PEA I and PEA II based implantable haemodynamic monitor: pre clinical studies in sheep

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Aims The aims of this study were first, to demonstrate that Peak Endocardial Acceleration during isovolumic systole (PEA I) is related to positive peak LVdP/dt, while Peak Endocardial Acceleration during isovolumic relaxation time (PEA II) is related to aortic diastolic pressure (ADP) and to negative peak LVdP/dt; and second, to test if the simultaneous recording of PEA I and PEA II offers a new chance to monitor indexes of LV systolic and diastolic function.

Methods An implantable haemodynamic monitor, based on PEA I and PEA II measurements via a microaccelerometer sensor located in the tip of a pacing lead, screwed into the right ventricle, was tested in nine sheep at baseline and during acute haemodynamic interventions: nitrate (0·1 mg/kg), metaraminol (0·15 mg/kg), dobutamine (5 µg/kg) infusion. ADP, positive and negative peak LVdP/dt were simultaneously recorded by an aortic and left ventricular Millar catheter.

Results PEA I changes were significantly related to positive peak LVdP/dt changes during dobutamine induced inotropic changes \((r=0·83, P<0·001)\). PEA II changes were significantly related to both ADP \((r=0·91, P<0·001)\) and negative peak LVdP/dt changes \((r=0·92, P<0·001)\) during nitrate induced hypotension and metaraminol induced hypertension.

Conclusion The simultaneous recording of PEA I and PEA II with an implantable system offers a new chance to monitor indexes of LV systolic and diastolic function.

Key Words: PEA I, contractility, PEA II, diastolic function.

Introduction

When the myocardium contracts isometrically, it generates vibrations which have audible components, responsible for the first heart sound\(^{[1,2,3]}\). Both the audible and non-audible spectrum of these vibrations can be measured with an implantable endocardial accelerometer. The peak of these myocardial vibrations (PEA, peak endocardial acceleration), occurring in the isovolumic contraction phase, is an index of myocardial contractility whose directional changes mirror very closely changes in left ventricular peak \(dP/dt\)\(^{[4,5]}\).

As observed for PEA I and the First Heart Sound (S1), PEA II, the maximum amplitude of vibrations measured by the endocardial accelerometer during the isovolumic ventricular relaxation phase, originates from the physical phenomenon (the abrupt deceleration of the moving aortic blood mass), that gives rise to the Second Heart Sound (S2)\(^{[6–10]}\).

The aims of this study were first, to demonstrate that Peak Endocardial Acceleration during isovolumic systole (PEA I) is related to positive peak LVdP/dt, while Peak Endocardial Acceleration during isovolumic relaxation time (PEA II) is related to aortic diastolic pressure (ADP) and to negative peak LVdP/dt; and second, to test if the simultaneous recording of PEA I and PEA II with an implantable system offers a new chance to monitor indexes of LV systolic and diastolic function.

Methods

We used a micromass uniaxial acceleration sensor (Sorin Biomedica Cardio SpA, Saluggia, Italy) located in the stimulating tip of a unipolar pacing lead; the mass is located inside a non-deformable capsule, and the device has a frequency response up to 1 kHz and a sensitivity of 7 mV/g \((g=9·81 \text{ m/s}^2)\)\(^{[11,12]}\). The research protocol was...
approved by the locally appointed ethic committee. The screw-in lead was inserted and fixed to the apex of the right ventricle in nine adult anesthetized sheep (63 ± 8 kg) instrumented with an aortic and a LV Millar catheter. The accelerometer was connected to an external signal amplifier with a frequency range of 0·05–1000 Hz. An analog peak-to-peak detector synchronized with the standard ECG scanned the first 150 ms following the R wave to record PEA I and the 100 ms following the T wave to record PEA II[10]. Positive and negative peak LVdP/dt were measured by the LV Millar catheter while aortic diastolic pressure (ADP) was measured at the dicrotic notch by the aortic Millar catheter[8,13]. All the data were collected and analyzed by a BIOPAC MP100 (Santa Barbara, CA, U.S.A.) digital acquisition system. All the parameters were acquired as instantaneous values at baseline and during acute hemodynamic interventions: first, nitrate (0·1 mg/kg in 1 min), then, metaraminol (0·15 mg/kg in 1 min), and last, dobutamine (5 μg/kg/min for 2 min) infusions. Each successive intervention was performed after drug wash-out (five half-lives) and return to a new baseline for the preparation.

