. Throughout that period, investigators and clinicians have sought to use the phenomenon for both diagnosis and treatment [2]. Recent research has confirmed old uses while presenting new ones. Consideration of these developments leads to the hypothesis of additional uses. The purpose of this paper is to review and introduce:

1. Actualized Applications of PESP Based on Empiric Studies.

2. Hypothetical Applications of PESP Based on Empiric Data.

3. Hypothetical Application of PESP Based on the Generalization of the Mechanism of PESP.

The PESP phenomenon is made up of the following intervals: S1-S1 interval=basic drive interval, 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). As can be seen in the figure, the contractility is potentiated from 1000 units to 1500 units.

The standard method of assessing the degree of potentiation is to calculate the ratio of contractility of the postextasystolic beat to the basic beat. In the example, this is the ratio of dp/dt of the potentiated beat to the basic beat: RP=1.5.

Until recently, the mechanism of PESP was largely unknown and hypothetical. However, extensive research has clarified the excitation-contraction elements behind the phenomenon, adding new impetus to research on the phenomenon [3,4].

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). Any factor which affects the uptake or release of this activator from this site will be manifested in the degree of potentiation [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).

One feature of the PESP phenomenon which was recognized early is that the shorter the S1-S2 (extrasystolic interval (ESI) or "coupling interval"), the greater the degree of potentiation at S3, all other intervals being equal. This is referred to as the "coupling interval phenomenon" [2,6]. It is a fundamental feature of PESP. We will see that it plays a significant role in the application of the phenomenon. 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 429 msec (HR=140), at S1-S2 of 350 msec, 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 curvilinear inverse relationship: y=0.00404X + 2.406 (X=Coupling interval (S1-S2)).

Actualized Applications of PESP Based on Empiric Studies

Detecting myocardial contractile reserve

The PESP phenomenon was early thought to provide information about myocardial reserve [2]. It was not until the recognition that the phenomenon is a function of all three intervals making up the response that this expectation was proven [6].

While it was at first appreciated that the augmentation of contractility occurred in the normal myocardium, it was soon found that such a response also occurs in some dysfunctional myocardium [2]. The most common application of this aspect of PESP has been in predicting the improvement of depressed function accompanying myocardial ischemia following revascularization [7].

More specifically, recent research has shown that ischemic myopathy falls into three categories: stunned myocardium, hibernating myocardium and necrotic myocardium [8-20]. Stunned myocardium refers to myocardial segments which have suffered low coronary perfusion leading to ischemia in the past but are now receiving normal perfusion. Hibernating myocardium refers to those myocardial segments which continue to suffer ischemia and respond by down regulation of function. There appears to be a continuum from stunning to hibernation [14]. PESP occurs in both forms of ischemia and predicts future recovery of function following re-perfusion [7,14]. Necrotic myocardium, being dead, fails to produce force in both a normal beat and after an extrasystole. This is often called "dyskinetic" myocardium, indicating that, instead of contracting and thus shortening, it actually bulges out [20].

Predicting prognosis in ischemic heart disease

In recent studies, Scognamiglio et al. were able to predict the return of contractile function following a myocardial infarction by exploiting the coupling interval phenomenon of PESP (introducing an extrasystole at varying coupling intervals [S1-S2]). Myocardial segments which potentiated at longer coupling intervals (S1-S2) recovered spontaneously, thereby predicting a better prognosis than if a shorter interval was required for potentiation [21,22]. This test appears to provide a dynamic test which can be used to uncover the potential of recovery of dysfunctional myocardium.

