Investigation of Causal Interactions between Ventricular Action Potential Duration, Blood Pressure and Respiration

S van Duijvenboden[1], M Orini [2], N Child [3], JS Gill [3], P Taggart [2], B Hanson [1]

[1] Department of mechanical engineering, UCL, London, UK
[2] Institute of cardiovascular science, UCL, London, UK
[3] Department of Cardiology, Guy's & St Thomas' Hospitals NHS Foundation Trust, UK

Abstract

Temporal variability of the ventricular action potential duration (APD) is an important electrophysiological parameter associated with arrhythmogenesis. Respiratory-related APD oscillations have recently been observed in humans. This study aims to investigate the underlying driving mechanisms by characterizing the causal interactions between APD, systolic blood pressure (SBP) and respiration in humans in vivo. In 12 subjects with normal ventricles undergoing clinical electrophysiological procedures, recordings were made of the endocardial unipolar electrogram, femoral artery pressure and respiration. The activation recovery interval (ARI) was derived from the electrogram as a conventional surrogate for APD. During the experiment, breathing and heart rate were maintained constant. Data was analyzed by computing the directed coherence between ARI, systolic blood pressure (SBP) and respiration at the respiratory frequency using a linear multivariate autoregressive model that describes both lagged and instantaneous effects. The pathways from respiration to ARI and SBP showed a high directed coherence: 0.68($\pm$0.22) and 0.75($\pm$0.12), respectively. In contrast, the mean directed coherence from SBP to ARI was small: 0.08($\pm$0.08). This suggests that APD oscillations at the respiratory frequency are not simply driven by a mechanical component but they are the result of more complex interactions.

1. Introduction

Temporal variability of the cardiac ventricular action potential duration (APD) is an important electrophysiological phenomenon that has been associated with arrhythmogensis [1]. Elucidation of the mechanisms that underlie modulation of ventricular APD is therefore an important challenge. In recent work, it has been observed that the ventricular APD in humans exhibits cyclical variation related to respiration [2,3]. At present, the underlying mechanisms are not fully understood. In humans, Blood pressure and heart period fluctuate with respiration . This is usually attributed to waxing and waning of neural activity to the sinus node [4]. The ventricular myocardium receives substantial vagal as well as sympathetic innervation [5]. Therefore, autonomic mediated baroreflex changes and respiratory reflexes may potentially drive respiratory-related APD oscillations. In the present study, we investigated the mechanisms underlying respiratory-related ventricular APD oscillations by characterizing the causal interactions between respiration, systolic blood pressure (SBP) and APD in humans in vivo. To this extent, we collected a unique database including measurements of femoral arterial pressure, respiration (chest movement), and endocardial unipolar electrograms (UEGs). Activation recovery intervals (ARIs) were measured from the UEGs as a conventional surrogate for ventricular APD. Both heart rate and breathing were maintained constant- The causal interactions between respiration, SBP and APD were studied in the frequency domain using the directed coherence based on linear multivariate autoregressive analysis.

2. Measurements

Studies were performed in 12 subjects during clinical ablation procedures for supraventricular arrhythmias. All patients had normal ventricular function. The study was approved by the local ethics committee and all patients gave written informed consent. Synchronous measurements were made of endocardial unipolar electrogram (UEG), femoral arterial blood pressure and chest movement (respiration). UEGs were measured using two decapolar electrode catheters (St Jude Medical 2-5-2mm spacing, 35 mm total span) positioned in the left and right ventricle as shown in Fig. 1. Both electrodes were referenced to a large skin surface electrode (100 x 150 mm) on the abdomen at the level of the naval. Arterial blood pressure was measured from a femoral artery with a continuous-flush pressure transducer system (Tru-Wave PX600F, Edwards

