Cardiorespiratory interactions in patients with atrial flutter

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Masè M, Disertori M, Ravelli F. Cardiorespiratory interactions in patients with atrial flutter. J Appl Physiol 106: 29–39, 2009. First published November 20, 2008; doi:10.1152/japplphysiol.91191.2008.—Cardiorespiratory interactions in patients with atrial flutter (AFL), a supraventricular arrhythmia based on a reentry, by using cross-spectral analysis and computer modeling. The coherence and phase between respiration and atrial ( \( \gamma_{\text{AA}} \) ) and ventricular \( \gamma_{\text{VR}} \) interval series were estimated in 20 patients with typical AFL (68.0 ± 8.8 yr) and some degree of atrioventricular (AV) conduction block. In all patients, atrial intervals displayed oscillations strongly coupled and in phase with respiration \( \gamma_{\text{AA}} = 0.97 \pm 0.03, \phi_{\text{AA}} = 0.71 \pm 0.31 \text{ rad} \), corresponding to a paradoxical shortening of intervals during inspiration. The modulation pattern was frequency independent, with in-phase oscillations and short time delays (0.40 ± 0.15 s) for respiratory frequencies in the range 0.1–0.4 Hz. Ventricular patterns were affected by AV conduction type. In patients with fixed AV conduction, ventricular intervals displayed oscillations strongly coupled \( \gamma_{\text{VR}} = 0.97 \pm 0.03 \) and in phase with respiration \( \phi_{\text{VR}} = 1.08 \pm 0.80 \text{ rad} \). Differently, in patients with variable AV conduction, respiratory oscillations were secondary to Wencheback rhythmicity, resulting in a decreased level of coupling \( \gamma_{\text{VR}} = 0.50 \pm 0.21 \). Simulations with a simplified model of AV conduction showed ventricular patterns to originate from the combination of a respiratory modulated atrial input with the functional properties of the AV node. The paradoxical frequency-independent modulation pattern of atrial interval, the short time delays, and the complexity of ventricular rhythm characterize respiratory arrhythmia during AFL and distinguish it from normal RSA. These peculiar features can be explained by assuming a direct mechanical action of respiration on AFL reentrant circuit.

The first report on an interaction between respiration and heart rate is ascribed to Ludwig and dates back as early as 1847 (34). The phenomenon, named respiratory sinus arrhythmia (RSA), was described as an acceleration of the heart rate during inspiration followed by a slowing during expiration. Since then, several studies have been performed that have revealed the complex nature of the interaction, characterized by frequency-dependent behaviors (1, 4, 13, 21, 55), and shed light on its origin. Several mechanisms have been proposed for the generation of RSA, including the direct interaction between central cardiorespiratory centers within the brain stem, pulmonary reflex pathways, respiratory gating of central arterial baroreceptor afferent input, an atrial reflex, and oscillations in arterial PCO2 and pH in arterial blood (15, 45, 60). These mechanisms would affect heart rate via fluctuations in cardiac parasympathetic efferent activity, acting mainly on the sinus node pacemaker (13, 29, 33, 58). Thus, at normal breathing frequencies (~0.25 Hz), the shortening of heart period during inspiration would be associated with the withdrawal of parasympathetic activity, whereas its lengthening during expiration would be associated with the strengthening of vagal activity.

The above findings depict a detailed picture of RSA; however, they pertain only to patients in normal sinus rhythm. Conversely, a paucity of data exists regarding the presence of cardiorespiratory interactions in patients with supraventricular arrhythmias, such as atrial fibrillation and atrial flutter, and even the existence of these interactions is a matter of debate. In fact, due to the complexity of the mechanisms underlying atrial activation during atrial arrhythmias (including reentrant activity, ectopic foci, and multiple-wavelet propagation) and to the presence of some degree of atrioventricular (AV) block, cardiorespiratory interactions are likely to involve the simultaneous modulation of several electrophysiological parameters at both atrial and AV levels. This may result in more complex and entangled interaction pathways, making respiratory modulation harder to detect. Several studies have investigated the presence of cardiorespiratory interactions during atrial fibrillation, focusing mostly on the respiratory modulation of ventricular rate. Data indicate that during normal breathing, the irregularity of ventricular intervals prevails over respiratory patterning, which is an infrequent finding and, when observed, exerts inconsistent effects on ventricular rhythm (10, 20, 39, 46, 51). More consistent respiratory effects on heart rate have been observed during Cheney-Stokes respiration and apnea (19, 32, 63), where heart rate has been shown to oscillate in synchrony with the slow breathing patterns. These studies suggest that respiration would influence ventricular rate in atrial fibrillation just at very low frequencies by causing cyclical changes in the electrophysiological properties of the AV node. Mostly because of technical issues, just few studies have analyzed the effect of respiration on atrial rate during atrial fibrillation (22, 23). In particular, Holmqvist et al. (23) have shown that controlled respiration at low rates (0.125 Hz) causes cyclic fluctuations in the atrial fibrillation frequency and have suggested the phenomenon to be related to parasympathetic modulations of the atrial fibrillation refractory period.

Differently from atrial fibrillation, evidence was gathered in favor of the existence of a respiratory modulation of atrial rate during atrial flutter, a common atrial tachyarrhythmia determined by a reentrant excitation wave in the atrium (65). Waxman et al. (67) observed the shortening of atrial flutter cycle length during respiratory maneuvers, such as the strain

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phase of Valsalva maneuver and expiration, which reduced cardiac volume. More recently, Ravelli et al. (50) showed the presence of a respiratory component in the overall variability of atrial flutter cycle length, which persisted after autonomic blockade. These studies constitute evidence of the presence of a respiratory-related variability in atrial flutter cycle length and suggest a direct mechanical action of respiration on atrial flutter reentrant circuit as a likely pathway of interaction. However, so far, an exhaustive picture of the respiratory modulation of atrial flutter rhythms and a quantification of its properties is still lacking.

