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The Effect of Head-up Tilt upon Markers of Heart Rate Variability in Patients with Atrial Fibrillation

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26	
27	Abstract
28	Background: Heart rate variability (HRV) analysis is uncommonly undertaken in patients
29	with atrial fibrillation (AF) due to an assumption that ventricular response is random. We
30	sought to determine the effects of head up tilt (HUT), a stimulus known to elicit an
31	autonomic response, on HRV in patients with AF; we contrasted the findings with those of
32	patients in sinus rhythm (SR).
33	Methods: Consecutive, clinically indicated tilt tests were examined for 207 patients: 176 in
34	SR, 31 in AF. Patients in AF were compared to an age-matched SR cohort (n=69). Five
35	minute windows immediately before and after tilting were analysed using time-domain,
36	frequency-domain and non-linear HRV parameters. Continuous, non-invasive assessment of
37	blood pressure, heart rate and stroke volume were available in the majority of patients.
38	Results: There were significant differences at baseline in all HRV parameters between AF
39	and age matched SR. HUT produced significant haemodynamic changes, regardless of
40	cardiac rhythm. Co-incident with these haemodynamic changes, patients in AF had a
41	significant increase in median [quartile 1, 2] DFA- α 2 (+0.14 [-0.03, 0.32], p<0.005) and a
42	decrease in sample entropy (-0.17 [-0.50, -0.01], p<0.005).
43	Conclusion: In the SR cohort, increasing age was associated with fewer HRV changes on
44	tilting. Patients with AF had blunted HRV responses to tilting, mirroring those seen in an age
45	matched SR group. It is feasible to measure HRV in patients with AF and the changes
46	observed on HUT are comparable to those seen in patients in sinus rhythm.
47	Keywords: Atrial Fibrillation; Heart Rate Variability; ECG Signal Processing; Head-up Tilt
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Heart rate variability (HRV) is a surrogate marker for the function of the autonomic nervous system (ANS) and the technique is widely available (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996). There are a variety of methods for the derivation of HRV, through the application of different mathematical functions to consecutive RR-intervals. These mathematical functions fall broadly into three groups: time domain, frequency domain and non-linear analysis (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996). A relationship between reduced HRV and prognosis has been shown in health (Hillebrand et al., 2013) and in numerous conditions, including after myocardial infarction and in patients with heart failure (Bilchick et al., 2002). HRV techniques are generally not applied to patients in atrial fibrillation (AF) (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996). This is an important limitation, as AF is not only very prevalent but it is present in 30-50% of the heart failure population, a condition in which HRV has been shown to be useful in predicting outcomes (Bilchick, et al., 2002). Recently, bridging this gap in knowledge has become even more pertinent due to the introduction of ablative interventions or device implantation (e.g. renal denervation, baroreceptor stimulators, vagal nerve stimulators, spinal cord stimulators) which modulate the ANS as a potential treatment strategy in heart failure and other diseases (Ardell et al., 2014; Patel et al., 2013). The argument against the use of HRV techniques in patients with AF is based upon the assertion that the RR intervals in AF are truly less dependent on physiological mechanisms

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74	measureable with HRV. Though in clinical examination AF is characterised crudely by an
75	irregularly irregular pulse, generally considered random, there is a growing body of evidence
76	that supports a different view (Carrara et al., 2015; Cygankiewicz et al., 2015; Hayano,
77	Sakata, Okada, Mukai, & Fujinami, 1998; Hayano et al., 1997; Rawles & Rowland, 1986).
78	Rawles and Rowland demonstrated in 74 patients in AF, using an auto-correlation technique,
79	that at rest approximately a third of patients had a non-random ventricular rhythm (Rawles &
80	Rowland, 1986). While the effect of the ANS on the sinus node is a major determinant of
81	HRV in sinus rhythm (SR), the ANS is equally important in AF, through its effects on the
82	refractory period and conductivity of the AV node, the frequency and irregularity of atrial
83	impulses and the degree of concealed conduction (Bollmann et al., 2006; Hayano, et al.,
84	1998; Lim et al., 2011).
85	
86	The purpose of this study was to determine the validity of measuring HRV in patients with
87	AF. To achieve this we used head-up tilt testing (HUT) as an intervention that predictably
88	activates the sympathetic nervous system (SNS) and leads to withdrawal of the
89	parasympathetic nervous system (PNS) (Mehlsen, Kaijer, & Mehlsen, 2008). We contrasted
90	the effects of HUT on HRV in a cohort of individuals with AF and a group in SR.

The ageing process is an important consideration in studies of autonomic physiology
(Petersen, Williams, Gordon, Chamberlain-Webber, & Sutton, 2000). Not only is increasing
age a risk factor for AF but it has also been shown to reduce HRV in cross sectional studies
(Laitinen, Niskanen, Geelen, Lansimies, & Hartikainen, 2004; Sosnowski, Macfarlane, &
Tendera, 2011; Task Force of the European Society of Cardiology and the North American
Society of Pacing and Electrophysiology, 1996). It is vital that we match for age and interpret
our findings in the context of a more elderly population. To aid this interpretation we carried

3	99	out additional analyses on a cohort in SR to establish the effect of aging on HRV responses to
4 5 6	100	tilt in our patients.
7 8	101	
9 10	102	Methods
11 12 13	103	Study Patients
13 14 15	104	We obtained data retrospectively on consecutive patients with permanent AF who underwent
16 17	105	clinically indicated tilt testing at two hospitals (over a cumulative 9 years). All patients in SR
18 19	106	from one of the hospitals also had their data analysed to provide the control population.
20 21	107	Patients were excluded from this analysis if they experienced syncope or pre-syncope in the
22 23 24	108	tilt phase or had a paced rhythm. Data was available for 176 patients in SR and 31 in AF.
24 25 26	109	National Health Service (UK) management permission for use of anonymised patient data for
27 28	110	ethical research was obtained.
29 30	111	
31 32	112	Tilt-test protocol
33 34 35	113	The tilt table examination was performed in a dedicated room. Patients were fasted for two
36 37	114	hours prior to the HUT and did not have medications stopped. A motorised bed with footplate
38 39	115	support was used to achieve tilt angles of 60-80°. Each patient had a 10 minute supine
40 41	116	baseline period after which they were subjected to 20 minutes of tilt.
42 43	117	
44 45 46	118	Data acquisition and pre-processing
47 48	119	Continuous, non-invasive, high resolution, beat-to-beat heart rate (1000 Hz sampling
49 50	120	frequency) and blood pressure monitoring (500 Hz sampling frequency) was performed at
51 52	121	both sites using either the Task Force® Monitor (CNS SystemsMedizintechnik AG, Graz,
53 54	122	Austria) or Nexfin® (BMEYE B.V, Amsterdam, Holland). The Task Force® Monitor also
55 56 57 58	123	estimates cardiac output and total peripheral resistance using impedance cardiography.

124	
125	Time series for heart rate (beat to beat NN intervals) were extracted and automatically filtered
126	to exclude artefacts and ectopics using a validated and freely available programme Kubios
127	HRV (<u>http://kubios.uef.fi</u>).
128	
129	Heart Rate Variability
130	We standardized our analysis windows to five minutes to minimize bias as it is known that
131	the total variance of HRV increases in proportion to the length of recording, in line with
132	international recommendations (Task Force of the European Society of Cardiology and the
133	North American Society of Pacing and Electrophysiology, 1996). Windows immediately
134	before and during the first five minutes of HUT were analysed. Time domain, frequency
135	domain and non-linear methods for determining HRV were applied to the data (Task Force of
136	the European Society of Cardiology and the North American Society of Pacing and
137	Electrophysiology, 1996).
138	
139	Time domain analysis involves application of simple statistical techniques straight to the
140	successive RR intervals. We elected to study only SDRR (standard deviation of successive
141	RR intervals) and RMSSD (root of the mean squared differences of successive RR intervals)
142	(Tarvainen, Niskanen, Lipponen, Ranta-Aho, & Karjalainen, 2014) as both of these
143	parameters can be used in 5 minute recordings of RR intervals and the other time domain
144	parameters are either derived from them or are highly correlated to them (Task Force of the
145	European Society of Cardiology and the North American Society of Pacing and
146	Electrophysiology, 1996).
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148	Frequency domain analysis required the RR interval time series to be converted to an
149	equidistantly sampled series and this was performed using the cubic spline interpolation
150	method (Tarvainen, et al., 2014). The power spectral density was estimated using parametric
151	autoregressive modelling (order number 16 without factorisation) and absolute power in the
152	low frequency (LF: 0.04-0.15 Hz) and high frequency (HF: 0.15-0.4 Hz) bands calculated
153	(Tarvainen, et al., 2014). These powers can be normalised to minimise the effects of changes
154	in total power on this parameters, e.g. normalised LF (LFnu) is calculated as: LF/(Total
155	power- very low frequency power). Due to the algebraic relationship with normalised
156	frequency domain parameters, whereby the sum of LFnu and HFnu is always equal to one,
157	we have opted to present only unique data and arbitrarily chose to present LFnu.
158	
159	Finally we also applied the following non-linear methods of HRV analysis: Poincaré plots,
160	detrended fluctuation analysis and entropy. Poincaré plots are a graphical representation of
161	the correlation between successive RR intervals. It can be assessed qualitatively by looking at
162	the shape of the plot and quantitatively by fitting an ellipse to the plot and calculating the
163	standard deviation of the points perpendicular to the line of identity (SD1) and along the line
164	of identity (SD2) (Tarvainen, et al., 2014).
165	
166	Detrended fluctuation analysis measures correlation with the signal for different time scales.
167	A series of RR intervals are integrated and are divided into a series of regular intervals. For
168	each interval the fluctuation of the data from a straight line of linear interpolation is
169	calculated. DFA- α 1 corresponds to short-term fluctuations within an interval range of 4-16
170	whereas DFA- α 2 characterises longer-term fluctuations within the interval range of 16-64
171	(Tarvainen, et al., 2014).
172	