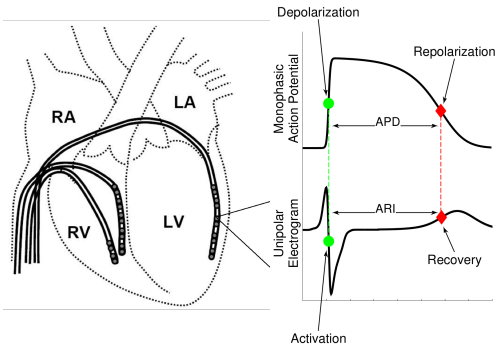

Figure 1. Left panel: Graphical illustration of the heart, showing the position of the endocardial leads and the pacing electrode (RV). Right panel: relationship between the action potential duration (APD) and the activation recovery interval (ARI).

Lifesciences, Irvine, CA, USA). The subjects breathing cycle was monitored using a custom-constructed tension sensor fixed to a freely-expandable band placed around the chest/abdomen . Subjects were instructed to breath at a fixed rate of 15 breaths/min (0.25Hz) aided by an animated visual display representing lung volume which cycled at the breathing rate. Confounding effects due to the cycle length dependency of APD were avoided by pacing from the right ventricular apex using a Biotronik (Berlin, Germany) stimulator (model UHS 3000) at a minimum cycle length necessary to maintain capture (median 500ms). A 2 min period for adaptation to the paced cycle length was applied before the experiment.

2.1. Data analysis

Electrograms, arterial pressure and respiration recordings were digitized at 1200Hz (Ensite 3000, Endocardial Solutions Inc.). Ventricular APDs were estimated from the UEGs by measuring activation-recovery intervals (ARIs) using the Wyatt method, which has been validated in theoretical, computational and experimental studies [6, 7] and used in many experimental set-ups [8]. Activation is measured at the moment of minimum dV/dt of the QRS complex and repolarization at the moment of maximum dV/dt of the T-wave. The relationship between APD and ARI is illustrated in Fig. 1. A total of 2x10 electrogram recordings were obtained from the left and right ventricle for every subject. The recordings were screened to identify and discount any cases where the T-wave was indistinct or corrupt. Any beat for which ARI measurements could not be determined were replaced by linear interpolation between the surrounding beats. Electrogram series were rejected if ARI measurements could not be determined for more than 10% of the total number of beats.

2.2. Assessment of causality

Causality was computed for ARI recordings sites that exhibited significant power at the breathing frequency. To this extent, we first determined the Thomson power spectrum of the respiration signal to identify the exact breathing frequency by finding the dominant frequency. Then, the significance of the power in the Thomson spectra of the ARI signal at this frequency was assessed using surrogate data analysis based on the 95th percentile of 10,000 surrogate series. Causality was measured by means of a linear extended multivariate (eMVAR) model that allows both lagged and instantaneous effects into the interactions [9, 10]:

$$Y(n) = \sum_{k=0}^{p} B(k)Y(n-k) + W(n), \qquad (1)$$

where $Y(n) = [y_1(n), \cdots, y_M(n)]^T$ is the vector of the recordings processes (ARI, SBP and respiration) sampled at every heart beat n, $B(k)$ are 3 x 3 coefficient matrices in which the elements $b_{ij}(k)$ describes the linear contribution of $y_j(n)$ on $y_i(n-k)$ $(i, j = 1, \cdots, M; k = 0, 1, \cdots, p)$. For example, $b_{13}(4)$ quantifies the contribution that systolic blood pressure (process 3) evaluated at beat $n-4$ has on ARI (process 1) at beat n. Finally, $W = [w_1, \cdots, w_M]^T$ is white and uncorrelated noise modeling electrical and muscular interferences. The extended model was preferred over a strictly causal model as instantaneous interactions (i.e. before arrival of the next heart beat) were expected to occur. The directed coherence is then defined as [9]:

$$\gamma_{ij}^{DC}(f) = \frac{\sigma_j H_{ij}(f)}{\sqrt{\sum_{n=1}^{M} \sigma_M^2 |H_{im}(f)|^2}} \qquad (2)$$

where $H(f) = B(f)^{-1}$, and $\gamma_{ij}^{DC}(f)$ can be interpreted as a measure of the influence of y_j onto y_i. The strength of the directed coherence is obtained by $|\gamma_{ij}^{DC}(f)|^2$, which is normalized ratio between part of the power spectrum of y_i ($S_{ii}(f)$) due to process j ($S_{i|j}(f)$). The coefficients of the MVAR model were estimated using the least-squares approach at a fixed model order of 10. The resulting residuals of the model were tested for white noise and independence.

