Pulse Arrival Time Accurately Detects Pacing-Induced Mechanical Alternans

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Abstract

Accurate cardiac risk stratification is crucial for preventing cardiac death, but still remains an unmet need. Mechanical alternans (MA), an oscillation of blood pressure that occurs on a beat-to-beat basis, has been recognized as a marker of cardiac instability and is associated with an increased risk of cardiac death. However, the use of MA for risk stratification is currently limited by the invasiveness and costs of continuous blood pressure monitoring. A non-invasive, cuffless and affordable method to detect MA is therefore highly desirable. The pulse transit time (PTT) and the pulse arrival time (PAT) are promising techniques for continuous blood pressure monitoring, particularly for detecting short-term blood pressure changes. In this work, we hypothesized that PAT, measured as the interval between the R-wave in the ECG and a distal arterial pulse, can be used to accurately track fast beat-to-beat blood pressure dynamics and detect MA.

A total of 42 ECG and femoral arterial pressure recordings from 12 patients with normal ventricles were analyzed. Patients were instructed to breath at a fixed respiratory rate and MA was induced by ventricular pacing. Both MA and PAT alternans were detected using spectral analysis. MA was present in 69% of blood pressure recordings (n=29). ROC analysis showed that PAT accurately detected MA, with an area under the curve was equal to $\mathrm{AUC} = 0.94$. *The optimal threshold for detecting MA by using PAT provided 90% sensitivity and 85% specificity. In conclusion, this study demonstrates that PAT can be used to accurately detect pacing-induced MA and may represent a first step toward non-invasive, cuff-less and affordable MA screening for cardiac risk assessment.*

1. Introduction

Cardiac alternans refers to either mechanical or electrical oscillations that occur on a beat-to-beat basis [1]. Electrical alternans generates at the cardiac myocyte level where it manifests as an oscillation of the action potential duration [2] and can be detected on the surface ECG as a beat-to-beat change in the T-wave morphology [3]. T-wave alternans is a well-established non-invasive marker of cardiac instability and a predictor of sudden cardiac death [3, 4]. Mechanical alternans (MA), first observed in the XIX century [1], usually refers to a repetitive sequence of strong and weak pulses and has been recognized as a marker of cardiac instability. Recent studies have shown that MA is associated with cardiac death in heart failure [5] and dilated cardiomyopathy [6] patients.

Accurate risk stratification in cardiac disease remains an unmet need, with both serious social and economic implications. At present, despite encouraging results [5, 6], the assessment and utilization of MA as a marker for cardiac risk stratification is limited by the invasiveness of continuous blood pressure monitoring and by the cost associated with invasive recordings. Therefore, a non-invasive and affordable method for detecting MA is needed to conduct studies to assess the prediction values of MA at a population level, with possibly great potential in terms of cardiac death prevention.

The Pulse transit time (PTT) and pulse arrival time (PAT) are promising non-invasive techniques for continuous blood pressure monitoring, particularly for detecting short-term perssure changes [7,8]. The PTT, defined as the the time delay for the pressure wave to travel between two arterial sites, and the PAT, defined as the interval between the R-wave in the ECG and a distal arterial pulse, are both negatively associated with blood pressure [9]. In recent years, photoplethysmography has provided the opportunity of measuring PAT from the body surface, therefore offering the possibility of non-invasive, cuff-less and affordable blood pressure monitoring. Although the accuracy of (absolute) blood pressure estimates based on PTT and PAT is controversial [10], we hypothesize that both methods can be used to track fast beat-to-beat blood pressure dynamics and detect MA. To the best of our knowledge the association between PAT and MA has never been studied. Therefore, this work aims to assess a novel and simple

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methodology to detect MA based on PAT in a database of patients with normal ventricles undergoing electrophysiological studies including surface ECG and invasive blood pressure monitoring. We consider this study a first step toward non-invasive, cuff-less and affordable MA screening.