The aim of the present study is to provide a quantitative and thorough characterization of the cardiorespiratory interactions during atrial flutter by application of cross-spectral analysis. Since atrial flutter is associated with some degree of AV block, the analysis is devoted not only to the description of the interactions at the atrial level but also to the patterns of interaction at the ventricular level. To shed light on the mechanisms originating the cardiorespiratory interactions at the ventricular level, we have integrated data analysis with computer simulations reproducing the response of the AV node to a respiratory modulated atrial input.

**MATERIALS AND METHODS**

*Study population.* Twenty patients (68.0 ± 8.8 yr) with typical atrial flutter constituted the study population. Fourteen patients had associated heart disease, including coronary artery disease, mitral valve disease, cardiomyopathy, and hypertensive heart disease. All patients showed some degree of AV conduction block, including stable 2:1, 3:1, or 4:1 ratios and variable degrees of block. In all patients, antiarrhythmic treatment was suspended at least five half-lives before the study. The study was approved by the Hospital Ethics Board, and all patients gave written informed consent.

*Electrophysiological study and data acquisition.* After light sedation with diazepam (10 mg im), a bipolar catheter was advanced into the esophagus for atrial electrogram recording (band width 30–500 Hz). Ventricular activity was recorded from a surface ECG, whereas respiratory activity was detected by a differential pressure transducer in the nose. All signals were recorded simultaneously on a FM magnetic tape (TEAC XR-510) with patients in the supine position. Baseline recordings were acquired in all patients during spontaneous respiration. In addition, in a subgroup of six patients, recordings were acquired during controlled respiration at increasing rates (0.1–0.4 Hz) following a metronome.

*Data processing and time series extraction.* Signals were digitalized at 1 kHz on a personal computer for interval measurement and analysis. A computer program was developed to automatically identify atrial electrogram complexes from the esophageal lead and QRS complexes from the surface ECG to provide a beat-to-beat measure of atrial (AA) and ventricular (RR) intervals. Specifically, to extract atrial activation times, atrial electrograms were band-pass filtered (40–250 Hz, order 40, Kaiser window) and the modulus of the filtered signal was further low-pass filtered (FIR, 20 Hz, order 40, Kaiser window) (8). Atrial depolarizations were detected in correspondence with the peaks of the filtered signal, which were larger than an adaptive threshold. For each detected depolarization, the activation time was set at the time of maximal, positive slope of the signal. The regular shape of the atrial waveform during atrial flutter allowed a high precision in the estimation of the activation times. Ventricular activation times were measured from the ECG by identifying the time of QRS maxima/minima, depending on the surface lead analyzed. Activation time series were visually checked and manually corrected if necessary.

Respiratory time series (i.e., respiograms) were obtained by sampling the respiratory signal in correspondence with the detected atrial or ventricular activation times. With this procedure, the respiratory signal could be constructed from a small number of samples, corresponding one to one to AA and RR series, respectively.

Time series were windowed to 200–300 points and characterized in the time domain by their mean and standard deviation (SD). Before spectral and cross-spectral analyses were performed, time series were detrended to fulfill stationarity criteria (5, 61).

*Spectral and cross-spectral analysis.* Power spectral analysis was applied to AA, RR, and respiratory series to determine the main oscillatory components of the series. Power spectral density (PSD) estimates were obtained by applying an autoregressive model (25). The model order was searched in the range 6–20 by means of Akaike’s criterion (2), obtaining model orders of 15.7 ± 2.5 and 10.8 ± 3.1 for AA and RR series, respectively. The power of the spectral peaks was calculated by evaluating the complex residues of the spectral density estimator, which allowed us to decompose the spectra into a sum of components. Each detected component was characterized by its central frequency, the peak spectral power (expressed in ms²), and the percent spectral power (i.e., peak spectral power over total spectral power). The power of the respiratory component in atrial (PAA) and ventricular (PVR) series was easily identified by coincidence with the peak of the respiratory spectrum, which was used as a reference. Since spectral analysis was performed over interval series, the abscissa of the spectra was expressed as cycles per beat. Conversion from cycles per beat to cycles per second (Hz) was achieved by dividing the frequency scale by the mean atrial and ventricular interval for atrial and ventricular spectra, respectively.

Cross-spectral analysis was applied to characterize the coupling and the phase relationship between interval series (atrial or ventricular) and respiration. The cross-spectrum was calculated by performing traditional cross-spectral analysis via a parametric autoregressive technique. The model order was chosen in the range 6–20 by minimizing Akaike’s figure of merit for the bivariate joint process (2), obtaining model orders of 9.9 ± 1.4 and 9.2 ± 2.0 for AA and RR series, respectively.

The coherence functions $\gamma_{AA}(f)$ and $\gamma_{RR}(f)$ were estimated from auto-PSD AA$(f)$, PSD RR$(f)$, PSD Resp$(f)$ and cross-spectral PSDAA Resp $(f)$, PSDRR Resp $(f)$ densities as:

$$\gamma_{AA}^2(f) = \frac{|PSD_{AA,Resp}(f)|^2}{PSD_{AA}(f)PSD_{Resp}(f)}$$

$$\gamma_{RR}^2(f) = \frac{|PSD_{RR,Resp}(f)|^2}{PSD_{RR}(f)PSD_{Resp}(f)}$$

and used to quantify the degree of linear coupling between synchronous oscillations in atrial/ventricular and respiratory series. The coherence function ranged between 0 and 1, with 0 indicating an absence of coupling and 1 indicating full coupling at the frequency $f$. The maxima ($\gamma_{AA}$ and $\gamma_{RR}$) of the coherence functions in the respiratory band (0.1–0.5 Hz) was assumed as a measure of the coupling strength between couples of series. To assess the significance of the coupling strength and distinguish effective from background coupling, we applied a statistical approach based on surrogate data generation, which yielded a specific significance threshold for each analyzed pair of series (18). Specifically, for each pair of investigated AA/RR and respiratory series, 100 surrogate series mimicking the individual properties of the original, but being completely uncoupled, were generated. The coherence was thus estimated for each surrogate pair, and the 95th percentile of the coherence distribution was taken as zero-coherence threshold.

