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Determination of aortic valve opening time and left ventricular peak filling rate from the peripheral pulse amplitude in patients with ectopic beats

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Short title: Aortic valve opening time and left ventricular peak filling rate

Abstract

Ectopic beats are common in patients who have heart disease and are associated with reduced peripheral pulse amplitude. This study determined the start of the peripheral pulse increase and from it the opening of the aortic valve. The left ventricular peak filling rate was also estimated from the peripheral pulse. Results were compared with published invasive and cardiac imaging data.

Twenty five subjects with ectopic beat electrocardiograms (ECGs) were studied. The ECGs and the peripheral pulses, detected optically at the right index finger by a simple photoplethysmography (PPG) technique, were recorded for subsequent analysis. Peripheral pulse amplitudes for ectopic beats, post-ectopic sinus beats and normal sinus beats were determined.

Ectopic beats induced a mean 68% decrease in pulse amplitude in comparison with sinus beats ($P<0.001$). In contrast, the mean pulse amplitude for post-ectopic sinus beats increased by 20% ($P<0.01$). Pulse amplitude changes were comparable with the published stroke volume differences for ectopic beats and post-ectopic sinus beats. The range of shortest coupling interval (CI) for ectopic beats with observable pulses was from 373 to 531 ms, with the mean value equivalent to 55% of the mean sinus RR interval, comparable with the opening of the aortic valve. Finally, as the CI increased, the pulse amplitude increased quickly from zero. The average rate of increase was equivalent to 4.8 times the normal sinus amplitude in one second, equal to 50% filling in 208 ms, showing diastolic rapid filling, comparable with published left ventricular peak filling rate data.

In conclusion, the effect of ectopic beat CI on peripheral pulse amplitude has been determined, providing useful information for developing a technique to determine the opening of the aortic valve and the peak filling rate non-invasively and peripherally in patients with frequent ectopic beats.

Keywords: Coupling interval; Ectopic beats; Left ventricular peak filling rate; Photoplethysmography (PPG); Pulse amplitude; Stroke volume.

1. Introduction

Ectopic beats arise ahead of the normal sinus beat and prematurely in the cardiac cycle. They are more common in the elderly and particularly in patients with heart disease. The prevalence of ectopic beats in the adult population increases with age. Rasmussen *et al* (1985) reported that, in three age groups (20-39, 40-59 and 60-79 years), ectopic beats detected from a 24-h ECG recording appeared in 31%, 68% and 84% of subjects respectively. Generally they go unnoticed until they become more frequent, and can cause an uncomfortable feeling or symptoms such as dizziness (Patterson and Treasure 2001).

Dizziness is associated with reduced blood flow and reduced tissue oxygenation. With early ectopic beats, the left ventricle during the rapid filling period receives less blood than for normal sinus beats, and hence the end-diastolic volume is low. Starling's Law of the heart shows that decreased ventricular diastolic filling (preload) then results in reduced cardiac stroke volume in comparison with normal sinus beats (Klabunde 2004).

Ventricular function has been studied invasively in patients during cardiac catheterization and angiography, or by Doppler echocardiography, or MRI techniques. Normalised left ventricular peak filling rate in normal subjects achieves 4.2 times end-diastolic volume per second (EDV/s) (Hui and Gibson 1983). Patients with cardiac disease respond differently. It was reported that, in patients with coronary artery disease, the peak filling rate is decreased to 2.0 EDV/s (Rokey *et al* 1985) and 2.4 EDV/s (Betocchi *et al* 1993), measured from Doppler echocardiography and

angiography respectively. Similarly, in patients with myocardial infarction and pulmonary arterial hypertension, the equivalent figures were reported to be 2.2 EDV/s (Gadsbøll et *al* 1991) and 2.7 EDV/s (Gan *et al* 2006) by angiography and MRI respectively. It has also been shown that premature ventricular contractions reduce stroke volume by an average of 71% compared with normal sinus beats, whereas the postextrasystolic beats increase stroke volume by only 18% over the sinus beats (Cohn and Kyrda 1981). However, the imaging or catheterization techniques involved in those studies are complex or invasive.