173	Sample entropy, which refers to the degree of irregularity or randomness with a series and are
174	estimates for the negative natural logarithm of the condition probability that a length of data
175	having repeated itself within a tolerance r for m points, will also repeat itself for $m+1$ points.
176	We used the default value of $m=2$ and $r=0.2$ SDRR (Tarvainen, et al., 2014).
177	
178	Statistics
179	Some of the HRV parameters were not normally distributed and so we adopted non-
180	parametric statistical analysis throughout for consistency. Continuous variables are
181	summarised as median (quartile 1, quartile 3) and compared using the Mann-Whitney U test
182	(independent samples), the Kruskal-Wallis test (more than two independent samples) and the
183	Wilcoxon signed rank test (dependent samples, i.e. comparing parameters before and after
184	HUT in the same cohort). Categorical variables are presented as counts or proportions (%)
185	and analysed using Fisher's exact text. Strength of correlation between variables are
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185	presented using the Pearson's product-moment correlation (r). A $P \le 0.05$ was considered
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186 187 188 189 190	presented using the Pearson's product-moment correlation (r). A P \leq 0.05 was considered statistically significant for analysis of baseline clinical features and haemodynamics of patients. This level of significance was made more stringent to P \leq 0.005 when analysing the HRV parameters using the Bonferroni method to correct for multiple testing. A concern with the Bonferroni method is that it can elevate the type II error rate (accepting the null
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186 187 188 189 190 191 192	presented using the Pearson's product-moment correlation (r). A P≤0.05 was considered statistically significant for analysis of baseline clinical features and haemodynamics of patients. This level of significance was made more stringent to P≤0.005 when analysing the HRV parameters using the Bonferroni method to correct for multiple testing. A concern with the Bonferroni method is that it can elevate the type II error rate (accepting the null hypothesis when the alternative is correct) and for that reason we have also provided complete P values or at least made a summative distinction between a parameter that changed
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	198	non-invasive beat to beat heart rate, blood pressure, stroke volume and peripheral resistance.
	199	Data for the remaining 12 patients in AF was obtained from another institution for whom
	200	non-invasive stroke volume or peripheral resistance measurements were not available.
)	201	Correlations between HRV variables at rest
2	202	
) - 	203	The effect of HUT in AF and SR
, ,	204	The demographics of the 31 patients in AF and 69 age-matched patients in SR are
;)	205	summarised in Table 1. Patients with AF were significantly more likely to have hypertension
)	206	and be on more medications (angiotensin converting enzyme inhibitor, angiotensin receptor
<u>}</u>	207	blocker, beta-blocker, calcium channel blocker and digoxin). Only 7 (22.6%) patients with
	208	AF were not on any of the six classes of medication detailed in Table 1, compared with 54
}	209	(78.3%) in the SR cohort.
)	210	
2	211	HUT causes a decrease in stroke volume, which is coupled with an increase in blood pressure
	212	(diastolic), heart rate and total peripheral resistance (Table 2). The magnitude and direction of
, ,	213	change, though similar for both cohorts, were statistically more convincing in patients with
}	214	SR.
)	215	
<u>-</u>	216	All HRV parameters at rest were significantly different between the AF and SR cohorts. On
5	217	HUT only 2 parameters (DFA- α 2 and sample entropy) changed significantly (P<0.005) in
, }	218	both groups (Table 2). SDRR, LFnu and SD2 increased in patients in SR on HUT, whereas
)	219	HF decreased in patients with AF at the uncorrected significance level of p<0.05. There was
	220	no overall difference in the direction of change between either group.
) - -	221	
) ,	222	The effect of aging on cardiovascular autonomic reflexes
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223	The cohort of 176 patients in SR was divided into tertiles of age (with median ages 22, 47
224	and 73 years). Their demographic data are detailed in Table 3 and suggests that the three
225	groups were balanced apart from there being proportionally more females in the youngest
226	cohort. In particular there were no differences with respect to prescribed medications.
227	
228	There were significant differences at rest between the 3 tertiles of age with respect to
229	haemodynamic function and HRV (Table 4). Stroke volume index decreased with age,
230	whereas resting heart rate did not change. With advancing age all of the HRV parameters
231	except for DFA- α 1 and DFA- α 2 were significantly attenuated (Table 4). Throughout the
232	tertiles of age, upon HUT, blood pressure, heart rate and total peripheral resistance index
233	increased whilst stroke volume index decreased. However, the augmentation in heart rate was
234	attenuated as was the decline in stroke volume index with increasing age. Furthermore, the
235	HRV response to HUT became blunted with age, with 11/12 HRV parameters changing at a
236	significance level of p< 0.005 in the youngest tertile, $9/12$ in the middle cohort and only $2/12$
237	in the oldest tertile.
238	
239	Correlations between each of the HRV parameters in the SR (N=176) and AF (N=31) cohorts
240	are shown in Table 5. There were strong correlations some of the non-linear parameters
241	(SD1, SD2 and DFA-α1) and linear parameters.
242	
243	Discussion
244	The main findings of this study are: 1) For patients in sinus rhythm, HRV at rest and in
245	response to HUT attenuates with age; 2) Patients in AF demonstrate similar changes in HRV

on HUT to an age-matched cohort in SR; 3) The non-linear measures of HRV appear more

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247	discriminatory in both AF compared with the conventional linear methods (time and
248	frequency domain).
249	
250	The effect of age on cardiovascular responses to HUT in SR patients
251	Haemodynamics
252	The process of shifting from a supine to an upright position results in an immediate reduction
253	in venous return and up to a 20% reduction in stroke volume. In response, there is an
254	activation of various homeostatic pathways, one of which is the ANS, which functions to
255	maintain cerebral blood flow and prevent syncope (Mourot et al., 2007). In our cohort, we
256	demonstrated that our HUT protocol was effective in inducing an adequate haemodynamic
257	stress. We observed a reduction in stroke volume index, which was associated with an
258	increase in blood pressure, heart rate and total peripheral resistance index.
259	
260	In the supine position, the oldest tertile had the lowest stroke volume and compared with the
261	youngest tertile had higher blood pressures and vascular resistance. Upon HUT, the increase
262	in heart rate was less pronounced in the older cohort as was the decrease in stroke index.
263	Cumulatively, these responses seek to maintain cardiac output (heart rate x stroke volume
264	indexed for body surface area). Laitinen and colleagues described the effect of ageing upon
265	response to HUT in 63 individuals and found results different from ours (Laitinen, et al.,
266	2004). Similar to our data they showed that elderly subjects had smaller increases in heart
267	rate, however, in contrast to our findings they showed that this cohort also had a larger
268	decrease in stroke volume and larger increase in total peripheral resistance upon HUT. The
269	most likely explanation is that the two studies have examined different populations. Laitinen
270	and colleagues studied a healthy population who were not on any medication compared with
271	our cohort who all had previously experienced syncope and at least a fifth had other

significant co-morbidities. Medications are known to influence cardiovascular responses but in our SR cohort there were no significant differences between the tertiles of age with respect to blood pressure lowering medications. Furthermore, there were differences between our studies with respect to when data were collected. In Laitinen's study all patients were rested supine for 3 hours before a 5 minute baseline recording of heart rate was obtained (our protocol mandated a 10 minute rest period) and were sampled at minutes 5-10 after HUT (our protocol mandated minutes 0-5). Heart rate variability

Ageing affects HRV both at rest and under dynamic testing using HUT. Consistent with the
wider literature our data confirm that HRV reduces with age, both at rest and in response to
HUT (Sosnowski, et al., 2011). At rest, we did not find a change in either DFA-α1 or DFAα2 with age. Others have reported similar results whilst some groups have shown a decrease

in DFA- α 1 and an increase in DFA- α 2 with advancing age in health volunteers (Shiogai,

286 Stefanovska, & McClintock, 2010; Voss, Schroeder, Heitmann, Peters, & Perz, 2015). The

287 likely contributors to this discrepancy are: 1) our study population were not healthy

288 volunteers; 2) approximately a fifth of our population in SR were on cardiovascular

medications (V. D. Corino et al., 2013); and 3) our study numbers were modest and hence our
investigation may be underpowered.

In the youngest tertile (0-30 years), seven of the nine HRV parameters changed significantly

on HUT. Only SDRR and its correlate SD2 did not change.(Hoshi, Pastre, Vanderlei, &

Godoy, 2013) In the 30-60 years of age cohort, RMSSD also failed to change significantly

295 with HUT. Finally in the 60 years and older cohort, only two HRV parameters changed (at

296 p<0.005), DFA- α 2 and sample entropy, both of them non-linear parameters. Studies

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3 4	297	examining the effect of HUT upon HRV, using time and frequency domain, mirror our
5 6	298	findings and have concluded that the response to HUT in younger individuals reflects
7 8	299	parasympathetic withdrawal at the cardiac level, which diminishes with ageing and is
9 10	300	associated with a concomitant increase in sympathetic tone to the periphery (Laitinen, et al.,
11 12	301	2004).
13 14 15	302	
16 17	303	Comparison of responses in patients with AF and SR
18 19	304	Frequency domain analyses of HRV in AF have failed to detect changes in response to
20 21	305	manoeuvres known to affect HRV in SR and our data lends further support to this assertion
22 23	306	(Hayano, et al., 1997; Leung et al., 2005). DFA- $\alpha 2$ and sample entropy are the only two HRV
24 25 26	307	parameters that changed significantly (p<0.005) in patients in AF and/or age-matched SR
27 28	308	upon HUT. Though the direction of change was identical between the two groups, the
29 30	309	magnitude of difference is likely to be different (though we are statistically underpowered to
31 32	310	demonstrate the latter). Furthermore there were three other HRV parameters that changed in
33 34 35	311	patients with SR but did not in AF, when the type 1 error rate was reduced to 0.05: SDRR,
36 37	312	SD2, LFnu (the former two have previously been shown to be well positively
38 39	313	correlated).(Hoshi, et al., 2013) It is not unexpected to see differences in HRV effects, since
40 41	314	our two populations are different and because of this we would always recommend analysing
42 43 44	315	HRV in patients with AF separately from those in SR. Nonetheless, our findings suggest that
44 45 46	316	though HRV data may be less interpretable in AF, certain parameters do have discriminatory
47 48	317	values rather than just the "random chaos" of ventricular response.
49 50	318	
51 52	319	However, a feature of note is how few HRV changes were actually observed on HUT, even in
53 54 55 56 57	320	the SR cohort. This highlights the importance of ageing on HRV as discussed above. In both

$$\begin{array}{c} 41\\ 42\\ 43\\ 44\\ 45\\ 46\\ 47\\ 48\\ 49\\ 50\\ 51\\ 52\\ 53\\ 55\\ 56\\ 57\\ 58\\ 59\\ 60\\ \end{array}$$

the oldest tertile in SR and the AF group, the non-linear measures were the only parametersthat changed significantly.

