Dynamics of AV coupling during human atrial fibrillation: role of atrial rate

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METHODS

Patient population and electrophysiological study. We investigated pacing-induced episodes of AF in 14 patients with paroxysmal AF (age, 56 ± 23 yr; 1 woman), referred for preablative electrophysiological evaluation. Nine of 14 of the analyzed episodes were self-terminating with a duration going from 5 to 30 min. Five AF episodes with longer duration were terminated by drug infusion. Associated diseases consisted of mitral valve disease, cardiomyopathy, and congenital heart disease in three patients. In the other cases, no associated cardiopathies were found. In all patients, antiarrhythmic treatment had been suspended at least five half-lives before the study. The study was approved by the local ethical committee, and all patients gave written, informed consent.

The electrophysiological study was performed by using a standard quadripolar catheter (Medtronic TorqR, 5-mm electrode spacing) positioned in the right atrium to record from the lateral wall. AF episodes were induced by burst atrial pacing, beginning at a cycle length of 400 ms and reducing by 20-ms intervals until atrial refractoriness. Bipolar atrial electrograms and surface ECGs were continuously monitored and stored on a computer-based digital amplifier/recorder system (Bard Electrophysiology). Intracardiac electrograms were band-pass filtered (30–500 Hz) and digitized at 1-kHz sampling frequency. All signals were exported for off-line measurement and analysis. The atrial signal from the lower bipolar was selected to detect atrial activity in the lower third of the right atrial free wall.

The importance of rate control strategies in atrial fibrillation (AF) is generally recognized, especially in the acute manifestations of the disease (20). Nevertheless, the determinants of ventricular response and the relationship between atrial and ventricular activity during AF remain partially understood.

During the arrhythmia, irregular atrial inputs uncoordinatedly impinge the atrioventricular (AV) node, where specific rate and time-dependent recovery properties generate conduction delays and blocks (5, 34, 36, 45, 46). In turn, concealed conduction of blocked beats can affect nodal refractoriness and influence the conduction of successive beats (9, 12, 25, 49). Nodal conduction is further complicated by dual-pathway physiology, which splits propagation into two distinct wavefronts with potential summation and annihilation effects (33, 51). The result of this complex interplay is a variable and usually high-rate ventricular rhythm, where the relation with the atrial input may appear lost.

Previous experimental (8, 21) and clinical studies (1, 11, 14, 24) supported the role of atrial activity as a determinant of the rate and regularity of ventricular rhythm during AF. Nevertheless, a quantitative description of the causal link (or coupling) between atrial and ventricular activity during human AF is still lacking. The reconstruction of AV coupling dynamics during AF may be helpful to reveal AV conduction mechanisms, as suggested by previous studies performed during regular atrial activation (30, 45).

This study aims to quantify the causal relationship between atrial and ventricular activation during human AF. The goal is pursued by analyzing the effects of spontaneous atrial rate changes on the dynamics of AV coupling. Transient instances of AV coupling are detected by the AV synchrogram method (31), which performs a beat-to-beat bivariate analysis of atrial and ventricular activation series. The analysis is applied to the onset and spontaneous evolution of AF episodes, when the atrial rhythm is known to undergo a spontaneous acceleration (41). This allows us to quantify AV coupling and reconstruct AV response at changing atrial rate under spontaneous arrhythmic conditions. The analysis is complemented with modular simulations by a difference-equation model of the AV node (28), to evaluate the potential contribution of atrial and nodal factors in the generation of the AV dynamics observed in patients.

