Relation of P-S₄ interval to left ventricular end-diastolic pressure

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SUMMARY Reports have suggested that the interval between P wave onset and the fourth heart sound (P-S₄ interval) reflects changes in left ventricular myocardial stiffness. We made simultaneous measurements of the P-S₄ or atrial electrogram to S₄ (A-S₄) interval and left ventricular pressure in 19 patients with coronary artery disease who were studied before and after atrial pacing. Thirteen patients developed angina accompanied by significant rises in their end-diastolic pressure and a consistent decrease in P-S₄ or A-S₄ interval; whereas the six patients who had atrial pacing without the development of angina had no changes in end-diastolic pressure, P-S₄, or A-S₄ interval. The resting data showed an inverse correlation between left ventricular end-diastolic pressure and the P-S₄ interval. In addition, the P-S₄ interval let us discriminate between patients with normal and abnormal end-diastolic pressure (>15 mmHg).

Although the fourth heart sound (atrial sound) was first described almost 100 years ago by Potain,¹ its clinical significance remains controversial. Traditionally, the atrial sound has been felt by some to be a reliable physical sign of ventricular dysfunction.²⁻⁵ Others, however, felt that the mere presence of an atrial sound was of little diagnostic value, since it was frequently recorded by phonocardiograms in normal patients as well as in those with ventricular dysfunction.^{6,7} The temporal relation of the atrial sound to the electrocardiogram and first heart sound (S₁) has been found to vary with clinical changes in patients with ischaemic heart disease and hypertension.⁸⁻¹⁰

Altered left ventricular pressure volume relations have been implicated as the common denominator in the production of the pathological fourth heart sound.^{4,5} More specifically, it has been postulated that decreasing left ventricular distensibility (as reflected by increased left ventricular end-diastolic pressure) is associated with decreasing P wave to atrial sound interval (P-S₄) and that it is this mechanism which leads to changes in the P-S₄ interval.^{4,10-13} It has been shown by McLaurin *et al.*,¹⁴ Barry *et al.*,¹⁵ and Mann *et al.*¹⁶ that increased left ventricular end-diastolic pressure during pacing-induced angina is the

result of altered left ventricular diastolic stiffness and left ventricular systolic performance during ischaemia.

We performed simultaneous phonocardiography and left ventricular pressure measurements and then used atrial pacing in patients with coronary disease to study the relation of atrial activation, timing of S₄ generation, and left ventricular pressure at end-diastole.

Methods

Nineteen normovolaemic patients ranging in age from 29 to 68 years were studied. All 19 patients had coronary artery disease but none had a history of chronic hypertension or electrocardiographic criteria for ventricular hypertrophy. These patients were selected because (1) they were to undergo routine cardiac catheterisation for evaluation of their presumed cardiovascular disease state, and (2) they had a fourth heart sound that could be recorded by phonocardiography. A fourth heart sound was defined as a phonocardiographically-recordable low frequency vibration occurring more than 70 ms after the onset of the P wave on the electrocardiogram.

After informed consent was obtained, cardiac catheterisations were performed with patients in the fasting state. The patients were premedicated with diazepam 10 mg orally. A 7.2 French pigtail angi catheter (Cook) was inserted via the femoral

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artery and positioned in the left ventricle. Pressures were recorded through the fluid-filled angiocatheter connected with either a Statham P23Db transducer, or a Micron MP15 pressure transducer. The Statham pressures were electronically filtered at 12 Hz; the pressures recorded using the Micron system were hydraulically filtered with a tuned connecting system which gave a linear amplitude response to 15 Hz. For the purposes of this study, a normal left ventricular end-diastolic pressure was taken as <15 mmHg and a raised left ventricular end-diastolic pressure as >15 mmHg. A No. 6 bipolar pacing catheter was inserted via a sheath into the femoral vein to position the tip of the catheter against the right atrial wall in 12 patients using a method similar to that of Barry *et al.*¹⁵

To test whether the P wave onset (as seen on the surface electrocardiogram) was an accurate indicator of atrial depolarisation for the purposes of this study, the remaining seven patients underwent an identical procedure with a quadripolar pacing catheter instead of the bipolar device. When positioned on the right atrial wall, two electrodes served as pacing leads and two as sensing leads.

