Autonomic influence on atrial fibrillatory process: head-up and head-down tilting

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Background: Changes in the autonomic nervous system (ANS) tone are present before, during, and after episodes of atrial fibrillation (AF). Atrial fibrillatory rate (AFR, the inverse of the atrial cycle length) has been used as a surrogate marker for local refractoriness and is a key characteristic of the fibrillatory process in patients with AF. Aim of this study is to assess changes in AFR, as an effect of autonomic balance change.

Methods: Forty patients undergoing cardiac cardioversion for symptomatic persistent AF were included in the study. Surface ECG was recorded during rest, head-down (HDT, -30°), and head-up tilt (HUT, $+60^\circ$). A median value of AFR was computed in each phase of the protocol.

Results: AFR decreased during HDT compared to the baseline (B) condition in all patients but three (median AFR_B = 391 fpm vs. AFR_{HDT} = 377 fpm, $p < .0001$). HUT increased AFR, making it significantly higher than HDT and baseline conditions (median AFR_{HUT} = 396 fpm, $p < .0001$ vs. B and HDT). Heart rate (HR) increased during HUT, but had a heterogeneous behavior in the population during HDT: about one third of the patients had an HR lower during HDT than during baseline, whereas the remaining two third had an increase in HR during HDT.

Conclusions: Dominant sympathetic/vagal tone during HUT/HDT significantly affects AFR, increasing/decreasing in respect to baseline. It may be worth exploring the possibility that patients with AF of shorter duration can convert to sinus rhythm during HDT.

KEYWORDS

atrial fibrillation, atrial fibrillatory rate, autonomic nervous system, head-down tilt, head-up tilt

Even though it is generally accepted that changes in the autonomic nervous system (ANS) tone are present before, during, and after episodes of AF; the exact role of ANS tone variations in the initiation (Bettoni & Zimmermann, 2002; Coccagna, Capucci, Bauleo, Boriani, & Santarelli, 1997; Herweg, Dalal, Nagy, & Schweitzer, 1998; Klingenberg, Grönfeld, Li, & Hohnloser, 1999; Tomita et al., 2003; Zimmermann & Kalusche, 2001), maintenance (Jayachandran et al., 2000; Liu & Nattel, 1997; Lombardi et al., 2004; Page, Wharton, & Prystowsky, 1996; Ramaswamy, 2003), and termination (Chen et al., 2000; Tomita et al., 2003) of AF remains controversial.

The ANS can alter atrial conduction and refractory period properties and can affect automaticity, reentry, fibrillatory conduction, and triggered automaticity. In 10 patients undergoing an electrophysiological study during sinus rhythm, a pacing protocol was applied before and after phenylephrine infusion, thus enhancing vagal tone. This leads to an increased number of functional obstacles, and hence wave breaks, resulting in a new wavelet formation and perpetuation of AF. Experimentally, it has been demonstrated that an increase in atrial pressure during tachycardia could activate cardiac mechanoreceptors leading to an increase in vagal activity (Liu & Nattel, 1997; Page et al., 1996). The increased incidence of AF in states of increased sympathetic

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activity suggests that the sympathetic nervous system plays an important role in the maintenance of AF too (Lombardi et al., 2004; Ramaswamy, 2003).

The atrial cycle length, related to the atrial refractory period, is a fundamental characteristic of the fibrillatory process during AF. Instead of assessing the atrial cycle length, the rate of fibrillation waves (as the inverse of the atrial cycle length) can be studied (Alcaraz, Hornero, & Rieta, 2011; Lankveld, Zeemering, Crijns, & Schotten, 2014; Platonov, Corino, Seifert, Holmqvist, & Sörnmo, 2014): after extraction of the atrial signal from the surface ECG, the largest peak in its power spectrum is determined. The location of this spectral peak (also known as the dominant atrial frequency or atrial fibrillatory rate, AFR) can be used as a measure of the average rate of fibrillation. AFR was shown to be a useful noninvasive marker for monitoring antiarrhythmic drug effect at atrial level (Aunes-Jansson et al., 2013; Corino, Holmqvist, Mainardi, & Platonov, 2014; Husser et al., 2005), and to be associated with outcome (Choudhary et al., 2013; Corino et al., 2013; Platonov et al., 2012a). Despite the increasing use of AFR in clinical studies, little data that show contradictory results exist with regard to assessment of ANS modulation effects on AFR achieved by carotid sinus massage (Bollmann, Wodarz, Esperer, Toepffer, & Klein, 2001), controlled respiration (Holmqvist et al., 2005; Stridh, Meurling, Olsson, & Sörnmo, 2003) or head-up tilt test (Corino, Sandberg, Lombardi, Mainardi, & Sörnmo, 2013).