Approaching the post-MI prognosis from another perspective, Sinnecker et al. [23,24] measured PESP of arterial blood pressure using a non-invasive photoplethysmographic device in 941 patients who survived the acute phase of an MI. They correlated the presence of what they thought to be PESP to all-cause 5 yrs mortality. PESP was defined as an increase in postextrasystolic pulse pressure of 3% or more compared with the mean of subsequent beats. The authors found a significantly higher mortality risk in patients in whom PESP was present compared with patients in whom PESP was absent, which is a counter-intuitive result. This measure of PESP remained a significant risk predictor after adjusting for left ventricular ejection fraction, the amount of ventricular premature beats and GRACE (Global Registry of Acute Coronary Events) score. The mechanism of how PESP is correlated with a worse prognosis was not made clear. However, there are several methodological problems with the studies [4]. The most important criticism is that the intervals making up the PESP response could not be controlled [6]. Another problem with the studies is that the PESP response was gauged by comparison of the first postextrasystolic beat to the subsequent beats. This is a non-standard way of assessing PESP. What they appear to actually be measuring is not the value of PESP but the decay of PESP, which would be equivalent to what has been designated the Recirculated Fraction (RF), a measure of the amount of activator calcium which is re-circulated from one beat to another [25]. This is a decaying exponential function and not the straight-line inverse function seen in the coupling phenomenon. Such a finding as they report would be consistent with a poorer prognosis because a reported "potentiation" would actually represent an increased rate of decay of RF, and thus would predict a poorer prognosis [25].

PESP and heart rate turbulence

Several recent studies have reported a relationship between PESP and heart rate turbulence, a parameter which gives some information about the prognosis of patients with idiopathic dilated cardiomyopathy [26-31]. Decreased heart rate turbulence is associated with a poor prognosis. It was found that pronounced PESP suppressed the typical baroreflex regulation pattern of heart rate variability in hearts with LV dysfunction. Again, these results might suggest that PESP actually indicates a poor prognosis, but it should be noted that the studies, by design, evaluated postextrasystolic potentiation of arterial blood pressure, rather than ventricular contractility because this is the physiologic effect which is thought to affect the baroreflex response. How these results are correlated with PESP of ventricular function is at present unexamined. Further studies clearly appear to be warranted.

Control of ventricular rate during atrial fibrillation

Coupled pacing (CP), a method for controlling ventricular rate during atrial fibrillation (AF), consists of a single electrical stimulation applied to the ventricle after each spontaneous activation. Because of retrograde conduction to the AV node, the manifest ventricular rate decreases and CP results in a mechanical contraction rate approximately one-half the rate during AF. In a canine model of AF, CP improved cardiac function and only moderately increased myocardial oxygen consumption, thus increasing cardiac efficiency [32]. A study in human patients confirmed that the technique reduced the mechanical contraction rate. The effect on contractility was not reported [33].

In several studies in canines with chronic atrial fibrillation, coupled pacing was shown to improve left ventricular contractility. In one study, a dual chamber pacemaker was programmed in its dual chamber synchronous pacing (DDD) mode to apply coupled pacing. The AV interval of the ventricular pacemaker was adjusted to alter the coupled pacing time delay to intervals ranging from 160 to 220 msec. After sustained coupled pacing had been applied for 3 to 4 weeks, left ventricular volumes and contractile rate were significantly reduced and returned towards the values measured prior to the induction of persistent AF [34]. It is unclear what the mechanism behind the improvement is. Tracings suggest a combination of effects: The first is PESP. An additional beneficial effect is due to "concealed conduction" of the triggered systole back into the AV node, making it refractory for further forward propagation of the fibrillatory impulse. What one sees, then, is regular 1:1 ventricular pacing where the AF waves do not conduct to the ventricle. How much the improved ventricular mechanics are due to this regularization of RR intervals [35] rather than PESP was unclear. In a follow-up study, the same investigators developed a more elaborate biventricular pacing protocol which confirmed that the beneficial effect was due to PESP [36]. Again, they demonstrated an increase in ejection fraction. It seems possible that such a technique might be applicable in the clinical setting with the use of biventricular pacing.

PESP and PVC cardiomyopathy

A recent retrospective study reported that, in presumed PVC-induced cardiomyopathy, the presence of potentiation of post-PVC systolic blood pressure was a marker for subsequent recovery of LV ejection fraction after ablation [37,38]. One might initially suspect that the investigators have merely fortuitously detected those ventricles with early coupling interval PVCs, leading to potentiation. While these investigators did not specifically address the relationship of cardiomyopathy to coupling interval of the PVC, other studies have not found such an association [39-41]. Follow-up studies will want to address the association of coupling interval of the PVC with potentiation and recovery post-ablation.