Statistical analysis

Data are expressed as mean ± 1 SD. Intrigroup comparisons were performed using the paired Student’s t-test. The ANOVA with Fischer post hoc pair-wise multiple comparisons was used to assess significance of intragroup repeated measures. Relations between variables were assessed using linear regression analysis and Pearson’s correlation coefficient. A P value of <0·05 was considered significant.

Results

A stable, reproducible and consistent PEA I and PEA II signal were obtained in all animals at baseline and during pharmacological interventions (Fig. 1).

The system was able to detect LV dP/dt variations ≥26 mmHg/s and ADP variations ≥3 mmHg.

Nitrate infusion significantly decreased PEA II (from 0·31 ± 0·10 to 0·21 ± 0·09 g) but not PEA I and HR (Fig. 2).

Metaraminol infusion significantly increased PEA I (from 0·69 ± 0·19 to 1·24 ± 0·39 g) and PEA II (from 0·26 ± 0·12 to 0·38 ± 0·14 g), without changing HR (Fig. 3).

Dobutamine infusion significantly increased PEA I (from 1·26 ± 0·01 to 3·34 ± 0·43 g), PEA II (from 0·22 ± 0·01 to 0·43 ± 0·06 g), and HR (from 90 ± 18 to 150 ± 18 bpm) (Fig. 4).

PEA I changes were significantly related to positive peak LVdP/dt changes during dobutamine induced inotropic changes (r=0·89, P<0·001).

PEA II changes were significantly related to both ADP (r=0·91, P<0·001) and negative peak LVdP/dt changes (r=0·92, P<0·001) during nitrate induced hypotension and metaraminol induced hypertension.
All the data are summarized in Table 1.

In the experimental sequence in each animal subsequent effects of the interventions were measured against the return to new baseline values after the previous infusion. Baseline values were considered values not exceeding ±10% the starting baseline data.

**Discussion**

**The endocardial acceleration signal**

A stable, reproducible and consistent endocardial acceleration signal was obtained in all animals.

Endocardial acceleration is easily recorded throughout the whole cardiac cycle[1], with the vibration peaks corresponding to the first heart sound (PEA I) and to the second heart sound (PEA II) (Fig. 1).

**The PEA I signal**

This high amplitude vibration is an expression of the tension wavefront produced during initial activation of the heart: it occurs at the onset of endocardial movement, an average of 20 msec before mitral valve closure[5,14,15], and, as positive peak LVdP/dt, is fairly consistent in sinus rhythm (Fig. 1).

Changes in the maximum rate of rise in ventricular pressure are highly sensitive to acute changes in contractility[16] and relatively independent of afterload. Up to date, positive peak LVdP/dt is universally accepted among catheter laboratory data as a good index to assess acute changes in contractility.

In our experimental model, changes of PEA I were strictly and linearly related to changes in positive peak LVdP/dt; although we appreciate that positive peak LVdP/dt, as PEA I, is not a gold standard of myocardial contractility, it can be used to assess directional changes in response to an intervention in an individual patient[17].

PEA I reflects advantages and disadvantages of positive peak LVdP/dt in monitoring beat-to-beat changes in ventricular function. PEA I in fact is very sensitive to contractility changes, relatively insensitive to afterload changes, but sensitive to preload changes, especially for

![Image](image-url)

**Figure 3** Simultaneous recording in a sheep of the PEA II and of ADP (upper panel), of the PEA II and of negative peak LVdP/dt (lower panel), during drug induced hypertension (metaraminol infusion). Curves show the close beat-to-beat correlation of PEA II, ADP and negative peak LVdP/dt.

![Image](image-url)

**Figure 4** Simultaneous recording in a sheep of the PEA I and of positive peak LVdP/dt (upper panel), of the PEA II, aortic diastolic pressure and of negative peak LVdP/dt (lower panel), during dobutamine infusion. Dobutamine inotropic stimulation increased positive peak LVdP/dt and PEA I. Dobutamine also increased ADP and negative peak LVdP/dt with an increase in the driving pressure and of the PEA II.