> One might ask why there is a differential effect depending on which measure of HRV is employed. There is no gold standard technique for measuring HRV and currently no one method can be described as superior to another; rather each provides complementary information (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996). Though many groups have attempted to attribute individual HRV parameters to a particular limb of the autonomic nervous system, to do so is an oversimplification of what is a complicated network. At best, HRV allows an insight into autonomic modulation; as tone increases, modulation increases but once tone remains elevated and saturation occurs, modulation decreases.

334 Non-linear measures of HRV

There is little doubt that heart rate and its variability are complex phenomena which arise from an intricate network of regulatory pathways. Heart rate is likely to be sensitive to initial conditions but this dependence is likely to diverge exponentially with time. In mathematics these types of systems are best described as non-linear, which are fundamentally different from linear systems (examples of which include time and frequency domain analyses). This description of the underlying principles of non-linear methods makes it immediately appealing as a technique for AF due to the apparent randomness of the latter. We examined three types of non-linear analysis: Poincaré plots (Hoshi, et al., 2013), DFA(Castiglioni et al., 2011) and entropy (Porta et al., 2007).

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3	345	SD1 and SD2 represent the standard deviation in the minor and major axis of a fitted ellipse
4 5 6	346	to a plot of RR interval against the subsequent RR interval. However, as derivation of these
6 7 8	347	variables is based on simple statistics, groups have questioned whether analysis of Poincaré
9 10	348	plots truly reflects a non-linear technique. Hoshi and colleagues performed linear correlation
11 12	349	amongst time domain, frequency domain and non-linear HRV parameters in 65 healthy
13 14 15	350	individuals and 114 patients with coronary artery disease. Their data showed that SD1 is
16 17	351	highly correlated to RMSSD (r=0.99) and SD2 to SDRR (r=0.95) (Hoshi, et al., 2013).
18 19	352	Tulppo and colleagues showed a strong correlation between SD1 and HF (r=0.94) as well as
20 21 22	353	SD2 and SDRR (r=0.99) (Tulppo, Makikallio, Takala, Seppanen, & Huikuri, 1996). Our data
22 23 24	354	similarly reproduced these correlations (Table 5).
25 26	355	
27 28	356	DFA detects self-similarity. An α value of 0.5 suggests that the signal is truly random
29 30	357	(white-noise) with larger values suggesting less noise (Brownian motion). When healthy
31 32 33	358	volunteers were sequentially challenged with atropine, propranolol and clonidine, it was
34 35	359	shown that DFA values rise with vagal blockade and decrease with sympathetic blockade
36 37	360	(Millar, Cotie, St Amand, McCartney, & Ditor, 2010).
38 39	361	
40 41	362	Sample entropy measures regularity or randomness of heart rate variations. Higher values
42 43 44	363	indicate greater irregularity and are commonly a feature of health. During HUT, it is expected
45 46	364	that sample entropy decreases and this has been shown to be proportional to the angle of
47 48	365	HUT (Porta, et al., 2007).
49 50	366	
51 52	367	Other data supporting the validity of using HRV in AF
53 54 55	368	Measuring HRV in AF is not implausible; however, there remains a marked under
56 57	369	appreciation of it. The most basic search on PubMed reveals >18000 articles containing the
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words 'heart rate variability' but only 402 articles using the combination of 'heart rate variability' and 'atrial fibrillation'. A selection of the key publications are summarised below, however, from a broader perspective, further work in this field is required especially using the less validated non-linear techniques. Just as in SR there is a circadian rhythm of HR, a similar one is found in AF (Bollmann, et al., 2006). Following on from this, the prognostic significance of HRV in large populations of SR patients has been widely published and though there is a similar trend in patients with AF, the literature is sparse (Frev et al., 1995; Platonov & Holmovist, 2011). Yamada and colleagues showed in 107 patients with AF and predominately a preserved left ventricular ejection fraction, that HRV (non-linear markers only) could predict mortality (Yamada et al., 2000). In the reduced ejection fraction population of MADIT-II, in a sub-group of patients with AF (n = 68), those with a pNN20 <87 had a higher mortality (V. D. Corino et al., 2015). Finally in a cohort of 155 patients with heart failure and AF who were enrolled into the Muerte Subita en Insufficiencia Cardiaca (MUSIC) study, only non-linear HRV parameters were found to be predictors of mortality, sudden cardiac death and heart failure progression.(Cygankiewicz, et al., 2015)

Our focus was on whether reactive changes in HRV could be identified in patient with AF after a dynamic challenge. Van den Berg and colleagues compared the role of vagal activity by using intravenous propanolol (SNS inhibitor) and methylatropine (PNS inhibitor) in 16 patients with chronic AF and 12 healthy men in SR (van den Berg et al., 1997). They demonstrated that though there were significant differences at baseline between the two groups in respect of HRV (SDRR, RMSDD, LF and HF), these parameters changed in patients with AF in a similar direction albeit visually different magnitudes to healthy

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individuals when subjected to pharmacological sequential autonomic blockade. In a subsequent blinded crossover trial in 60 patients with permanent AF, it was shown that both beta-blockers and rate limiting calcium channel blockers lower heart rate and time domain parameters (SDRR, RMSDD), whilst beta-blockers also increased irregularity (sample entropy)(V. D. Corino, et al., 2015). Nagayoshi and colleagues documented RR interval and SDRR in 23 patients (mean age 61 years) in response to tilt, Valsalva, hand grip and showed that the response in patients with AF was similar to those of a historic SR population (Nagayoshi, Janota, Hnatkova, Camm, & Malik, 1997).

404 Limitations

This is a retrospective study and is exposed to the inherent biases that are common with this design. We have tried to minimise selection bias by sampling consecutive patients. Observer bias was limited as the tilt-time around which the analysis was performed was based upon what was recorded at the time of the HUT. Ideally we would have wanted to study more patients with AF but we were surprised to find only 31 patients in total at two centres spanning in combination, 9 years of data in total. Our findings are applicable to patients with permanent AF who are above the age of 60 and likely to be on heart rate lowering or blood pressure lowering medications. Drugs, duration of AF (often difficult accurately to ascertain if the condition is asymptomatic) and other diagnoses (hypertension, heart failure, diabetes mellitus) are all known to induce autonomic remodelling and it is likely to account for the heterogeneity in response to HUT in our study. However, due to our limited sample size of patients with AF, we are unable confidently to perform further subgroup analyses to investigate the relative contributions of each of these explanatory variables on HRV. Comparisons of HRV and response to HUT between the population in AF and SR are confounded by the significantly increased use of cardiovascular medications and prevalence

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420	of hypertension in the AF group (Table 1). A larger and prospective study, with a broad
421	spectrum of AF patients matched by an equally broad spectrum of SR patients, might
422	overcome a number of these problems. Others have analysed blood pressure variability in
423	patients with AF and found less 'white-noise' artefact when compared to spectral analysis of
424	heart rate (V. D. A. Corino, Lombardi, & Mainardi, 2014). Future work may also study blood
425	pressure variability and baroreceptor function as markers of the ANS in patients with AF.
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427	We corrected for multiple statistical testing using a Bonferroni correction. However, an
428	accepted weakness is that it often results in a reduction in power, i.e. a conclusion that there
429	is no change, when one genuinely exists. To demonstrate the effects of this correction
430	explicitly, we have also provided those results that achieved significance at the conventional
431	critical p value of 0.05.
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Conflict of interests

None.