The finding that PESP predicted recovery from cardiomyopathy post-ablation might suggest that the mechanism of PVC cardiomyopathy is not related to the EC-coupling elements which affect PESP (uptake and release of calcium by and from the SR). However, this result appears to conflict with those studies previously reported which suggest abnormalities in EC-coupling in tachycardia-mediated cardiomyopathy [42-44]. Alternatively, the presence of PESP might indicate an early compensatory phase of the development of the cardiomyopathy before the development of the failure phase. This would be consistent with the natural history of rapid pacing induced dilated cardiomyopathy and heart failure [45].

If confirmed, this study would have great significance because of the wide-spread nature of PVCs in the population. Coupling this study with the technique of prospective induction of PESP [46,47] might develop into a meaningful diagnostic test for the selection of patients with PVCs and cardiomyopathy who should be considered for ablation.

Force-frequency pacing: paired pacing and non-excitatory stimulation (NES) to treat myocardial dysfunction paired-pacing

Since the mid-20th century, there has been considerable interest in the utilization of PESP for the treatment of heart failure by the application of PESP as repetitive coupled extrasystoles programmed to occur following each basic beat, called "coupled pacing" or "paired pacing" [2]. Since that report, there have appeared several preliminary studies reporting the application of the technique to patients with heart failure [48-51]. Prior to these reports, the major concerns of applying paired pacing were: (i) the difficulty of weaning the failing ventricle from paired pacing, (ii) the increase in oxygen consumption, (iii) the increased risk of the development of ventricular arrhythmias, and (iv) the risk of increasing ventricular failure. None of these problems was manifest in these studies. All of the investigations showed that paired pacing improved left ventricular hemodynamics and increased contractility. Furthermore, myocardial oxygen consumption was not increased [48]. No adverse effects were reported, although the studies were preliminary and of short-term duration. Close examination of the protocols of the studies reveals that there are possibilities of enhancing the results with creative programming of the intervals involved. The results are certainly promising enough to warrant further study. Also, given what has been found in the application of PESP in various etiologies of cardiomyopathy, it is clear that the careful selection of the appropriate patients for these studies is increasingly important.

Non-excitatory stimulation (NES)

Electrical stimulation of the myocardium during the refractory period can also result in an increase in contractility [2,52]. The change in contractility is a function of the amplitude and polarity of the stimulation and the location of the stimulating electrodes [53-55]. The stimulation is not conducting, it does not depolarize the myocardium, and is referred to as "non-excitatory stimulation" (NES). Over the course of the last few years there have been multiple studies of an implantable device which applies NES to the ventricles [56-100]. The proprietary device is called "OPTIMIZER" and the result is referred to as "Cardiac Contractility Modulation," or CCM. The device has been shown to improve functional capacity, quality of life and parameters of myocardial contractility. Beneficial effects have been reported on morbidity and mortality in heart failure patients [95,97,98]. Chronic changes accruing to CCM include reversion from fetal to adult gene expression profiles in the heart, improved calcium handling, restorative ventricular remodeling, and improved cardiac function [88]. The 2016 ESC/HFA guidelines considers CCM to be worthy of consideration in selected patients with heart failure. This is based on a demonstrated improvement in exercise tolerance and quality of life [86].

While there have been multiple studies to determine the mechanism(s) of action of the CCM device, at present, it has not been conclusively shown that the effective function of the device is substantially different from what would be expected from PESP with the CI phenomenon carried to the extreme of introducing the extra stimulus within the refractory period. Basic studies have shown that the experimental permutations which affect the features of EC-coupling known to be associated with PESP affect NES similarly, and in the same direction. That is, the augmentation by NES is abolished by caffeine and by decreasing the inflow of calcium via sodium/calcium exchange (NCX); it is blunted by exposure to ryanodine and by the calcium channel blocker, verapamil [59,64,66,75,83]. Clearly, NES leads to improved SR calcium uptake, as does PESP. To clearly distinguish the two, more basic studies with direct comparisons of all of the intervals involved will be required. Some of the proprietary data about the OPTIMIZER will have to be shared for such studies to be carried out. It seems important for these studies to be undertaken because of the voluminous literature about PESP which would be available when extending the clinical application of NES [92].