In the presence of significant coupling, the phase functions $\phi_{AA}(f)$ and $\phi_{RR}(f)$, given by

$$\phi_{AA}(f) = \arctan \frac{\text{Im}[P_{AA,Resp}(f)]}{\text{Re}[P_{AA,Resp}(f)]}$$

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\[ \phi_{\text{RR}}(f) = \text{arctg} \left( \frac{\text{Im}[P_{\text{RR},\text{Resp}}(f)]}{\text{Re}[P_{\text{RR},\text{Resp}}(f)]} \right) \]  

where Im and Re indicate the imaginary and real part of the cross-spectral density functions, were calculated to estimate the phase shift between synchronous oscillations at the frequency \( f \) in the interval and respiratory series. The phase function ranged between \(-\pi\) and \(+\pi\), with 0 indicating oscillations in phase and \( \pm \pi \) oscillations in antiphase. Positive phase values indicated a delay in interval oscillations with respect to respiratory oscillations. The phase values (\( \phi_{\text{AA}} \) and \( \phi_{\text{RR}} \)) in correspondence of maximal coherence were used to characterize the phase relation between the processes. The time delay (in seconds) between coupled oscillations was obtained by dividing the phase shift for \( 2\pi \).

**Computer simulations.** To investigate the mechanisms originating cardiorespiratory interactions at the ventricular level and, specifically, to evaluate the hypothesis that the dynamics of interactions observed in patients can be explained by the combination of a respiratory modulated atrial input with the functional properties of the AV node, we ran simulations using a simple model of interaction among atrial, ventricular, and respiratory activity, according to the scheme drawn in Fig. 1. The model simply represents respiratory activity at the frequency \( 1/T \), by the harmonic function

\[ \text{Resp}(t) = \cos \left( \frac{2\pi}{T} t \right) \]  

Similarly, with a previous model (37), respiration was assumed to exert a direct influence on atrial activity, harmonically modulating atrial intervals around a mean value \( A_{\text{Am}} \); i.e.,

\[ A_{A_j} = A_{\text{Am}} + \Delta A_{A_j} = A_{\text{Am}} + A \cos \left( \frac{2\pi}{T_r} t_{j-1} - \phi \right) \]  

where \( 2A \) is the amplitude of the respiratory modulation, \( t_{j-1} \) is the timing of the \( A_{j-1} \) beat, \( 1/T_r \) is the respiratory frequency, and \( \phi \) is a constant phase delay.

To simulate ventricular variability, the modulated atrial input given by Eq. 6 was filtered by the simplified AV model proposed by Mangin et al. (36), which includes, together with the basic properties of nodal conduction and refactoriness, the contribution of concealed conduction (i.e., the effect of nonconducted beat on the transmission of successive beats (31)).

The conduction of an atrial beat impinging the AV node at time \( A_{j+2} \) was assumed to depend solely on the preceding recovery time \( V_A \) (i.e., time interval from the preceding conducted beat \( V_i \)). For recovery times \( V_A \) shorter than the nodal refractory period \( \theta \), the beat was blocked. Conversely, for recovery times exceeding the refractory period, the beat was conducted to the ventricles, generating the ventricular beat \( V_{i+1} \) after a conduction time \( AV_{i+1} \) given by the recovery curve (57)

\[ AV_{i+1} = AV_{\text{min}} + a e^{-V_A/\tau} \]  

where \( AV_{\text{min}} \) is the minimum conduction time corresponding to propagation in a fully recovered tissue and \( a \) and \( \tau \) are positive constants.

As shown in Fig. 1, the recovery time \( V_A \) can be expressed as a function of the previous conduction time and the modulated atrial intervals of Eq. 6:

\[ V_A = \sum_{j=1}^{k} A_{A_j} - A_{V_i} \]  

where atrial intervals \( A_{A_j} \) are numbered from the last conducted beat, \( k \) is the first beat for which the recovery time exceeded the refractory period, and \( A_{V_i} \) is the previous conduction time.

To include in the model the effects of concealed conduction, the refractory period \( \theta \) of the node was assumed to be lengthened by the presence of nonconducted beats (36). Thus the refractory period was defined as the sum of a basic refractory period \( \theta_0 \) and a normally distributed concealed conduction term, \( \Delta_{j+1} \), produced by each nonconducted beat \( A_{j+1} \); i.e.,

\[ \theta = \theta_0 + \Delta_{j+1} = \theta_0 + \Omega_{j+1} \Delta_{\text{std}} + \Delta_{\text{mean}} \]  

where \( \Omega_{j+1} \) is a normally distributed random number, with a mean of 0 and a standard deviation of 1, and \( \Delta_{\text{mean}} \) and \( \Delta_{\text{std}} \) are positive constants.

Output sequences of simulated ventricular intervals were iteratively generated once parameter values were set, and cross-spectral parameters (coherence and phase) between simulated respiratory and ventricular series were estimated. Simulations were run by setting model parameters to \( AV_{\text{min}} = 90 \) ms, \( \theta_0 = 200 \) ms, and \( \tau = 100 \) ms, according to values determined in previous studies (36). The refractory period and the atrial parameters were set to \( \theta_0 = 405 \) ms, \( A_r = 5 \) ms, \( \phi = 0.5 \) rad, and \( T_r = 5,000 \) ms to mimic our patients. The mean atrial interval \( A_{\text{Am}} \) was varied in the range 120–320 ms, with \( 2A_r \), \( \theta_0 \), and \( \tau_0 \) being set to 5 ms, \( 0.5 \) rad, and \( 5,000 \) ms, respectively.

