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Mechanical modulation of atrial flutter cycle length

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Abstract

Although atrial flutter (AFL) is considered a highly regular rhythm, small fluctuations in cycle length have been described. The mechanisms responsible for these interval oscillations have been investigated by recent studies in humans which have shown that cyclic variations in atrial volume and pressure following ventricular contraction may account for the spontaneous variability of AFL. Other studies have shown that variations in the dimensions of the atria, caused by hemodynamical alterations due to imposed manoeuvres, directly modify the rate of AFL. All this evidence has led to the development of the mechano-electrical feedback (MEF) hypothesis, which assumes that changes in atrial volume directly affect AFL cycle length variability by modifying the conduction properties of the circulating impulse in the atrium.

In the present study, we re-examined the variability pattern of typical AFL by spectral analysis aiming to support the MEF hypothesis for AFL cycle length variability. In a study population of 30 patients with typical AFL, we observed that AFL cycle length presented a spontaneous beat-to-beat variability, composed of two oscillations: a main oscillation at the frequency of ventricular contraction (1.70 ± 0.48 Hz, spectral power: $15.4 \pm 17.6\,ms^2$) and a second oscillation at the frequency of respiration (0.32 ± 0.07 Hz, spectral power: $2.9 \pm 2.6\,ms^2$). Both ventricular and respiratory oscillations persisted after pharmacologic autonomic blockade (ventricular spectral power: $17.7 \pm 14.7\,ms^2$ (before block) vs $20.2 \pm 18.3\,ms^2$ (after block), $p = NS$; respiratory spectral power: $6.0 \pm 3.8\,ms^2$ (before block) vs $5.0 \pm 3.4\,ms^2$ (after block), $p = NS$), suggesting a non-neurally mediated underlying mechanism. Contrary to respiratory modulation of heart rate during sinus rhythm, respiratory AFL cycle length oscillations displayed a reverse pattern, with longer cycle lengths during inspiration and shorter during expiration ($AA_{insp} = 223.2 \pm 28.6$ ms vs $AA_{exp} = 221.1 \pm 28.2$ ms, $p < 0.0005$), which was consistent with a mechanical modulation of AFL reentry.

The use of spectral analysis techniques applied to ventricular interval series and combined with computer simulations of atrioventricular conduction showed that the respiratory oscillation of atrial cycle length determined an oscillation in ventricular intervals with longer intervals during inspiration and shorter during expiration ($VV_{insp} = 639.9 \pm 186.0$ ms vs $VV_{exp} = 634.8 \pm 182.9$ ms, $p < 0.05$). Ventricular interval oscillations resulted amplified by a factor 1.8 with respect to corresponding atrial cycle length oscillations. Thus, the mechanical fluctuations in AFL cycle length, although of small amplitude, might become clinically relevant through a magnified effect on ventricular variability.

Keywords: Atrial flutter; Cycle length variability; Stretch; Mechano-electrical feedback; Reentry

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Contents

1. Introduction

After atrial fibrillation, atrial flutter (AFL) is the most important and most common atrial tachyarrhythmia. Atrial flutter is a reentrant arrhythmia which requires anatomic or functional barriers to maintain its activation (Waldo, 2000; Saoudi et al., 2001). Typical AFL is caused by a reentrant excitation in the right atrium which rotates around the tricuspid annulus with the crista terminalis and tricuspid annulus as barriers. Atypical AFL may originate from the right or left atrium without involving the cavotricuspid isthmus (Waldo, 2000). Although AFL is considered a highly regular rhythm, small fluctuations in cycle length have been documented (Lewis, 1920; Wells et al., 1979; Lammers et al., 1991). The variability of AFL cycle length has been evaluated to be approximately 5 ms (standard deviation, S.D.). The mechanisms responsible for these cycle length oscillations were investigated showing that spontaneous AFL cycle length variations were not randomly distributed, but rather occurred on a beat-to-beat basis in association with the QRS complex (Lammers et al., 1991; Ravelli et al., 1994). The pattern of typical AFL cycle length comprised a phase of cycle length increase, the reaching of a maximum value 400–500 ms after the onset of the QRS complex and a phase of decrease (see Fig. 1). The prolongation of AFL cycle coincided with the increase in atrial pressure and volume during the ventricular ejection phase (Ravelli et al., 1994). The synchronism between changes in AFL cycle length and atrial pressure/volume indicated that cyclic variations in atrial pressure/volume following ventricular contraction modulated AFL cycle length, accounting for the spontaneous variability of the arrhythmia (Ravelli et al., 1994; Yamashita et al., 1994).

The existence of a relationship between atrial size and AFL rate was outlined by several studies many decades ago. In dogs, the rate of experimentally induced AFL varied with atrial size and distension. Acute or chronic atrial enlargement slowed the flutter rate (Hayden et al., 1967; Boyden and Hoffman, 1981). Similarly, AFL rate was lower in humans with markedly enlarged atria (Rytand et al., 1958). The role of atrial volume in the determination of AFL rate was pointed out by Waxman's studies (Waxman et al., 1991, 1992). The first study examined changes in AFL rate in response to three manoeuvres (passive tilting, Valsalva manoeuvre and

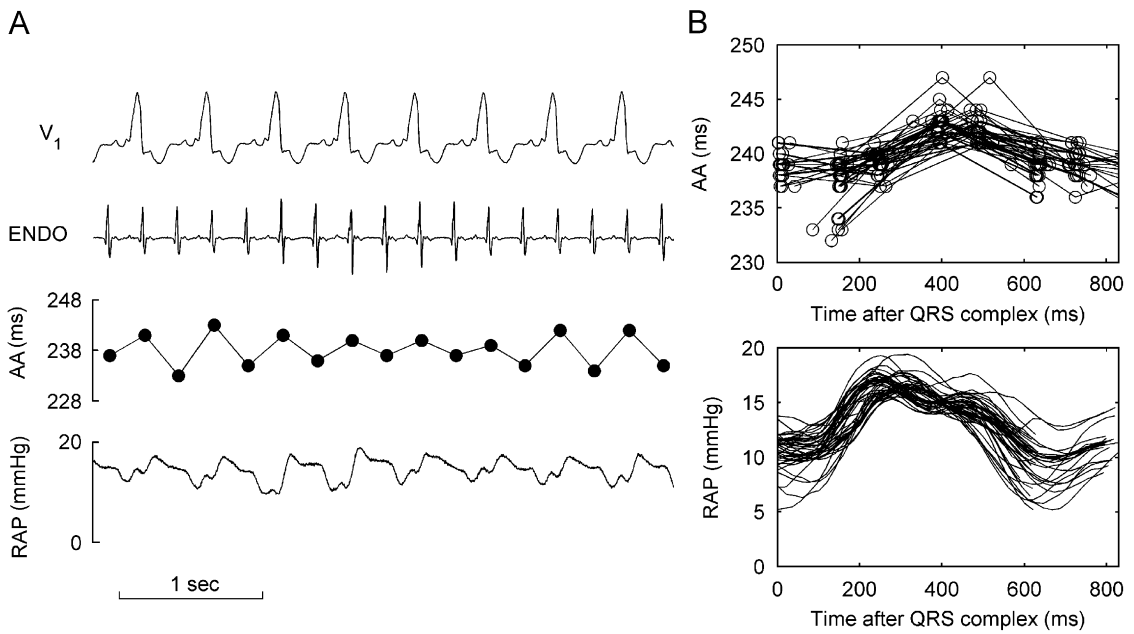

Fig. 1. Beat-to-beat fluctuations in atrial flutter cycle length and correlation with atrial pressure changes during ventricular cycle. Panel A: ECG (V_1), atrial electrogram (ENDO), atrial cycle length series (AA) and right atrial pressure (RAP) signal during atrial flutter in a patient with 2:1 AV conduction. Panel B: Comparison between atrial flutter cycle length variations and changes in atrial pressure after the onset of QRS in a patient with variable AV conduction. Note the synchronism between atrial flutter cycle length variations and atrial pressure changes. Modified from Ravelli et al. (1994); with permission from *Circulation*.