Phonocardiograms were obtained from all patients in the supine position with a Maico contact microphone secured at the cardiac apex with a strap. Phonocardiograms were performed with an Irex Continutrace 101 recorder and filtered through an Irex 150–102 heart sound module. The phonocardiograms were recorded using low frequency filters (50–250 Hz) with a gentle roll-off (6 decibels per octave).

The limb lead on the electrocardiogram with the longest PR interval was sought and was most commonly lead II. The electrocardiogram was scrutinised to assess the P wave onset and the lead in which this was best seen was monitored. The P wave onset was defined as a consistent deviation from the baseline noted on 50 mm/s recordings from this lead. By observing the slower speed tracing, the P wave onset could be defined consistently on 100 and 200 mm/s recordings despite less clear-cut deviations from the baseline at these speeds.

The electrocardiogram, left ventricular pressure, and phonocardiogram were recorded simultaneously in the resting state at 50, 100, and 200 mm/s paper speed (Fig. 1). The right atrium was paced with step-

Fig. 1 Resting phonocardiogram (Phono) in case 6 with electrocardiogram (ECG) and left ventricular pressure (LVP) showing a P-S₄ interval (P-S₄) of 110 ms, a PR interval (PR) of 164 ms, and a left ventricular end-diastolic pressure of 20 mmHg. P, P wave; S₄, fourth heart sound; S₁, first heart sound.

wise increases in heart rate in order to induce angina pectoris. When either definite angina was induced, or the heart rate reached 150 beats/min for three minutes, the pacing was abruptly terminated, with return of the heart rate to control level. Beginning 15 to 30 seconds after cessation of pacing, at a time when angina (if induced) was still present, the electrocardiogram, electrogram (in seven patients), ventricular diastolic pressure, and phonocardiogram were simultaneously recorded again at 50, 100, and 200 mm/s paper speed (Fig. 2).

The resting and post-pacing data were analysed for (1) the interval between the onset of the P wave on the electrocardiogram or atrial depolarisation on the electrogram and the positive deflection of the main low frequency component of the fourth heart sound on the phonocardiogram; (2) the post-"a" wave left ventricular end-diastolic pressure; (3) heart rate, and (4) PR interval. The post-"a" wave left ventricular end-diastolic pressure was taken at that point (approximately 50 mm/s after the QRS onset) where the oscilloscope beam trace thinned and changed its slope

toward the major systolic ventricular pressure rise. Often this was quite clear because of a plateau before the major pressure rise.

For all interval and pressure determinations the average of at least four consecutive cardiac cycles was used. The first five to six beats after termination of atrial pacing were not used for analysis, as the left ventricular end-diastolic pressure does not stabilise until after this initial post-pacing period.¹⁷ Statistical methods used χ^2 , linear regression, and multiple regression analysis where appropriate.

Results

Table 1 summarises the resting and post-pacing data obtained for the left ventricular end-diastolic pressure, P-S₄ interval, PR interval, heart rate, and development of angina pectoris in the 12 patients with only the surface electrocardiogram recorded. Table 2 displays similar data for the seven patients with atrial depolarisation to S₄ (A-S₄) interval determinations. PR, AV (interval between atrial and ventricular

Fig. 2 Phonocardiogram in the same patient and format as Fig. 1 showing a reduced (as compared to the resting value) immediate post-pacing P-S₄ interval (P-S₄) of 90 ms. The post-pacing PR interval (PR) of 162 ms is virtually unchanged from the resting P-R interval. Note the increase in ST segment depression which occurred during pacing-induced angina. Other abbreviations as in Fig. 1.

Table 1 Patient data

Case No.	Pacing		Angina		LVEDP		P-S ₄ interval (ms)		PR interval (ms)		Heart rate (beats/min)	
	Before pacing	After pacing	Before pacing	After pacing	Before pacing	After pacing	Before pacing	After pacing	Before pacing	After pacing	Before pacing	After pacing
1	Yes	Yes	8	11	141	133	128	133	93	93		
2	Yes	Yes	8	14	154	149	138	141	64	65		
3	Yes	Yes	18	37	128	95	156	159	75	76		
4	Yes	Yes	8	31	164	119	200	199	74	75		
5	Yes	Yes	31	42	134	127	148	150	75	76		
6	Yes	Yes	20	29	110	90	164	162	61	61		
7	Yes	Yes	30	35	95	80	146	150	82	80		
8	Yes	Yes	10	15	152	136	164	162	84	86		
9	Yes	Yes	12	17	140	95	130	134	96	98		
10	Yes	No	12	13	165	167	213	216	72	74		
11	Yes	No	11	11	136	138	145	146	73	70		
12	Yes	No	17	18	109	110	138	138	73	75		
Mean	16.1†	25.8†			135.3‡	113.8‡	155.8‡	157.5‡	76.8‡	77.4‡		
Standard deviation	9.3†	11.5†			21.9‡	24.3‡	25.3‡	24.6‡	10.0‡	10.2‡		
P value*		<0.005			<0.005		NS			NS		

LVEDP, left ventricular end-diastolic pressure.

