Post-extrasystolic Blood Pressure Potentiation as a Risk Predictor in Cardiac Patients

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Abstract

For more than 100 years physicians have observed that heartbeats following extrasystolic beats are characterised by augmented myocardial contractility. This phenomenon was termed post-extrasystolic potentiation (PESP). In the 1970s it was first noted that PESP measured at the blood pressure level is typically pronounced in heart failure patients. Only recently, it was shown that PESP measured non-invasively as post-extrasystolic blood pressure potentiation was a strong and independent predictor of death in survivors of myocardial infarction and in patients with chronic heart failure. A similar parameter (PESP_{Afib}) can be also assessed in patients with atrial fibrillation. PESP and PESP_{Afib} can be understood as non-invasive parameters that indicate myocardial dysfunction. They have the potential to improve risk stratification strategies for cardiac patients.

Keywords

Post-extrasystolic potentiation, risk prediction, myocardial infarction

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In 1885, Oscar Langendorff was the first person to describe the increase in contractility ('Pulsverstärkung') that follows an extrasystole.¹ Langendorff experimented with spontaneously beating isolated frog hearts. He recorded the heartbeats by using a lever that transferred the contractile movements of the heart to a rotating drum. Electrical stimulation resulted in premature contractions that were followed by compensatory pauses. In these experiments, he noticed that myocardial contractility during the first post-ectopic beats was typically stronger compared with the normal beats (see *Figure 1A*). Decades later, this phenomenon was termed post-extrasystolic potentiation (PESP).²

PESP is present at the level of the myocardium, independently of pre- or afterload conditions.³ The driving force behind the augmented post-extrasystolic contractility is augmented calcium release from the intracellular stores during the post-extrasystolic action potential.^{4,5}

Historically, PESP has been studied intensively with regard to two possible clinical applications (reviewed in Cooper³):

- PESP was induced during contrast ventriculography with the aim of identifying ischaemic but viable myocardial regions that might benefit from revascularisation.
- PESP was elicited by paired pacing with the aim of augmenting myocardial contractility in heart failure patients.

Besides these now widely abandoned applications, several studies have documented an interesting relationship between PESP and myocardial dysfunction.

Post-extrasystolic Potentiation and Heart Disease: A Forgotten Association?

PESP can be measured as post-extrasystolic augmentation of the maximum left-ventricular pressure rise (LV dP/dt) or as systolic blood pressure potentiation. The parameter that is most closely related to myocardial contractility is LV dP/dt. At the level of LV dP/dt, PESP was observed both in healthy people and in heart failure patients.⁶ However, potentiation of LV dP/dt was typically more pronounced in failing than in healthy hearts.^{7–10} At the level of blood pressure, it has to be taken into account that systolic blood pressure is not only determined by cardiac output, but also by vascular factors, such as peripheral vascular resistance. When PESP was measured at the level of maximum systolic blood pressure (or maximum LV pressure, which are roughly equivalent in the absence of aortic stenosis), the typical finding in healthy probands was that the first post-ectopic heartbeat elicited a lower pulse wave than the regular ones. By contrast, in heart failure patients, PESP of systolic blood pressure could generally be observed.^{6–10} In a series of 100 consecutive patients with coronary artery disease, the pattern of post-extrasystolic blood pressure potentiation was associated with an increased prevalence of congestive heart failure and cardiomegaly as well as with higher left-ventricular end-diastolic pressure, lower cardiac output and lower left-ventricular ejection fraction (LVEF).¹¹

At the cellular level, PESP of contractility is caused by an increased magnitude of the post-extrasystolic systolic calcium transient.^{4,5} During the premature heartbeat, calcium release from the intracellular stores is reduced due to refractoriness of the calcium release channels (ryanodine receptors) located in the membrane of the intracellular