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 448 References: 449 Ardell, J. L., Cardinal, R., Beaumont, E., Vermeulen, M., Smith, F. M., & Andrew Armour, J. (2014). Chronic spinal cord stimulation modifies intrinsic cardiac synaptic efficacy in the suppression of atrial fibrillation. <i>Auton Neurosci</i>, <i>186</i>, 38-44. doi: 10.016/j.auton.2040.9017 452 453 Bilchick, K. C., Fetics, B., Djoukeng, R., Fisher, S. G., Fletcher, R. D., Singh, S. N., Berger, R. D. (2002). Prognostic value of heart rate variability in chronic congestive heart failure. <i>Nan J Cordiol</i>, 90(1), 24-28. Bollmann, A., Husser, D., Mainardi, L., Lombardi, F., Langley, P., Murray, A., Sornmo, L. (2006). 453 Bollmann, A., Husser, D., Mainardi, L., Lombardi, F., Langley, P., Murray, A., Sornmo, L. (2006). 454 Analysis of surface electrocardiograms in atrial fibrillation: techniques, research, and clinical applications. <i>Europeace</i>, 8(11), 911-926. doi: 10.1093/europace/eu113 460 461 Carrara, M., Carozzi, L., Moss, T. J., de Pasquale, M., Cerutti, S., Ferrario, M., Moorman, J. R. 462 (2015). Heart rate dynamics distinguish among atrial fibrillation, normal sinus rhythm and sinus rhythm with frequent ectopy. <i>Physiological Measurement</i>, <i>36</i>(9), 1873-1888. doi: 463 10.1088/0967-3334/36/9/1873 465 466 Castiglioni, P., Parati, G., Di Rienzo, M., Carabalona, R., Cividjian, A., & Quintin, L. (2011). Scale exponents of blood pressure and heart rate during autonomic blockade as assessed by detrended fluctuation analysis. <i>J Physiol</i>, <i>589</i>(Pt 2), 355-369. doi: 467 470 471 Corino, V. D., Cygankiewicz, I., Mainardi, L. T., Stridh, M., Vasquez, R., Bayes de Luna, A., Platonov, P. G. (2013). Association between atrial fibrillator, <i>Ann Noninvasive Electrocardiol</i>, 473 474 475 476 477 478 478 479 <	1		
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 Chronic spinal cord stimulation modifies intrinsic cardiae synaptic efficacy in the suppression of atrial fibrillation. Auton Neurosci, 186, 38-44. doi: 10.1016/j.autneu.2014.09.017 Bilchick, K. C., Fetics, B., Djoukeng, R., Fisher, S. G., Fletcher, R. D., Singh, S. N., Berger, R. D. (2002). Prognostic value of heart rate variability in chronic congestive heart failure (Veterans Affairs' Survival Trial of Antiarchythmic Therapy in Congestive Heart Failure. <i>J. An J Cardiol</i>, 90(1), 24-28. Bollmann, A., Husser, D., Mainardi, L., Lombardi, F., Langley, P., Murray, A., Sornmo, L. (2006). Analysis of surface electrocardiograms in atrial fibrillation: techniques, research, and clinical applications. <i>Europace</i>, 8(11), 911-926. doi: 10.1093/europace/eul113 Carrara, M., Carozzi, L., Moss, T. J., de Pasquale, M., Cerutti, S., Ferrario, M., Moorman, J. R. (2015). Heart rate dynamics distinguish among atrial fibrillation, normal sinus rhythm with frequent ectopy. <i>Physiological Measurement</i>, <i>36</i>(9), 1873-1888. doi: 10.1088/0967-3334/36/9/1873 Castiglioni, P., Parati, G., Di Rienzo, M., Carabalona, R., Cividjian, A., & Quintin, L (2011). Scale exponents of blood pressure and heart rate during autonomic blockade as assessed by detrended fluctuation analysis. <i>J Physiol</i>, <i>58</i>(9): 2), 355-369. doi: 10.1113/jphysiol.2010.196428 Corino, V. D., Cygankiewicz, I., Mainardi, L. T., Stridh, M., Vasquez, R., Bayes de Luna, A, Platonov, P. G. (2013). Association between atrial fibrillatory rate and heart rate variability in patients with atrial fibrillation. <i>J Cardioxes Electrophysiol</i>, <i>26</i>(2), 137-141. doi: 10.1111/jee.12580 Corino, V. D., Ulimoen, S. R., Enger, S., Mainardi, L. T., Veit, A., & Platonov, P. G. (2015). Ret-control drugs affect variability in cytoricular Response During Atrial Fibrillation and Long-term Outcome in Patients with atrial fibrillation. <i>J Cardiovs Electrophysiol</i>, <i>26</i>(2), 137-141. doi: 10.1111/			
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 Bilchick, K. C., Fetics, B., Djoukeng, R., Fisher, S. G., Fletcher, R. D., Singh, S. N., Berger, R. D. (2002). Prognostic value of heart rate variability in chronic congestive heart failure (Veterans Affier's Survival Trial of Antiarrhythmic Therapy in Congestive Heart Failure). <i>Am J Cardiol,</i> 90(1), 24-28. Bollmann, A., Husser, D., Mainardi, L., Lombardi, F., Langley, P., Murray, A., Sornmo, L. (2006). Analysis of surface electrocardiograms in atrial fibrillation: techniques, research, and clinical applications. <i>Europace,</i> 8(11), 911-926. doi: 10.1093/europace/eul113 Carrara, M., Carozzi, L., Moss, T. J., de Pasquale, M., Cerutti, S., Ferrario, M., Moorman, J. R. (2015). Heart rate dynamics distinguish among atrial fibrillation, normal sinus rhythm and sinus rhythm with frequent ectopy. <i>Physiological Measurement,</i> 36(9), 1873-1888. doi: 10.1088/0967-334/36/9/1873 Castiglioni, P., Parati, G., Di Rienzo, M., Carabalona, R., Cividjian, A., & Quintin, L. (2011). Scale exponents of blood pressure and heart rate during autonomic blockade as assessed by detrended fluctuation analysis. <i>J Physiol,</i> 589(Pt 2), 355-369. doi: 10.1113/jphysiol.2010.196428 Corino, V. D., Cygankiewicz, I., Mainardi, L. T., Stridh, M., Vasquez, R., Bayes de Luna, A, Platonov, P. G. (2013). Association between atrial fibrillatory rate and heart rate variability in patients with atrial fibrillation and congestive heart failure. <i>Ann Noninvasive Electrocardiol, 18</i>(1), 41-50. doi: 10.1111/janec.12019 Corino, V. D., Ulimoen, S. R., Enger, S., Mainardi, L. T., Tveit, A., & Platonov, P. G. (2015). Rate-control drugs affect variability and irregularity measures of RR Intervals in patients with permanent drugs affect variability and irregularity measures of RR Intervals in patients with theart fibrillation. <i>J Cardiovasc Electrophysiol,</i> 26(2), 137-141. doi: 10.1111/jce.12580 Corino, V. D. A., Lombardi, F., & Mainardi, L. T., Zotti		450	
 433 binlink, K. C., Felks, B., Djoueng, K., Fishel, S.G., Hether, N.G., Jingly, J.K., Delgel, N.G. 434 (2022). Prognostic value of heart rate variability in chronic congestive heart failure! (Veterans) 435 Affairs' Survival Trial of Antiarrhythmic Therapy in Congestive Heart Failure!. <i>Am J Cardiol</i>, 436 90(1), 24-28. 437 Bollmann, A., Husser, D., Mainardi, L., Lombardi, F., Langley, P., Murray, A., Sornmo, L. (2006). 438 Analysis of surface electrocardiograms in atrial fibrillation: techniques, research, and clinical 439 applications. <i>Europace</i>, 8(11), 911-926. doi: 10.1093/europace/eul113 440 451 Carrara, M., Carozzi, L., Moss, T. J., de Pasquale, M., Cerutti, S., Ferrario, M., Moorman, J. R. 452 (2015). Heart rate dynamics distinguish among atrial fibrillation, normal sinus rhythm and 453 sinus rhythm with frequent ectopy. <i>Physiological Measurement</i>, 36(9), 1873-1888. doi: 454 10.1088/0967-3334/36/9/1873 455 465 465 Castiglioni, P., Parati, G., Di Rienzo, M., Carabalona, R., Cividjian, A., & Quintin, L. (2011). Scale 468 exponents of blood pressure and heart rate during autonomic blockade as assessed by 469 detrended fluctuation analysis. <i>J Physiol, 589</i>(Pt 2), 355-369. doi: 10.1113/jphysiol.2010.196428 470 471 Corino, V. D., Cygankiewicz, I., Mainardi, L. T., Stridh, M., Vasquez, R., Bayes de Luna, A., 472 Platonov, P. G. (2013). Association between atrial fibrillatory rate and heart rate variability in 473 474 474 475 476 477 478 478 479 479 479 479 470 471 472 473 474 474			Bilebiels K.C. Feties D. Disultanz D. Fisher C.C. Flatcher D.D. Singh C.N. Bargar D.D.
 454 (2002). Frogrosol and control of the analogity in Congestive Heart Failure). <i>Am J Cardiol</i>, 90(11), 24-28. 455 Bollmann, A., Husser, D., Mainardi, L., Lombardi, F., Langley, P., Murray, A., Sormon, L. (2006). 458 Analysis of surface electrocardiograms in atrial fibrillation: techniques, research, and clinical applications. <i>Europace</i>, 8(11), 911-926. doi: 10.1093/europace/eul113 460 Carrara, M., Carozzi, L., Moss, T. J., de Pasquale, M., Cerutti, S., Ferrario, M., Moorman, J. R. (2015). Heart rate dynamics distinguish among atrial fibrillation, normal sinus rhythm and sinus rhythm with frequent ectopy. <i>Physiological Measurement</i>, 36(9), 1873-1888. doi: 10.1088/0967-334/36/9/1873 465 Castiglioni, P., Parati, G., Di Rienzo, M., Carabalona, R., Cividjian, A., & Quintin, L. (2011). Scale exponents of blood pressure and heart rate during autonomic blockade as assessed by detrended fluctuation analysis. <i>J Physiol</i>, 589(Pt 2), 355-369. doi: 10.1113/jphysiol.2010.196428 470 Corino, V. D., Cygankiewicz, I., Mainardi, L. T., Stridh, M., Vasquez, R., Bayes de Luna, A., Platonov, P. G. (2013). Association between atrial fibrillatory rate and heart rate variability in patients with atrial fibrillation and congestive heart failure. <i>Ann Noninvasive Electrocardiol</i>, <i>18</i>(1), 41-50. doi: 10.1111/janec.12019 476 Corino, V. D., Ulimoen, S. R., Enger, S., Mainardi, L. T., Tveit, A., & Platonov, P. G. (2015). Rate-control drugs affect variability and irregularity measures of RR intervals in patients with permanent atrial fibrillation. <i>J Cardiovasc Electrophysiol</i>, <i>26</i>(2), 137-141. doi: 10.1111/jce.12580 479 Corino, V. D. A., Lombardi, F., & Mainardi, L. T., Zotti, Blood pressure variability in patients with atrial fibrillation. <i>J Cardiovasc Electrophysiol</i>, <i>26</i>(2), 137-141. doi: 10.1111/jce.12580 479 Corino, V. D. A., Lombardi, F., & Mainardi, L. T. (2014). Blood pressure variability in patien			
 Affairs Survival Inal of Antiarrhytimic Therapy in Congestive Heart Falure?, <i>Am J Carabio</i>, 90(1), 24-28. Bollmann, A., Husser, D., Mainardi, L., Lombardi, F., Langley, P., Murray, A., Sornmo, L. (2006). Analysis of surface electrocardiograms in atrial fibrillation: techniques, research, and clinical applications. <i>Europace</i>, 8(11), 911-926. doi: 10.1093/europace/eu113 Carrara, M., Carozzi, L., Moss, T. J., de Pasquale, M., Cerutti, S., Ferrario, M., Moorman, J. R. (2015). Heart rate dynamics distinguish among atrial fibrillation, normal sinus rhythm and sinus rhythm with frequent ectopy. <i>Physiological Measurement</i>, 36(9), 1873-1888. doi: 10.1088/0967-3334/36/9/1873 Castigioni, P., Parati, G., Di Rienzo, M., Carabalona, R., Cividjian, A., & Quintin, L. (2011). Scale exponents of blood pressure and heart rate during autonomic blockade as assessed by detrended fluctuation analysis. <i>J Physiol</i>, 599(Pt 2), 355-369. doi: 10.1113/jphysiol.2010.196428 Corino, V. D., Cygankiewicz, L., Mainardi, L. T., Stridh, M., Vasquez, R., Bayes de Luna, A., Platonov, P. G. (2013). Association between atrial fibrillatory rate and heart rate variability in patients with atrial fibrillation and congestive heart failure. <i>Ann Noninvosive Electrocardiol,</i> <i>18</i>(1), 41-50. doi: 10.1111/anec.12019 Corino, V. D., Ulimoen, S. R., Enger, S., Mainardi, L. T., Tveit, A., & Platonov, P. G. (2015). Rate-control drugs affect variability and irregularity measures of RR intervals in patients with permanent atrial fibrillation. <i>J Cardiovasc Electrophysiol, 26</i>(2), 137-141. doi: 10.1111/jce.12580 Corino, V. D. A., Lombardi, F., & Mainardi, L. T. (2014). Blood pressure variability in patients with atrial fibrillation. <i>J Cardiovasc Electrophysiol, 26</i>(2), 137-141. doi: 10.1111/jce.12580 Key, B., Heinz, G., Binder, T., Wutte, M., Schneider, B., Schmidinger, H.,, Pacher, R. (1995). Diurnal variation of ventricular response Durin			