respiration) which predictably affected venous return and hence cardiac volume. Passive upright tilting, the strain phase of the Valsalva manoeuvre and expiration, three interventions which reduced cardiac size, increased the rate of AFL independently of autonomic tone (Waxman et al., 1991). The subsequent study (Waxman et al., 1992) examined the effects of 1:1 atrioventricular (AV) conduction on AFL rate in patients and dogs. The development of 1:1 AV conduction during AFL increased atrial pressure, which in turn slowed down AFL rate. Moreover, inferior vena cava occlusion in dogs consistently shortened the average AFL cycle length (Waxman et al., 1992). All these effects were independent of vagus nerve activity or adrenergic agonist administration, implying that changes in atrial pressure and volume directly affected the characteristics of AFL circuit, and thus could modulate the AFL rate. A correlation between atrial volume and mean AFL period was observed also by Vulliemin et al. (1994), who underlined the importance of the right heart preload and atrial size for the electrophysiological characteristics of type I AFL. Thus, alterations in the dimensions of the atrial walls, whether caused by imposed manoeuvres or by spontaneous ventricular beats, directly modified the cycle length of AFL.

All these studies have led to the development of the mechano-electrical feedback (MEF) hypothesis, which assumes that changes in atrial volume directly affect AFL variability by modifying the conduction properties of the circulating impulse in the atrium (Lammers et al., 1991; Ravelli et al., 1994).

The aim of the work presented here is to re-examine the variability pattern of AFL by spectral analysis to elucidate the mechanisms of beat-to-beat variations in AFL cycle length and to support the MEF hypothesis for AFL cycle length variability. Firstly spectral analysis and power band interpretation were used for a thorough characterization of the oscillations composing AFL cycle length variability, including a detailed analysis of the less described respiratory-related oscillation. Then, the effects of autonomic blockade on AFL cycle length variability were analyzed to test the role of autonomic tone in the generation of AFL cycle length variations. Finally the impact of the small AFL cycle length variations on ventricular rate variability was examined. A preliminary version of part of this study was presented in abstract form (Ravelli et al., 1995).

2. Materials and methods

2.1. Patient population and electrophysiological study

Thirty patients (68.0 ± 8.8 years) with typical AFL and 2:1 or 4:1 AV conduction were studied. In all patients antiarrhythmic treatment had been suspended at least five half-lives before the study. The study was performed in the hospital Electrophysiology Laboratory in Trento, in accordance with the principles outlined in the Declaration of Helsinki. All patients gave written informed consent.

After light sedation with diazepam 10 mg IM, a bipolar catheter was advanced into the oesophagus for atrial electrogram recording (band-width, 30–500 Hz). Ventricular activity was recorded from surface ECG, while 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).

After 10 min baseline recordings were acquired in all 30 patients, the following specific protocols were applied to subgroups of patients to better disclose the sources of atrial and ventricular variability. *Protocol 1.* To study the effects of ventricular contraction on atrial cycle length variability, recordings were obtained during ventricular pacing at different rates in five patients with a previously implanted permanent VVI programmable pacemaker. *Protocol 2.* To study the effects of respiration on atrial and ventricular interval variability, recordings were acquired in 10 patients during controlled respiration at increasing rates following a metronome. *Protocol 3.* To study the involvement of the autonomic nervous system in AFL variability, recordings were obtained after autonomic blockade in 12 patients. Beta-adrenergic receptor blockade was accomplished by intravenous propanolol (0.2 mg/kg), while muscarinic receptor blockade was achieved by intravenous atropine (0.04 mg/kg) (Jose and Taylor, 1969). Propanolol was administered first to avoid the potential induction of 1:1 AV conduction by atropine.

2.2. Data measurement and analysis

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 oesophageal lead and QRS complexes from the surface ECG in order to provide a beat-to-beat measure of atrial (AA) and ventricular (VV) intervals. Specifically to extract atrial activation times, atrial electrograms were bandpass 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) (Botteron and Smith, 1995). Atrial depolarizations were detected in correspondence with the peaks of the filtered signal, which were larger than an adaptative 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 AFL allowed a high precision in the estimation of activation times. Ventricular activation times were measured from the ECG by identifying the time of QRS maxima/minima, depending on the surface lead analysed.

2.3. Time domain and frequency domain analysis

Atrial and ventricular series of 300 consecutive intervals were constructed and characterized in the time domain by computing their mean value, S.D. and range. In addition mean values and S.D. were provided separately for intervals occurring during inspiration and expiration.

The main oscillatory components of atrial and ventricular interval series were determined by spectral analysis. Power spectral density (PSD) estimates were obtained applying an autoregressive model (Johnsen and Andersen, 1978). The model order was set to 16 and 12 for atrial and ventricular interval series, respectively. The power of the peaks was calculated by evaluating the complex residues of the spectral density estimator, which allowed decomposition of the spectra into a sum of components. Each detected component was characterized by its central frequency, the peak spectral power (PSP, expressed in ms^2) and the percentage spectral power (i.e. peak spectral power over total spectral power). As for temporal analysis, power spectra were calculated over 300 consecutive intervals, which yielded a reliable estimate of the spectral parameters (Marple, 1987; Task Force, 1996). 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. Ventricular and respiratory frequencies were estimated by applying spectral analysis to windows of the ECG and respiratory signals synchronous with the interval analysed windows. The signals were down-sampled at the mean frequency of atrial activation.

2.4. Statistical analysis

Student's two-tailed *t*-test for paired and unpaired data were applied where appropriate to test statistical significance. A value of $p<0.05$ was considered statistically significant.

2.5. Computer simulation

In order to estimate the amount of ventricular variability originating from atrial variability, simulated ventricular series were calculated by applying an atrioventricular node model (Shrier et al., 1987) to real atrial series. The model included the basic properties of nodal conduction and refractoriness. It assumed that an atrial beat was conducted to the ventricles only if the recovery time VA_{i-1} from the previous conducted beat was longer than a constant refractory period θ, otherwise the beat was blocked. If conduction occurred, the nodal conduction time AV_i was assumed to depend on the previous recovery time VA_{i-1} according to the exponential function:

$$AV_i = AV_{min} + \alpha\, e^{-VA_{i-1}/\tau} \quad \text{for } VA_{i-1} > \theta,$$

where the parameter AV_{min} was the minimal conduction time through the AV node and α and τ were positive constants. For a given set of model parameters and a given atrial input series, the model iteratively determined the sequence of ventricular beats, providing a simulated series of ventricular intervals.

Simulated ventricular series were calculated in each patient and quantitatively compared with the corresponding real ventricular series. The agreement between real and simulated series was estimated on a beat-to-beat basis by calculating the average distance *D* between the series (Jorgensen et al., 2002). The minimization of *D* over the (AV_{min}, α, τ, θ) parameter space was used as criterion to identify in each patient the set of parameters in the model which provided the best agreement with real data. The percentage of ventricular variability arising from atrial variability was estimated by the ratio of simulated to real ventricular interval S.D.s.