**Table 1** PEA I and PEA II changes during acute haemodynamic interventions

<table>
<thead>
<tr>
<th></th>
<th>HR (bpm)</th>
<th>PEA I (g)</th>
<th>Pos. peak LVdP/dt (mmHg/s)</th>
<th>PEA II (g)</th>
<th>Neg. peak LVdP/dt (mmHg/s)</th>
<th>ADP (mmHg)</th>
</tr>
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<tbody>
<tr>
<td>Baseline</td>
<td>90 ± 18</td>
<td>0·66 ± 0·3</td>
<td>682 ± 188</td>
<td>0·26 ± 0·1</td>
<td>1316 ± 268</td>
<td>55 ± 15</td>
</tr>
<tr>
<td>Nitrates (% change)</td>
<td>+3 ± 6</td>
<td>+3 ± 20</td>
<td>+62 ± 37</td>
<td>−30 ± 18*</td>
<td>−25 ± 13*</td>
<td>−29 ± 11*</td>
</tr>
<tr>
<td>Dobutamine (% change)</td>
<td>+7 ± 20</td>
<td>+105 ± 58*</td>
<td>+166 ± 37*</td>
<td>+40 ± 23*</td>
<td>+91 ± 41*</td>
<td>+79 ± 16*</td>
</tr>
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*P<0·01 vs baseline.
shorter diastolic preceding intervals, in which the Frank Starling mechanism plays a primary role\cite{19}.

To be broadly useful for monitoring failing hearts, the PEA signal set would need to behave appropriately when regions other than the septum are compromised or when ventricular function has become dysynchronous.

Attempts have been made by other authors to assess the usefulness of PEA I changes for monitoring global left ventricular contractility changes during acute regional left ventricular wall dysfunction. In 1994 Wood et al.\cite{24} studied the regional effects of myocardial ischemia on the epicardially recorded first heart sound in dogs, demonstrating that the amplitude of cardiac vibrations in isovolumic systole are sensitive to global left ventricular contractility and independent of the site of application of the accelerometer sensor (normal contracting or ischaemic non-contracting LV area).

Padeletti et al.\cite{26} has previously determined the correlation PEA I vs changes in LV positive peak dP/dt, during and after temporary occlusion of left descending coronary artery in pigs. Data processing, including 3 min of basal time, the occlusion time (5 min), and 3 min of recovery time, and showed a good correlation between these variables (r=0.75).

Bombardini et al.\cite{25} demonstrated that PEA I changes during dobutamine or diprydamole induced contractility changes were well assessed both in patients with normal (wall motion score index=1) or dysynchronous (wall motion score index>1) left ventricular function.

Clementy et al.\cite{27} assessed the haemodynamics of multisite ventricular pacing by echocardiography and PEA I in heart failure patients. During various ventricular pacing configurations, PEA I measurements were consistent with echocardiographic data, showing comparable haemodynamic effects of biventricular and left ventricular pacing.

The PEA II signal

PEA II, the maximum amplitude of vibrations measured by the endocardial accelerometer during the isovolumic ventricular relaxation phase, originates from the physical phenomenon (the abrupt deceleration of the moving aortic blood mass), that gives rise to the Second Heart Sound (S2) (Fig. 1).

Our data in anaesthetized sheep showed that PEA II, measured by the endocardial (BEST) accelerometer, during vasoactive and inotropic stimulations, is correlated with Aortic Diastolic Pressure (ADP) (r=0.91 ± 0.03) and with negative peak LVdP/dt (r=0.92 ± 0.02)\cite{10}.

Early studies of the haemodynamic determinants of the amplitude of the S2 have related the aortic component amplitude (A2) of the S2 vibration to the aortic diastolic pressure, in agreement with clinical findings that hypertensive patients frequently have loud second heart sounds\cite{7,8,18}. This does not explain, however the clinical observation that patients suffering from myocardial infarction and/or heart failure, often exhibit reduced A2 amplitude, even when the aortic pressure is normal\cite{19}.

In their proposed mechanism for the origin of the second heart sound, Sabbah and Stein\cite{13} showed a relation between the amplitude of S2 and the driving pressure. Driving pressure, in the heart, refers to the instantaneous difference between arterial and ventricular pressure shortly after semilunar closure (likewise, PEA I is related to the first derivative of the pressure gradient that develops during isovolumetric contraction between atrium and ventricle, that can be approximated by the first derivative of the ventricular gradient).

Kusawa and associates\cite{9} previously found a good correlation of the amplitude of the second heart sound with the difference of pressure between the aorta and the left ventricle coincident with the dicrotic notch.

Assuming that the amplitude of S2 is related to the first derivative of the pressure gradient that develops between aorta and ventricle, other studies\cite{19} explained the cause of the low intensity aortic component of S2 in non-hypotensive patients with poor ventricular performance. They showed that the amplitude of S2 was linearly related to the rate of change of the pressure gradient that develops across the aortic valve during diastole (r=0.82). The latter is also correlated with negative dP/dt (r=0.62).

In normotensive patients with poor ventricular performance, the rate of isovolumic relaxation may be compromised and this would cause a reduction in negative dP/dt which in turn causes a reduction of the rate of change of the pressure gradient, that develops across the valve during diastole. A diminished S2, therefore, would result due to the more slowly developing driving pressure, which directly affects the characteristics of valvular vibration.