**RESULTS**

**Respiratory fluctuations of atrial rate.** The existence of a respiratory component in the variability pattern of atrial flutter interval is shown in Fig. 2A, whereas the corresponding cross-spectral parameters are displayed in Fig. 2B. Atrial intervals (Fig. 2A, top left) oscillated around a mean value of 216.6 ms, presenting a standard deviation of 3.1 ms. The variability pattern showed the presence of two oscillations, a faster one at the frequency of ventricular contraction (49) and a slower one at the frequency of respiration. In particular, the presence of the
significant coupling (comprising 21.4 variability was observed in the power spectrum of all patients, showed a high significant value (from the power spectrum of the series (Fig. 2 respiratory oscillation in atrial interval variability was evident from the power spectrum of the series (Fig. 2A, top right), which displayed a well-defined peak at the frequency of respiration ($f = 0.25 \text{ Hz}$), as shown by comparison with the respiratory spectrum (Fig. 2A, bottom right). Respiratory oscillations generated 52.1% ($P_{AA} = 4.89 \text{ ms}^2$) of the total spectral power, whereas the remaining variability originated from a high-frequency oscillation at the frequency of ventricular contraction ($f = 2.31 \text{ Hz}$, not visible in the displayed frequency range). The coherence function (Fig. 2B, left) showed a high significant value ($\gamma_{AA} = 0.988$), which indicates the presence of strong coupling between atrial interval and respiratory oscillations at the frequency of respiration. The corresponding small value of the phase function (Fig. 2B, right), $\phi_{AA} = 0.42 \text{ rad}$, indicates that the two oscillations occurred almost in phase. Referring to the atrial interval time series displayed in Fig. 2A, top left, this corresponds to a paradoxical/reverse modulation of atrial intervals by respiration, characterized by longer intervals during inspiration and shorter intervals during expiration ($218.5 \pm 2.4 \text{ vs. } 214.3 \pm 2.5 \text{ ms, } P < 0.001$).

The results from the overall population of patients, summarized in Table 1, confirm these observations. In fact, a respiratory ($f = 0.31 \pm 0.07 \text{ Hz}$) oscillation in atrial interval variability was observed in the power spectrum of all patients, comprising 21.4 $\pm 21.6\%$ of the total spectral power. High significant coupling ($\gamma_{AA} = 0.97 \pm 0.05$) and in-phase oscillations ($\phi_{AA} = 0.71 \pm 0.31 \text{ rad}$, corresponding to a time delay of $t_{AA} = 0.40 \pm 0.15 \text{ s}$) characterized the interaction between respiration and atrial activity in all patients, thus proving the presence of a strong and reverse modulation of atrial intervals by respiration.

To investigate the presence of frequency-dependent phenomena or phase inversion behaviors in the interaction between respiration and atrial electrical activity, we calculated the phase between the series as a function of the respiratory frequency during controlled respiration in a subgroup of six patients. The atrial phase (Fig. 3A) remained bounded to small values ($\phi_{AA} = 0.52 \pm 0.22 \text{ rad}$, corresponding to $t_{AA} = 0.35 \pm 0.18 \text{ s}$), indicating a reverse respiratory modulation of atrial intervals at all tested respiratory frequencies, although a small increase (slope $= 1.23 \text{ rad/Hz}$, $r = 0.57$) in phase values was observed at increasing respiratory rate.

Respiratory fluctuations of ventricular rate. The variability of ventricular intervals during atrial flutter is displayed in Figs. 4 and 5 in two representative patients with fixed and variable AV conduction ratios, respectively. The patient with fixed AV conduction ratio showed a marked (SD = 18.5 ms) ventricular interval oscillation (Fig. 4A, top left) synchronous with respiratory oscillation (Fig. 4A, bottom left). The power spectrum of the series (Fig. 4A, top right) shows that this respiratory oscillation ($f =

Table 1. Time and frequency domain characterization of the respiratory variability of atrial and ventricular intervals during atrial flutter

<table>
<thead>
<tr>
<th></th>
<th>AA</th>
<th>Fixed AV</th>
<th>Variable AV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>20</td>
<td>16</td>
<td>4</td>
</tr>
<tr>
<td>Mean interval, ms</td>
<td>229.2$\pm$38.0</td>
<td>620.0$\pm$191.7</td>
<td>643.9$\pm$140.2</td>
</tr>
<tr>
<td>SD interval, ms</td>
<td>4.6$\pm$2.3</td>
<td>7.0$\pm$5.3</td>
<td>83.2$\pm$28.8</td>
</tr>
<tr>
<td>R peak power, ms$^2$</td>
<td>3.75$\pm$3.31</td>
<td>49.4$\pm$85.9</td>
<td>2,418.3$\pm$1990.7</td>
</tr>
<tr>
<td>R peak power, %</td>
<td>21.4$\pm$21.6</td>
<td>61.3$\pm$19.1</td>
<td>31.3$\pm$7.7</td>
</tr>
<tr>
<td>Coherence</td>
<td>0.97$\pm$0.05</td>
<td>0.97$\pm$0.03</td>
<td>0.50$\pm$0.21</td>
</tr>
<tr>
<td>Phase, rad</td>
<td>0.71$\pm$0.31</td>
<td>1.08$\pm$0.80</td>
<td>$-1.24\pm0.97$</td>
</tr>
<tr>
<td>Temporal delay, s</td>
<td>0.40$\pm$0.15</td>
<td>0.67$\pm$0.51</td>
<td>$-0.88\pm0.77$</td>
</tr>
</tbody>
</table>

Values are means $\pm$ SD. AA, atrial intervals; RR, respiratory intervals; AV, atrioventricular; R, respiratory.
0.21 Hz) constituted the main source of ventricular variability (PRR = 263.67 ms², 77.3% of the total spectral power) in the patient. Consistently, ventricular and respiratory oscillations were strongly coupled with high significant coherence, \( \gamma_{RR}^2 = 0.96 \), at the frequency of respiration (Fig. 4B, left). The corresponding small phase value, \( \phi_{RR} = 0.73 \text{ rad} \), indicates in-phase oscillations (Fig. 4B, right) and thus reverse modulation, as in the case of atrial intervals.