 456 90(1), 24-28. Bollmann, A., Husser, D., Mainardi, L., Lombardi, F., Langley, P., Murray, A., Sornmo, L. (2006). Analysis of surface electrocardiograms in atrial fibrillation: techniques, research, and clinical applications. <i>Europace</i>, 8(11), 911-926. doi: 10.1093/europace/eu113 460 461 Carrara, M., Carozzi, L., Moss, T. J., de Pasquale, M., Cerutti, S., Ferrario, M., Moorman, J. R. (2015). Heart rate dynamics distinguish among atrial fibrillation, normal sinus rhythm and sinus rhythm with frequent ectopy. <i>Physiological Measurement</i>, <i>36</i>(9), 1873-1888. doi: 10.1088/0967-334/36/9/1873 465 Castiglioni, P., Parati, G., Di Rienzo, M., Carabalona, R., Cividjian, A., & Quintin, L. (2011). Scale exponents of blood pressure and heart rate during autonomic blockade as assessed by detrended fluctuation analysis. <i>J Physiol</i>, <i>589</i>(Pt 2), 355-360. doi: 10.1113/jphysiol.2010.196428 470 Corino, V. D., Cygankiewicz, I., Mainardi, L. T., Stridh, M., Vasquez, R., Bayes de Luna, A., Platonov, P. G. (2013). Association between atrial fibrillatory rate and heart rate variability in patients with atrial fibrillation and congestive heart failure. <i>Ann Noninvosive Electrocardiol, 18</i>(1), 41-50. doi: 10.1111/nec.12019 475 Corino, V. D., Ulimoen, S. R., Enger, S., Mainardi, L. T., Tveit, A., & Platonov, P. G. (2015). Rate-control drugs affect variability and irregularity measures of RR intervals in patients with permanent atrial fibrillation. <i>J Cardiovasc Electrophysiol, 26</i>(2), 137-141. doi: 10.1111/j.ec.12580 476 Corino, V. D. A., Lombardi, F., & Mainardi, L. T. (2014). Blood pressure variability in patients with atrial fibrillation. <i>J Cardiovasc Electrophysiol, 26</i>(2), 137-141. doi: 10.1111/jcc.12580 478 479 Cygankiewicz, I., Corino, V., Vazquez, R., Bayes-Genis, A., Mainardi, L., Zareba, W., Platonov, P. G. (2015). Reduced Irregularity of Ventricular Respon			
 Analysis of surface electrocardiograms in atrial fibrillation: techniques, research, and clinical applications. Europace, 8(11), 911-926. doi: 10.1093/europace/eul113 Garrara, M., Carozzi, L., Moss, T. J., de Pasquale, M., Cerutti, S., Ferrario, M., Moorman, J. R. (2015). Heart rate dynamics distinguish among atrial fibrillation, normal sinus rhythm and sinus rhythm with frequent ectopy. Physiological Measurement, 36(9), 1873-1888. doi: 10.1088/0967-3334/36/9/1873 Castiglioni, P., Parati, G., Di Rienzo, M., Carabalona, R., Cividjian, A., & Quintin, L. (2011). Scale exponents of blood pressure and heart rate during autonomic blockade as assessed by detended fluctuation analysis. J Physiol. 589(Pt 2), 355-369. doi: 10.1113/jphysiol.2010.196428 Corino, V. D., Cygankiewicz, I., Mainardi, L. T., Stridh, M., Vasquez, R., Bayes de Luna, A., Platonov, P. G. (2013). Association between atrial fibrillatory rate and heart rate variability in patients with atrial fibrillation and congestive heart failure. Ann Noninvasive Electrocardiol, 18(1), 41-50. doi: 10.1111/nec.12019 Corino, V. D., Ulimoen, S. R., Enger, S., Mainardi, L. T., Tveit, A., & Platonov, P. G. (2015). Rate-control drugs affect variability and irregularity measures of RR intervals in patients with permanent atrial fibrillation. J Cardiovasc Electrophysiol, 26(2), 137-141. doi: 10.1111/jce.12580 Corino, V. D. A., Lombardi, F., & Mainardi, L. T. (2014). Blood pressure variability in patients with atrial fibrillation. J Cardiovasc Electrophysiol, 26(2), 137-141. doi: 10.1111/jce.12580 Cygankiewicz, I., Corino, V., Vazquez, R., Bayes-Genis, A., Mainardi, L., Zareba, W., Platonov, P. G. (2015). Reduced Irregularity of Ventricular Response During Atrial Fibrillation and Long-term Outcome in Patients With Heart Failure. Am J Cardiol, 116(7), 1071-1075. doi: 10.1016/j.amicat.2015.06.043 Frey, B., Heinz, G., Binder, T., Wutte, M., Schneider, B., Schmidi			
 Analysis of surface electrocardiograms in atrial fibrillation: techniques, research, and clinical applications. <i>Europace</i>, 8(11), 911-926. doi: 10.1093/europace/eu113 Carrara, M., Carozzi, L., Moss, T. J., de Pasquale, M., Cerutti, S., Ferrario, M., Moorman, J. R. (2015). Heart rate dynamics distinguish among atrial fibrillation, normal sinus rhythm and sinus rhythm with frequent ectopy. <i>Physiological Measurement</i>, 36(9), 1873-1888. doi: 10.1088/0967-3334/36/9/1873 Castiglioni, P., Parati, G., Di Rienzo, M., Carabalona, R., Cividjian, A., & Quintin, L. (2011). Scale exponents of blood pressure and heart rate during autonomic blockade as assessed by detrended fluctuation analysis. <i>J Physiol</i>, 589(Pt 2), 355-369. doi: 10.1113/jphysiol.2010.196428 Corino, V. D., Cygankiewicz, I., Mainardi, L. T., Stridh, M., Vasquez, R., Bayes de Luna, A., Platonov, P. G. (2013). Association between atrial fibrillatory rate and heart rate variability in patients with atrial fibrillation and congestive heart failure. <i>Ann Noninvasive Electrocardiol</i>, <i>18</i>(1), 41-50. doi: 10.1111/jnec.12019 Corino, V. D., Ulimoen, S. R., Enger, S., Mainardi, L. T., Tveit, A., & Platonov, P. G. (2015). Rate-control drugs affect variability and irregularity measures of RR intervals in patients with permanent atrial fibrillation. <i>J Cardiovasc Electrophysiol</i>, <i>26</i>(2), 137-141. doi: 10.1111/jce.12580 Corino, V. D. A., Lombardi, F., & Mainardi, L. T. (2014). Blood pressure variability in patients with atrial fibrillation. <i>J Cardiovasc Electrophysiol</i>, <i>26</i>(2), 137-141. doi: 10.1111/jce.12580 Cygankiewicz, I., Corino, V., Vazquez, R., Bayes-Genis, A., Mainardi, L., Zareba, W., Platonov, P. G. (2015). Reduced irregularity of Ventricular Response During Atrial Fibrillation and Long-term Outcome in Patients With Heart Failure. <i>Am J Cardiol</i>, <i>116</i>(7), 1071-1075. doi: 10.1016/j.amicard.2015.06.043 Frey, B., Heinz, G., Binder, T., Wutte, M., Schneider, B., Schmidinger, H.			
17459applications. Europace, 8(11), 911-926. doi: 10.1093/europace/eul1131846020461Carrara, M., Carozzi, L., Moss, T. J., de Pasquale, M., Cerutti, S., Ferrario, M., Moorman, J. R.21461Carrara, M., Carozzi, L., Moss, T. J., de Pasquale, M., Cerutti, S., Ferrario, M., Moorman, J. R.24463sinus rhythm with frequent ectopy. Physiological Measurement, 36(9), 1873-1888. doi:25466Castiglioni, P., Parati, G., Di Rienzo, M., Carabalona, R., Cividjian, A., & Quintin, L. (2011). Scale26466castiglioni, P., Parati, G., Di Rienzo, M., Carabalona, R., Cividjian, A., & Quintin, L. (2011). Scale27467exponents of blood pressure and heart rate during autonomic blockade as assessed by28468detrended fluctuation analysis. J Physiol. 589(Pt 2), 355-369. doi:2940910.1113/jphysiol.2010.196428301470Corino, V. D., Cygankiewicz, I., Mainardi, L. T., Stridh, M., Vasquez, R., Bayes de Luna, A.,31470Platonov, P. G. (2013). Association between atrial fibrillatory rate and heart rate variability in32473patients with atrial fibrillation and congestive heart failure. Ann Noninvosive Electrocardiol,33476Corino, V. D., Ulimoen, S. R., Enger, S., Mainardi, L. T., Tveit, A., & Platonov, P. G. (2015). Rate-control34478atrial fibrillation. J Cardiovasc Electrophysiol, 26(2), 137-141. doi: 10.1111/jce.1258034479Atrial fibrillation. Auton Neurosci, 185(0), 129-133. doi:48http://dx.doi.org/10.1016/j.autneu.2014.08.00247484(2yg		458	Analysis of surface electrocardiograms in atrial fibrillation: techniques, research, and clinical
 460 461 461 462 463 464 464 465 465 465 465 466 466 466 467 468 468 469 469 469 469 469 460 460 461 462 463 464 464 464 465 465 465 465 466 466 467 468 468 468 468 468 468 468 469 469 469 469 469 460 460 460 461 474 470 474 470 474 475 475 476 477 477 478 478 479 479 470 471 470 471 471 471 472 473 474 474 474 475 475 476 477 478 478 479 479 474 474 474 475 475 476 477 478 478 479 479 474 474 474 474 475 475 476 477 478 478 478 479 479 479 474 470 474 474 474 475 475 476 477 478 478 478 479 479 479 471 471 474 474 474 475 475 476 476 477 478 478 478 478 479 479 479 479 470 471 471 471 471 471 471 472 474 474 474 475 476		459	applications. Europace, 8(11), 911-926. doi: 10.1093/europace/eul113
 Carrara, M., Carozzi, L., Moss, T. J., de Pasquale, M., Cerutti, S., Ferrario, M., Moorman, J. R. (2015). Heart rate dynamics distinguish among atrial fibrillation, normal sinus rhythm and sinus rhythm with frequent ectopy. <i>Physiological Measurement, 36</i>(9), 1873-1888. doi: 10.1088/0967-3334/36/9/1873 Castiglioni, P., Parati, G., Di Rienzo, M., Carabalona, R., Cividjian, A., & Quintin, L. (2011). Scale exponents of blood pressure and heart rate during autonomic blockade as assessed by detrended fluctuation analysis. <i>J Physiol, 589</i>(Pt 2), 355-369. doi: 10.1113/jphysiol.2010.196428 Corino, V. D., Cygankiewicz, I., Mainardi, L. T., Stridh, M., Vasquez, R., Bayes de Luna, A., Platonov, P. G. (2013). Association between atrial fibrillatory rate and heart rate variability in patients with atrial fibrillation and congestive heart failure. <i>Ann Noninvasive Electrocardiol,</i> <i>18</i>(1), 41-50. doi: 10.1111/anec.12019 Corino, V. D., Ulimoen, S. R., Enger, S., Mainardi, L. T., Tveit, A., & Platonov, P. G. (2015). Rate-control drugs affect variability and irregularity measures of RR intervals in patients with permanent atrial fibrillation. <i>J Cardiovasc Electrophysiol, 26</i>(2), 137-141. doi: 10.1111/jce.12580 Corino, V. D. A., Lombardi, F., & Mainardi, L. T. (2014). Blood pressure variability in patients with atrial fibrillation. <i>J Cardiovasc Electrophysiol, 26</i>(2), 137-141. doi: 10.1111/jce.12580 Cygankiewicz, I., Corino, V., Vazquez, R., Bayes-Genis, A., Mainardi, L., Zareba, W., Platonov, P. G. (2015). Reduced Irregularity of Ventricular Response During Atrial Fibrillation and Long-term Outcome in Patients With Heart Failure. <i>Am J Cardiol, 116</i>(7), 1071-1075. doi: 10.1016/j.amjcard.2015.06.043 Frey, B., Heinz, G., Binder, T., Wutte, M., Schneider, B., Schmidinger, H., Pacher, R. (1995). Diurnal variation of ventricular response to atrial fibrillation in patients with advanced heart failure. <i>Am Heart J,</i> 129(18		
 462 (2015). Heart rate dynamics distinguish among atrial fibrillation, normal sinus rhythm and sinus rhythm with frequent ectopy. <i>Physiological Measurement</i>, <i>36</i>(9), 1873-1888. doi: 463 10.1088/0967-3334/36/9/1873 465 466 Castiglioni, P., Parati, G., Di Rienzo, M., Carabalona, R., Cividjian, A., & Quintin, L. (2011). Scale exponents of blood pressure and heart rate during autonomic blockade as assessed by detrended fluctuation analysis. <i>J Physiol</i>, <i>589</i>(Pt 2), 355-369. doi: 469 10.1113/jphysiol.2010.196428 470 471 Corino, V. D., Cygankiewicz, I., Mainardi, L. T., Stridh, M., Vasquez, R., Bayes de Luna, A., Platonov, P. G. (2013). Association between atrial fibrillatory rate and heart rate variability in patients with atrial fibrillation and congestive heart failure. <i>Ann Noninvasive Electrocardiol,</i> <i>18</i>(1), 41-50. doi: 10.1111/anec.12019 475 476 Corino, V. D., Ulimoen, S. R., Enger, S., Mainardi, L. T., Tveit, A., & Platonov, P. G. (2015). Rate-control drugs affect variability and irregularity measures of RR intervals in patients with permanent atrial fibrillation. <i>J Cardiovasc Electrophysiol, 26</i>(2), 137-141. doi: 10.1111/jce.12580 479 480 Corino, V. D. A., Lombardi, F., & Mainardi, L. T. (2014). Blood pressure variability in patients with atrial fibrillation. <i>Auton Neurosci, 185</i>(0), 129-133. doi: http://dx.doi.org/10.1016/j.autneu.2014.08.002 484 Cygankiewicz, I., Corino, V., Vazquez, R., Bayes-Genis, A., Mainardi, L., Zareba, W., Platonov, P. G. (2015). Reduced Irregularity of Ventricular Response During Atrial Fibrillation and Long-term Outcome in Patients With Heart Failure. <i>Am J Cardiol, 116</i>(7), 1071-1075. doi: 10.1016/j.amjcard.2015.06.043 488 489 Frey, B., Heinz, G., Binder, T., Wutte, M., Schneider, B., Schmidinger, H., Pacher, R. (1995). Diurnal variation of ventricular response to atrial fibrillation in patients with advanced heart failure. <i>Am Heart </i>	19		