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Signal preprocessing and time series extraction. Beat-to-beat AV coupling was evaluated during the short-term acceleration of the atrial rate starting from the first AF complex for a time interval of 5 min. Atrial and ventricular activation time series were automatically extracted from the recorded atrial electrograms and ECGs, as previously described (18, 32). Briefly, after electrogram preprocessing to remove ventricular artifacts (18, 42), atrial depolarizations were identified by signal filtering and adaptive threshold crossing (18, 32). For each detected depolarization, the activation time was defined as the barycenter of the local activation waveforms (i.e., time that divided in two equal parts the local area of the modulus of the signal), to guarantee accurate estimation of atrial activation, even in the presence of fragmented atrial activity (18). Ventricular activation times were measured from the ECG by identifying the time of QRS maxima/minima, depending on the considered lead (32). Activation detection was visually supervised to verify proper identification, and the activation times were manually corrected in case of false-positive or false-negative detections. Following the identification of activation series, atrial (AA) and ventricular (VV) cycle lengths were obtained as intervals between consecutive atrial and ventricular activation times, respectively.

AV synchrogram analysis and AV response reconstruction. AV synchrogram analysis was applied to atrial and ventricular activation series to assess the dynamics of AV coupling and to reconstruct AV response as a function of atrial rate. The construction of the AV synchrogram, schematized in Fig. 1, has been detailed elsewhere (31). Briefly, the technique identifies instances of AV coupling between atrial and ventricular activations by evaluating the timing of atrial beats in subsequent ventricular cycles. To identify n:m coupling conditions (where n is the number of atrial beats, and m the number the ventricular cycles), the ventricular phase \( \Psi_m \) between m subsequent ventricular cycles (see Fig. 1C, for m = 1) was modeled by a linear function of time (17, 27). \( \Psi_m \) was sampled at discrete times given by atrial activations \( A_k \), yielding the discrete series \( \Psi_m(A_k) \). Coupling conditions were automatically detected in presence of sequence repetitions in \( \Psi_m(A_k) \). In the displayed case, a repeated sequence of three phase values indicates a 3:1 coupling epoch (open squares), while the repeatition of four phase values identifies a 4:1 coupling epoch (open triangles).

In each patient, AV synchrogram analysis was performed for 1 ≤ m ≤ 3, detecting coupling conditions up to order 3. To identify even short instances of AV coupling, coupled epochs were detected starting from two repetitions of the phase sequences. The statistical significance of the coupling patterns was case-by-case assessed by a surrogate data test (31, 44). Specifically, for each detected n:m coupled epoch, the probability of obtaining an ordered n:m phase sequence of equal (or longer) length was computed from 1,000 surrogate phase series, obtained by a random permutation of the order of the original \( \Psi_m(A_k) \) series. Coupling patterns were considered statistically significant if the probability of obtaining them from random series was <0.05.

The results of the analysis were summarized by the conduction ratio (CR) series, which displayed the CR = \( m/n \) of each coupled epoch as a function of time (Fig. 1D). AV coupling was quantified by three indexes: the percentage of significantly coupled beats (pc), the maximal length of the coupled epochs (\( I_{\text{max}} \)), and the average CR (CR\(_m\)) (Fig. 1E), defined respectively by:

\[
\text{pc} = \frac{\sum_{i=1}^{M} (A_{ij} - A_{ij})}{T} \cdot 100\% \quad (1)
\]

\[
I_{\text{max}} = \max_i (A_{ij} - A_{ij}) \quad (2)
\]

\[
\text{CR}_m = \frac{1}{M} \sum_{j=1}^{M} \left( \frac{m/n_j}{M} \right) \cdot (A_{ij} - A_{ij}) \quad (3)
\]

where \( A_{ij} \) and \( A_{ij} \) are the first and last atrial activation times, respectively, of the jth coupling segment, \( M \) is the total number of coupling segments, and \( T \) is the total duration of the analyzed window. The first two parameters quantified the occurrence and stability of the coupling patterns, whereas the third gave an average measure of the degree of AV conduction. To point out the role of atrial rate in determining AV dynamics, the AV response curve was reconstructed in each patient. The curve displayed the CR of each detected pattern as a function of the atrial cycle length at which it was observed (Fig. 1E).

Statistical analysis. Data are expressed as means ± SD. Statistical differences between parameter values at the onset vs. stabilization of the episodes were assessed by paired Student’s t-test, given the normality of index distributions (Shapiro-Wilk test, \( P > 0.05 \)).