A different scenario characterized patients with variable AV conduction, where high-amplitude oscillations of ventricular intervals (SD = 113.6 ms) and more complex variability patterns were observed (Fig. 5A, top left). This condition is reflected in the power spectrum of the series (Fig. 5A, top right), where different sources of variability can be distinguished. A respiratory oscillation \( f = 0.25 \text{ Hz} \) was still observed, but it comprised just 22.8% (PRR = 2,904.20 ms²) of the total power, whereas the remaining variability was associated with the presence of Wencheback rhythms due to AV block. Specifically, two spectral peaks, associated with 7:3 and 5:2 AV conduction ratios, were observed at the frequencies of 0.52 and 0.74 Hz, which comprised 23.3% (2,965.3 ms²) and 18.7% (2,385.2 ms²) of the total variability, respectively. Consistent with the increased complexity, the coherence between respiratory and ventricular activity (Fig. 5B, left) decreased to \( \gamma_{RR}^2 = 0.55 \), slightly above the significance threshold (0.47). The corresponding value of the phase function, \( \phi_{RR} = -1.92 \text{ rad} \), indicates almost antiphase oscillations (Fig. 5B, right).

The results from the overall population of patients corroborate these findings (Table 1). In fact, a respiratory oscillation was observed in the ventricular spectrum of all patients. It represented the main oscillation (61.3 ± 19.1% of the total spectral power) in patients with fixed AV conduction ratios, whereas in patients with variable conduction, it was secondary (31.3 ± 7.7% of the total spectral power) to Wencheback rhythmicity. High significant coherence values and in-phase oscillations (Fig. 4B, right) were observed in all patients with fixed AV conduction.
were repeated in the absence (basic model) and presence of the generation of ventricular modulation patterns, simulations modulated atrial interval with the functional properties of the patients could arise from the combination of a respiratory spectral properties of ventricular interval series observed in antiphase oscillations.

The results are depicted in Fig. 3B. Ventricular phases were more dispersed than atrial phases due to the presence of variable AV conduction ratios. Focusing on fixed AV conduction ratios (filled circles), phase values display an increase with increasing respiratory frequency. The linear fit shows a higher slope (2.46 rad/Hz) than the atrial curve (Fig. 3A), which is consistent with a higher time delay, and a linear correlation coefficient of 0.62 (P < 0.05). As in the atrial case, however, the increase of the phase was not sufficient to induce a change in the patterns of modulation (φ_{RR} = 0.89 ± 0.46 rad, corresponding to a temporal delay τ_{RR} = 0.61 ± 0.35 s), and ventricular intervals were paradoxically modulated at all respiratory frequencies. Variable AV conduction ratios (open circles) display scattered phase values (φ_{RR} = −0.99 ± 2.18 rad) with a prevalence of antiphase oscillations.

**Simulation results.** To evaluate the hypothesis that the cross-spectral properties of ventricular interval series observed in patients could arise from the combination of a respiratory modulated atrial interval with the functional properties of the AV node, we ran simulations with a simplified model of AV conduction. In particular, to assess the possible roles played by AV recovery properties and concealed conduction effects in the generation of ventricular modulation patterns, simulations were repeated in the absence (basic model) and presence of concealed conduction (complete model).

The results of the simulations are displayed in Fig. 6, where the coherence γ^2_{RR} (top) and phase φ_{RR} (bottom) between simulated ventricular interval and respiratory series obtained using the basic model (A) are compared with those obtained using the complete model including concealed conduction (B). Cross-spectral indexes are displayed as a function of the stimulating atrial period A_Am to evidence their trend for changing levels of AV block.

The basic AV model was able to reproduce the behavior of the phase function observed in patients. In fact, as shown in Fig. 6A, the phase presented small values (φ_{RR} = 1.14 ± 0.38 rad), corresponding to in-phase oscillations, for fixed AV conduction ratios (i.e., in 2:1, 3:1, and 4:1), whereas in the presence of variable AV conduction ratios, values were closer to ±π (φ_{RR} = −1.99 ± 0.70 rad) and antiphase oscillations were dominant. The basic model instead could not depict the decrease of the coherence function observed in patients with variable AV conduction. As shown in Fig. 6A, the coherence function attained high values for either fixed (γ^2_{RR} = 1) or variable (γ^2_{RR} = 0.9988 ± 0.0019) AV conduction ratios.

Conversely, the behavior of the coherence function observed in patients could be reproduced by introducing the effects of concealed conduction in the model. In fact, as shown in Fig. 6B, top, the presence of concealed conduction affected coherence values differently in fixed and variable AV conduction ratios. Although the range of stability of fixed AV conduction ratios was narrowed by concealed conduction, the coherence function maintained high values (γ^2_{RR} = 0.98 ± 0.04) in 2:1, 3:1, and 4:1 AV conduction ratios. Differently, coherence values underwent a significant decrease (γ^2_{RR} = 0.61 ± 0.14) in variable AV conduction ratios.
To provide a direct qualitative comparison with results obtained in patients, Fig. 7 displays simulated ventricular interval series (left), obtained using the complete model, with the corresponding results of cross-spectral analysis (right). Figure 7A shows a condition of fixed AV conduction, obtained at a mean atrial period of AA\textsubscript{m} = 305 ms. Similarly to what was observed in patients (see for comparison Fig. 4), the interval series displays a clear periodic pattern (SD = 19.3 ms) synchronous with respiration (bottom trace), and a high value of coherence (\(\gamma^2_{RR} = 0.98\)) with in-phase oscillations (\(\phi_{RR} = 0.62\) rad) was observed between the series and respiration. Differently, Fig. 7B displays a condition of variable AV conduction, obtained at a mean atrial period of AA\textsubscript{m} = 280 ms. As observed in patients (see for comparison Fig. 5), the ventricular series presented a higher variability (SD = 126.1 ms) and a more complex pattern of variability, which resulted in a reduced value of coherence (\(\gamma^2_{RR} = 0.69\)). The corresponding value of the phase, \(\phi_{RR} = -2.51\), indicates almost antiphase oscillations.