Hypothetical Applications of PESP Based on Empiric Data

PESP of atria to augment pre-load

A recent study demonstrated PESP of the atria with paired pacing which resulted in an augmentation of LV systolic performance by affecting an increase in LV preload [99]. The presence of PESP is not surprising given the extensive presence of sarcoplasmic reticulum in atrial myocytes [100]. One might expect that this atrial PESP might be programmable in a pacing device for beneficial augmentation of ventricular function.

Use of LV PESP to augment the treatment of heart failure with preserved ejection fraction (HFpEF)

In HFpEF, systolic function is normal but there is increased diastolic pressure during relaxation. The ventricle become stiff and cannot relax. The filling pressure increases even further during exercise, causing the symptoms of heart failure. Medications that help improve outcomes in systolic heart failure have unfortunately not worked in HFpEF. Thus, the treatment remains largely empiric. On the other hand, the issue of ventricular relaxation following an extrasystole is fraught with confusion [2]. One recent study, however, looked at this issue in more detail and showed that failing hearts showed potentiated relaxation following an extrasystole, compared to a non-failing heart [101]. This finding seems to warrant further investigations, particularly to determine if this might be a factor to be exploited in the application of the devices being tested to treat heart failure. This result could have significant bearing on the utilization of a Force-frequency device (paired-pacing, NES) on heart failure with preserved ejection fraction (HFpEF) [102].

Use of LV PESP to predict the response to force-frequency pacing in myocardial dysfunction

As noted under new uses of PESP, Force-frequency pacing (Paired pacing and non-excitatory stimulation (NES)) have been shown to augment contractility in myocardial dysfunction [48-100]. However, recent studies have shown that some cardiomyopathies do not respond to PESP with augmentation of contractility. In other words, there is no PESP. So it would be important to know which cardiomyopathies do, and which do not, show PESP following an extrasystole.

Table 1 lists non-ischemic cardiomyopathies which have been reported to respond to an extrasystole with PESP. To this list could be added ischemic cardiomyopathy when the myocardium is either stunned or hibernating. From these results, it would appear that these cardiomyopathies might be expected to benefit from Force-frequency pacing (Paired pacing or NES).

	Cause of CM	Response to PESP	Reference
Autonomic Nervous System Dysfunction	Abn Autonomic NS	Present	[103-105]
Taurine Depletion	Decr. Actin/myosin	Present	[106]
Chagas disease	Microvasc. Abn	Present	[107-109]
Calcium Overload	Incr.SERCA2A	Incr.RF	[110]

Table 1: Non-ischemic cardiomyopathies which have been reported to respond to an extrasystole with PESP. Abn: Abnormal; Incr: Increased; NS: Nervous System; Microvasc: Microvascular; RF: Recirculated Fraction.

Table 2 lists cardiomyopathies which have been reported to fail to augment contractility following an extrasystole or responded with decreased function. Again, theoretically, these cardiomyopathies would not be expected to respond optimally to Force-frequency pacing. These results do not necessarily mean that these cardiomyopathies will not respond at all to Force-frequency pacing, since the context of the study in which PESP was tested was not controlled. These results may merely mean that the degree of myocardial dysfunction has progressed beyond the threshold where PESP was operative, as has been reported with prolonged hibernation in ischemic cardiomyopathy [8,9].

	Cause of CM	Response to PESP	Reference
Bartter's Syndrome	Abn Ca homeostasis	Absent	[111,112]
Profound Catecholamine Stimulation: Takotsubu	SR Ca depletion	Absent	[113,114]
Carnitine deficient cardiomyopathy	Abn. Mito, SR	Absent	[115]
Cyclopiazonic acid cardiomyopathy	Abn. SR Ca uptake	Decr.RF	[116,117]
Tachycardia- induced cardiomyopathy	Abn.SR uptake/release	Abn MRC	[42-44]
Doxorubicin cardiomyopathy	Abn. SR release	Absent	[118,119]
Hypertrophic cardiomyopathy	Decr. SERCA2A	Decr RF	[120-122]
Cyclosporine	Incr.Ca release	Decr PESP	[123]

Table 2: List of cardiomyopathies which have been reported to fail to augment contractility following an extrasystole or responded with decreased function. Abn: Abnormal; Incr: Increased; Decr: Decreased; Mito: Mitochondria; Microvasc: Microvascular; RF: Recirculated Fraction; SR: Sarcoplasmic Reticulum; MRC: Mechanical Restitution of Contractility.