The aim of this study was to assess the dynamic change in AFR associated with autonomic tone changes using head-up (HUT) and head-down (HDT) tilt test in patients with persistent AF.

1 | METHODS

1.1 | Patients

Patients admitted with persistent AF and planned for elective cardioversion were screened for participation in this study from 2011 to 2014. Patients with abnormal levels of thyroid hormones, severe renal failure requiring dialysis, or heart valve disease were excluded as well as were patients ablated for AF or on any of the Class I or Class III antiarrhythmic drugs. Of the 70 screened patients, 40 fulfilled the inclusion and exclusion criteria and were included in the study. All patients were on anticoagulant therapy.

This study was approved by the local ethics committee and all patients gave informed consent.

1.2 | Tilt test protocol

The tilt test was performed between 1 and 3 pm in a quiet study room. The tilt table used was manually operated with foot board support for the head-up tilt and hand grip and ankle support for the head-down tilt. The recordings of the surface ECG started with the supine position with an initial 5 min registration, followed by a 5 min registration in the head-down position (-30°), and finally a 5 min registration in head-up tilt position ($+60^\circ$).

1.3 | Atrial fibrillatory rate computation

Atrial fibrillatory rate was estimated from lead V_1 on the digital 12-lead ECG using software provided by CardioLund Research AB (Lund, Sweden).

The ECG signals were preprocessed to remove baseline wander removal, and then atrial activity was extracted, using spatiotemporal QRST cancelation (Stridh & Sörnmo, 2001). Briefly, using spatiotemporal QRST cancelation, an average QRST complex is computed as a weighted combination of the average beat of the lead subjected to analysis with the average beats of adjacent leads. The average QRST complex is then subtracted from the ECG signals, and the resulting residual ECG contains mainly the atrial activity. The residual ECG was analyzed performing time-frequency analysis on overlapping 2–5 s segments. The time-frequency distribution of the atrial signal (obtained by short-term Fourier transform) was decomposed such that each spectrum can be modeled as a frequency-shifted and amplitude-scaled version of the spectral profile. This procedure is based on a spectral profile, dynamically updated from previous spectra, which was matched to each new spectrum using weighted least squares estimation (Stridh, Sörnmo, Meurling, & Olsson, 2004). The frequency shift needed to achieve optimal matching then yields a measure of instantaneous fibrillatory rate of a 2.5-s ECG segment and was trended as a function of time. Frequencies were converted into fibrillatory rates with its unit fibrillations per minute (fpm, i.e., rate = frequency $\times 60$). Mean fibrillatory rate (in fpm) was defined as the average of the instantaneous fibrillatory rates over 1-min ECG segment. The software provides a value of AFR only if the residual atrial signal is of sufficient quality.

1.4 | Statistical analysis

Variables are presented as mean ± 1 SD, or as median (interquartile range). Wilcoxon sign-rank test was used to compare the three phases of the protocol. A p -value $< .05$ was considered significant.

2 | RESULTS

2.1 | Patients

The studied population comprised 40 patients (25 men), mean age 64 ± 12 years. Detailed clinical characteristics and medication are listed in Table 1. For the majority of patients ($n = 27$, 67.5%), the index AF episode was the first ever experienced symptomatic AF. Most of the patients (80%) had hypertension; no patient had antiarrhythmic drugs, but most of them (77.5%) were on beta-blockers therapy and a few of them (17.5%) were taking digoxin.

