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Autonomic influence on atrial fibrillatory process: tilt up and tilt down maneuvers

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Short title: Atrial fibrillatory rate during tilt up and tilt down tests

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Abstract

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.

Objective Aim of the present 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°). 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, $p < 0.0001$). HUT increased AFR, making it significantly higher than HDT and baseline conditions (median AFR_HUT= 396 fpm, $p < 0.0001$ 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.

Conclusion 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; autonomic nervous system; head-up tilt; head-down tilt

Abbreviations:

AF, atrial fibrillation; **AFR**, atrial fibrillatory rate; **ANS**, autonomic nervous system; **HDT**, head down tilt; **HR**, heart rate; **HUT**, head up tilt.

Introduction

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[1–6], maintenance[7–11], and termination[6,12] 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 ten 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 wavebreaks, 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[7,8]. The increased incidence of AF in states of increased sympathetic activity suggests that the sympathetic nervous system plays an important role in the maintenance of AF too[9,10].

Atrial fibrillatory rate (AFR, the inverse of the atrial cycle length) is a fundamental characteristic of the fibrillatory process during AF[13], and was shown to be a useful non-invasive marker for monitoring antiarrhythmic drug effect at atrial level[14–16], and to be associated with outcome[17–19]. Despite the increasing use of AFR in clinical studies, little data that show contradictory results exist in regard to assessment of ANS modulation effects on AFR achieved by either carotid sinus massage[20], controlled respiration[21,22] or head-up tilt test[23].

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.

Methods

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, forty fulfilled the inclusion and exclusion criteria and were included in the study.

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

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 tile 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 five minutes registration, followed by a five minutes registration in the head down position (-30°) and finally a five minute registration in head up tilt position (+60°).

Atrial fibrillatory rate computation

Atrial fibrillatory rate was estimated from lead V1 on the digital 12-lead ECG using software provided by CardioLund Research AB (Lund, Sweden).

The ECG signals were pre-processed to remove baseline wander removal, and then atrial activity was extracted, using spatiotemporal QRST cancellation[24]. Briefly, using spatiotemporal QRST cancellation, 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[25]. The frequency shift needed to achieve optimal matching then

yields a measure of instantaneous fibrillatory rate of a 2.5-seconds ECG segment and was trended as a function of time. Frequencies were converted to fibrillatory rates with its unit fibrillations per minute (fpm, i.e., rate = frequency × 60). Mean fibrillatory rate (in fpm) was defined as the average of the instantaneous fibrillatory rates over 1-minute ECG segment. The software provides a value of AFR only if the residual atrial signal is of sufficient quality.

Statistical analysis

Variables are presented as mean ± one standard deviation, or as median (interquartile range). Wilcoxon sign-rank test were used to compare the three phases of the protocol. A p-value < 0.05 was considered significant.

Results

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 mot of them (77.5%) were on beta-blockers therapy and a few of them (17.5%) were taking digoxin.

AFR during HDT and HUT

Figure 1 shows the residual atrial signals obtained after QRST cancellation 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 position of the maximum peak in the power spectrum multiplied by 60 to obtain the fpm) decreases during HDT in 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 Figure 2, that presents the mean AFR (average of 5 one-minute 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 over 40 (7.5%) the patients that 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 Figure 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 Figure 3 that presents the values of HR and AFR over time. In Figure 3(a), left column, it can be noted that median HR increased during HDT test and further increased during HUT. On the contrary, in Figure 3(b), 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 Figure 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.

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 in regard to the duration of AF episode, whether the AF attack was first ever experienced or not and as a result 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.

Discussion

To the best of our knowledge, this is the first study designed to assess the effect of a both HDT and HDT 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 employed for assessment of atrial electrophysiology during AF[23,26]. 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[27]. On the contrary, arterial blood pressure and heart rate did not change significantly from supine baseline levels in response to HDT[27–30], while baroreflex sensitivity was improved during HDT[29,30].

The effect of vagal dominance by using 15° and 30° HDT was assessed in 12 healthy volunteers by Nagaya et al.[28]who reported stroke volume increase during both 15° and 30° HDT 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.[20], 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 8 patients AFR increased from 384 to 408 fpm ($p = 0.012$) while in 9 patients AFR decreased from 390 fpm to 366 fpm ($p = 0.008$) 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[23,26] and during exercise[31]. Fourteen patients with chronic AF were included in the study by Ingemansson et al.[26], and a HUT of 80° was performed. Similarly to the findings in our study, 80° HUT was associated with significant

reduction of the dominant atrial cycle length (the inverse of AFR) from 160 to 150 ms ($p < 0.01$), corresponding to a 6% increase from 375 fpm to 400 fpm. The relative AFR increase in our study was not as prominent as in the study by Ingemansson et al.[26] (about 1.3%), which may be due to the differences in tilt-test protocols and patient characteristics. Heart rate in[26] increased from 91 bpm during baseline to 106 bpm during HUT ($p < 0.01$), corresponding to a increase of 16%, similarly 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 employs an different mechanism of sympathetic activation, which may explain the differences in AFR dynamics reported by Husser et al.[31] using the same methodology of AFR estimation. In their study, seven patients (29%) responded to exercise with an increase in AFR of 26 fpm ($p < 0.001$), three (13%) with a decrease of -21 fpm ($p < 0.001$), while the remaining 14 patients (58%) did not show a response (defined as a rate change higher than 2.5%). A more recent study[23] showed an increase in AFR in 25 patients with permanent AF during HUT at 75°: AFR increased from 365 bpm to 372 bpm, corresponding to an increase of about 2%, more similar to our results.