3. Results

3.1. Sources of AFL cycle length variability

The time series and power spectral density of AFL cycle lengths in a representative patient are shown in Fig. 2. Atrial cycle lengths (top left panel) present a spontaneous beat-to-beat variability, ranging from 214 to 240 ms. The variability of atrial cycle lengths is not random, since two periodic patterns underlie the series. This is evident in the power spectrum of atrial cycle length (top right panel), where the variability of atrial cycle lengths is shown to be composed of two main peaks: a low-frequency peak at 0.21 Hz and a high-frequency peak at 1.11 Hz. The high-frequency peak is dominant and comprises 71.8% (27.9 ms^2) of the total spectral power, while the low-frequency peak includes 21.3% (8.3 ms^2) of the total power.

To give a correct interpretation of the two spectral components, the AFL cycle length spectrum was compared with the spectra of the corresponding ECG (central right panel) and respiratory signal (bottom right panel). It is evident that the AFL cycle length high-frequency peak (*V* peak) is aligned with the peak of the ventricular rate in the ECG, while the low-frequency peak (*R* peak) is aligned with the peak of the respiratory signal.

The time and frequency analysis on the overall population of 30 patients confirmed these results. In the overall population atrial cycle lengths presented a spontaneous variability of 4.3 ± 2.2 ms (range 1.8–8.0 ms). Ventricular and respiratory oscillations composed the atrial variability spectrum, with the *V* peak, at the

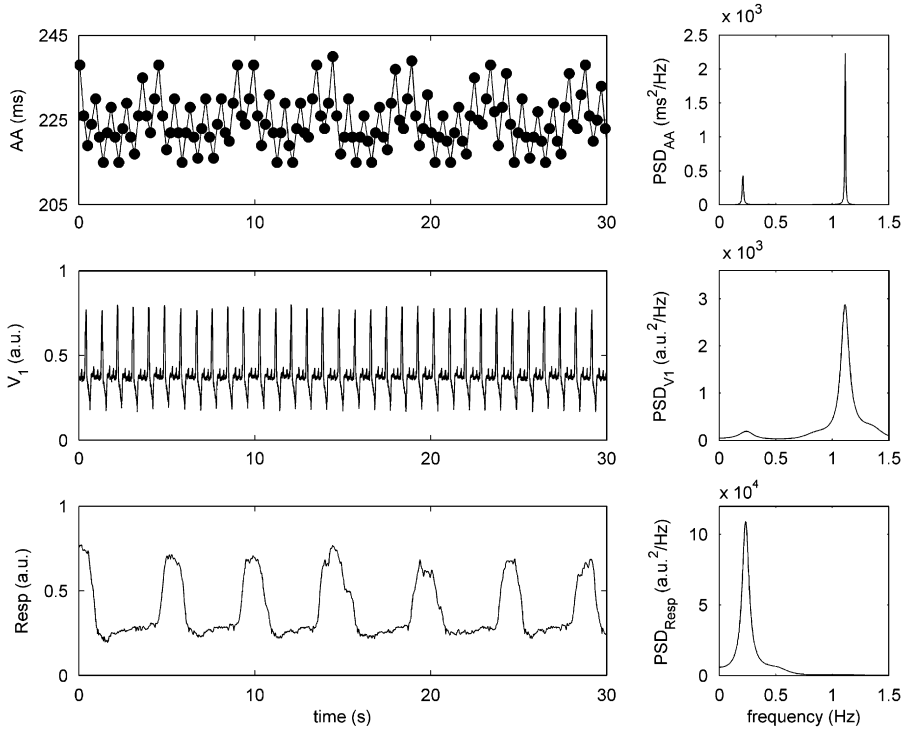

Fig. 2. Sources of atrial flutter cycle length variability. Left panels: Atrial cycle length series (top) and corresponding ECG, lead V_1 (middle), and respiratory signal (bottom) in a representative patient. Right panels: Power spectral density of atrial cycle length series (top), ECG (middle) and respiratory (bottom) signals. Note that the atrial cycle length spectrum shows two mayor spectral components, in correspondence with the respiratory (0.21 Hz) and ECG (1.11 Hz) peaks, respectively.

frequency of 1.70 ± 0.48 Hz, comprising $54.5 \pm 25.1\%$ of the total spectral power ($15.4 \pm 17.6\,ms^2$) and the *R* peak, at the frequency of 0.32 ± 0.07 Hz, comprising $22.0 \pm 24.8\%$ ($2.9 \pm 2.6\,ms^2$) of the total power, thus showing the prevalence of the ventricular oscillation in spontaneous conditions.

3.2. Modulation of AFL cycle length by ventricular activity

The correlation between the high-frequency peak of the AFL cycle length spectrum and the ventricular rate was evidenced during ventricular pacing at different rates in five patients with a previously implanted programmable pacemaker. The results of the analysis in a representative patient are displayed in Fig. 3, for pacing frequencies of 60, 70, 80 and 90 bpm. Different patterns of atrial variability (left panels) emerged when the ventricular pacing frequency was progressively increased. The increase in ventricular frequency involved a progressive shift toward higher frequencies of the atrial high-frequency peak (right panel), while the low-frequency peak remained unchanged. This behaviour was observed in all five patients with implantable pacemaker and confirmed the ventricular origin of the high-frequency oscillation.

3.3. Modulation of AFL cycle length by respiratory activity

The correlation between the low-frequency peak of the spectrum and the respiratory rate was pointed out in 10 patients under controlled, metronomic respiration. The results of the analysis in a representative patient are displayed in Fig. 4, for respiratory frequencies of 0.1, 0.2, 0.3 and 0.4 Hz (from top to bottom). Periodic patterns of atrial variability (left panels) with decreasing periods emerged when the respiratory frequency was progressively increased. The increase in respiratory frequency involved a progressive shift toward higher frequencies of the atrial low-frequency peak (right panel), while the high-frequency peak remained unchanged.