Figure 1: Post-extrasystolic Potentiation

A: The first description of post-extrasystolic potentiation in the scientific literature (Source: Langedorff, 1885). The contractions of an isolated, spontaneously beating frog heart (*Rana temporaria*) were recorded on a rotating drum by using a lever lying on the heart. Premature ventricular contractions were elicited by electrical stimulation (arrows). The contractions following the premature beats (arrowheads) were stronger than the regular contractions. B: Determination of post-extrasystolic blood pressure potentiation. Typical ECG and blood pressure recordings from a patient who died during follow-up (upper panel) and a long-term survivor (lower panel). Sequences elicited by a ventricular ectopic beat (asterisk) are shown. The systolic blood pressure of the first post-ectopic heart beat (P_1) and the mean systolic blood pressure of the nine subsequent heartbeats (P_{2-10}) are shown. Post-extrasystolic potentiation (PESP) was considered to be present if the ratio P_1/P_{2-10} exceeded 1.03. Based on data published in Iribé et al., 2006.

calcium stores. Accordingly, more calcium remains in the intracellular stores. In the post-extrasystolic pause, the calcium content of the intracellular stores is further increased due to activity of the sarcoplasmic reticulum calcium ATPase (SERCA). Since the amplitude of the systolic calcium transient largely depends on the filling state of the intracellular stores, it is augmented in the first post-ectopic heartbeat.

Both animal experiments¹² and simulation studies¹³ indicate that increased PESP might result from heart failure-induced alterations of intracellular calcium cycling. In failing myocardium, the steady-state calcium content of the intracellular stores is reduced due to increased diastolic calcium leak via the ryanodine receptors. Starting from this lower steady state, the relative augmentation after an ectopic beat may be increased as compared with non-failing myocardium.

Already in 1971, Beck et al.⁶ reported that the potentiation of the first post-extrasystolic blood pressure wave is typically seen in failing ventricles but rarely in healthy hearts. The authors concluded that PESP measured on the level of blood pressure could be used to detect 'abnormal' left ventricles. However, the use of PESP as a diagnostic tool for myocardial dysfunction has not been pursued further for many years.

Post-extrasystolic Potentiation as a Risk Predictor in Cardiac Patients

To investigate whether PESP at the blood pressure level is associated with adverse outcome in cardiac patients, we prospectively analysed its correlation with mortality in a cohort of 941 survivors of acute myocardial infarction (MI).¹⁴ To establish a new, simply applicable, non-invasive risk predictor, we decided to investigate PESP at the blood pressure level using non-invasive measurements. On days 5–9 after MI, patients underwent a 30-minute recording of ECG and blood pressure. Blood pressure was continuously recorded using a photoplethysmographic finger cuff device. PESP was assessed after spontaneously occurring ventricular premature contractions (VPCs).

Of the 941 patients, 220 (23.4 %) exhibited at least one VPC suitable for PESP quantification during the 30-minute recording period. In these patients, we calculated the ratio of the systolic blood pressure of the first post-ectopic beat (P_1) divided by the average blood pressure of the nine following beats (P_{2-10} ; see Figure 1B). We considered PESP present if the ratio was >1.03 (i.e. if the post-VPC pulse wave exceeded the mean of the nine subsequent pulse waves by more than 3 %). According to this definition, PESP was present in 62 (28.2 %) and absent in 158 (71.8 %) of the 220 patients in whom PESP could be quantified.

The presence of PESP was associated with a marked increase of 5-year all-cause mortality (see Figure 2A), which amounted to 29.4 % in patients with PESP present and 5.8 % in patients with PESP absent. Patients in whom PESP could not be measured due to lack of suitable VPCs had a low mortality rate of 6.3 %, almost indistinguishable from that of patients with PESP absent (see Figure 2A). Therefore, we merged the patient categories PESP absent and PESP not detectable, which allowed us to base the analyses on the whole dataset of 941 patients.

In multivariable analysis considering LVEF, VPC count and GRACE (Global Registry of Acute Coronary Events) score as independent variables, PESP remained a strong independent predictor of mortality with a hazard ratio of 3.2 (95 % confidence interval 1.8–5.7; see Figure 2B). If applied together for post-MI risk stratification, PESP and LVEF provided complementary information (see Figure 2C). Patients in whom both parameters were normal were at a low 5-year mortality risk of 5.1 %. Patients, in whom one of the parameters was abnormal, had a substantially higher risk of 18.2 % (LVEF abnormal) or 23.8 % (PESP abnormal). The small group of patients in whom both parameters were abnormal had an excess 5-year mortality risk of 46.7 % (see Figure 2C).