If we assume that aortic pressure is constant during the isovolumic relaxation phase, the first derivative of the pressure gradient that develops during isovolumetric relaxation between aorta and ventricle is inversely related to left ventricular pressure decay rate, while PEA II measurements are linearly related to driving pressure variations.

PEA I and PEA II changes during pharmacological interventions

Intravenous nitrates are largely used as unloading agents: their dilating effects are more pronounced on veins than on arterioles: nitrates do reduce the afterload, but especially the preload of the heart\cite{20}. With the used infusion dosages positive peak LVdP/dt and PEA I were insensitive to nitrate induced preload changes; otherwise ADP fall and decrease of negative peak LVdP/dt were closely and linearly sensed by the PEA II. Heart rate was constant in all animals (Fig. 2).

Pressure agents such as metaraminol increase afterload and ADP; theoretically, if the afterload is
increased, systolic wall stress rises, which leads to increased diastolic volume and a compensatory increase in the stroke volume, which is restored to its prior value[21]. Consequently, positive peak LVdP/dt increases without changes in heart rate, also for an induced vagal baroreflex. PEA I and PEA II increased during infusion of the drug, linearly with positive peak LVdP/dt and ADP (Fig. 3).

Dobutamine increases heart rate and ventricular contractility. Its major characteristic is that it exerts a potent inotropic effect. The inotropic response is co-mediated by beta-1 and alpha-adrenoreceptors, the latter causing an inotropic component that is independent of any chronotropic effect[22]. Furthermore, dobutamine accelerates diastolic filling because it enhances the uptake of calcium into the sarcoplasmic reticulum[23]. In our experimental setting dobutamine inotropic stimulation increased positive peak LVdP/dt and PEA I. Dobutamine also increased ADP and negative peak LVdP/dt with an increase in driving pressure and PEA II (Fig. 4).

PEA II was significantly \((r=0.92)\) related to peak negative LVdP/dt changes

The correlation between ADP and PEA II was low at the start of dobutamine infusion: in these first 30–40 s there was both a sudden afterload decrease and a sudden lusitropic response with a negative peak LVdP/dt increase greater than the ADP decrease; that explains PEA II and ADP trends, with an increase of PEA II and a decrease of ADP, in these first seconds of infusion the vasoconstrictive alphal-mediated effect of dobutamine was offset by the beta2-mediated vasodilatation.

PEA I and PEA II demonstrated to be linearly sensitive to changes in positive and negative peak LVdP/dt, both with constant (nitrates or metaraminol infusion) heart rate, or increased heart rate (dobutamine infusion).

The capability of the system to detect inotropic changes is consistent with that of Langenfeld[11] and Clementy[12] demonstrating that PEA I is highly sensitive to exercise induced inotropic changes in a large number of patients.

Conclusions

Simultaneous PEA I and PEA II monitoring is feasible with a single implantable lead and quantitatively documents the left ventricular inotropic and lusitropic response, in a totally automatic, operator-independent fashion.

The results obtained in this study confirm the increasing amount of data[5,11,12,24,25] suggesting that PEA I is a good signal for assessing intra-individual changes in myocardial contractility.

PEA II might represent ADP with an accuracy determined by the quality of the sensed signal, and is sensitive to changes in negative peak LVdP/dt.

PEA II, like PEA I, is sensitive to energy-dependent events: PEA II occurs in the first phase of diastole, the isovolumic relaxation phase, that is an active process, requiring ATP for the uptake of calcium ions by the sarcoplasmic reticulum.

Whereas a decreased inotropic state (decreased contractility) is a classic feature of myocardial failure, current emphasis has swung to the realization that changes in the lusitropic state (ability to relax) are at least equally important and often may occur before systolic abnormalities are evident[22].

The simultaneous recording of PEA I and PEA II with an implantable system offers a new chance to monitor indexes of LV systolic and diastolic function, especially in failing hearts and/or hearts exposed to drugs.

In this experimental protocol we used a micromass uniaxial acceleration sensor located in the stimulating tip of a unipolar pacing lead up to date implanted in a large number of patients[11,12] where PEA I is used as driving control for a rate responsive pacemaker (BEST Living System-Sorin).

The same sensor can be used to detect PEA II, when the dedicated algorithm to recognize the data will be adjunct to the system.

To establish fully the advantages and limits of this new method, comparisons with LV pressure-volume loops in humans and multicentre study data are needed.

References