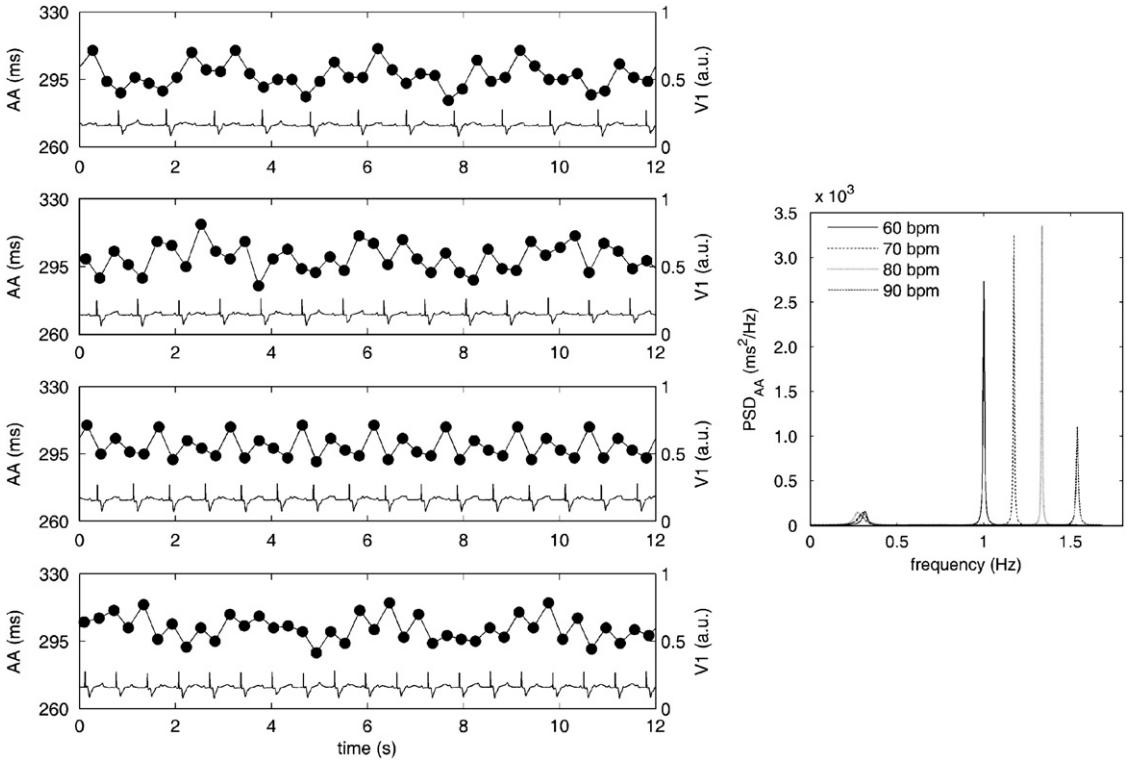

Fig. 3. Atrial flutter cycle length series (left panels) and corresponding power spectral density (right panels) during ventricular pacing by VVI programmable pacemaker at increasing frequency (60, 70, 80, and 90 bpm, from top to bottom) in a representative patient. ECG traces are displayed under corresponding atrial series. The increase in ventricular frequency changes the pattern of AA variability and progressively shifts the ventricular peak in atrial power spectrum toward higher frequencies.

This behaviour was observed in all 10 patients under controlled respiration and confirmed the respiratory origin of the low-frequency oscillation.

The relationship between the respiratory pattern of AFL cycle lengths and the inspiratory/expiratory phases was studied in the overall population of 30 patients.

As shown in the representative example in Fig. 5, the oscillation of atrial cycle lengths with respiration displayed a reverse pattern with longer intervals during inspiration than expiration. The lengthening of AFL cycle length during inspiration and its shortening during expiration was observed in all 30 patients ($AA_{insp} = 223.2 \pm 28.6$, $AA_{exp} = 221.1 \pm 28.2$, $p < 0.0005$).

3.4. Autonomic blockade

The involvement of autonomic tone variations in the generation of AFL cycle length variability was tested by autonomic blockade. Panel (A) of Fig. 6 compares atrial variability in basal condition (upper panels) and after autonomic blockade (lower panels) in a representative patient. The overall variability (S.D.) of atrial cycle lengths was not significantly affected by autonomic blockade (before block: 6.3 ms, after block: 6.0 ms) and the two oscillation peaks were preserved. In fact the ventricular and respiratory powers were, respectively, 27.7 and 8.4 ms^2 in basal condition and 24.9 and 7.4 ms^2 after autonomic blockade.

The results of the analysis on the population of patients under autonomic blockade ($N = 12$), displayed in panel (B), confirmed that both time and frequency indexes were not significantly altered by pharmacological denervation. In fact the S.D. of atrial series was not significantly different after autonomic blockade (before block: 5.4 ± 2.1 ms, after block: 5.2 ± 2.3 ms, $p =$ NS), as well as the powers of the ventricular (before block: 17.7 ± 14.7 ms^2 ($49.3 \pm 20.2\%$), after block: 20.2 ± 18.3 ms^2 ($54.7 \pm 23.1\%$), $p =$ NS) and respiratory peaks (before block: 6.0 ± 3.8 ms^2 ($24.1 \pm 20.1\%$), after block: 5.0 ± 3.4 ms^2 ($23.1 \pm 21.8\%$), $p =$ NS).

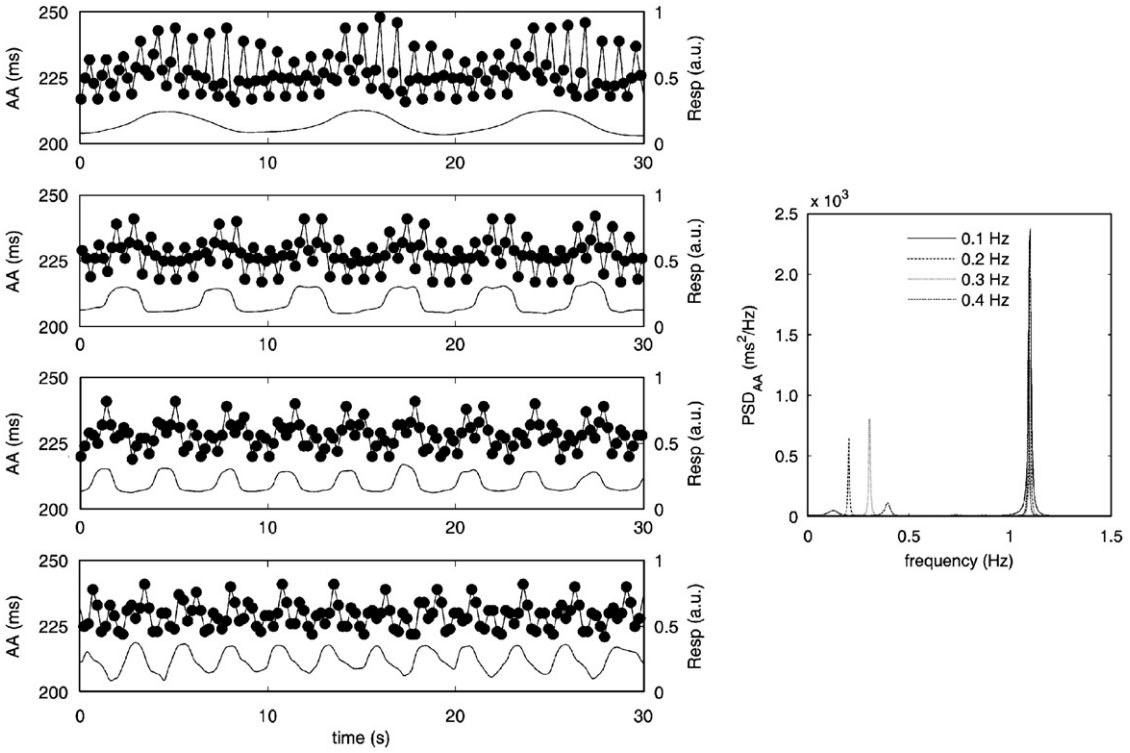

Fig. 4. Atrial flutter cycle length series (left panels) and corresponding power spectral density (right panels) during controlled, metronomic respiration at increasing frequency (0.1, 0.2, 0.3, 0.4 Hz, from top to bottom) in a representative patient. Respiration traces are displayed under corresponding atrial series. The increase in respiratory frequency changes the patterns of AA variability and progressively shifts the respiratory peak in atrial power spectrum toward higher frequencies.

3.5. Sources of ventricular interval variability

The series of ventricular intervals during AFL in a representative patient with 2:1 AV conduction is shown in Fig. 7. Ventricular intervals display a spontaneous beat-to-beat variability (central panel), ranging from 438 to 453 ms. The variability is characterized by a slow oscillation synchronous with the respiratory oscillation of atrial cycle lengths (top panel), with longer ventricular intervals during inspiration and shorter intervals during expiration (447.8 ± 1.2 ms vs 441.9 ± 2.1 ms, $p < 0.05$). Ventricular interval oscillations are amplified by a factor 1.26 (expressed as S.D.s ratio) with respect to atrial cycle length oscillations.