Furthermore, from these results, it is clear that abnormal handling of calcium by the SR is the prominent EC-coupling element associated with the loss of PESP. These studies, do not, however, conclusively rule out other elements of EC-coupling being affected in the cardiomyopathy, since more rigorously detailed investigations would be required for such a conclusion.

Use of LV PESP to guide cancer therapy

Cardiovascular disease represents the main competing cause of death in cancer survivors [124]. Moreover, one of the major causes of cardiovascular mortality in cancer survivors is left ventricular dysfunction secondary to the treatment of the cancer with anthracycline drugs, one of which is doxorubicin [125]. The standard method of monitoring the cancer treatment with doxorubicin is to follow the echocardiogram for evidence of myocardial dysfunction prior to and during the course of therapy [126].

We have seen earlier (Table 2) that the cardiomyopathy associated with doxorubicin does not respond to PESP, which is thought to be due to abnormal release of calcium from the SR. However, anthracycline cardio toxicity is strongly dose-related [125] and the conditions of these studies of PESP with doxorubicin cardiomyopathy were not strictly correlated with the clinical situation. Presumably, the absent PESP response is that which develops after a full course of therapy, after the full-blown cardio toxicity has become manifest. One might

hypothesize that the PESP response could be studied at earlier stages of treatment to predict early cardiomyopathy before the condition becomes irreversible.

Additionally, again theoretically, one could perhaps implant one of the Force-frequency pacemakers before there is the loss of PESP. This might delay the onset of cardiomyopathy and possibly even allow the use of higher doses of anthracycline.

Use of LV PESP to predict the degree of obstruction in hypertrophic cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is the most common hereditary disease of the heart [127]. The disease is characterized by excessive thickening of the left ventricular myocardium. There are two types of HCM: a more common, obstructive type in which there is left ventricular outflow obstruction (HOCM) and a less common, non-obstructive type (HNCM). The obstruction can be reliably quantified using Doppler echocardiography by determining the increased systolic flow velocities in the left ventricular outflow tract or by calculating the pressure gradients at catheterization. Provocation of obstruction is mandatory and can be induced by postextrasystolic potentiation, which is known as the "Brockenbrough sign" [128].

One might reliably speculate that, since there is an indirect relationship between the coupling interval and the PESP, varying the coupling interval of the extrasystole (S1-S2) would result in a variable and predictable degree of obstruction. The curve generated by such a technique might provide information regarding the degree of obstruction as well as provide information about prognosis and indications for surgical or ablative therapy.

Hypothetical Application of PESP Based on the Generalization of the Mechanism of PESP

Use of PESP and other pacing modalities to augment the function of other organs or systems

Building on the observations that the potentiation associated with PESP, including other patterns of electrical stimulation, as well as Non-excitatory Stimulation (NES), leads to the modulation of the intracellular calcium which produces the functional output, recently there have appeared several proposals which seek to exploit this phenomenon in systems other than the cardiovascular system. The systems to be augmented include the neurological system [129], the endocrine system (blood glucose level control) [130], intracellular calcium control [131], gastrointestinal system (gastrointestinal motility stimulation) [132] and genetic system (modify gene expression [133]). Even non-biological systems have come to be considered to be potentially enhanced by modifying the electrical stimulation pattern (touch detector for a digitizer [134]). There are at present no specific empiric data to support such applications Future studies to confirm or deny these hypothetical applications of the force-frequency relationship appear to be warranted.

Conclusion

In this paper, the uses of PESP have been introduced and reviewed. These uses were found to fall into the two categories of: actualized applications derived from empiric studies which support the application and hypothetical applications which are derived from the application of the phenomenon in empiric studies. Further research into the mechanism and applications of PESP seems to clearly be warranted because of the recent observations of successful applications in clinical medicine.

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