Computer simulations. Simulations were run by a simplified AV conduction model to evaluate the potential contribution of atrial and nodal properties to AV coupling dynamics in AF patients. The model, schematized in Fig. 2, predicted ventricular activations for a given
ATRIAL RATE DETERMINES AV DYNAMICS IN HUMAN AF

Fig. 2. Schematic representation of the mathematical model of AV conduction during AF. Fibrillatory atrial inputs impinge the AV node at normally distributed intervals $AA_i$. An atrial beat ($A_{i+1}$) is conducted through the AV node generating the ventricular beat ($V_{i+1}$), provided that its recovery time (RT) exceeds the nodal refractory period $\theta$; otherwise it is blocked. Due to concealed conduction effects, blocked beats ($A_i$) determine the lengthening of the basic nodal refractory period $\theta_0$ by a normally distributed amount $\Delta_r$.

atrial sequence by assuming basic nodal properties, such as the slow recovery of nodal excitability and concealed conduction (28, 45). The irregular atrial beat sequence during AF was modeled by using random atrial intervals:

$$A_{i+1} = A_i + AA_i = A_i + (AA_{min} + \Delta_i \Delta_{AA})$$

where $AA_i$ is a normally distributed random number, with mean 0 and SD 1; and $AA_{min}$ and $\Delta_{AA}$ are positive constants, which control the mean period and the variability of the atrial activity, respectively.

Nodal recovery was modeled assuming an exponential decrease of the conduction time $AV_{i+1}$ at the increase of the recovery time (RT) from the preceding conducted beat $V_i$:

$$AV_{i+1} = \alpha + \beta \cdot e^{-RT/\theta} \text{ if } RT > \theta$$

where $\alpha$ is the conduction time in a fully recovered tissue, $\beta$ and $\gamma$ are positive constants, and $\theta$ is the refractory period (45). For recovery times shorter than $\theta$, the beat was blocked (e.g., beat $A_i$).

To model concealed conduction effects, $\theta$ was defined by the sum of a basic period $\theta_0$ and a variable concealed conduction term, $\Delta_r$, produced by nonconducted atrial beats $A_i$. The latter included a random component to mimic different changes in nodal refractoriness induced by different beat penetration (degree of concealment) into the node (28):

$$\theta = \theta_0 + \Delta_r = \theta_0 + \Omega_i \Delta_{RT} + \Delta_n$$

where $\Omega_i$ is a normally distributed random number with mean 0 and SD 1; and $\theta_0$, $\Delta_{RT}$, and $\Delta_n$ are positive constants.

Simulated ventricular series of 60-s length were generated for different atrial series and parameter sets and submitted to AV synchrogram analysis. AV coupling properties were thus quantified at changing atrial rate and atrial/nodal variability levels. Specifically, model parameters were set to $\alpha = 166$ ms, $\beta = 200$ ms, and $\gamma = 100$ ms, $\theta = 154$ ms, $\Delta_r = 54$ ms, according to previously determined values (28). To assess atrial rate effects on AV coupling, the mean atrial interval $AA_{min}$ was varied in the range 100–250 ms (step 0.5 ms). To investigate the effects of variability sources, simulations were run in a modular fashion: 1) in the absence of variability (pacing model: $\Delta_{AA} = 0$ ms; $\Delta_{RT} = 0$ ms); 2) in the presence of the sole atrial variability (AF1 model: $\Delta_{AA} = 25$ ms, average variability value in the patient population; $\Delta_{RT} = 0$ ms); 3) in the presence of both atrial and concealed conduction variability (AF2 model: $\Delta_{AA} = 25$ ms, $\Delta_{RT} = 50$ ms according to previous studies (28)). Because of the stochastic terms in the model, results were averaged over 20 trials for each parameter set.