The results on the overall population of 30 patients showed ventricular intervals oscillating at the respiratory frequency with an average S.D. of 7.6 ± 6.0 ms (range 2.4–22.6 ms) and $67.7 \pm 26.9\%$ (68 ± 133 ms^2) of the spectral power in the respiratory frequency band. Ventricular intervals were significantly longer during inspiration than expiration in all patients ($VV_{insp} = 639.9 \pm 186.0$ ms vs $VV_{exp} = 634.8 \pm 182.9$ ms, $p < 0.05$, $N = 30$). Higher variability in ventricular intervals was observed in 4:1 patients with respect to 2:1 patients (S.D. $= 9.9 \pm 7.8$ ms vs 5.29 ± 1.5 ms), although the difference was not statistically significant. In all patients the amplitude of ventricular oscillations resulted significantly higher ($p < 0.05$) than that of corresponding atrial cycle lengths, with a ratio of ventricular to atrial series S.D.s of 1.8 ± 0.9.

To quantify the amount of ventricular variability originating from atrial variability, simulated ventricular series were calculated by applying a model of AV conduction to real atrial series. Simulated series (empty dots) were able to reproduce on a beat-to-beat basis the variability of real ventricular series (filled dots), as shown in the example of Fig. 7 (central panel), where simulated and real series are superimposed. In this case the simulated series, obtained setting the model parameters to $AV_{min} = 24$ ms, $\alpha = 0$ ms, $\theta = 200$ ms, reproduced 73.4% of ventricular variability. The results on the overall population of 30 patients confirmed the ability of the model to reproduce $67.4 \pm 23.4\%$ of ventricular variability with a good beat-to-beat agreement testified by

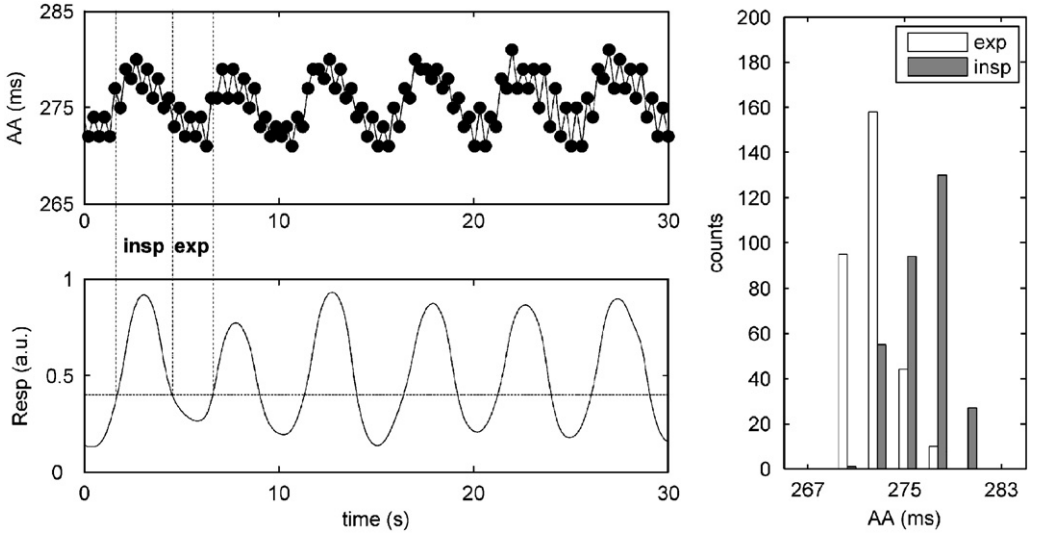

Fig. 5. Dependence of atrial flutter cycle length on respiratory phase. Left panels: Atrial cycle length series (top) and corresponding respiratory signal (bottom) in a representative patient. Inspiration (insp) and expiration (exp) phases are indicated and divided by the horizontal line in the respiratory signal. Right panel: Distributions of atrial cycle lengths occurring during expiration (white bars) and inspiration (grey bars). Note the paradoxical lengthening of atrial cycle lengths during inspiration with respect to expiration.

the small distance $D = 3.2 \pm 2.1$ ms. Better results were obtained in 2:1 patients vs 4:1 patients, where $78.2 \pm 23.1\%$ vs $59.1 \pm 21.2\%$ ($p < 0.05$) of the variability was predicted. Model parameter values in the population were estimated in $AV_{min} = 210 \pm 166.7$ ms, $\alpha = 89 \pm 130.7$ ms, $\tau = 333 \pm 344.5$ ms, $\theta = 291 \pm 181.7$ ms. Significantly longer conduction times ($AV_{min} = 285.1 \pm 182.9$ ms vs 114 ± 75.0 ms, $p < 0.05$) and refractory periods ($\theta = 361.1 \pm 205.8$ ms vs 201 ± 96.7 ms, $p < 0.05$) were observed in patients with 4:1 AV conduction than in patients with 2:1 AV conduction, which might be attributed to a different contribution of concealed conduction in the two groups.

4. Discussion

The data presented support our initial hypothesis that AFL cycle length oscillations are mechanically mediated.

The main results of the present paper can be summarized as follows:

(1) Atrial flutter cycle length presents a beat-to-beat variability, composed of two oscillations: the prevalent at the frequency of ventricular contraction and the other at the frequency of respiration.
(2) Both ventricular and respiratory AFL cycle length oscillations persist after autonomic blockade, suggesting the two oscillations to be independent of autonomic tone.
(3) Respiratory AFL cycle length oscillations show longer cycle lengths during inspiration than expiration, opposite to the usual respiratory modulation observed in sinus arrhythmia; this reverse phase relation adds evidence to the mechanical origin of respiratory AFL cycle length oscillations.
(4) The respiratory mechanical modulation of atrial cycle lengths gives rise to amplified respiratory oscillations in ventricular intervals, which also show a reverse variability pattern.

In this study we presented a thorough characterization of the spontaneous variability of AFL. The quantification of AFL cycle length variability was accomplished by time domain and frequency domain techniques. In particular frequency domain analysis was performed by an autoregressive model, which provided power spectral density distribution and automatically identified the number, amplitude and central