2.2 | AFR during HDT and HUT

Figure 1 shows the residual atrial signals obtained after QRST cancelation in a 2.5-s segment and the respective power spectra, during the three phases of the protocol. It can be observed that AFR (i.e., the

TABLE 1 Clinical characteristics in the study population

Variable	Value
Age (years)	64 ± 12
Gender (male/female)	25/16
AF duration (days)	90 (1–350)
Congestive heart failure	8
Hypertension	32
Ischemic heart disease	4
Diabetes mellitus	3
Beta-blockers	32
Digoxin	7

position of the maximum peak in the power spectrum multiplied by 60 to obtain the fpm) decreases during HDT with respect to baseline (398 fpm vs. 434 fpm, HDT vs. baseline), whereas during HUT, AFR increases to 445 fpm. This trend during the three phases is confirmed in the whole population as shown in Fig. 2 that presents the mean AFR (average of five 1-min value) per patient in the three phases of the protocol. It can be observed that AFR decreased during HDT compared to the baseline condition, in almost all the patients, being only 3 of 40 (7.5%) patients who had a slightly higher AFR during HDT. HUT increased AFR, making it significantly higher than HDT and baseline conditions. There was only one patient who responded with AFR

reduction during HDT compared to HUT. From Fig. 2, it can be observed that one patient had a very high AFR during all phases of the tilt test when compared to all the others, so results on the whole population are presented using median and interquartile values as shown in Table 2. The same trend was observed also for the three patients, who underwent tilt test while being on amiodarone therapy.

While AFR had a consistent behavior, heart rate (HR) demonstrated heterogeneous behavior in different patients, as it is shown in Fig. 3 that presents the values of HR and AFR over time. In Fig. 3A, left column, it can be noted that median HR increased during HDT test and further increased during HUT. On the contrary, in Fig. 3B, left column, it can be noted that median HR decreased during HDT test but increased during HUT. However, for both patients, AFR decreased during HDT and increased during HUT, as shown in Fig. 2 as well for all the population. The result on HR is reflected on the whole population, as about one third of the patients had an HR lower during HDT than during baseline, whereas the remaining two third had an increase in HR during HDT.

2.3 | Clinical characteristics on AFR

We have assessed possible impact of factor that may affect atrial electrical remodeling and thus AFR, but found no difference in AFR in response to HDT or HUT with regard to the duration of AF episode, whether the AF attack was first ever experienced or not and as a result

FIGURE 1 (A, C, E) The residual atrial signals obtained after QRST cancellation in 2.5-s segments, during baseline, HDT, and HUT, respectively. (B, D, F) The respective power spectra, the vertical line shows the position of the maximum peak in the power spectrum (this frequency is then multiplied by 60 to obtain the AFR in fpm). See text for details. HDT = Head-down tilt; HUT = Head-up tilt

FIGURE 2 Trends of heart rate (HR, left column) and atrial fibrillatory rate (AFR, right column) for two patients, (A) and (B). Both patients showed a similar AFR response to tilting, whereas HR increased during head-up tilt but showed different response during head-down tilt. Circles indicate baseline, asterisks head-down tilt, and squares head-up tilt, the lines represents the median values in each phase

TABLE 2 Atrial fibrillatory rate and heart rate during the three phases of the protocol

	Baseline	HDT	HUT
Atrial fibrillatory rate			
Median	391	377*	396*,***
IQR	363–421	350–399	366–430
Heart rate			
Median	86	89**	92*,***
IQR	81–99	81–100	82–110

HDT, head-down tilt; HUT, head-up tilt; IQR, interquartile range.

* $p < .0001$ vs. Baseline.

** $p < .05$ vs. Baseline.

*** $p < .0001$ vs. HDT.

or beta-blocker therapy (Table 3). None of other clinical relevant characteristics such as gender, the presence of heart failure, hypertension, or digoxin therapy showed any effect on response to HDT or HUT.