3. Results

Fig. 2 shows an example of respiration, ARI and SBP in both time and frequency domain. Clear oscillatory behavior is observed in ARI and SBP at the respiratory frequency (0.25Hz). The causal interactions between the signals of this example are investigated in Fig. 3. In the upper panel, a graphical representation shows the possible interactive

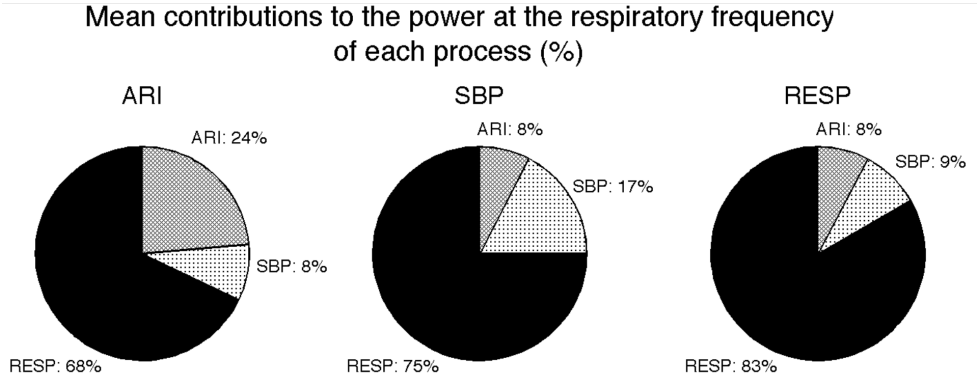

Figure 4. Mean decomposition of the power spectrum of activation recovery interval (ARI), systolic blood pressure (SBP) and respiration (RESP) at the respiratory frequency into contributions from each process (directed coherence).

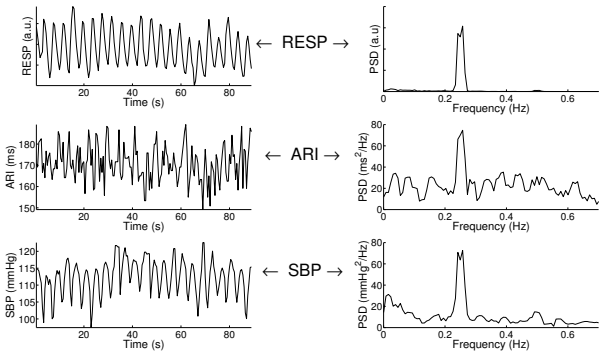

Figure 2. Example of time series and corresponding spectra of respiration (RESP), activation recovery interval (ARI) and systolic blood pressure (SBP) during controlled breathing at 0.25Hz.