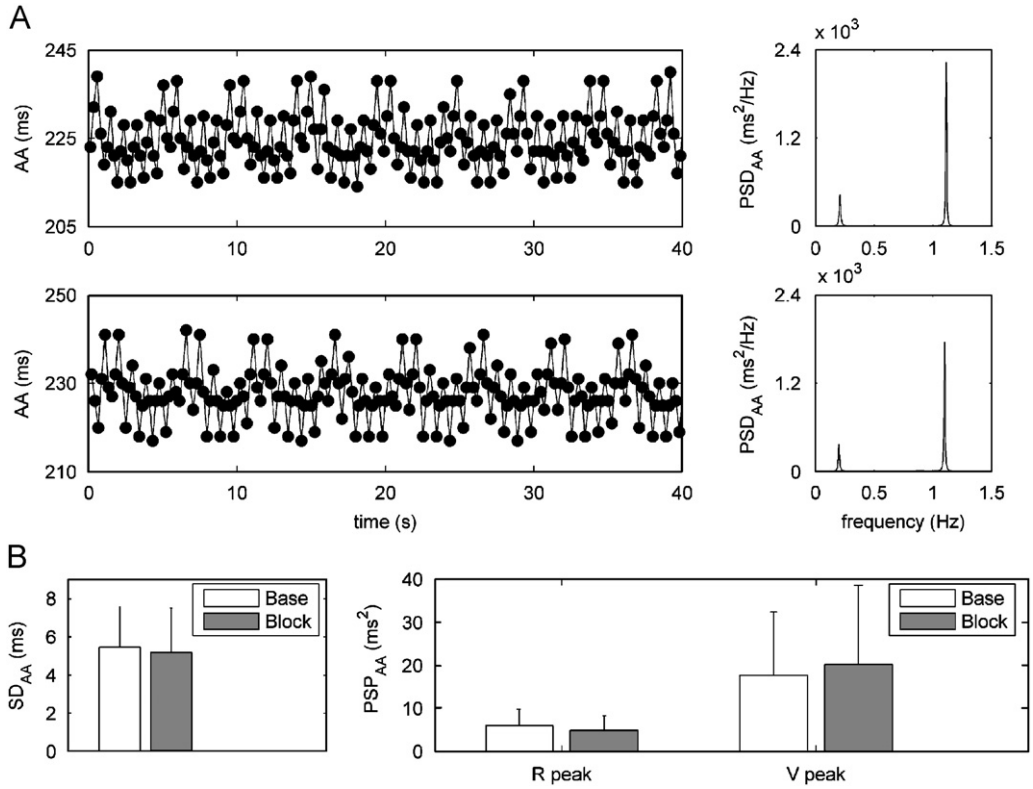

Fig. 6. Comparison of atrial flutter cycle length variability in basal condition and after autonomic blockade in a representative patient (A) and in the overall group ($N = 12$) (B). (A) Atrial cycle length series (left panels) and corresponding power spectral densities (right panels) in basal condition (upper panels) and after autonomic blockade (lower panels) show that atrial variability patterns persist after autonomic blockade and the two main oscillation peaks are preserved. (B) The atrial cycle length S.D.s (left panel) and the spectral powers (PSP) of the ventricular (*V* peak) and respiratory peaks (*R* peak) (right panel) remain almost unaffected after autonomic blockade (grey bars) with respect to basal condition (white bars).

frequency of the oscillatory components (Johnsen and Andersen, 1978), thus allowing a complete, quantitative description of AFL variability. Spectral analysis has been widely applied to cardiovascular series to quantify heart rate variability, thus leading to the identification of the main oscillations of cardiovascular rhythms (Akselrod et al., 1981; Eckberg, 2000; Malliani, 2005). More recently spectral techniques have been used in the context of atrial arrhythmias, where dominant frequency analysis has been applied to atrial electrograms for the analysis of atrial rate during atrial fibrillation (Sanders et al., 2005).

The application of parametric spectral analysis techniques to AFL cycle length series in this study allowed us to identify two main oscillatory components in atrial variability, to quantify their spectral power and to correlate them with ventricular and respiratory activities. In fact, the spontaneous variability of AFL cycle length was shown to be composed of a dominant oscillation at the frequency of ventricular contraction, which constituted 54% of the total spectral power, and a second oscillation at the frequency of respiration, which represented 22% of the power. The correlation of AFL variability with ventricular and respiratory activities was dynamically evidenced by performing driven manoeuvres. Ventricular pacing in patients with implanted pacemaker showed that changes in ventricular frequency shifted the high-frequency oscillation peak in atrial cycle lengths. Similarly in patients under controlled respiration changes in respiratory frequency shifted the low-frequency cycle length oscillation peak.

Spectral analysis was applied to atrial series measured before and after autonomic blockade to quantitatively evaluate the involvement of the autonomic nervous system in AFL cycle length variability. The results of the analysis showed the variability to persist after autonomic blockade, since no significant decrease in atrial cycle length spectral powers and standard deviations was observed after administration of

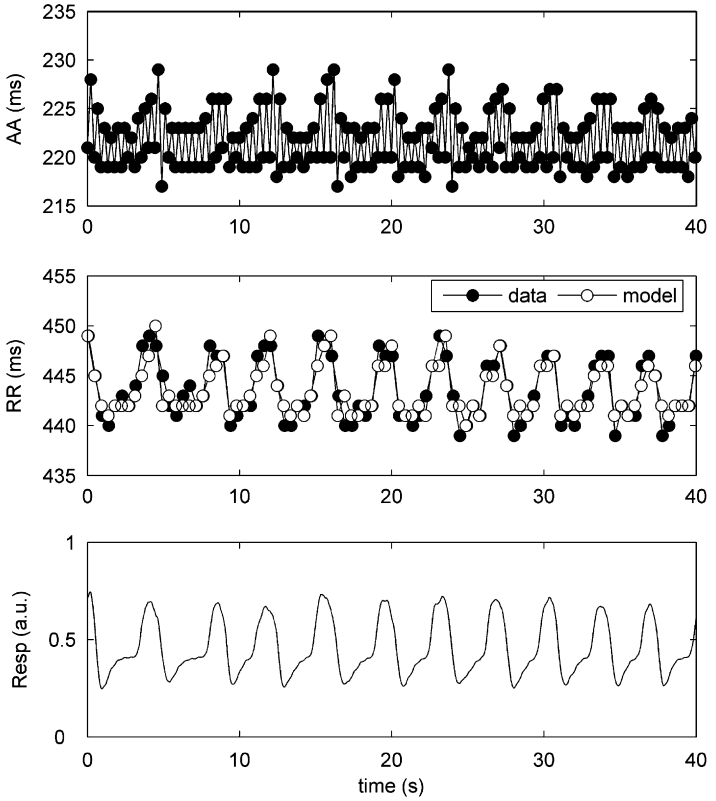

Fig. 7. Sources of ventricular interval variability during atrial flutter. Atrial (upper panel) and ventricular (central panel) interval series and corresponding respiratory signal (lower panel) in a representative patient with 2:1 AV conduction. Simulated ventricular interval series (empty dots) are superimposed to real series (filled dots).

blocking agents. This finding supports the conclusion that the effect of ventricular contraction and respiration on AFL cycle length variability is not mediated via a neural mechanism. The results are consistent with the study of Waxman et al. (1991), which showed that autonomic blockade did not significantly alter the effects of tilt and Valsalva manoeuvres on AFL mean rate, and with the study of Stambler and Ellenbogen (1996), who showed the presence of ventricular and respiratory components in AFL cycle length variability in heart transplant recipients.

In agreement with Waxman et al.'s results (1991) showing a reduction of atrial rate by expiration, the present study demonstrates that respiration paradoxically affects AFL cycle length, since inspiration prolongs AFL cycle length and expiration shortens it. This is opposite to the effects of respiration during sinus rhythm (respiratory sinus arrhythmia), where heart rate increases during inspiration and decreases during expiration (Yasuma and Hayano, 2004).

Several mechanisms have been proposed for the generation of respiratory sinus arrhythmia, including direct and/or indirect interaction of respiratory and cardiac control centres in the brain or hemodynamically induced changes in autonomic nervous control (Eckberg, 2003). These mechanisms would affect heart rate via fluctuations in cardiac parasympathetic efferent activity (Piepoli et al., 1997; Eckberg, 2003). Nevertheless the presence, although reduced, of respiratory sinus arrhythmia in heart transplant recipients (Bernardi et al., 1989) suggested that non-neurally mediated, intrinsic, mechano-sensitive mechanisms may partially contribute to the phenomenon (Kohl et al., 1999). In particular, since respiratory changes in intrathoracic pressure alter systemic venous return to the heart, thus changing right atrial preload in synchrony with respiratory cycle, respiration may mechanically modulate heart rate by stretch of the sinus node pacemaker (Kohl et al., 1999; Cooper and Kohl, 2005).