2. Methods

Data collection

Studies were performed in 12 patients (10 males, 2 females, aged 4868, median 54) during in the unsedated state before the routine clinical procedure for radiofrequency ablation for atrial fibrillation at St Thomas' Hospital, London, as described previously [11, 12]. None of the subjects was known to have ventricular scar or disordered conduction due to bundle branch abnormality. Cardioactive medications were discontinued for 5 days before the study. Invasive arterial blood pressure was measured using a continuous-flush pressure transducer system (Tru-Wave PX600F; Ed- wards Lifesciences, Irvine, CA). Both limb leads ECGs and arterial blood pressure were recorded at a sampling frequency of 1200 Hz. During the study, heart rate was clamped by ventricular pacing at a fixed cycle length (median, 500 ms) from the right ventricular apex using a Biotronik (Berlin, Germany) stimulator (model UHS 3000). Patients were breathing at four fixed rates (6, 9, 15, and 30 breaths/min) for 90 s each, in random order.

Parameter extraction

ECG and blood pressure signals were band-pass filtered between 0.5 and 35 Hz, and ECG R-waves were identified and systolic blood pressure, $SBP(n)$, measured for each heartbeat n. The pulse arrival time, $PAT(n)$, was measured as the time between the R-wave peak and the maximum first derivative of the upstroke in the pulse of the same heartbeat (see Fig. 1).

Detection of mechanical and PAT alternans

The presence of alternans was investigated using spectral analysis, as described previously [13, 14]. The first step of this method is to apply a detrending filter to enhance changes in the SBP and PAT signal on a beat-to-beat basis:

$$y(n) = SBP(n+1) - SBP(n) \tag{1}$$

Next, spectral analysis was applied to quantify the magnitude of the oscillation that appears every other beat, i.e. at a frequency equal to 0.5 cycles per beat [13]. The spectrum

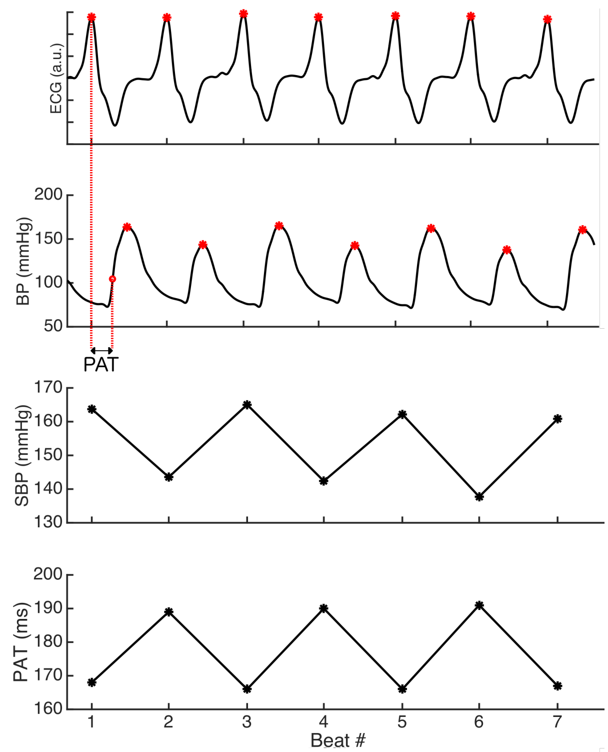

Figure 1. Representative example of pulse arrival time (PAT) alternans occurring as the same time as mechanical alternans. PAT was measured from the R-wave to the maximum upstroke of the corresponding pulse.

was estimated in a moving window of length L = 64 beats:

$$P_{\mathrm{SBP}}(n,f) = \left| \sum_{l=-L/2+1}^{l/2} y(n+l) e^{-2\pi i l} \right|^2 \tag{2}$$

A SBP recording was classified as exhibiting MA if $P_{\mathrm{SBP}}(n, f = 0.5) > 4$ mmHg^2, i.e. if the magnitude of MA was higher than 2 mmHg in at least one sliding window.

PAT alternans was computed as in (1)-(2), but using $PAT(n)$ time series instead of $SBP(n)$. The optimum threshold to detect MA based on PAT alternans was established by ROC analysis, scanning PAT alternans magnitude from 1 to 30 ms.