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 %)[32], esmolol and its combination with tecadenoson reduces AFR of about 6%[15], AZD7009 (a combined potent potassium and sodium channel blocker) decreases AFR from 394 vs 225 (a decrease of 42%) in patients with permanent AF[16], flecainide lowers AFR from 378 to 270 fpm in patients with persistent lone AF (a decrease of 27%)[14].

Moreover, a drop in AFR was observed before spontaneous conversion of the AF episode to sinus rhythm, being the drop either a gradual slowing in patients with lone paroxysmal AF[33] or abrupt[34].

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 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.

Limitations:

Most of the patients (77.5%) were on beta-blockers therapy during the study and it may have been better examined 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.

Conclusions

Modulation of autonomic tone by head-up and head-down tilt, significantly affects atrial electrophysiological properties assessed non-invasively by increase and decrease of 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 administration thus warranting further studies of possible cardioversion effect of HDT in selected patient cohorts.

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Table 1: Clinical characteristics in the study population

Variable	Value
Age (yrs)	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

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; †† $p < 0.0001$ vs. Baseline; † $p < 0.05$ vs. Baseline; ‡ $p < 0.0001$ vs. HDT.

Table 3: Atrial Fibrillatory Rate (mean ± one standard deviation) in subgroups of patients with different clinical characteristics.

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

HDT = Head-down tilt; HUT = Head-up tilt.

† $p < 0.05$ vs. Baseline; †† $p < 0.0001$ vs. Baseline; ‡ $p < 0.05$ vs. HDT; ‡‡ $p < 0.0001$ vs. HDT.

Figures caption

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: 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.

Figure 3: 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.