Simulation results showed that the wide spectrum of modulation patterns observed in ventricular time series could be consistently reproduced by combining a respiratory modulated atrial input with a simple model of AV conduction, including the AV recovery properties and the effects of concealed conduction. In particular, the first factor determined phase properties, whereas the second affected the level of coupling.

**DISCUSSION**

In the present study, we analyzed the cardiorespiratory interactions during atrial flutter at the atrial as well as the ventricular level, providing a quantitative description of the phenomenon by cross-spectral analysis and computer modeling. The main results of the study can be summarized as follows: 1) strong, significant coupling is observed between atrial intervals and respiration at the frequency of respiration in all patients, regardless of the AV conduction type; 2) the atrial respiratory modulation pattern is paradoxical, frequency independent, and involves short temporal delays so that atrial intervals oscillate in phase with respiration at all respiratory frequencies, with longer intervals during inspiration than expiration; 3) the coupling and phase relations between ventricu-
ular intervals and respiration are affected by the AV conduction type; indeed, strong coupling and in-phase oscillations are observed in patients with fixed AV conduction ratios, whereas the linear coupling is reduced and antiphase oscillations are mainly observed in patients with variable ratios; and 4) as shown by computer simulations, the combination of a respira-
tory modulated atrial input with the conductive and refractory properties of the AV node (i.e., AV recovery curve and concealed conduction) may consistently explain the patterns of ventricular variability observed in patients.

These results define the cardiorespiratory interactions during atrial flutter as a sound phenomenon, evident in all patients, with well-defined and repetitive features at both the atrial and ventricular levels. This clear evidence distinguishes atrial flutter from atrial fibrillation, where the irregularity of the rhythm prevails over respiratory patterning and even the presence of respiratory arrhythmia is a matter of debate (10, 20, 39, 46, 51).

In atrial flutter, the simple reentrant mechanism underlying atrial activation determines a more regular rhythm, which makes the respiratory modulation apparent. Similarly to atrial flutter, evident respiratory modulations of the heart rate have indeed been identified during atrial tachycardias, where regular, high-frequency rhythms are generated by focal activity (24).

Use of spectral and cross-spectral analysis in the characterization of atrial flutter cardiorespiratory interactions. The quantitative characterization of the cardiorespiratory interactions during atrial flutter in this study was accomplished by cross-spectral analysis. Spectral and cross-spectral analyses have been used widely in the context of cardiovascular oscillations to characterize heart rate variability during normal sinus rhythm, thus leading to the identification of the main oscillations of cardiovascular rhythms (3, 14, 35, 38), and to quantify the degree of linear coupling and phase relation between cardiovascular variables (5, 42, 62). Nevertheless, frequency-domain techniques have been applied to a less extent in the characterization of cardiovascular oscillations during atrial arrhythmias (50, 54, 59). Spectral and cross-spectral analyses have been applied to individuate the presence of a respiratory modulation of heart rate and blood pressure in atrial fibrillation (23, 46), whereas spectral analysis has been used to characterize the overall variability of atrial flutter cycle length (50, 59).

Focusing on the respiratory modulation of atrial flutter rhythms, in the present study we applied cross-spectral analysis to both atrial and ventricular interval series to test effectively the presence of coupling between atrial/ventricular series and res-
piration and to characterize the phase relation of the interaction. Specifically, the calculation of the coherence function and its comparison with the zero-coherence threshold generated by surrogate data allowed us to measure the linear coupling between time series and to assess its statistical significance, distinguishing effective coupling from independent narrow-band oscillations at nearby frequencies (18). The comparison with the zero-coherence threshold was critical in assessing the coupling between ventricular intervals and respiration in pa-
tients with variable AV conduction, where the degree of coupling was weaker, but significant interactions could still be identified and distinguished from background coupling.

Features of the cardiorespiratory interactions at the atrial level. By applying cross-spectral analysis to atrial interval and respiratory series, we provided a quantitative description of the respiratory modulation of atrial activity during atrial flutter. The analysis evidenced three main features characterizing the cardiorespiratory interactions at the atrial level. First, the respiratory modulation of atrial intervals assumed a reversed pattern characterized by longer atrial intervals in inspiration than expiration. Second, atrial intervals and respiration oscillator in phase, with a small temporal delay ($t_{AA} = 0.40 \pm 0.15$ s) between coupled oscillations. Third, the reverse modulation pattern was frequency independent, and in-phase oscillations were observed at all respiratory frequencies in the range 0.1–0.4 Hz.

These features portray respiratory arrhythmia in atrial flutter and distinguish it from normal RSA. In fact, RSA at typical breathing frequencies (~0.25 Hz) is characterized by the lengthening of heart period during expiration and its shortening during inspiration (15, 21, 45, 68), corresponding to the waxing and waning of vagal modulation to the sinus node pacemaker.

The modulation is associated with longer temporal delays (1.5 s) and characterized by frequency-dependent behaviors, with both amplitude and phase relation strongly affected by the respiratory rate (1, 4, 13, 21, 55).