The time between the sinus beat and the ectopic beat (coupling interval, CI) affects diastolic filling and hence systolic aortic pressure and peripheral arterial pressure. Davies *et al* (2001) and Roach *et al* (2002) have assessed blood pressure turbulence following ectopic beats using the beat-to-beat blood pressure recorded by a Finapres device, and reported a qualitative initial decrease in blood pressure, following by an increase and a return to the resting state, but did not make an investigation on the association with CI. Watanabe *et al* (2002) reported that pulse pressure was steeply and positively related to the ectopic beat CI, with the pulse pressure changing from 100 to 20 mmHg for CI changes from 900 to 400 ms. Unfortunately, there is little further quantitative data about the effect of ectopic beats.

A simple non-invasive technique for investigating cardiac function during frequent ectopic beats would be of value, especially in patients experiencing dizziness without asystolic pauses. Electrical thoracic impedance cardiography techniques have been used to estimate stroke volume (Raaijmakers *et al* 1999, Vonk-Noordegraaf *et al*

2000), but have not presented the relationship between stroke volume and peripheral pulse amplitude. Photoplethysmography (PPG) is an optical technique which can record the peripheral pulse, and its pulse amplitude includes information attributed to cardiac synchronous changes in the blood volume with each heart beat (Allen 2007). However, we are unaware of any investigation of ectopic CI on pulse amplitude.

This study therefore investigated how ectopic beats influenced the peripheral pulse by studying pulse amplitude for ectopic beats and post-ectopic sinus beats in comparison with normal sinus beats. The shortest CI for ectopic beats with observable pulses was studied to determine the opening of the aortic valve. Pulse amplitude as a function of ectopic beat CI was then investigated to estimate left ventricular peak filling rate. These determinations were then compared with published data.

2. Methods

2.1 Subjects

25 subjects were recruited from the Freeman Hospital, Newcastle upon Tyne. All subjects gave their written informed consent. Their age range was 35 to 92 years, with 18 male and 7 female. Other subject information details were given in an earlier publication (Zheng *et al* 2007). The investigation conformed to the principles in the Declaration of Helsinki. The research study was approved by the Local Research Ethics Committee.

2.2 Measurement system and protocol

A PPG system was used to record right index finger PPG at a sample rate of 2500 Hz for at least 150 s. A single channel ECG was recorded simultaneously to

provide a timing reference for the finger PPG pulses. More details of the measurement system and measurement protocol have been described (Allen and Murray 2000, Zheng *et al* 2007).

2.3 Ectopic ECG sequences with or without a peripheral pulse

ECG sequences with two sinus beats on either side of a single ectopic beat were extracted from the recordings for off-line analysis, as shown in figure 1. These are referred to simply as the five-beat sequences, with the third beat an ectopic beat, the fourth beat a post-ectopic sinus beat and the other three beats normal sinus beats. Due to the expected lower stroke volume, the ectopic beats were followed by a smaller (figure 1(A)) or unobservable (figure 1(B)) finger PPG pulse in comparison with sinus beats.

2.4 Ectopic beat coupling interval

For all sequences, the ectopic beat CI was calculated from the Q wave of the sinus beat preceding the ectopic beat to the Q wave of the ectopic beat, using interactive software developed with Matlab 7.1 (MathWorks Inc), as shown in figure 1(A). The corresponding RR interval was also calculated between the Q wave of the first and second sinus beat.

For each subject, the shortest ectopic beat CI associated with an observable finger PPG pulse was determined to estimate the opening of the aortic valve. For subjects with pulseless ectopic beats (figure 1(B)), the longest ectopic beat CI for ectopic beats without pulse was also determined.

2.5 Pulse amplitude: ectopic beat versus sinus beat

PPG pulse amplitudes for each beat in the five-beat sequences were calculated from the PPG pulse peak less the preceding pulse foot (figure 1(A)). This amplitude was divided by the PPG amplifier gain setting used. Then the pulse amplitudes were referenced to the first sinus beat to obtain the percentage change, described below as normalised pulse amplitude.

The normalised pulse amplitudes for ectopic beats and post-ectopic sinus beats were first plotted against their corresponding ectopic beat CI for all beat data. Summary data for each subject was then calculated, and as each subject had different numbers of ectopic beat sequences, each subject's average pulse and normalised pulse amplitudes for each beat of the five-beat sequences were determined. The pulse amplitude for ectopic and sinus beats (paired to the first sinus beat) were analysed for all subjects using paired t-test. A $P<0.05$ was considered to be statistically significant.