RESULTS

**AV coupling patterns in AF patients.** Figure 3 shows the results of AV synchrogram analysis (C) and the reconstruction of AV response curve (D) in a representative patient. Atrial intervals (Fig. 3A) showed a progressive decrease in the first minutes (150 s) of the episode, passing from 137 ± 19 to 124 ± 16 ms ($P < 0.001$). Concurrently, ventricular intervals (Fig. 3B) increased from 535 ± 134 to 567 ± 139 ms ($P < 0.05$). AV synchrogram analysis detected the presence of epochs of coupled activity of different orders along the evolution of the episode (Fig. 3C). Significantly coupled epochs (dark gray) involved $pc = 26.3\%$ of the atrial beats with $l_{max} = 4.2$ s. A deterioration in the occurrence and stability of coupled epochs was observed at the shortening of atrial cycle length. From episode onset to stabilization, the pc decreased from 28.9 to 25.1%, and the $l_{max}$ decreased from 535 ms to 4.2 s. In terms of AV response, the 9.5% shortening of atrial cycle length induced a 16.4% decrease in CRs, which passed from $CR_{max} = 0.27$ to 0.23.

The dependence of AV conduction from atrial rate is evidenced in the reconstructed AV response curve (Fig. 3D), which points out an underlying structure in the ordering of coupled epochs. $nm$ patterns with progressively lower $mn$ ratios appeared at the shortening of atrial cycle length, and higher order rhythms, such as $n:2$ and $n:3$, occurred in between main $n:1$ patterns. For instance, $3:1$, $4:1$, $5:1$, and $6:1$ patterns were progressively encountered passing from $AA = 143 ± 8$ to 120 ± 11 ms. Higher order $n:2$ patterns were present at intermediate frequencies (e.g., $7:2$ pattern between $3:1$ and $4:1$), or as higher order manifestation of $n:1$ rhythms (e.g., $8:2$ pattern). $n:3$ patterns were sporadically encountered, such as the 11:3 pattern between the $7:2$ and $4:1$ regions. Despite differences in atrial cycle length and coupling orders, all patients displayed organized structures in AV response, with decreasing CR at atrial cycle length shortening (see examples in Fig. 4).

The global results of AV synchrogram analysis in our patient population (Fig. 5) confirmed the effects of atrial interval shortening on AV coupling properties. In the whole dataset of episodes, the atrial cycle length (Fig. 5A, left) underwent a 10.8% decrease in the first minutes of AF, passing from $AA_{min} = 185 ± 32$ to 165 ± 24 ms ($P < 0.001$), while atrial variability (right) did not show significant changes. The increase of atrial rate led to a significant increase of ventricular rate variability (Fig. 5B, right), while no consistent variations in mean ventricular rate was observed (left) in the population. The ventricular interval variability increased by 8.3%, passing from $VV_{std} = 123 ± 52$ to 133 ± 55 ms ($P < 0.05$). Concurrently with the atrial rate acceleration, all AV coupling indexes displayed a significant decrease (Fig. 5C). The occurrence (Fig. 5C, left) and stability of the patterns (center) decreased from $pc = 27.1 ± 8.0$ to 21.8 ± 6.9% ($P < 0.05$) and from $l_{max} = 3.9 ± 1.5$ to 2.8 ± 0.7 s ($P < 0.01$),
respectively. The CRs (right) decreased on average by 14.7%, passing from \( CR_{m} = 0.34 \pm 0.09 \) to \( 0.29 \pm 0.08 \) (\( P < 0.01 \)).

Simulation results. The contribution of atrial and nodal properties to AV coupling features is analyzed in Fig. 6. The occurrence (top) and stability (bottom) of simulated AV coupling patterns were calculated by combining nodal recovery with a regular atrial activation (pacing model, A), irregular atrial activation (AF1 model, B), and irregular atrial activation with variable concealed conduction effects (AF2 model, C).