Consistently with previous works suggesting a mechanically mediated mechanism underlying atrial flutter cycle length variability (50, 67), the peculiar features of the cardiorespiratory interactions during atrial flutter can be explained by assuming a direct mechanical action of respiration on atrial flutter reentrant circuit. It is well known that respiration exerts a mechanical effect on cardiac performance (53). Specifically, cyclical changes in intrathoracic pressure associated with respiratory phases alter systemic venous return to the heart, and thus right atrial preload, in synchrony with respiratory cycle.

Mechanical respiratory effects on cardiac volume are present during normal sinus rhythm and might affect heart rate by stretching of the sinus node pacemaker (12, 27), thus potentially contributing to RSA. Indeed, a mechanical modulation of heart rate has been suggested to determine RSA in heart transplant recipients (6, 7) and to contribute significantly to RSA in conditions associated with reduced vagal tone, as observed in patients with mild heart failure (17) and in healthy subjects during exercise (7, 9). Nevertheless, in normal physiological resisting conditions, mechanical mechanisms are secondary to autonomic ones in the modulation of the sinus node pacemaker activity and thus in the determination of RSA.

Conversely, during atrial flutter, where the mechanism of atrial activation is constituted by a reentrant circuit, right atrial volume changes induced by respiratory mechanics are likely to significantly affect atrial flutter properties. Indeed, several studies have evidenced the role of atrial volume in the determination of atrial flutter rate and interval variability. In particular, Waxman et al. (67) showed an increase in atrial flutter rate in response to maneuvers reducing cardiac size, such as passive upright tilting, the strain phase of Valsalva maneuver, and expiration. A correlation between atrial volume and mean atrial flutter period was observed by Vulliemin et al. (64), who underlined the importance of the right heart preload and atrial size for the electrophysiological characteristics of type I atrial flutter. Finally, the mechanical origin of atrial flutter interval variability was suggested by the study of Ravelli et al. (50), who showed the persistence of the overall variability of atrial flutter intervals after autonomic blockade. All these studies have contributed to the formulation of the hypothesis that
changes in atrial volume directly affect atrial flutter variability by modifying the conduction properties of the circulating impulse in the atrium (50).

Assuming the hypothesis of a mechanical modulation of atrial flutter circuit by respiration, we can provide an explanation of the features of respiratory arrhythmia during atrial flutter. In fact, the reverse modulation of atrial intervals by respiration is consistent with the effects of atrial volume variations on atrial flutter reentrant circuit. By reducing the intrathoracic pressure, inspiration produces an increase of the right atrial volume, due to the increase of both the venous return to the heart and the afterload of the ventricles, whereas expiration has the opposite effect (53). Thus the lengthening of atrial intervals during inspiration and the shortening during expiration could be explained by an increase/decrease of the size of the reentrant circuit underlying atrial flutter. In addition to changes in circuit size, stretch-induced variations in conduction velocity (11, 16) also may explain the changes in atrial flutter rate related to respiration. Experimental and clinical studies have indeed demonstrated that an increase in mechanical loading conditions may modulate atrial electrophysiological properties (16, 40, 48) and specifically decrease conduction velocity (11, 16) via mechanoelectrical feedback (28, 30, 52). Thus both a lengthening of atrial flutter anatomical circuit and a slowed conduction velocity caused by atrial volume increase may consistently explain the increase in atrial interval observed during inspiration, thus supporting the mechanical origin of cardiorespiratory interactions during atrial flutter.

The short temporal delays observed between atrial/ventricular interval oscillations and respiration, which resulted in $t_{AA} = 0.40 \pm 0.15$ s (in all patients) and $t_{RR} = 0.67 \pm 0.51$ s (in patients with constant AV conduction ratios), also are consistent with the presence of an intrinsic mechanical mechanism. In fact, mechanoelectrical feedback has been demonstrated to operate on a beat-to-beat basis (26, 30) and to occur rapidly, involving a time lag of just 10–20 ms (26). Moreover, the observed temporal delays are similar to those observed by Bernardi et al. (7) in transplanted patients ($0.52 \pm 0.13$ s), where an intrinsic mechanism is invoked to explain the presence of RSA, whereas they are significantly shorter than those involved in RSA in normal patients (~1.5 s (7, 56)).

The presence of a short temporal delay between atrial interval and respiratory oscillations can explain the absence of significant phase-dependent or phase-inversion behaviors in the respiratory modulation of atrial intervals. In normal RSA, several authors (4, 13, 55) observed a linear increase in the phase angle with the respiratory frequency, whose slope was associated with the temporal delay between oscillations. In the presence of large temporal delays, changes in the phase angle at increasing respiratory frequencies can be consistent and result in different, even reverse, modulation patterns, which makes the typical picture of RSA, determining an increase of heart rate during inspiration, just a punctual description of the phenomenon (4). Conversely, the small temporal delay observed in atrial flutter patients determines a small rate of change of the phase with the respiratory frequency, resulting in no significant alterations of the modulation pattern. Thus the fast response allows the system to follow the respiratory modulation even at high frequencies, without consistent changes in the paradoxical nature of the modulation. Thus the reverse modulation of atrial intervals by respiration, the small temporal delay between the oscillations, and the absence of significant frequency-dependent behaviors in the phase between atrial and respiratory oscillations, beyond constituting the fingerprint of the cardiorespiratory interactions during atrial flutter, concur to give evidence to the mechanical origin of the phenomenon.

Features of cardiorespiratory interactions at the ventricular level. In the present study, the analysis of cardiorespiratory interactions was performed at both the atrial and ventricular level, to determine how the tiny modulation of atrial intervals affect the variability of ventricular rhythm. The analysis performed on ventricular intervals revealed the presence of a wider spectrum of respiratory patterns at the ventricular level despite the common modulation pattern observed at the atrial level. Specifically, the strength of coupling and the phase between oscillations was strongly influenced by the AV conduction type, with strong coupling and in-phase oscillations for fixed AV conduction and reduced coupling and mainly antiphase oscillations for variable AV conduction. The presence of different modulation patterns at different heart levels constitutes an additional peculiarity of respiratory arrhythmia in atrial flutter with respect to RSA in normal sinus rhythm, where similar modulation patterns are observed at the atrial and ventricular levels (41).