2.6 Pulse amplitude: function of coupling interval

To allow the effect of ectopic beat CI on pulse amplitude to be determined, only pulses with normalised amplitudes less than 0.85 were used for linear regression analysis, because Klabunde (2004) has shown that, at the end of rapid filling period, the ventricle is about 85% full. The regression line was drawn through the longest CI for pulseless ectopic beats (substituted by the shortest CI for ectopic beats with observable pulses for those subjects without pulseless ectopic beats). For statistical analysis, only those subjects with at least eight ectopic beats followed by observable pulses were retained. This left 15 subjects out of the original 25. The slope of

normalised pulse amplitude versus CI, relating to the left ventricular peak filling rate, was calculated for each individual subject, and also the mean slope from all analysable subjects, with the unit of normalised pulse amplitude change in one second. The significance of the linear relation and the square of the correlation coefficient were also presented.

3. Results

3.1 Ectopic ECG sequences with or without a peripheral pulse

In the 25 subjects the effect of 443 ectopic beats was studied. Table 1 gives the CI for the opening of the aortic valve. The range of shortest CI for ectopic beats with observable pulses was from 373 to 531 ms, with the mean ± SD of 451 ± 39 ms, equivalent to 55 ± 8% of the mean sinus RR interval.

There were 12 subjects having pulseless ectopic beats. In these subjects, 143 out of 277 (52%) ectopic beats without pulses were observed. The mean ± SD of longest CI for pulseless ectopic beats was 428 ± 31 ms, with the mean of only 11 ms less than the shortest CI for ectopic beats with observable pulses.

3.2 Pulse amplitude: ectopic beat versus sinus beat

With all the data for the normalised pulse amplitudes for ectopic beats and post-ectopic sinus beats plotted together against their corresponding ectopic beat CIs, as shown in figure 2, the differences of pulse amplitude in ectopic beats and post-ectopic sinus beats in comparison with normal sinus beats were clearly shown. Figure 3 shows for all subjects the overall mean and SD of finger PPG pulse amplitude and normalised pulse amplitude for each beat of the five-beat sequence.

The pulse amplitudes for the ectopic beats were significantly less than for the sinus beats ($P<0.001$), with a mean 68% decrease. In addition, the post-ectopic sinus beats had a significantly increased pulse amplitude in comparison with the preceding sinus beats of 20% ($P<0.01$).

3.3 Pulse amplitude: function of coupling interval

Figure 4 shows individually for 15 analysable subjects the normalised ectopic beat pulse amplitude as a function of ectopic beat CI for all ectopic beats with pulses. Their relationships were significant, with all $P<0.001$ (except one subject $P=0.011$) and with R square of correlation coefficient larger than 0.65. As the CI increased, the pulse amplitude increased quickly from zero. After excluding one subject with only atrial ectopic beats and another subject with a very high heart rate, both with very fast diastolic filling, the average rate of increase was equivalent to 4.8 times the normal sinus amplitude per second, equal to 50% filling in 208 ms, showing diastolic rapid filling. However, the relationship differed between subjects, ranging from 2.3 to 9.6 times the normal sinus amplitude per second. These results are compared in the discussion section with published data for left ventricular peak filling rate.

4. Discussion and conclusion

Our results are consistent with preload as one of the main determinants of stroke volume. When ectopic beats occur during the rapid ventricular filling period, there will be reduced stroke volume from a lower preload (Ghuran *et al* 2002, Welch *et al* 1989). This results in a lower blood volume pulse in the peripheral arteries which has been detected by the blood volume pulse. Overall, the ectopic beats resulted in a mean

68% decrease in pulse amplitude, followed by a mean 20% increase for the sinus beat after the ectopic beat. The average amplitude changes were comparable with the published stroke volume changes evoked by premature ventricular contractions (Cohn and Kyrda 1981), with an average of 71% decrease and 18% increase for ectopic beats and post-ectopic sinus beats respectively.