Figure 1

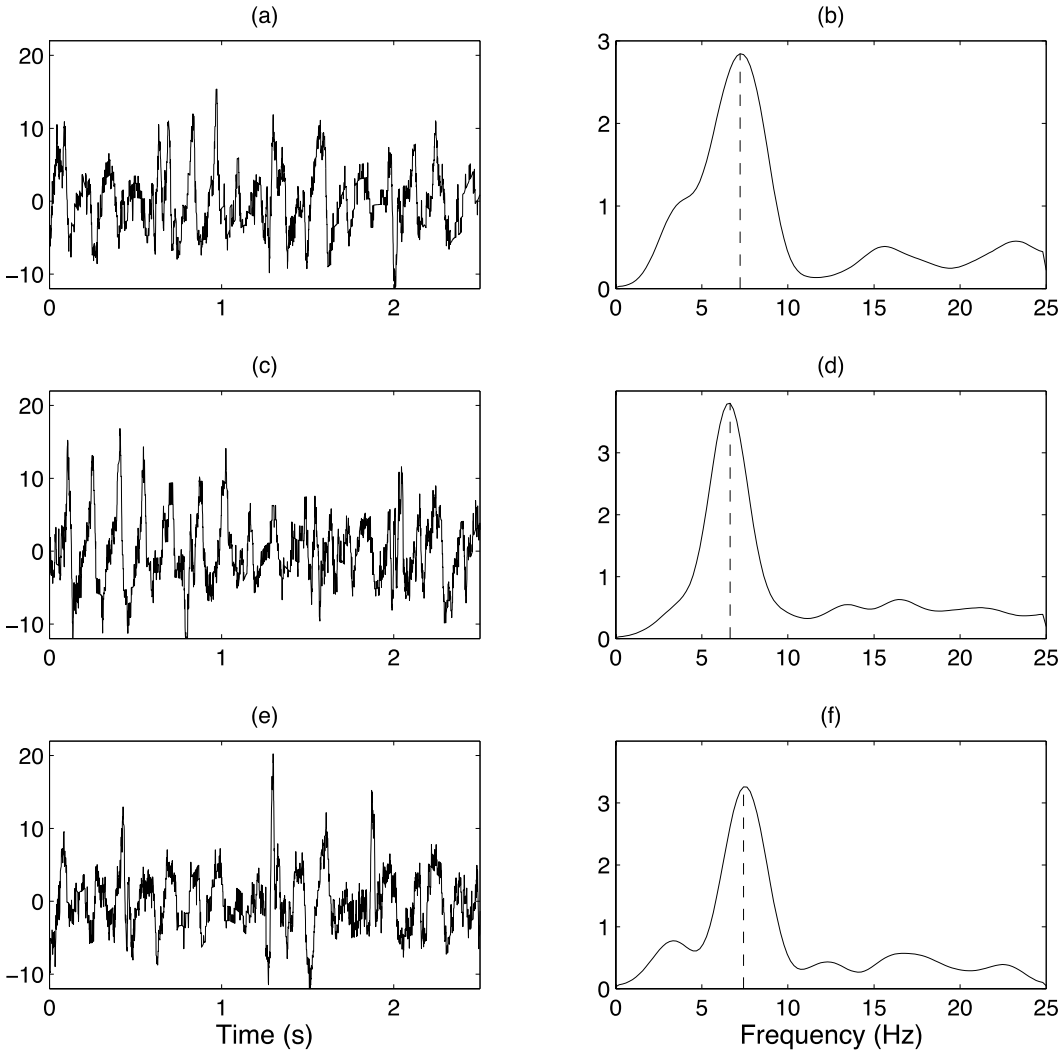

Figure 2

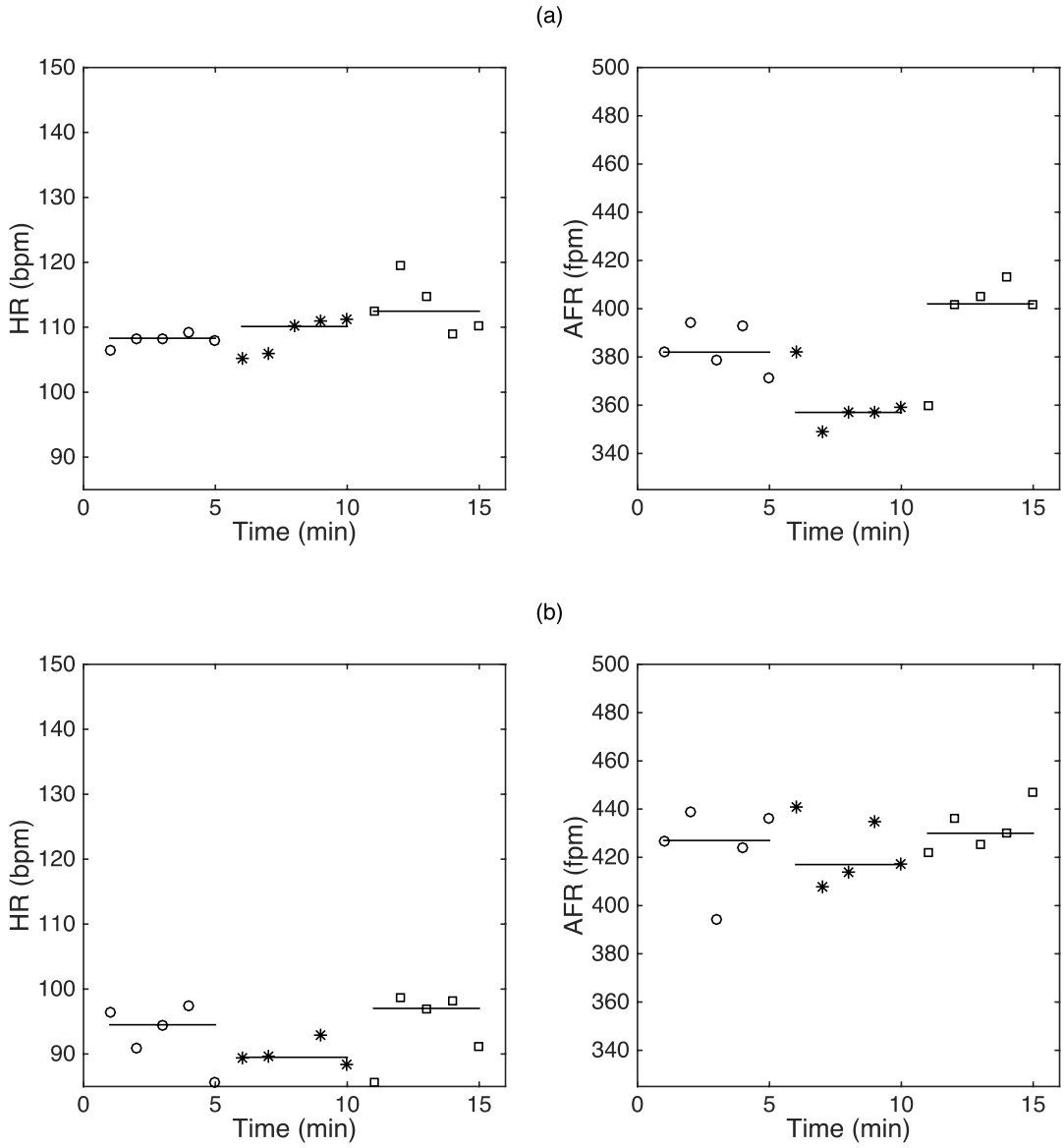
(a)
HR (bpm)
AFR (fpm)
Time (min)
Time (min)
(b)
HR (bpm)
AFR (fpm)
Time (min)
Time (min)

Figure 3