There was no evidence for relevant confounding by baseline variables such as age, sex, diabetes mellitus or baseline medical therapy (use of β -blockers, ACE inhibitors, statins, diuretics, acetylsalicylic acid or clopidogrel). If any of these variables was additionally included in a Cox regression model consisting of PESP, LVEF, VPC count and GRACE score, the association of PESP and mortality remained highly significant.¹⁴

To validate these findings in a different patient population, we analysed data from a previously reported cohort of 146 patients with chronic heart failure,¹⁵ who were followed up for 2.7 years. At inclusion, all patients also underwent a continuous blood pressure measurement allowing PESP assessment. The mortality rate during follow-up was 28.8 %. Also in this cohort of heart failure patients, presence of PESP was a strong and independent risk predictor, with mortality amounting to 42 % and 20 % in patients with PESP present and absent/not calculable, respectively.¹⁴

PESP as described above can only be assessed in patients with sinus rhythm. However, in atrial fibrillation, the myocardial force-interval relationship translates the random variability of beat-to-beat intervals into a corresponding pulse pressure variability.^{16,17} We hypothesised that a parameter analogous to PESP could also be determined in atrial fibrillation. Therefore, we developed a PESP-analogous parameter ($PESP_{Afib}$) and evaluated its association with mortality in a small cohort of 32 MI survivors with atrial fibrillation.¹⁸ The ECGs were screened for short-long sequences, in which a heartbeat interval shorter than 80 % of the local average (P_i) was followed by an interval longer than 140 % of the local average (P_{i+1}). Based on the systolic blood pressure values elicited by P_i and P_{i+1} and the corresponding RR intervals (RR_i and RR_{i+1}), we calculated $PESP_{Afib}$ as $(P_{i+1}-P_i) / (RR_{i+1}-RR_i)$, i.e. by relating the systolic pressure change to the RR interval change.¹⁸

$PESP_{Afib}$ values were significantly higher in non-survivors than in survivors. When dichotomised at its median, $PESP_{Afib}$ distinguished between patient groups with 5-year mortality rates of 63 % and 19 %, respectively. The association of $PESP_{Afib}$ with mortality was independent from established risk factors such as LVEF, diabetes mellitus, age or the mean heart rate.

Taken together, these results indicate that PESP (and $PESP_{Afib}$ in atrial fibrillation) is a promising new risk predictor for cardiac patients.

Future Directions

One explanation for the close association of PESP and mortality in cardiac patients is that PESP is a surrogate parameter for myocardial dysfunction. It remains to be investigated whether PESP will be useful for clinical applications beyond risk stratification.

If changes in the clinical status of a patient translate into changes of PESP, PESP might become a tool to monitor the therapy of heart failure patients. This would be especially interesting since, in theory, sensors and algorithms necessary to quantify PESP might be incorporated into implantable cardiac devices such as pacemakers, ICDs or event recorders.

To test the hypothesis that PESP could be used to monitor the clinical status of heart failure patients, we initiated a study in which patients with acutely decompensated heart failure undergo PESP assessments at admission, before discharge and after 4 weeks. In addition, NT-proBNP (N-terminal of the prohormone brain natriuretic peptide) plasma levels are determined. Preliminary data from two patients are shown in Figure 3. Numerical PESP ratios (i.e. P_i/P_{2-10}) at admission were >1.03 in both patients, meaning that both patients would be classified as 'PESP present' according to the definition used in the post-MI study described above.¹⁴ In one of the patients (Patient 1), PESP numerical ratio at discharge decreased to 0.98, re-classifying the patient as 'PESP absent' at this time point. Concomitantly, the NT-proBNP plasma level was also lower at discharge than at admission. In the other patient (Patient 2), both PESP numerical ratio and plasma NT-proBNP level increased from admission to discharge. While the correlation of PESP with natriuretic peptide levels in these examples is encouraging, it is necessary to include additional patients before any solid conclusions can be drawn.