The effects of alteration of venous return/right atrial volume by respiration may indeed explain the modulation of AFL cycle length, since respiratory oscillations persisted after autonomic blockade. In the case of AFL, the mechanical modulation is exerted on a reentrant circuit, which results in a paradoxical modulation. In fact the lengthening of the cycle length during inspiration is associated with the increase in right atrial volume, consistent with inspiratory augmented venous return to the heart (Robotham et al., 1978; Ferguson et al., 1989), while opposite effects are associated to expiration. The transduction mechanisms by which changes in atrial volume may affect AFL reentrant mechanism and thus AFL cycle length are discussed in Section 5.2.

In addition to the study of atrial variability, this work presents an analysis of ventricular variability during AFL. The application of spectral analysis to ventricular interval series showed ventricular variability during AFL to be composed of a main oscillation at the frequency respiration, which represented 68% of the ventricular spectral power.

Ventricular activation is the result of the interplay between the atrial input and the filtering action of the AV node region. The filtering of the AV node can result in a wide variety of delays and patterns of beat-to-beat changes in delays, due to both intrinsic functional properties of the AV node (Billette and Nattel, 1994) and extrinsic factors. Concerning functional properties, AV nodal conduction time has been shown to be rate-dependent (Billette et al., 1976) and mainly determined by the previous recovery time (Teague et al., 1976; Shrier et al., 1987). According to the concept of recovery curve, a reduction in atrial cycle interval might slow or inhibit AV conduction, while a prolongation in cycle interval might facilitate conduction. Moreover, AV conduction can be influenced by the history of stimulation, through fatigue and facilitation mechanisms (Sun et al., 1995), and by the presence of concealed conduction (Langendorf, 1948). Finally AV node properties can be modulated by extrinsic factors such as autonomic tone (Levy and Zieske, 1969; Prystowsky et al., 1981; Page et al., 1991, 1996; Nollo et al., 1994), with vagal activity exerting a negative dromotropic effect and sympathetic activity a positive one.

In this work the origins of ventricular variability were investigated by simulations with a simplified AV node model (Shrier et al., 1987), mimicking the recovery properties of the AV node. Simulations run with real atrial series as input reproduced most (67%) of ventricular variability, thus showing that the respiratory oscillation in atrial cycle lengths, combined with nodal recovery properties, was the main determinant of ventricular rhythm during AFL. Thus, although indirectly, respiration exerted a mechanical modulation on ventricular rhythm during AFL. The interplay between the respiratory modulated atrial input and the refractory and conductive properties of the AV node resulted in a magnified (1.8 times larger) variability of ventricular intervals with respect to atrial cycle lengths. In our study population, composed of patients with fixed 2:1 and 4:1 AV conduction, a mean ventricular interval S.D. of 7.6 ms (mean range 36 ms) was obtained. In patients with variable AV conduction it is likely that respiratory modulations may exert more pronounced effects, since the tiny variations in AFL intervals might be tuned to differentiate between conduction or block through the node. In these conditions, complex patterns of VV variability may be generated by the composition of respiratory modulation and Wenckeback rhythms.

5. Potential contribution of MEF to AFL cycle length variability

5.1. Concurrent hypothesis for the origin of AFL cycle length oscillations

Ventricular and respiratory activities involve changes in the hemodynamical state of the heart which may affect the electrophysiological properties of the atria both directly by changes in atrial pressure and/or volume and indirectly by reflex mechanisms.

During one ventricular cycle, atrial filling and atrial emptying phases alternate in concomitance with closure/opening of AV ventricular valves, which causes consequent variations in atrial dimensions. With the onset of ventricular systole and AV valve closure, the blood flows into the atria, producing an increase in volume accompanied by a continuous rise in pressure (v wave), while with the opening of the AV valves the atrial size decreases through atrial emptying (Jarvinen et al., 1996; Gaynor et al., 2005). As well respiratory phases involve alterations of the venous return. Specifically inspiration increases both the venous return to the

heart and the afterload of the ventricles by reducing the ventricular diastolic pressure relative to the extrathoracic arterial pressures, and expiration has the opposite effect (Robotham et al., 1978). These cyclic variations in venous return produce an increase in right atrial volume during inspiration and a decrease during expiration (Ferguson et al., 1989).

Hemodynamical variations associated with ventricular and respiratory activities may cause reflex responses. In fact the rise in arterial pressure elicited by ventricular systole and the changes in arterial pressure due to the inspiratory increase in venous return to the heart result in stimulation of arterial baroreceptors, which in turn causes reflex responses (Triedman and Saul, 1994). Additional reflexes may originate from stimulation of atrial mechanoreceptors due to changes in the atrial volume induced by both ventricular contraction and respiration (Paintal, 1973; Baertschi and Gann, 1977) and from stimulation of lung receptors by respiration (Taha et al., 1995). Alterations in neural tone associated to reflex changes provoked by ventricular and respiratory activities may hypothetically cause the changes in AFL cycle length. Changes in autonomic nervous activity are indeed known to influence the electrophysiological properties of the atria, which may affect AFL rate. Parasympathetic activity has been shown to shorten the atrial refractory period (Rensma et al., 1988; Liu and Nattel, 1997), while increased sympathomimetic activity has less clear-cut effects on atrial electrophysiology with both shortened (Farges et al., 1977; Liu and Nattel, 1997) and unchanged (Vargas et al., 1975; Rensma et al., 1988) refractoriness reported. Differently, conduction velocity has been reported to be either not changed (Rensma et al., 1988) or slightly increased (Liu and Nattel, 1997) by both sympathetic and parasympathetic activity. Since AFL rate in typical atrial flutter is governed by the conduction velocity (Allessie et al., 1987; Waldo, 2000), small or no effects on the rate are expected to be produced by autonomic changes. Two further observations suggest that the changes in AFL rate are not neurally mediated. First the combined use of muscarinic and beta-adrenergic receptor blockade in our patients did not affect AFL cycle length variability associated to ventricular contraction and respiration. Second the latency between the onset of ventricular contraction and the initial lengthening of the flutter cycle, estimated in about 50 ms (Lammers et al., 1991), was too short to involve nervous reflex mechanisms. Having ruled out the neurally mediated mechanism, the observation of the striking parallel time course of the changes in AFL cycle length and the variations of atrial volume suggests the direct influence of stretch/volume variations on AFL reentry as the most likely mechanism responsible for the modulation in AFL cycle length due to ventricular and respiratory activities.

5.2. *Potential contribution of MEF to the modulation of atrial flutter reentry*

The specific mechanisms by which stretch may directly modulate AFL reentrant circuit, inducing the described changes in atrial cycle length, are still hypothetical. Different parameters determine AFL rate, depending on the mechanism of AFL. Specifically the revolution time of a macroreentry with excitable gap is governed directly by the length of the circuit and inversely by the conduction velocity, while moderate changes in refractory period are not expected to produce rate variations (Allessie et al., 1987). Differently, the revolution time of a functional reentry is governed solely by the refractory period (Allessie et al., 1987). Since, as previously observed, the underlying mechanism of typical AFL is a macroreentry with large excitable gap (Waldo, 2000), changes in atrial volume associated with ventricular cycle and respiration may modulate the revolution time of the reentry (and thus the observed AFL cycle lengths) through a modification of both geometric (i.e. circuit size) and electrophysiological factors (i.e. conduction velocity).