In the presence of a regular high-frequency atrial activation (Fig. 6A), the slow recovery of nodal excitability determined AV coupling patterns with a well-defined structure as a function of atrial rate. Similarly to the dynamics observed in patients, patterns with decreasing CRs appeared at the shortening of atrial cycle length, and higher order \( n:2 \) and \( n:3 \) rhythms were present for a limited set of atrial cycle lengths between dominant \( n:1 \) rhythms (top). The sequence of AV patterns as a function of atrial rate can be suitably described by the mathematical concept of the Farey sequence (3, 23), which can explain specific rhythm transitions in our patients. The Farey sequence predicts the appearance of \( (n + N):(m + M) \) patterns at frequencies intermediate to those of \( n:m \) and \( N:M \).

Fig. 3. Temporal evolution of AV coupling dynamics and reconstruction of the AV response curve at the onset of AF in a representative patient. A–C: atrial (AA; A) and ventricular interval series (VV; B), and synchrogram-derived \( m/n \) ratios (CR; C) of coupling epochs are displayed as a function of time. A: the gray line represents the moving average of the series, which evidences the shortening of AA intervals over time. B: light and dark gray differentiate nonsignificantly from significantly coupled epochs, as assessed by surrogate data analysis. C: AV response curve obtained displaying the \( CR = m/n \) of significantly coupled epochs as a function of the corresponding AA. Note the progressive decrease of CRs at the shortening of AA, and the appearance of high-order \( n:2 \) and \( n:3 \) rhythms in between \( n:1 \) rhythms.

Fig. 4. A–C: AV response curves reconstructed by AV synchrogram analysis in three representative AF patients. Note the progressive decrease of CRs at the shortening of AA, and the appearance of high-order \( n:2 \) and \( n:3 \) coupling patterns in between \( n:1 \) patterns.
patterns. Consistently with this ordering, a (4 + 3):(1 + 1) or 7:2 pattern was observed between 3:1 and 4:1 patterns in Figs. 3D and 4B, while a (7 + 3):(2 + 1) or 10:3 pattern was observed between 7:2 and 3:1 patterns in Fig. 4B. The pacing model predicted AV patterns with maximal occurrence (top) and length (bottom) at all frequencies. Thus the sole recovery properties of the node could not explain the reduced occurrence and stability of AV coupling occurring in our patients, especially at higher atrial rates.

AV coupling instability in AF patients could be reproduced by including a variable atrial input into the model (Fig. 6B). With respect to the pacing model, pattern occurrence (top) and stability (bottom) displayed an overall decrease, with more pronounced reduction at higher atrial rates. In the presence of variability, the occurrence and stability of AV coupling were further reduced. The persistence of n:m pattern ordering in the presence of variability sources suggests that the deterioration of AV coupling is not due to the loss of a single component but rather to a complex interplay of multiple factors.

Fig. 6. A–C: simulated AV coupling properties as a function of atrial rate in the absence and presence of variability sources. The occurrence of n:m coupling patterns (top) and $l_{\text{max}}$ of coupled segments (bottom) were calculated by the AV recovery model during regular atrial activation (pacing model; A), irregular atrial activation (AF1 model; B), and irregular atrial activation with variable beat concealment (AF2 model; C). The parameters used in the simulations are reported in the text. Note the deterioration of AV coupling, but the persistence of n:m pattern ordering, in the presence of variability sources.
atrial variability, \(nm\) patterns displayed a normal instead of uniform distribution. Patterns could partially superimpose, and higher order \(2n:2m\) patterns could spurious occur. Nevertheless, it is important to notice that the Farey sequence ordering of AV coupling at changing atrial rate was maintained. The addition of the concealed conduction term (Fig. 6C) amplified the effects of atrial variability, leading to further decrease of pattern occurrence and stability, especially at higher atrial rates.

The results of computer simulations suggest that nodal recovery properties may underlie AV coupling transitions in AF patients, while the irregularity of atrial inputs and, additionally, of beat concealment may explain the reduced occurrence and stability of AV coupling patterns.