3 | DISCUSSION

To the best of our knowledge, this is the first study designed to assess the effect of both HDT and HUT maneuver and resulting modulation of the autonomic tone on the atrial fibrillatory process. The main

finding is that the dominant sympathetic and vagal tone during HUT and HDT, respectively, significantly affects AFR. In particular, AFR is reduced as a result of HDT and increased during HUT in respect to baseline, the finding that appeared to be very consistent in the studied population.

Sympathetic stimulation using HUT test approach has been frequently used earlier and in a few studies it was used for assessment of atrial electrophysiology during AF (Corino et al., 2013; Ingemansson, Holm, & Olsson, 1998). The effects of the reverse stimulation using HDT, however, are less well explored and no previous studies have reported the effect of vagal dominance resulting from HDT of atrial fibrillatory process. Applied in the clinical settings on healthy subjects during sinus rhythm, HDT has been shown to increase peripheral venous pressure, forearm blood flow, and forearm vascular conductance, while decreasing muscle sympathetic nerve activity and forearm vascular resistance (Tanaka, Davy, & Seals, 1999). On the contrary, arterial blood pressure and heart rate did not change significantly from supine baseline levels in response to HDT (Harrison, Rittenhouse, & Greenleaf, 1986; Kardos, Rudas, Simon, Gingl, & Csanády, 1997; Nagaya, Wada, Nakamitsu, Sagawa, & Shiraki, 1995; Tanaka et al., 1999), whereas baroreflex sensitivity was improved during HDT (Harrison et al., 1986; Kardos et al., 1997).

The effect of vagal dominance by using 15° and 30° HDT was assessed in 12 healthy volunteers by Nagaya et al. (Nagaya et al., 1995), who reported stroke volume increase during both 15° and 30° HDT

FIGURE 3 Mean atrial fibrillatory rate (AFR) per patient in the three phases of the protocol. HDT, head-down tilt; HUT, head-up tilt. Filled circles indicate patients not taking any rate- or rhythm-control drugs, circles indicate patients taking beta-blockers

without accompanying changes in the heart rate or blood pressure. These results can be interpreted as in line with our findings, showing that heart rate decreased in some patients and increased in other. An alternative approach to explore the effects of vagal stimulation was used by Bollmann et al. (Bollmann et al., 2001), who performed carotid sinus massage in 19 patients with AF using similar methodology for AFR estimation. The study reported two different responses of AFR to carotid sinus massage that were equally common: in eight patients AFR increased from 384 to 408 fpm ($p = .012$), whereas in nine patients AFR decreased from 390 fpm to 366 fpm ($p = .008$) without AF termination and the remaining two patients showed no change in AFR. On the contrary, in our study on a larger cohort we found a consistent

response of AFR to HDT, with a decrease in AFR during HDT in the vast majority of patient with persistent AF.

The effect of sympathetic tone was assessed in patients with AF during HUT (Corino et al., 2013; Ingemansson et al., 1998) and during exercise (Husser et al., 2007). Fourteen patients with chronic AF were included in the study by Ingemansson et al. (Ingemansson et al., 1998), and a HUT of 80° was performed. Similarly to the findings in our study, 80° HUT was associated with significant reduction in the dominant atrial cycle length (the inverse of AFR) from 160 to 150 ms ($p < .01$), corresponding to a 6% increase from 375 to 400 fpm. The relative AFR increase in our study was not as prominent as in the study by Ingemansson et al. (Ingemansson et al., 1998) (about 1.3%), which may be due to the differences in tilt-test protocols and patient characteristics. Heart rate in Ingemansson et al. (1998) increased from 91 bpm during baseline to 106 bpm during HUT ($p < .01$), corresponding to an increase of 16%, similar to AFR results, the increase in HR in our patients was smaller (about 7%), but still in line with our observations.