 463 sinus rhythm with frequent ectop. <i>Physiological Measurement</i>, <i>36</i>(9), 1873-1888. doi: 10.1088/0967-3334/36/9/1873 464 10.0088/0967-3334/36/9/1873 465 466 Castiglioni, P., Parati, G., Di Rienzo, M., Carabalona, R., Cividjian, A., & Quintin, L. (2011). Scale exponents of blood pressure and heart rate during autonomic blockade as assessed by detrended fluctuation analysis. <i>J Physiol</i>, <i>589</i>(Pt 2), 355-369. doi: 10.1113/jphysiol.2010.196428 467 Corino, V. D., Cygankiewicz, I., Mainardi, L. T., Stridh, M., Vasquez, R., Bayes de Luna, A., Platonov, P. G. (2013). Association between atrial fibrillatory rate and heart rate variability in patients with atrial fibrillation and congestive heart failure. <i>Ann Noninvasive Electrocardiol, 18</i>(1), 41-50. doi: 10.1111/anec.12019 475 Corino, V. D., Ulimoen, S. R., Enger, S., Mainardi, L. T., Tveit, A., & Platonov, P. G. (2015). Rate-control drugs affect variability and irregularity measures of RR intervals in patients with permanent atrial fibrillation. <i>J Cardiovasc Electrophysiol, 26</i>(2), 137-141. doi: 10.1111/jce.12580 479 480 Corino, V. D. A., Lombardi, F., & Mainardi, L. T. (2014). Blood pressure variability in patients with atrial fibrillation. <i>J Cardiovasc Electrophysiol, 26</i>(2), 137-141. doi: 10.1111/jce.12580 481 atrial fibrillation. <i>Auton Neurosci, 185</i>(0), 129-133. doi: http://dx.doi.org/10.1016/j.autneu.2014.08.002 483 Cygankiewicz, I., Corino, V., Vazquez, R., Bayes-Genis, A., Mainardi, L., Zareba, W., Platonov, P. G. (2015). Reduced Irregularity of Ventricular Response During Atrial Fibrillation and Long-term Outcom in Patients With Heart Failure. <i>Am J Cardiol, 116</i>(7), 1071-1075. doi: 10.1016/j.amjcard.2015.06.043 484 Frey, B., Heinz, G., Binder, T., Wutte, M., Schneider, B., Schmidinger, H., Pacher, R. (1995). Diurnal variation of ventricular response to atrial fibrillation in patients with advanced heart failure. <i>Am Heart J, 12</i>	20		
 464 10.1088/0967-3334/36/9/1873 465 466 Castiglioni, P., Parati, G., Di Rienzo, M., Carabalona, R., Cividjian, A., & Quintin, L (2011). Scale exponents of blood pressure and heart rate during autonomic blockade as assessed by detrended fluctuation analysis. J Physiol, 589(Pt 2), 355-369. doi: 10.1113/jphysiol.2010.196428 470 470 471 Corino, V. D., Cygankiewicz, I., Mainardi, L. T., Stridh, M., Vasquez, R., Bayes de Luna, A., Platonov, P. G. (2013). Association between atrial fibrillatory rate and heart rate variability in patients with tartial fibrillation congestive heart failure. Ann Noninvasive Electrocardiol, 18(1), 41-50. doi: 10.1111/anec.12019 475 476 Corino, V. D., Ulimoen, S. R., Enger, S., Mainardi, L. T., Tveit, A., & Platonov, P. G. (2015). Rate-control drugs affect variability and irregularity measures of RR intervals in patients with permanent atrial fibrillation. J Cardiovasc Electrophysiol, 26(2), 137-141. doi: 10.1111/jce.12580 479 Corino, V. D. A., Lombardi, F., & Mainardi, L. T. (2014). Blood pressure variability in patients with atrial fibrillation. Auton Neurosci, 185(0), 129-133. doi: http://dx.doi.org/10.1016/j.autneu.2014.08.002 474 483 Cygankiewicz, I., Corino, V., Vazquez, R., Bayes-Genis, A., Mainardi, L., Zareba, W., Platonov, P. G. (2015). Reduced Irregularity of Ventricular Response During Atrial Fibrillation and Long-term Outcome in Patients With Heart Failure. Am J Cardiol, 116(7), 1071-1075. doi: 10.1016/j.auficar.2015.06.043 489 Frey, B., Heinz, G., Binder, T., Wutte, M., Schneider, B., Schmidinger, H., Pacher, R. (1995). Diurnal variation of ventricular response to atrial fibrillation in patients with advanced heart failure. Am Heart J, 129(1), 58-65. 	21	462	(2015). Heart rate dynamics distinguish among atrial fibrillation, normal sinus rhythm and
 Castiglioni, P., Parati, G., Di Rienzo, M., Carabalona, R., Cividjian, A., & Quintin, L. (2011). Scale castiglioni, P., Parati, G., Di Rienzo, M., Carabalona, R., Cividjian, A., & Quintin, L. (2011). Scale exponents of blood pressure and heart rate during autonomic blockade as assessed by detrended fluctuation analysis. <i>J Physiol</i>, <i>589</i>(Pt 2), 355-369. doi: 10.1113/jphysiol.2010.196428 Corino, V. D., Cygankiewicz, I., Mainardi, L. T., Stridh, M., Vasguez, R., Bayes de Luna, A., Platonov, P. G. (2013). Association between atrial fibrillatory rate and heart rate variability in patients with atrial fibrillation and congestive heart failure. <i>Ann Noninvasive Electrocardiol</i>, <i>18</i>(1), 41-50. doi: 10.1111/jnec.12019 Corino, V. D., Ulimoen, S. R., Enger, S., Mainardi, L. T., Tveit, A., & Platonov, P. G. (2015). Rate-control drugs affect variability and irregularity measures of RR intervals in patients with permanent atrial fibrillation. <i>J Cardiovasc Electrophysiol</i>, <i>26</i>(2), 137-141. doi: 10.1111/jce.12580 Corino, V. D. A., Lombardi, F., & Mainardi, L. T. (2014). Blood pressure variability in patients with atrial fibrillation. <i>Auton Neurosci</i>, <i>185</i>(0), 129-133. doi: http://dx.doi.org/10.1016/j.autneu.2014.08.002 Cygankiewicz, I., Corino, V., Vazquez, R., Bayes-Genis, A., Mainardi, L., Zareba, W., Platonov, P. G. (2015). Reduced Irregularity of Ventricular Response During Atrial Fibrillation and Long-term Outcome in Patients With Heart Failure. <i>Am J Cardiol</i>, <i>116</i>(7), 1071-1075. doi: 10.1016/j.amjcard.2015.06.043 Frey, B., Heinz, G., Binder, T., Wutte, M., Schneider, B., Schmidinger, H., Pacher, R. (1995). Diurnal variation of ventricular response to atrial fibrillation in patients with advanced heart failure. <i>Am Heart J</i>, <i>129</i>(1), 58-65. 	22	463	sinus rhythm with frequent ectopy. Physiological Measurement, 36(9), 1873-1888. doi:
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 469 10.113/jphysiol.2010.196428 471 Corino, V. D., Cygankiewicz, I., Mainardi, L. T., Stridh, M., Vasquez, R., Bayes de Luna, A., 472 Platonov, P. G. (2013). Association between atrial fibrillatory rate and heart rate variability in 473 patients with atrial fibrillation and congestive heart failure. Ann Noninvasive Electrocardiol, 474 18(1), 41-50. doi: 10.1111/anec.12019 475 476 Corino, V. D., Ulimoen, S. R., Enger, S., Mainardi, L. T., Tveit, A., & Platonov, P. G. (2015). Rate-control 477 drugs affect variability and irregularity measures of RR intervals in patients with permanent 478 atrial fibrillation. <i>J Cardiovasc Electrophysiol, 26</i>(2), 137-141. doi: 10.1111/jce.12580 479 480 Corino, V. D. A., Lombardi, F., & Mainardi, L. T. (2014). Blood pressure variability in patients with 4181 atrial fibrillation. Auton Neurosci, 185(0), 129-133. doi: 429 484 Cygankiewicz, I., Corino, V., Vazquez, R., Bayes-Genis, A., Mainardi, L., Zareba, W., Platonov, P. G. 483 484 Cygankiewicz, I., Corino, V., Vazquez, R., Bayes-Genis, A., Mainardi, L., Zareba, W., Platonov, P. G. 485 486 486 487 Frey, B., Heinz, G., Binder, T., Wutte, M., Schneider, B., Schmidinger, H., Pacher, R. (1995). 488 489 5448 489 Frey, B., Heinz, G., Binder, T., Wutte, M., Schneider, B., Schmidinger, H., Pacher, R. (1995). 490 Diurnal variation of ventricular response to atrial fibrillation in patients with advanced heart 491 failure. Am Heart J, 129(1), 58-65. 	27	467	exponents of blood pressure and heart rate during autonomic blockade as assessed by
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 476 Corino, V. D., Olimoen, S. R., Enger, S., Mainfardi, L. T., Ivelt, A., & Platonov, P. G. (2015). Referentiation drugs affect variability and irregularity measures of RR intervals in patients with permanent a trial fibrillation. <i>J Cardiovasc Electrophysiol, 26</i>(2), 137-141. doi: 10.1111/jce.12580 479 480 Corino, V. D. A., Lombardi, F., & Mainardi, L. T. (2014). Blood pressure variability in patients with atrial fibrillation. <i>Auton Neurosci, 185</i>(0), 129-133. doi: http://dx.doi.org/10.1016/j.autneu.2014.08.002 473 483 49 484 483 49 484 486 487 488 489 480 480 480 481 483 483 484 483 484 485 486 487 488 488 55 489 489 484 488 55 489 484 488 55 489 484 488 55 489 484 488 56 57 490 484 487 488 58 59 		475	
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 40 478 atrial fibrillation. J Cardiovasc Electrophysiol, 26(2), 137-141. doi: 10.1111/jce.12580 42 479 43 480 Corino, V. D. A., Lombardi, F., & Mainardi, L. T. (2014). Blood pressure variability in patients with atrial fibrillation. Auton Neurosci, 185(0), 129-133. doi: http://dx.doi.org/10.1016/j.autneu.2014.08.002 484 483 49 484 Cygankiewicz, I., Corino, V., Vazquez, R., Bayes-Genis, A., Mainardi, L., Zareba, W., Platonov, P. G. (2015). Reduced Irregularity of Ventricular Response During Atrial Fibrillation and Long-term Outcome in Patients With Heart Failure. Am J Cardiol, 116(7), 1071-1075. doi: 10.1016/j.amjcard.2015.06.043 54 488 55 489 Frey, B., Heinz, G., Binder, T., Wutte, M., Schneider, B., Schmidinger, H., Pacher, R. (1995). Diurnal variation of ventricular response to atrial fibrillation in patients with advanced heart failure. Am Heart J, 129(1), 58-65. 			
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 482 <u>http://dx.doi.org/10.1016/j.autneu.2014.08.002</u> 47 483 49 484 Cygankiewicz, I., Corino, V., Vazquez, R., Bayes-Genis, A., Mainardi, L., Zareba, W., Platonov, P. G. 50 485 (2015). Reduced Irregularity of Ventricular Response During Atrial Fibrillation and Long-term 51 486 Outcome in Patients With Heart Failure. <i>Am J Cardiol, 116</i>(7), 1071-1075. doi: 52 487 10.1016/j.amjcard.2015.06.043 53 54 488 55 489 Frey, B., Heinz, G., Binder, T., Wutte, M., Schneider, B., Schmidinger, H., Pacher, R. (1995). 56 490 Diurnal variation of ventricular response to atrial fibrillation in patients with advanced heart 57 491 failure. <i>Am Heart J, 129</i>(1), 58-65. 			
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 484 Cygankiewicz, I., Corino, V., Vazquez, R., Bayes-Genis, A., Mainardi, L., Zareba, W., Platonov, P. G. 485 (2015). Reduced Irregularity of Ventricular Response During Atrial Fibrillation and Long-term 486 Outcome in Patients With Heart Failure. <i>Am J Cardiol, 116</i>(7), 1071-1075. doi: 487 10.1016/j.amjcard.2015.06.043 53 54 488 55 489 Frey, B., Heinz, G., Binder, T., Wutte, M., Schneider, B., Schmidinger, H., Pacher, R. (1995). 56 490 Diurnal variation of ventricular response to atrial fibrillation in patients with advanced heart 57 491 failure. <i>Am Heart J, 129</i>(1), 58-65. 		483	
 485 (2015). Reduced Irregularity of Ventricular Response During Atrial Fibrillation and Long-term 486 Outcome in Patients With Heart Failure. <i>Am J Cardiol, 116</i>(7), 1071-1075. doi: 487 10.1016/j.amjcard.2015.06.043 53 54 488 55 489 Frey, B., Heinz, G., Binder, T., Wutte, M., Schneider, B., Schmidinger, H., Pacher, R. (1995). 56 490 Diurnal variation of ventricular response to atrial fibrillation in patients with advanced heart 57 491 failure. <i>Am Heart J, 129</i>(1), 58-65. 			Cygankiewicz, I., Corino, V., Vazquez, R., Bayes-Genis, A., Mainardi, L., Zareba, W., Platonov, P. G.
 486 Outcome in Patients With Heart Failure. Am J Cardiol, 116(7), 1071-1075. doi: 487 10.1016/j.amjcard.2015.06.043 488 488 489 Frey, B., Heinz, G., Binder, T., Wutte, M., Schneider, B., Schmidinger, H., Pacher, R. (1995). 490 Diurnal variation of ventricular response to atrial fibrillation in patients with advanced heart 491 failure. Am Heart J, 129(1), 58-65. 			
5248710.1016/j.amjcard.2015.06.043535448855489Frey, B., Heinz, G., Binder, T., Wutte, M., Schneider, B., Schmidinger, H., Pacher, R. (1995).56490Diurnal variation of ventricular response to atrial fibrillation in patients with advanced heart57491failure. Am Heart J, 129(1), 58-65.5859			
 53 54 488 55 489 Frey, B., Heinz, G., Binder, T., Wutte, M., Schneider, B., Schmidinger, H., Pacher, R. (1995). 56 490 Diurnal variation of ventricular response to atrial fibrillation in patients with advanced heart 57 491 failure. <i>Am Heart J</i>, 129(1), 58-65. 58 59 			
5448855489Frey, B., Heinz, G., Binder, T., Wutte, M., Schneider, B., Schmidinger, H., Pacher, R. (1995).56490Diurnal variation of ventricular response to atrial fibrillation in patients with advanced heart57491failure. Am Heart J, 129(1), 58-65.5859		407	10.1010/J.amjca10.2013.00.043
 489 Frey, B., Heinz, G., Binder, T., Wutte, M., Schneider, B., Schmidinger, H., Pacher, R. (1995). 490 Diurnal variation of ventricular response to atrial fibrillation in patients with advanced heart 491 failure. <i>Am Heart J</i>, <i>129</i>(1), 58-65. 58 59 		488	
56490Diurnal variation of ventricular response to atrial fibrillation in patients with advanced heart57491failure. Am Heart J, 129(1), 58-65.5859			Frey B. Heinz G. Binder T. Wutte M. Schneider B. Schmidinger H. – Pacher R. (1995)
57 491 failure. Am Heart J, 129(1), 58-65. 58 59			
58 59			
59		491	ianuie. Ann neurij, 123(1), 30-03.
	60		20