To understand the origin of the cardiorespiratory patterns at the ventricular level, we performed a simulation study. We assumed that the interplay between the respiratory modulated atrial input and the functional properties of the AV node could consistently explain the features observed in patients and tested our hypothesis using a simplified model of AV conduction, including the recovery properties of the node and the contribution of concealed conduction. The comparison of simulation results obtained in the absence and presence of concealed conduction allowed us to evaluate the contribution of the two AV properties in the generation of ventricular patterns. Specifically, simulations showed that the recovery properties of the AV node could consistently produce the antiphase modulation pattern observed in patients with variable AV conduction, clarifying the electrophysiological origin of the phenomenon. In patients with variable AV conduction, the conduction ratio usually oscillates between two adjacent levels of AV block (e.g., 2:1 and 3:1, or 3:1 and 4:1). In these conditions, tiny variations in the timing of atrial inputs impinging the AV node could discriminate between conduction or block of the beats. During inspiration, the lengthening of atrial intervals results in longer recovery times and thus in a higher probability of conduction. Conversely, expiration, producing a shortening of atrial intervals and thus a shortening of recovery times, is associated with a lower probability of conduction. Thus inspiration can consistently result in a lower level of block corresponding to shorter ventricular intervals, and expiration can result in a higher degree of block with longer ventricular intervals. Differently, in patients with fixed AV conduction, the rhythm is stable and the tiny modulation of atrial intervals do not change the level of AV block. In this case, ventricular intervals are mainly determined by the sum of atrial intervals and thus a shortening of recovery times, is associated with a lower probability of conduction. Thus inspiration can consistently result in a lower level of block corresponding to shorter ventricular intervals, and expiration can result in a higher degree of block with longer ventricular intervals. Differently, in patients with fixed AV conduction, the rhythm is stable and the tiny modulation of atrial intervals do not change the level of AV block. In this case, ventricular intervals are mainly determined by the summation of atrial intervals (see Fig. 1); thus the prolongation of atrial intervals in inspiration results in a lengthening of ventricular intervals, whereas expiration has the opposite effect.

The inclusion of the concealed conduction term in the basic AV model was necessary to reproduce the presence of different levels of coherence between respiration and ventricular activ-
ity, suggesting that concealed conduction could influence the level of cardiorespiratory coupling at the ventricular level. In fact, concealed conduction was shown to significantly affect variable AV conduction ratios, whereas it influenced constant AV conduction ratios to a less extent. Thus more stable conduction rhythms are less exposed to the effect of concealed conduction with preservation of a high level of linear coupling, whereas variable AV conduction ratios, being intrinsically more unstable, may undergo a significant reduction of coherence, which is consistent with the different levels of linear coupling observed in patients.

In our model we assumed cardiorespiratory interactions to occur solely at the atrial level by a respiratory modulation of atrial intervals, which constituted the input of the AV node. Nevertheless, since the conduction through the AV node also can be influenced by extrinsic factors, such as autonomic tone (41, 43, 44, 47), it is plausible that respiration may exert a secondary modulation on ventricular activity through additional pathways. Previous work indeed showed that, in conditions of atrial pacing at low frequencies, the AV conduction time presented an oscillation at the frequency of respiration (41, 66). The oscillation was explained with the waxing and waning of vagal activity to the AV node occurring in association with respiration, resulting in a negative dromotrophic effect during expiration and a positive effect during inspiration. Thus respiratory autonomic effects could hypothetically counterbalance the lengthening and shortening of ventricular intervals in patients with constant AV conduction ratios, whereas they could enhance the pattern of ventricular intervals in patients with variable AV conduction. However, the study of Warner et al. (66), performing atrial pacing over a wide range of frequencies, showed that the respiratory modulation was significant at low heart rates, whereas at higher rates, such as those observed during atrial flutter, blood pressure effects became dominant. On the whole, however, the ability of the model to depict the main features of cardiorespiratory interactions at the atrial level suggests that mechanically mediated respiratory modulations of atrial activity, filtered by the AV node, play a main role in the determination of ventricular modulation patterns, whereas other factors should be of secondary importance.

Potential clinical implications. Although the physiological role of RSA remains uncertain, an emerging hypothesis suggests that RSA functions to improve the pulmonary gas exchange, synchronizing the heartbeat with respiratory rhythm (68). The increase of the heart rate during inspiration and its decrease during expiration would match alveolar ventilation with perfusion within each respiratory cycle, providing a higher number of heartbeats when alveolar ventilation is maximal, while suppressing unnecessary heartbeats when ventilation is minimal, thus saving energy. In this perspective, the reversal, paradoxical respiratory arrhythmia observed in atrial flutter patients might result in increased physiological dead space and intrapulmonary shunt, exacerbating overall ventilation-perfusion mismatch and therefore contributing to worsen the compromised hemodynamics of atrial flutter patients.

Conclusions. In this study, cross-spectral analysis was used to characterize the presence of cardiorespiratory interactions during atrial flutter. The reverse modulation of atrial intervals by respiration, the small temporal delay, and the absence of significant frequency-dependent behaviors constitute the fingerprint of the interaction at the atrial level, whereas more complex behaviors and phase-inversion phenomena, imputable to the intrinsic functional properties of the AV node, characterize the phenomenon at the ventricular level. The potential significance of this interaction still has to be evaluated; nevertheless, assuming that normal RSA functions to optimize pulmonary gas exchange, the inversion of a normal cardiorespiratory interaction may have deleterious effects on the already hemodynamically compromised conditions of atrial flutter patients.

GRANTS

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REFERENCES