Exercise-induced increase in the sympathetic tone in patients with persistent AF uses a different mechanism of sympathetic activation, which may explain the differences in AFR dynamics reported by Husser et al. (Husser et al., 2007) using the same methodology of AFR estimation. In their study, seven patients (29%) responded to exercise with an increase in AFR of 26 fpm ($p < .001$), three (13%) with a decrease of -21 fpm ($p < .001$), whereas the remaining 14 patients (58%) did not show a response (defined as a rate change higher than 2.5%). A more recent study (Corino et al., 2013) showed an increase in AFR in 25 patients with permanent AF during HUT at 75°: AFR increased from 365 to 372 bpm, corresponding to an increase of about 2%, more similar to our results.

3.1 | Clinical relevance of AFR reduction during HDT

It has been shown that AFR can monitor antiarrhythmic drug effects in patients with AF, as the drugs have been shown to increase atrial cycle length that corresponds to increased refractoriness of the atrial myocardium, thus decreasing AFR. In particular, it has been shown that amiodarone decreases AFR from 410 to 339 fpm in patients with persistent AF (decrease of 17%) (John et al., 2013), esmolol, and its combination with tecadenoson reduces AFR of about 6% (Corino et al., 2014), AZD7009 (a combined potent potassium and sodium channel blocker) decreases AFR from 394 vs. 225 (a decrease of 42%) in patients with permanent AF (Aunes-Jansson et al., 2013), and flecainide lowers AFR from 378 to 270 fpm in patients with persistent lone AF (a decrease of 27%) (Husser et al., 2005).

Moreover, a drop in AFR was observed before spontaneous conversion of the AF episode into sinus rhythm, being the drop either a gradual slowing in patients with lone paroxysmal AF (Platonov et al., 2012b) or abrupt (Petrutiu, Sahakian, & Swiryn, 2007).

In this study we reported that HDT affects atrial electrophysiological properties during AF in the same direction as antiarrhythmic drugs used for pharmacological cardioversion and similarly to what is observed just before spontaneous restoration of sinus rhythm. The magnitude of AFR drop as a consequence of HDT is much lower than

TABLE 3 Atrial fibrillatory rate (mean $\pm$ 1 SD) in subgroups of patients with different clinical characteristics

	Baseline	HDT	HUT
AF episode duration <90 days ($n = 28$)	403 $\pm$ 40	384 $\pm$ 42**	409 $\pm$ 39*,****
AF episode duration >90 days ($n = 12$)	369 $\pm$ 27	357 $\pm$ 29*	374 $\pm$ 28*,***
First AF ($n = 29$)	390 $\pm$ 39	373 $\pm$ 40**	396 $\pm$ 40*,****
Not first AF ($n = 11$)	400 $\pm$ 41	384 $\pm$ 40*	406 $\pm$ 39*,***
Beta-blockers ($n = 32$)	397 $\pm$ 40	380 $\pm$ 41**	402 $\pm$ 41*,****
No beta-blockers ($n = 8$)	374 $\pm$ 33	359 $\pm$ 30*	384 $\pm$ 33*,***

HDT, head-down tilt; HUT, head-up tilt.

* $p < .05$ vs. Baseline.

** $p < .0001$ vs. Baseline.

*** $p < .05$ vs. HDT.

**** $p < .0001$ vs. HDT.

the one observed in the studies using rhythm-control drugs; however, this may be due to the fact that patients included in our study had long-standing persistent AF with a priori low chances of spontaneous conversion. Moreover, the tilt test was not intended to convert AF. However, it may be worth exploring the possibility that patients with AF of shorter duration and thus less advanced electrical remodeling may have a different response to the tilt test and more pronounced AFR drop during HDT with AF converting potential.

3.2 | Limitations

Most of the patients (77.5%) were on beta-blockers therapy during the study and it may have been better examined on them after beta-blockade washout, but they all needed beta-blockade for clinical reasons and no withdrawal was approved by Institutional Review Board. Moreover, no difference between patients taking and not taking beta-blockers was found in terms of AFR trend during the different phases of the protocol.

4 | CONCLUSIONS

Modulation of autonomic tone by head-up and head-down tilt significantly affects atrial electrophysiological properties assessed non-invasively by increase and decrease in AFR, respectively. The drop in AFR during HDT was similar, even though not as prominent, to the decrease observed as a result of rhythm-control drug.

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