1		
2		
3	492	Hayano, J., Sakata, S., Okada, A., Mukai, S., & Fujinami, T. (1998). Circadian rhythms of
4	493	atrioventricular conduction properties in chronic atrial fibrillation with and without heart
5	494	failure. J Am Coll Cardiol, 31(1), 158-166.
6	495	Hayano, J., Yamasaki, F., Sakata, S., Okada, A., Mukai, S., & Fujinami, T. (1997). Spectral
7	496	characteristics of ventricular response to atrial fibrillation. Am J Physiol, 273(6 Pt 2), H2811-
8 9	497	2816.
9 10	498	Hillebrand, S., Gast, K. B., de Mutsert, R., Swenne, C. A., Jukema, J. W., Middeldorp, S., Dekkers,
10	499	O. M. (2013). Heart rate variability and first cardiovascular event in populations without
12	500	known cardiovascular disease: meta-analysis and dose-response meta-regression. Europace,
13	501	15(5), 742-749. doi: 10.1093/europace/eus341
14		
15	502	
16	503	Hoshi, R. A., Pastre, C. M., Vanderlei, L. C., & Godoy, M. F. (2013). Poincare plot indexes of heart rate
17	504	variability: relationships with other nonlinear variables. Auton Neurosci, 177(2), 271-274.
18	505	doi: 10.1016/j.autneu.2013.05.004
19		
20	506	
21	507	Laitinen, T., Niskanen, L., Geelen, G., Lansimies, E., & Hartikainen, J. (2004). Age dependency of
22	508	cardiovascular autonomic responses to head-up tilt in healthy subjects. J Appl Physiol, 96(6),
23	509	2333-2340. doi: 10.1152/japplphysiol.00444.2003
24		
25	510	
26	511	Leung, R. S., Bowman, M. E., Diep, T. M., Lorenzi-Filho, G., Floras, J. S., & Bradley, T. D. (2005).
27	512	Influence of Cheyne-Stokes respiration on ventricular response to atrial fibrillation in heart
28	513	failure. <i>J Appl Physiol, 99</i> (5), 1689-1696. doi: 10.1152/japplphysiol.00027.2005
29		
30	514	
31	515	Lim, P. B., Malcolme-Lawes, L. C., Stuber, T., Koa-Wing, M., Wright, I. J., Tillin, T., Kanagaratnam,
32	516	P. (2011). Feasibility of multiple short, 40-s, intra-procedural ECG recordings to detect
33	517	immediate changes in heart rate variability during catheter ablation for arrhythmias. Journal
34	518	of Interventional Cardiac Electrophysiology, 32(2), 163-171. doi: 10.1007/s10840-011-9580-2
35		
36	519	
37	520	Mehlsen, J., Kaijer, M. N., & Mehlsen, A. B. (2008). Autonomic and electrocardiographic changes in
38	521	cardioinhibitory syncope. <i>Europace, 10</i> (1), 91-95. doi: 10.1093/europace/eum237
39 40		
40 41	522	
42	523	Millar, P. J., Cotie, L. M., St Amand, T., McCartney, N., & Ditor, D. S. (2010). Effects of autonomic
43	524	blockade on nonlinear heart rate dynamics. Clin Auton Res, 20(4), 241-247. doi:
44	525	10.1007/s10286-010-0058-6
45		
46	526	
47	527	Mourot, L., Bouhaddi, M., Gandelin, E., Cappelle, S., Nguyen, N. U., Wolf, JP., Regnard, J. (2007).
48	528	Conditions of autonomic reciprocal interplay versus autonomic co-activation: Effects on non-
49	529	linear heart rate dynamics. Auton Neurosci, 137(1–2), 27-36. doi:
50	530	http://dx.doi.org/10.1016/j.autneu.2007.06.284
51		
52	531	
53	532	Nagayoshi, H., Janota, T., Hnatkova, K., Camm, A. J., & Malik, M. (1997). Autonomic modulation of
54	533	ventricular rate in atrial fibrillation. Am J Physiol, 272(4 Pt 2), H1643-1649.
55	534	Patel, H. C., Rosen, S. D., Lindsay, A., Hayward, C., Lyon, A. R., & di Mario, C. (2013). Targeting the
56	535	autonomic nervous system: Measuring autonomic function and novel devices for heart
57	536	failure management. Int J Cardiol, 170(2), 107-117. doi: 10.1016/j.ijcard.2013.10.058
58		
59		
60		21