*P value obtained by Student's paired t test.

†Statistics derived from those patients who developed angina with pacing.

‡Statistics derived from all patients.

Table 2 Patient data, A-S₄ interval

Case No.	Angina with pacing	LVEDP (mmHg)		A-S ₄ interval (ms)	
		Before pacing	After pacing	Before pacing	After pacing
1	Yes	15	21	132	107
2	Yes	6	14	151	118
3	Yes	7	11	142	130
4	Yes	14	22	134	110
5	No	20	21	118	114
6	No	12	12	144	142
7	No	13	12	136	132
Mean		12.4	16.1	136.7	121.9
Standard deviation		4.4	4.6	9.75	12.03
P value*			<0.01		<0.02

A-S₄, interval between atrial depolarisation and fourth heart sound.

*Student's paired t test, patients developing angina.

depolarisation on atrial electrogram), and heart rate did not change significantly after pacing in either group.

Fig. 3 shows an inverse correlation of the P-S₄ interval and the left ventricular end-diastolic pressure with a correlation coefficient of -0.727 ($F = 14.5$, $p < 0.005$) by multiple regression analysis. In addition, multiple regression analysis showed no significant correlation between the P-S₄ interval and the PR interval ($F = 1.372$, $p < 0.5$), nor was there any significant relation between the PR interval and the left ventricular end-diastolic pressure ($F = 0.001$, $p < 0.975$). Fig. 4 shows the addition of the post-pacing P-S₄ interval and left ventricular end-diastolic pressure data and confirms the correlation ($r = -0.672$, $p < 0.001$) between the two variables. As shown in Table 1, nine of the 12 patients (without electrogram) developed angina pectoris during pacing. These nine patients had a significant decrease in

P-S₄ interval ($p < 0.005$) and a significant increase in their ventricular end-diastolic pressure ($p < 0.005$) compared with pre-pacing values. In contrast, the other three patients who were paced, but did not develop angina, had no significant change in their P-S₄ interval in relation to left ventricular end-diastolic pressure. The change in the P-S₄ interval in relation to the left ventricular end-diastolic pressure was $\Delta P-S_4/\Delta$ left ventricular end-diastolic pressure = 2.8 ms/mmHg. As also seen in Table 1, there was no significant change in resting as compared with post-pacing heart rates or PR intervals. In addition, there was no significant change in the post-pacing left ventricular systolic pressure.

The results for the seven patients with atrial electrograms were similar to those with surface electrocardiogram only. Fig. 5 illustrates the values for such a patient before (resting) and after pacing. The A-S₄ interval correlated closely with left ventricular

end-diastolic pressure for both the resting and post-pacing conditions (Fig. 6). Four of the seven patients developed angina during pacing; these subjects displayed significant ($p < 0.02$) increases in left ventricular end-diastolic pressure and corresponding decreases in A-S₄ interval. As in the surface electrocardiogram subjects, PR interval, AV interval (atrial to ventricular depolarisation interval), and intrinsic heart rate did not change after pacing. P wave to atrial electrogram interval did not change after pacing.

Discussion

The atrial sound has been the subject of considerable controversy in regard to its pathophysiology and clinical significance.^{3 6 7 11} In an excellent review, Craige¹¹ has put this controversy into perspective and concluded: (1) the basic mechanism involved in the production of the atrial gallop is exaggerated left ventricular stiffness during the time of atrial systole, and (2) the atrial gallop is a valuable sign of altered left ventricular function. The present study examines the temporal relation of the P-S₄ interval to two basic variables: (1) the PR interval of the electrocardiogram, and (2) left ventricular end-diastolic pressure

Fig. 3 Correlation of resting P-S₄ interval (P-S₄) and left ventricular end-diastolic pressure (LVEDP) for the 12 patients not having atrial electrograms are shown. The vertical dashed line indicates the border of abnormal left ventricular end-diastolic pressure (>15 mmHg) and normal pressures (≤ 15 mmHg). The horizontal dashed line divides the P-S₄ interval into two zones of interest.