In addition, it has also been shown that ectopic beats with CIs below the threshold, where the ventricular rapid filling initiates, resulted in no peripheral pulse. The mean shortest ectopic beat CI for ectopic beats with observable pulses was 55% of the sinus RR interval. It is known that the duration of electromechanical systole is measured from the onset of the ECG-Q wave to the first high frequency vibrations of the aortic component of the second heart sound, whose value is slightly less than the time delay between the onset of the ECG-Q wave and the opening of aortic valve for rapid filling period. Our results are consistent with the published duration of electromechanical systole of 52% of the mean RR interval (Weissler *et al* 1968).

The effect of different ectopic beat CIs on peripheral pulse amplitude has been investigated in this present study, and to our knowledge this is the first study to investigate the effect of ectopic beat CI non-invasively on the peripheral pulse. However, since these data were collected retrospectively, the actual stroke volume for the ectopic beats was not known, which is a limitation of this study. However, we have shown that different ectopic beat CIs result in different peripheral pulse amplitudes, with an average pulse amplitude increased by 4.8 times the normal sinus amplitude per second. This changing rate is comparable with the published

normalised left ventricular peak filling rate around 4.2 EDV/s (Bacharach *et al* 1979, Gadsbøll *et al* 1991, Hui and Gibson 1983). Therefore, investigating peripheral pulse amplitude change with CI also provides a simple potential procedure for assessing left ventricular peak filling rate non-invasively, and indicates when ectopic beats are likely to be associated with reduced cardiac output.

In conclusion, the effect of ectopic beat CI on the resulting peripheral pulse amplitude has been determined, which could provide useful information to determine the opening of the aortic valve and the left ventricular peak filling rate non-invasively and peripherally, especially in patients with frequent ectopic beats.

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Table and figures legends:

Table 1: Opening of the aortic valve determined from the shortest CI for ectopic beats with observable pulses from all 25 subjects.

Figure 1: (A) Ectopic beat coupling interval and ectopic beat pulse amplitude for a typical example of a five-beat sequence containing an ectopic beat. (B) One example of a five-beat sequence with an ectopic beat that is not followed by any observable pulse on the finger PPG.

Figure 2: The normalised pulse amplitude for ectopic beats (A) and post-ectopic sinus beats (B) against their corresponding ectopic beat CI from all beat data.

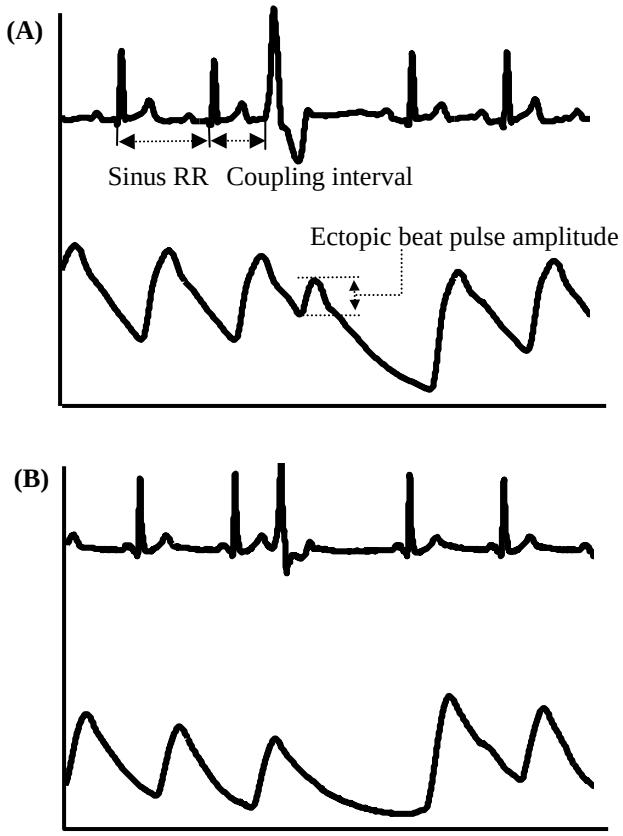
Figure 3: Mean and SD values (arbitrary units) of finger PPG pulse amplitude (A) and its relative value to the first sinus beat within five-beat sequences (B) for all subjects, shown for each beat of the five-beat sequences (beat 1, 2 and 5 sinus; beat 3 ectopic; beat 4 post-ectopic sinus). SD values are for population relating to between-subject variability.