It is also possible that PESP could be used in the general population to predict cardiac events or to identify patients with unrecognised cardiac conditions. This hypothesis is currently being addressed in

Figure 2: Post-extrasystolic Potentiation Predicts Mortality after Myocardial Infarction

A: Incidence of death during a follow-up period of 5 years in patients stratified according to the presence or absence of post-extrasystolic potentiation (PESP) (red and green curve, respectively). The mortality of those patients, who did not have suitable VPCs for PESP assessment is also shown (grey curve). B: Hazard ratios with 95 % confidence intervals obtained by multivariable Cox regression analysis for 5-year all-cause mortality are shown. All shown variables were included in the model. The grey line indicates a hazard ratio of 1.0. C: Mortality in patients stratified by the combination of PESP (absent or present) and LVEF (≤ 35 % or > 35 %). In panels (A) and (C), the number of patients at risk at 0, 1, 2, 3, 4, 5 years are shown below the graphs in the same colour coding and P values for the overall comparison at 5 years are indicated. Based on data published in Iribe et al., 2006. GRACE = Global Registry of Acute Coronary Events; LVEF = left-ventricular ejection fraction; PESP = post-extrasystolic potentiation; VPC = ventricular premature contraction.

the ongoing INVADE (Prevention of Stroke and Dementia in Primary Care) study,¹⁹ in which PESP was determined in a general population sample of 1,900 patients aged ≥ 65 years, who are now followed up for cardiovascular events. Follow-up of this study will be completed in late 2016.

Another open question is whether PESP might improve patient selection for primary prophylactic ICD therapy. The limitations of LVEF in this regard are well known²⁰ and the complementary nature of the prediction

Figure 3: Monitoring Decompensated Heart Failure with Post-extrasystolic Potentiation

Post-extrasystolic potentiation numerical ratios (left panel, blue symbols), NT-proBNP plasma levels (left panel, red symbols) and body weight (right panel) measured at admission and at discharge in two patients presenting with acute decompensated heart failure. NT-proBNP = N-terminal of the prohormone brain natriuretic peptide.

of post-MI mortality by LVEF and PESP (see Figure 2C) suggests that this might be the case. However, it should be noted that, in this study, the primary endpoint was all-cause mortality. While PESP was also significantly associated with cardiac death and with sudden cardiac death (with p values of 5.9×10^{-5} and 1.9×10^{-4} , respectively), the numbers of events (38 and 14, respectively) were too small to investigate whether the association of PESP with these more specific endpoints was independent from established risk predictors or whether PESP is differentially associated with sudden and non-sudden cardiac death. It is, therefore, possible that presence of PESP identifies a patient group

that typically dies from a cause (e.g. progressive heart failure) that cannot be prevented by ICD therapy. Accordingly, larger studies are necessary to investigate the utility of PESP to identify ICD candidates.

Conclusion

Post-extrasystolic blood pressure potentiation is a strong and independent risk predictor in survivors of MI and in heart failure patients. An analogous parameter (PESP_{Afib}) can be determined in patients with atrial fibrillation. Open questions are whether PESP is suitable as a parameter for therapy monitoring and whether it may aid patient selection for prophylactic ICD therapy. ■

Clinical Perspective

- Post-extrasystolic potentiation (PESP) is the increase of myocardial contractility in the heartbeat that follows a premature beat. PESP can also be measured at the blood pressure level as post-extrasystolic blood pressure potentiation.
- At the blood pressure level, PESP is typically pronounced in heart failure patients.
- In survivors of myocardial infarction and in patients with chronic heart failure, PESP at the blood pressure level is an independent predictor of mortality.
- The suitability of PESP as a parameter to monitor heart failure treatment and as a predictor of efficacy of ICD implantation remains to be investigated.