Fig. 4 Plot showing resting and post-pacing P-S₄ interval (P-S₄) versus left ventricular end-diastolic pressure (LVEDP) with data on angina development in the 12 patients of Fig. 3.

possibly reflecting left ventricular diastolic stiffness. It is important to note that (1) in the post-pacing record there was no significant change in PR interval or heart rate as compared with the resting data, and (2) there was no significant correlation between the P-S₄ interval and the PR interval or heart rate in our study group.

Although left ventricular end-diastolic pressure is an imperfect index of left ventricular diastolic stiffness, Mirsky and co-workers¹⁸ found a good correlation between left ventricular diastolic stiffness and left ventricular end-diastolic pressure in patients with coronary artery disease. The intervention of rapid atrial pacing to produce angina pectoris in patients with coronary disease increases left ventricular end-diastolic pressure primarily as a result of increasing left ventricular diastolic stiffness.¹⁴⁻¹⁷ Thus, we may choose to view the range of left ventricular end-diastolic pressures in the resting condition and the increment during pacing-provoked angina as reflecting differing states of ventricular stiffness altered by ischaemia.

The present study showed an inverse relation between the P-S₄ or A-S₄ interval and left ventricular end-diastolic pressure in the resting state. The 13 patients with coronary artery disease who had atrial pacing-induced angina pectoris then showed an increase in left ventricular end-diastolic pressure and a consistent decrease in their P-S₄ or A-S₄ interval, with each patient serving as his own control. This suggests that the P-S₄ and A-S₄ interval are related to

Fig. 5 Resting and post-pacing phonocardiogram (Phono) [case 1 from Table 2]. Note the change in A-S₄ interval and corresponding LVEDP. Abbreviations as in Fig. 1 and 2; AEG, atrial electrogram.

ischaemia-induced changes in the left ventricle. These findings corroborate earlier work which noted shortening of the P-S₄ interval in patients who had deterioration in their clinical status.⁸⁻¹⁰ Also, these data are consistent with the observations of Craige¹¹ who has noted shortening of the P-S₄ interval when the ventricle demonstrates increased stiffness. One may postulate that the bolus of blood entering the ventricle, as a result of atrial contraction, eventually encounters forces resisting ventricular dilatation. If the ventricle is relatively stiff, then this resistance may occur abruptly and early after the P wave. Such checking of this bolus might produce the vibrations recorded as S₄. This circumstance of a stiff ventricle may be envisioned as producing raised end-diastolic pressure, as well as an "early" S₄, in response to the bolus of blood from the atrium.

The P-S₄ intervals in our study can be divided into three zones: (1) ≤ 130 ms, usually associated with abnormal left ventricular end-diastolic pressure; (2) >130 ms but <140 ms cannot clearly discriminate between normal and abnormal left ventricular end-diastolic pressure; and (3) ≥ 140 ms, usually associated with normal left ventricular stiffness as reflected by left ventricular end-diastolic pressure. The correlation between the P-S₄ interval and the left ventricular

Fig. 6 Plot showing resting and post-pacing values for the atrial electrogram of fourth sound interval (A-S₄) and left ventricular end-diastolic pressure (LVEDP) for the seven patients with atrial electrograms. Abbreviations as in Fig. 3, symbols as in Fig. 4.

end-diastolic pressure is not adequate to attempt to quantify left ventricular end-diastolic pressure accurately. Experience with more patients will be needed to assess the limits of these categories but there were recordable fourth heart sounds in seven patients with normal left ventricular pressures in this study, and yet the temporal relations of the P wave to the fourth heart sound distinguished these patients from those with apparently abnormal left ventricular function. It is possible that our conclusions may not be applicable either to patients with extremely early diastolic P waves, very short or prolonged PR intervals, or distorted P waves caused by interatrial conduction defects.

We believe that this study clarifies previous concepts and observations concerning the pathophysiological significance of the timing of the fourth heart sound. In addition, we have documented the effects of ischaemia-induced changes in left ventricular diastolic pressure upon the P-S₄ interval. These measurements may prove useful in clinical phonocardiography as a further means of non-invasive classification of left ventricular function.

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