Figure 4: The normalised ectopic beat pulse amplitude as a function of ectopic beat CI from 15 subjects. Some subjects had pulseless ectopic beats. The slope for each is also given, where the amplitude change in one second is referenced to the normal sinus pulse amplitude, with the unit expressed as '/s'. (▼ pulseless ectopic beats; ● ectopic beats; ○ sinus beats).

* with only atrial ectopic beats; ** with high heart rate.

Subject	Opening of the aortic valve (ms)	Mean RR (ms)	Opening of the aortic valve /Mean RR (%)
1	442	834	53
2	416	738	56
3	426	586	73
4	449	952	47
5	442	917	48
6	486	1090	45
7	418	872	48
8	427	874	49
9	428	628	68
10	432	882	49
11	531	874	61
12	373	693	54
13	440	1087	40
14	486	1136	43
15	478	937	51
16	518	818	63
17	472	912	52
18	436	750	58
19	434	713	61
20	511	951	54
21	426	737	58
22	440	840	52
23	484	774	63
24	393	757	52
25	495	761	65
Mean ±SD	451 ±39	845 ±137	55 ±8

Table 1: Opening of the aortic valve determined from the shortest CI for ectopic beats with observable pulses from all 25 subjects.



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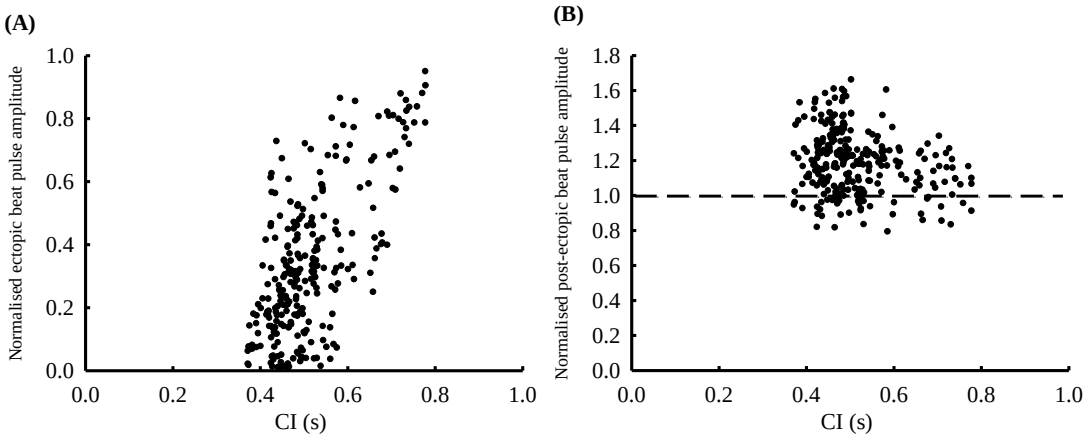

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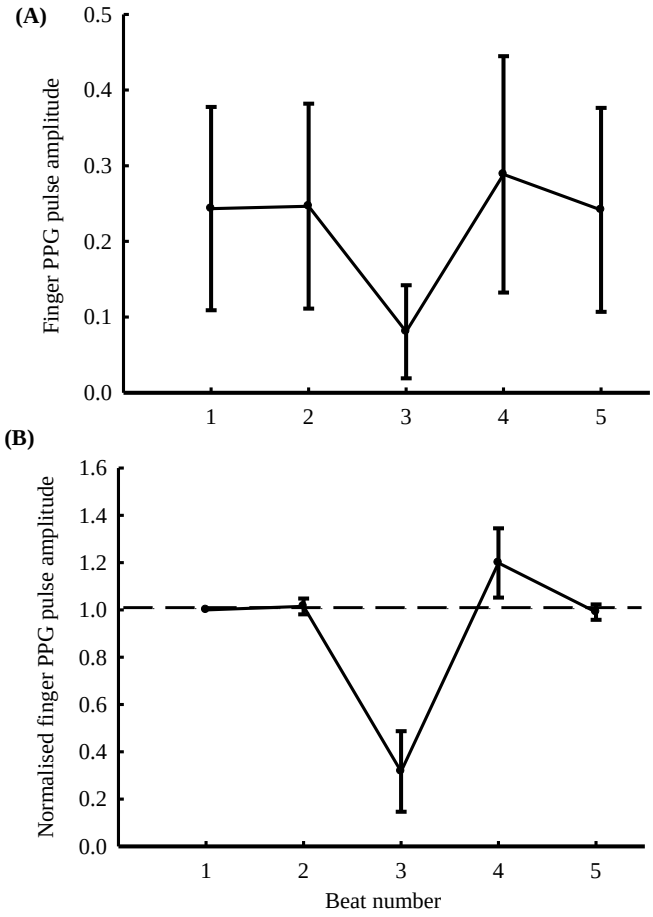