5.2.1. *Mechanical modulation of circuit size*

The mechanical modulation of AFL cycle length by ventricular activity might be consistently explained by a geometrical deformation of the reentrant circuit associated with changes in atrial volume. Jarvinen et al. (1996) found that during a cardiac cycle, the atrial volume should vary by around 70%. Approximating the right atrium by a sphere with volume proportional to r^3 and the circuit size with a circumference of length r and assuming a uniform increase in atrial volume, the length of the circuit should increase by 19% in a ventricular cycle. Provided a constant conduction velocity along the reentrant circuit, the same increase should be observed in the conduction time and thus in AFL cycle length. The maximal increase in atrial cycle length observed in our study group during the ventricular cycle was of 13%, implying that a geometrical deformation

could consistently produce the observed changes in AFL rate. The discrepancy between the increase in cycle length and in circuit size could in part be ascribed to the assumed approximations. In fact the increase in volume of the right atrium is likely to be not homogeneous, due to the presence of bundles, and the conduction velocity is expected to vary in a complex way around the circuit. A slow conduction zone is indeed present within the tricuspid annulus–inferior vena cava isthmus (Shah et al., 1997). Smaller deformations of critical parts of AFL circuit could partially explain the smaller variability observed.

Similarly to the effect of ventricular contraction, deformations of the reentrant circuit associated with changes in atrial volume during the respiratory phases (Ferguson et al., 1989) may hypothetically account for the respiratory AFL cycle length oscillation. However, the lack of specific data describing the extent of changes in atrial dimensions during a respiratory cycle hinders a quantitative evaluation of this hypothesis.

5.2.2. Mechanical modulation of electrophysiological parameters

Stretch may change the AFL rate also by changing atrial electrophysiological variables. Experimental and clinical studies have demonstrated that changes in mechanical loading conditions may modulate the electrophysiological properties of the atria (Nazir and Lab, 1996a; Franz and Bode, 2003; Ravelli, 2003). This phenomenon has been demonstrated to operate on a beat-to-beat basis (Kaufmann et al., 1971; Lab, 1980, 1982) and to occur rapidly, involving a time lag of just 10–20 ms (Kaufmann et al., 1971). The major part of studies in the atria has considered the effects of stretch on atrial refractoriness. While in vivo studies provided divergent results due to the variety of loading conditions and neurohumoral influences (Kaseda and Zipes, 1988; Solti et al., 1989; Klein et al., 1990; Calkins et al., 1992; Sideris et al., 1994; Wijffels et al., 1997; Chen et al., 1999; Tse et al., 2001; Manios et al., 2006), experimental studies in isolated preparations clearly showed that atrial refractory period (Ravelli and Allessie, 1997; Bode et al., 2000; Zarse et al., 2001; Ninio et al., 2005) and action potential duration at early levels of repolarization (Nazir and Lab, 1996b; Tavi et al., 1998; Kamkin et al., 2000) were shortened by acute atrial dilatation. As concerns the effects of acute atrial dilatation on conduction velocity, consistent results were obtained in the isolated rabbit heart. Specifically, high-density mapping studies by Chorro et al. (1998) showed a global decrease of conduction velocity of about 25% by balloon inflation in the right atrium, while Eijsbouts et al. (2003) showed that acute atrial dilatation not only depressed atrial conduction, but also promoted spatial heterogeneity in conduction by causing conduction blocks parallel to the boundaries of large trabeculae.

Electrophysiological changes in the atria in response to hemodynamical load may be explained, at least in part, by activation of stretch-activated ion channels (SACs). SACs have been identified in ventricular and atrial myocytes of a number of different species (Hu and Sachs, 1997; Niu and Sachs, 2003). SACs may theoretically account for the voltage-dependent modulation of action potential shape as found in atrial preparations, since they have equilibrium potentials which are positive to resting membrane potential (Hu and Sachs, 1997). However, the use of inhibitors of stretch-activated channels yielded differing results. While stretch-induced APD shortening was suppressed by streptomycin (Babuty and Lab, 2001), shortening of the refractory period in the isolated rabbit heart remained unchanged by gadolinium (Bode et al., 2000) and by a SAC-blocking peptide from tarantula venom (Bode et al., 2001). The possible role of SACs in stretch-induced conduction disturbances has been evidenced in a recent simulation study by Kuijpers et al. (2007). In a model of atrial tissue the authors showed that a depolarized resting membrane potential produced by SAC currents could result in a slowing of conduction velocity through inactivation of Na^+ channels and lowering of the maximum upstroke velocity.

5.3. The MEF paradigm for AFL cycle length oscillations

All this evidence concurs in the formulation of the MEF paradigm for AFL cycle length oscillations, which is schematized in Fig. 8. According to this, the observed increase in AFL cycle length during ventricular systole and inspiration may be explained by the corresponding increase in atrial volume and stretch. Stretch indeed may produce the prolongation of the revolution time of the reentry via both a lengthening of the anatomical pathway of the circuit and a decrease of the conduction velocity along the circuit. The opposite effects are expected during ventricular diastole and expiration, when atrial volume decreases, thus producing the shortening of AFL cycle length.

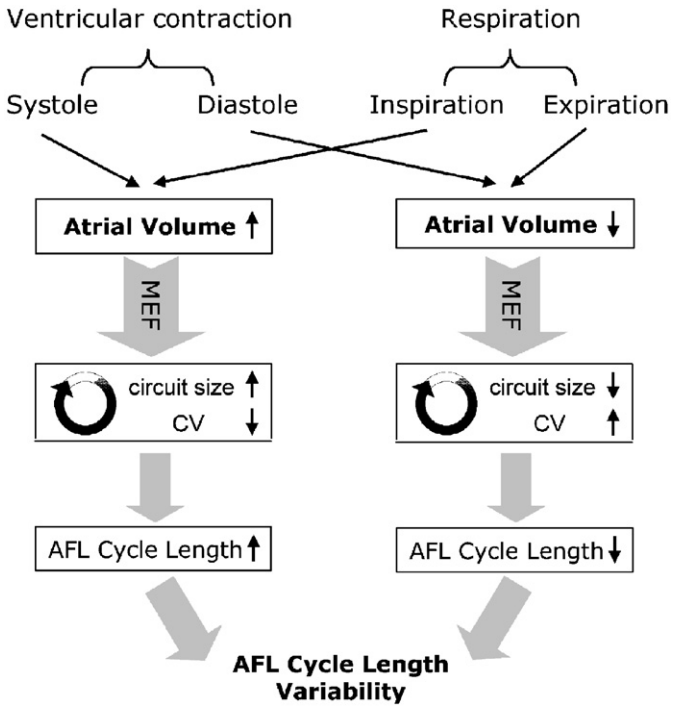

Fig. 8. Schematic diagram showing the potential contribution of MEF to the cycle length variability of typical atrial flutter. CV: conduction velocity. See text for further details.

Modulation of refractory period by stretch is not expected to influence the rate of the macroreentry with large excitable gap underlying typical AFL. SACs might be in part involved in the mechanical modulation of AFL cycle length by stretch-induced slowing of conduction (Kuijpers et al., 2007). However, the possible role of SACs in the occurrence of AFL cycle length variability must still be evaluated.

6. Conclusion

The spontaneous variability of atrial cycle length in typical AFL is composed of two oscillations, caused by ventricular contraction and respiration via mechanical modulation. Further studies should be performed to understand how changes in atrial stretch are translated into changes in the conduction properties of the underlying reentrant circuit. These would involve beat-to-beat measurements of conduction velocity, refractory period and circuit pathway during AFL, which are technically challenging in patients. The mechanically induced fluctuations in AFL cycle length are of small magnitude and thus might be not clinically relevant. However, since the mechanical respiratory oscillation in atrial cycle length gives rise to amplified oscillations in ventricular intervals, this mechanical phenomenon occurring at the atrial level might become relevant at the ventricular level.

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Editor's note

Please see also related communications in this issue by McNary et al. (2008) and Ninio and Saint (2008).

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