- Langendorff O. Ueber elektrische Reizung des Herzens. *Du-Bois-Reymond's Archiv f. Physiologie* 1885;**8**:284–7.
- Hoffman BF, Bindler E, Suckling EE. Postextrasystolic potentiation of contraction in cardiac muscle. *Am J Physiol* 1956;**185**:95–102. PMID: 13313754
- Cooper MW. Postextrasystolic potentiation: Do we really know what it means and how to use it? *Circulation* 1993;**88**:2962–71. PMID: 7504591
- Wier WG, Yue DT. Intracellular calcium transients underlying the short-term force-interval relationship in ferret ventricular myocardium. *J Physiol* 1986;**367**:507–30. PMID: 2432238; PMCID: PMC1182812
- Rice JJ, Jafri MS, Winslow RL. Modeling short-term interval-force relations in cardiac muscle. *Am J Physiol Heart Circ Physiol* 2000;**278**:H989–31. PMID: 10710361
- Beck W, Chesler E, Schrire V. Postextrasystolic ventricular pressure responses. *Circulation* 1971;**44**:523–33. PMID: 4106154
- Kvasnicka J, Liander B, Broman H, Varnauskas E. Quantitative evaluation of postectopic beats in the normal and failing human heart using indices derived from catheter-tip manometer readings. *Cardiovasc Res* 1975;**9**:336–41. PMID: 1175180
- Merrill JP, Motte G, Aumont MC, et al. Post-extrasystolic left ventricular peak pressure with and without left ventricular failure. *Cardiovasc Res* 1979;**13**:338–44. PMID: 89910
- Seed WA, Noble MIM, Walker JM, et al. Relationships between beat-to-beat interval and the strength of contraction in the healthy and diseased human heart. *Circulation* 1984;**70**:799–805. PMID: 6488494
- Voss A, Baier V, Schumann A, et al. Postextrasystolic regulation patterns of blood pressure and heart rate in patients with idiopathic dilated cardiomyopathy. *J Physiol* 2002;**538**:271–8. PMID: 11773334; PMCID: PMC2290033 DOI: 10.1016/0002-8703(78)90086-8; PMID: 79308
- Hamby RJ, Aintablian A, Roberts G, Kramer RJ. Postextrasystolic aortic pressure pulse response in coronary artery disease. *Am Heart J* 1978;**96**:195–202. DOI: 10.1016/0002-8703(78)90086-8; PMID: 79308
- Hoit BD, Tramuta DA, Kadambi R, et al. Influence of transgenic overexpression of phospholamban on postextrasystolic potentiation. *J Mol Cell Cardiol* 1999;**31**:2007–15. PMID: 10591027
- Iribe G, Kohl P, Noble D. Modulatory effect of calmodulin-dependent kinase II (cAMKII) on sarcoplasmic reticulum Ca²⁺ handling and interval-force relations: a modelling study. *Philos Trans A Math Phys Eng Sci* 2006;**364**:1107–33. PMID: 16608699
- Sinnecker D, Dirschinger R, Barthel P, et al. Postextrasystolic blood pressure potentiation predicts poor outcome of cardiac patients. *J Am Heart Assoc* 2014;**3**:e000857. DOI: 10.1161/JAHA.114.000857. PMID: 24895163; PMCID: PMC4309081
- Bauer A, Morley-Davies A, Barthel P, et al. Bivariate phase-rectified signal averaging for assessment of spontaneous baroreflex sensitivity: pilot study of the technology. *J Electrocardiol* 2010;**43**:649–53. DOI: 10.1016/j.jelectrocard.2010.05.012; PMID: 20638668
- Hardman SMC, Noble MIM, Seed WA. Postextrasystolic potentiation and its contribution to the beat-to-beat variation of the pulse during atrial fibrillation. *Circulation* 1992;**86**:1223–32. PMID: 1382889
- Endoh M. Force-frequency relationship in intact mammalian ventricular myocardium: physiological and pathophysiological relevance. *Eur J Pharmacol* 2004;**500**:73–86. PMID: 15464022
- Sinnecker D, Barthel P, Huster KM, et al. Force-interval relationship predicts mortality in survivors of myocardial infarction with atrial fibrillation. *Int J Cardiol* 2015;**182**:315–20. DOI: 10.1016/j.ijcard.2015.01.018; PMID: 25585377
- Bickel H, Ander KH, Brönnner M, et al. Reduction of long-term care dependence after an 8-year primary care prevention program for stroke and dementia: the INVADE trial. *J Am Heart Assoc* 2012;**1**:e000786. DOI: 10.1161/JAHA.112.000786; PMID: 23130154; PMCID: PMC3487359
- Dagres N, Hindricks G. Risk stratification after myocardial infarction: is left ventricular ejection fraction enough to prevent sudden cardiac death? *Eur Heart J* 2013;**34**:1964–71. DOI: 10.1093/eurheartj/ehh10; PMID: 23644180