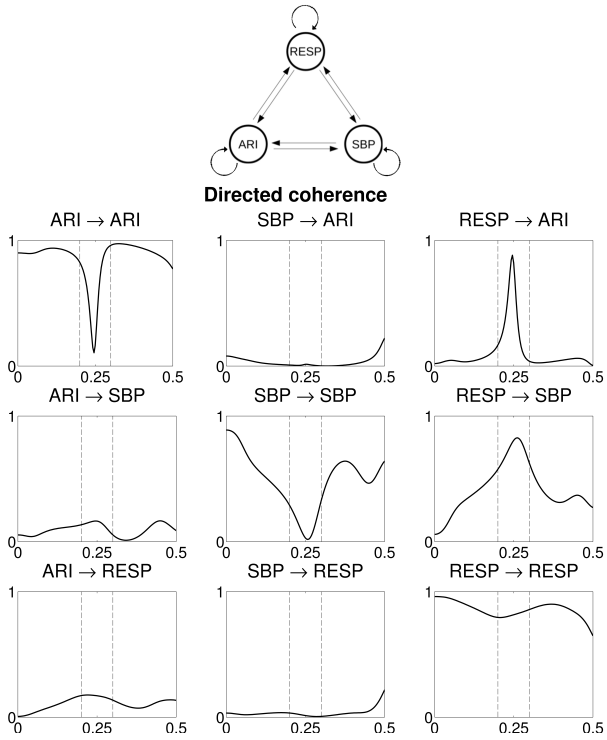

Figure 3. Characterization of the causal interactions between the processes shown in Fig. 2. Top: possible interactive pathways. Bottom: Directed coherence between ARI, SBP and RESP, see text for details.

pathways. The graphs below show for each signal how its power spectrum is decomposed into contributions from other signals. For example, the contributions to the ARI spectrum are shown in the upper row. A clear peak for the interaction $RESP \rightarrow ARI$ indicates that the ARI signal is receiving information at the respiratory frequency from the respiratory signal. In contrast, the function $SBP \rightarrow ARI$ is almost uniformly zero around the respiratory frequency, suggesting minimal contribution of SBP to the observed ARI oscillations. As expected, the contribution of ARI and SBP towards respiration was marginal.

The mean decompositions of the ARI, SBP and respiratory power spectra into power contributions related to all processes are presented in Fig. 4. For example, the directed coherence from RESP to ARI was 0.68, which means that, on average, 68% of the ARI power spectrum at the breathing frequency could be explained by the respiratory signal. High directed coherences were found for $RESP \rightarrow ARI$ and $RESP \rightarrow SBP$: 0.68($\pm$0.22) and 0.75($\pm$0.12), respectively. In contrast, the strength of the pathway $SBP \rightarrow ARI$ was found to be marginal: 0.08($\pm$0.08).

4. Discussion

To the best of our knowledge, this work is the first application to study the causal cardiorespiratory interactions between ventricular endocardial APD (ARI), arterial SBP

and respiration. We measured the strength of linear coupling between ARI, SBP and respiratory signals in specific causal directions at the respiratory frequency using the directed coherence. The results show that the directed coherence from respiration to ARI and to SBP was high, while the influence of SBP on ARI was marginal. Mechanisms that may play a role in the genesis of respiratory-related APD oscillations include respiratory reflexes, the baroreflex and mechanoelectric feedback (MEF). Mechanical action of respiration causes change in arterial pressure that may trigger the baroreflex, thereby modulating autonomic input to individual myocytes and hence APD. Previous studies have shown that respiratory-induced changes in heart rate are indeed partly driven by arterial pressure during rest [11–13]. In the presented work, however, we found low mutual influence between SBP and ARI, suggesting that other mechanisms than the baroreflex feedback might be more important in driving the observed APD oscillations. Our results may support a possible role of APD modulation due to respiratory reflexes. For instance, respiration modulates sympathetic neuronal and vagal motorneurone activity which may modulate APD. On the other hand, the direct coherence findings may also support the theory of MEF, which is the process whereby mechanical forces on the myocardium alter its electrical properties [14]. There is a general consensus that voluntary breathing causes variation of ventricular filling and hence stretch of the myocardium [15]. Cyclical variation of ventricular filling could therefore possibly result in cyclical variation of APD via MEF. This mechanism may act almost instantaneously (i.e. before arrival of the next heart beat). Consequently, to achieve a full description of the correlation structure of the observed signals, we used the extended MVAR model that includes both instantaneous and lagged effects. Future work is needed to further investigate the origin of respiratory-related ventricular APD oscillations, as well as to assess possible interactions between conduction and repolarization dynamics [16].

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