**DISCUSSION**

**Main results.** This study quantified the dynamic relationship between atrial and ventricular activities at the increase of atrial rate during human AF. AV synchrogram analysis demonstrated that atrial and ventricular activities displayed a variety of \(nm\) coupling patterns (ranging from 2:1 to 7:1, with higher order intermediates) at changing atrial rate. The increase in AF rate determined transitions toward AV patterns with smaller CRs, lower occurrence, and higher instability, which were associated with an increased variability of the ventricular response. Computer simulations showed that the structure of AV transitions and the instability of coupling in patients could be predicted, assuming the filtering of high-rate irregular atrial beats with different nodal concealment by the slow recovery of nodal excitability.

**Role of atrial rate in AV dynamics and ventricular response during AF.** The causal relationship between atrial rate and ventricular response during AF has been previously investigated in experimental (8, 21) and clinical studies (11, 15, 16, 28), where changes in atrial/nodal properties were obtained by specific pacing protocols (8, 21), drug administration (11, 15, 28), autonomic maneuvers (16), or spontaneous circadian long-term oscillations (11). Differently in this work, the effects of atrial rate were quantified during the spontaneous short-term evolution of AF episodes, when the atrial cycle length undergoes a progressive shortening (41) due to accommodation of atrial electrophysiological parameters and alterations in atrial metabolism after arrhythmia onset (2, 41). Coherently with a black-box description of AV conduction (4, 36, 45), the contribution of atrial rate to the generation of ventricular response was pointed out by reconstructing AV response curves by AV synchrogram analysis (31). The technique performs a beat-to-beat analysis of both atrial and ventricular series and thus allows direct exploration of the relationship between the two measures of the fibrillatory process (40) with respect to methods based on the analysis of the sole ventricular interval series (6, 7, 13, 19, 43, 50).

The spontaneous shortening of atrial cycle length in our patients led to higher instability of AV coupling and advanced levels of AV block, which determined an increased variability of ventricular response. The role of atrial rate in determining AV coupling properties and ventricular response is consistent with previous experimental (8, 21) and clinical findings (1, 11, 14, 24). Studies in the rabbit model during irregular atrial pacing and/or AF showed the ventricular response to be determined, not only by the AV node properties, but also by the rate and irregularity of the atrial activity (8, 21). Similarly, clinical studies in AF patients showed ventricular variability and more probable ventricular intervals to be multiples of atrial variability and dominant atrial intervals (11, 24), respectively. In particular, drug-induced shortening of atrial cycle length was shown to reduce AV CRs and induce a shift of the dominant ventricular interval peaks (11). AV response curves in our patients extend these results, since they pointed out not only the decrease of AV CRs at higher atrial rates, but also the existence of a subtle structure of \(nm\) coupling patterns between dominant \(n:1\) coupling regions. As concerns pattern stability, the lower stability of AV coupling and the increased variability of ventricular response at higher atrial rate observed in our patients is consistent with previous studies in patients with atrial flutter (29, 30) and AF (1, 14). A decreased stability of AV coupling patterns was indeed observed during the transitions from slow to rapid atrial flutter forms (30), and an increased irregularity of ventricular interval series occurred at higher atrial rates in patients with AF and congestive heart failure (14).

**Potential mechanisms underlying AV coupling during AF.** In all patients, the reconstructed AV response curves showed a progressive decrease of the CRs at increasing atrial rates, with a Farey sequence ordering of the transitions (3, 23). This rhythm structure can be predicted by deterministic models, which assume a monotonically decreasing recovery curve (23). Our simulation results showed the persistence of this ordering in the presence of atrial rate and concealed conduction variability. Thus rhythm transitions in our AF patients are consistent with rhythms at low AV block levels (CR \(\approx 0.5\)) during atrial pacing (23, 26, 35, 45), and with AV rhythm transitions at higher AV block levels in atrial flutter patients (30). This suggests that AV conduction during AF is based on similar mechanisms to those occurring during atrial pacing and regular atrial tachycardias, where the slow recovery of nodal tissue plays a major role in filtering out the high-frequency atrial inputs. Simulation results suggested also that atrial variability and, additionally, concealed conduction may be responsible for the unstable nature of AV coupling during AF. In the presence of these factors, an overall decrease in the occurrence and length of AV coupling was observed, with more severe effects at shorter atrial cycle lengths. This may be explained by the fact that high-rate rhythms, associated with advanced levels of AV block, are stable for a limited range of atrial cycle lengths. Thus even small changes in the atrial input timing or in the refractory period (due to concealed beats) may lead to higher levels of block and instability of conduction patterns. The shift toward advanced levels of AV block, with an increased contribution of concealed conduction, may thus contribute to the increased variability/irregularity of ventricular rhythm at higher atrial rates (14).