Statistical analysis

True positvie and false positive detections were defined as when PAT alternans was or was not detected in recordings exhibiting significant MA, respectively. False positive and negative detections were defined as when PAT alternans was or was not detected in recordings not exhibiting significant MA. The confusion matrix was constructed and

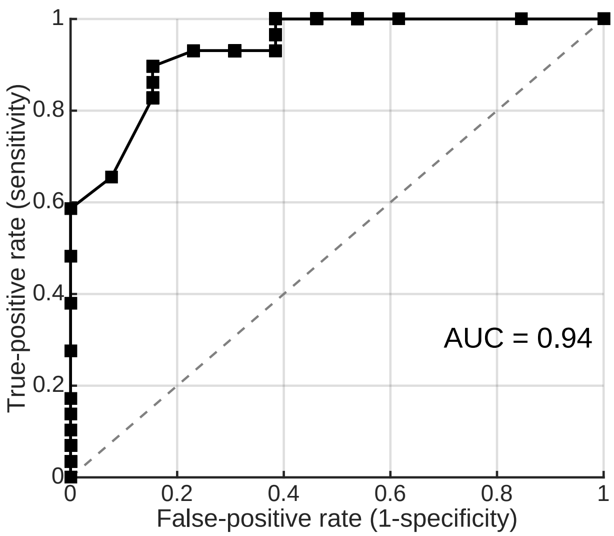

Figure 2. ROC curve showing the accuracy of PAT to predict mechanical alternans.

		PAT Alternans +	PAT Alternans -	
Mechanical Alternans	+	26	3	$Se = 90\%$
	-	2	11	$Sp = 85\%$
		$PPV = 93\%$	$NPV = 79\%$	

Table 1. Confusion matrix for MA detection using PAT for the optimal detection threshold. *PPV: Positive Predictive Value, NPV: Negative Predictive Value, Se: Sensitivity, Sp: Specificity.*

sensitivity, specificity, positive and negative predictive values as well as total accuracy were estimated.

3. Results

A total of 42 ECGs and blood pressure recordings from 12 patients were analyzed. Each recording was 90 s long and the respiratory frequency was fixed. The mean SBP was 137 $\pm$ 19 mmHg. MA was observed in 29 recordings (69%). The mean MA magnitude was 4.1 mmHg (range: 2.1-12.8 mmHg). Figure 2 shows the ROC curve for MA detection using PAT. The area under the curve was $\mathrm{AUC} = 0.94$ and the optimal threshold (PAT alternans magnitude) for detecting MA was equal to 3.1 ms, which provided a 90% sensitivity, 85% specificity and an accuracy of 88%. The positive and negative predictive values (PPV & NPV) were 93% and 79%, respectively. For this threshold, the mean PAT alternans magnitude was 5.3 ms (range: 3.1 - 13.6 ms). The corresponding confusion matrix for this threshold is shown in Table 1.

4. Discussion

To the extent of our knowledge, this study is the first to demonstrate that the PAT can accurately detect pacing induced MA. This is an important finding since MA has been linked with poor prognosis, ischemia, disordered left ventricular function and cardiac arrhythmias [15]. In a prospective study conducted by Hirashiki et al, pacing induced MA was identified as an important prognostic factor for poor outcome in patients with idiopathic dilated cardiomyopathy [6]. PAT and PTT have already shown to conceivably permit continuous, noninvasive, and cuffless BP monitoring in the acute setting. The results of this study strongly suggests that non-invasive measurements based on PAT and potentially PTT may be utilised to improve cardiac risk stratification by enabling non-invasive and cuff-less monitoring of MA.

Although the exact mechanism underlying MA is not fully understood, there is general consensus that MA is associated with beat-to-beat variation of the left ventricular stroke volume, either caused by changes in myocardial contraction or left end-diastolic volume [16, 17] probably due to calcium handling imbalance [1]. In this study, MA was detected by measuring the systolic arterial pressure for each beat. To investigate whether estimation of MA could be improved, we extended our analysis by extracting multiple data points from the arterial waveform instead of only a single systolic value. This provided similar results. The presented work is based on invasive arterial blood pressure measurements. Further work is needed to determine whether PAT measured through photoplethysmography can be used to accurately detect MA and whether the methodology proposed in this paper can be also utilised to detect MA in sinus rhythm.

5. Conclusion

This work demonstrates that simple spectral analysis of the PAT can provide accurate detection of pacing-induced MA. This findings has implications for screening of MA for cardiac risk assessment.

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