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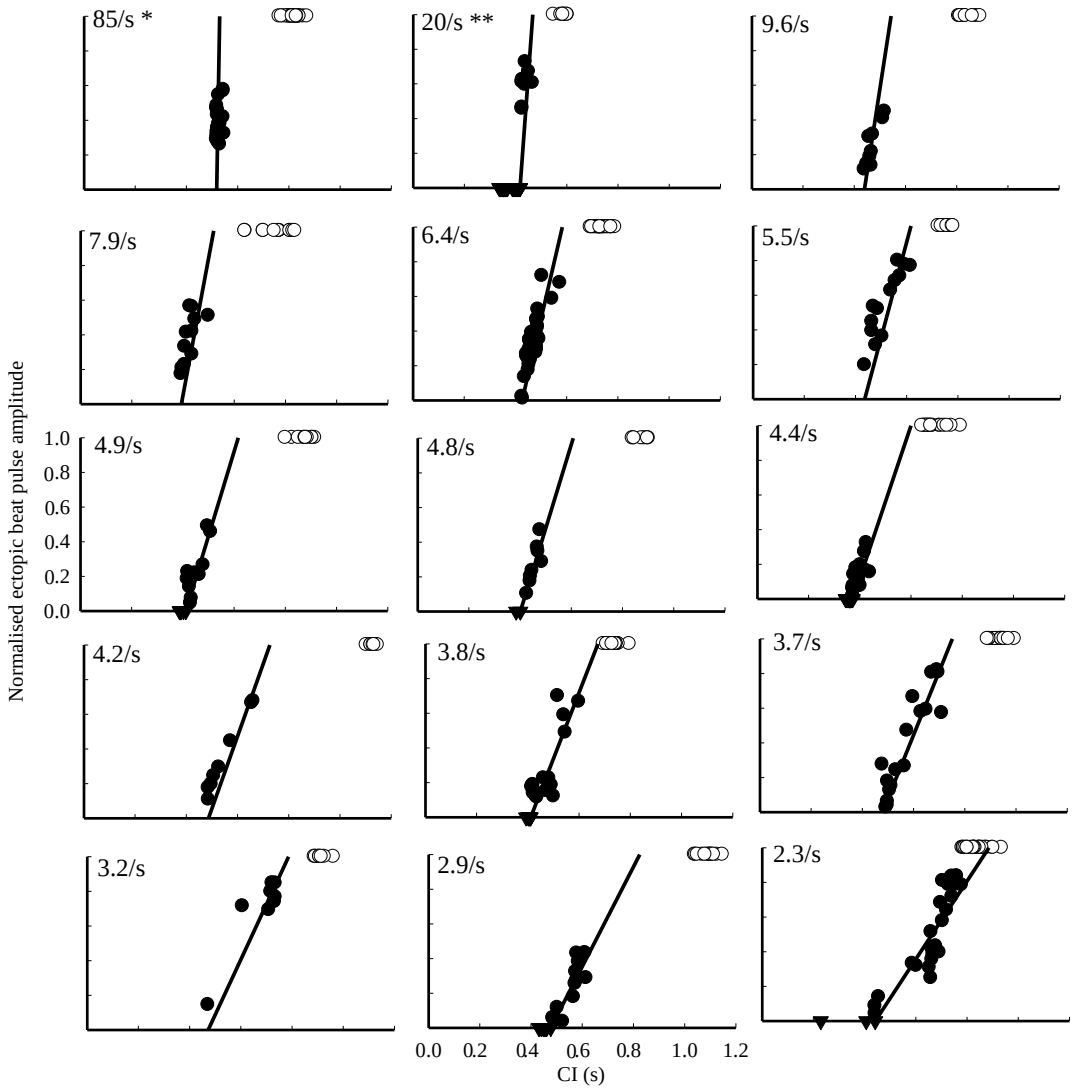

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* with only atrial ectopic beats; ** with high heart rate.