Although the global features of AV coupling during AF may be ascribed to the combination of an irregular atrial input with the recovery properties of the AV node, other atrial, nodal, and/or extrinsic factors may modulate AV coupling. As concerns atrial factors, the complexity of multiple wavelet pathways during AF may lead to a variable spatial pattern of AV node engagement, affecting ventricular response. Higher complexity of ventricular output was induced by nodal input asynchrony in experimental models (8, 21). Similarly, lower
levels of AV synchronization were observed in the presence of disorganized atrial activation in patients with persistent AF (1). Among nodal factors, dual-pathway nodal physiology may affect AV coupling by introducing two functionally distinct propagating waves through the AV node (33). Although our results did not provide direct evidence of dual-pathway propagation, its participation to AV coupling during atrial arrhythmias is supported by several experimental (51, 52) and clinical studies (30, 43). Ablation of the slow pathway significantly modified the distribution of ventricular intervals in AF patients (43). As well, dual-pathway physiology was suggested to underlie stable high-order alternating AV patterns in patients with regular atrial tachyarrhythmias (30). Finally, among extrinsic factors, autonomic tone is known to exert dromotropic effects on nodal conduction and to modulate concealed conduction (37–39, 48). Changes in autonomic balance induced by AF onset may have partially contributed to the increased pattern instability observed at high atrial rates.

Clinical implications. The results of this study support the role of atrial rate, filtered by nodal recovery properties, in determining ventricular response during AF. This suggests that similar mechanisms determine ventricular activation during atrial pacing, regular atrial tachycardias, and AF, which may have implications for the conception and development of AF rate-control approaches (20). In addition, the study showed that the increase in atrial rate during the onset of AF episodes led to advanced levels of AV block and higher variability of ventricular response. Since an increased ventricular variability has adverse effects on hemodynamic regulation (10, 40), acute changes occurring in the first minutes of AF may increase hemodynamic risks in AF patients.

Study limitations. Atrial activity was determined from electrodes in the lower part of the right atrium, which may be partially representative of the atrial input to the AV node. Although our analysis pointed out the global features of AV coupling in human AF, further mapping studies and a detailed description of the AV node region are necessary to clarify the spatio-temporal pattern of AV node engagement during AF and the local dynamics of AV conduction.

Conclusions. This paper points out the existence of AV coupling during human AF and supports the role of atrial rate in determining AV coupling and ventricular response. The increase of atrial rate determined instability in AV patterns and increased levels of AV block, which resulted in higher variability in ventricular response. Despite higher complexity and instability, AV coupling transitions in AF are similar to those occurring during atrial pacing and regular tachycardias, which suggests the filtering of atrial beats by the slow recovery of nodal excitability. The similarity of mechanisms operating during AF and atrial tachycardias may have implications in the conception of efficacious rate-control strategies.

GRANTS

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

Author contributions: M. Masè and F.R. conception and design of research; M. Masè analyzed data; M. Masè, M. Marini, M.D., and F.R. interpreted results of experiments; M. Masè prepared figures; M. Masè drafted manuscript; M. Masè, M.D., and F.R. edited and revised manuscript; M. Masè, M. Marini, M.D., and F.R. approved final version of manuscript; M. Marini performed experiments.

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