1 2		
2 3	537	
3	538	Datarson M.E. Williams T.P. Cardon C. Chambarlain Wabbar P. & Sutton P. (2000) The normal
5	538	Petersen, M. E., Williams, T. R., Gordon, C., Chamberlain-Webber, R., & Sutton, R. (2000). The normal
6		response to prolonged passive head up tilt testing. <i>Heart, 84</i> (5), 509-514.
7	540	Platonov, P. G., & Holmqvist, F. (2011). Atrial fibrillatory rate and irregularity of ventricular response
8	541	as predictors of clinical outcome in patients with atrial fibrillation. <i>J Electrocardiol,</i> 44(6),
9	542	673-677. doi: 10.1016/j.jelectrocard.2011.07.024
10	543	
11	543 544	Darta A. Craachi Duccana T. Tahaldini F. Curretti C. Furlan D. 8 Mantana N. (2007)
12		Porta, A., Gnecchi-Ruscone, T., Tobaldini, E., Guzzetti, S., Furlan, R., & Montano, N. (2007).
13	545	Progressive decrease of heart period variability entropy-based complexity during graded
14	546	head-up tilt. <i>J Appl Physiol, 103</i> (4), 1143-1149. doi: 10.1152/japplphysiol.00293.2007
15	547	
16	548	Powley I. M., & Powland, F. (1986). Is the pulse in atrial fibrillation irregularly irregular? Dr. Haget I
17		Rawles, J. M., & Rowland, E. (1986). Is the pulse in atrial fibrillation irregularly irregular? <i>Br Heart J</i> ,
18	549	56(1), 4-11.
19	550	Shiogai, Y., Stefanovska, A., & McClintock, P. V. E. (2010). Nonlinear dynamics of cardiovascular
20	551	ageing. Physics Reports, 488(2-3), 51-110. doi: 10.1016/j.physrep.2009.12.003
21	552	
22	553	Socrowski M. Macfarland D.W. & Tandara M. (2011) Determinants of a reduced heart rate
23		Sosnowski, M., Macfarlane, P. W., & Tendera, M. (2011). Determinants of a reduced heart rate
24	554	variability in chronic atrial fibrillation. <i>Ann Noninvasive Electrocardiol, 16</i> (4), 321-326. doi:
25	555	10.1111/j.1542-474X.2011.00458.x
26	556	
27	557	Tarvainen, M. P., Niskanen, J. P., Lipponen, J. A., Ranta-Aho, P. O., & Karjalainen, P. A. (2014). Kubios
28	558	HRVheart rate variability analysis software. Comput Methods Programs Biomed, 113(1),
29 20		
30 31	559	210-220. doi: 10.1016/j.cmpb.2013.07.024
32	560	
33	561	Task Force of the European Society of Cardiology and the North American Society of Pacing and
33 34	562	Electrophysiology. (1996). Heart rate variability. Standards of measurement, physiological
35	563	interpretation, and clinical use. Task Force of the European Society of Cardiology and the
36		
37	564	North American Society of Pacing and Electrophysiology. <i>Eur Heart J, 17</i> (3), 354-381.
38	565	Tulppo, M. P., Makikallio, T. H., Takala, T. E., Seppanen, T., & Huikuri, H. V. (1996). Quantitative beat-
39	566	to-beat analysis of heart rate dynamics during exercise. <i>Am J Physiol, 271</i> (1 Pt 2), H244-252.
40	567	
41	568	van den Berg, M. P., Haaksma, J., Brouwer, J., Tieleman, R. G., Mulder, G., & Crijns, H. J. (1997). Heart
42	569	rate variability in patients with atrial fibrillation is related to vagal tone. Circulation, 96(4),
43	570	1209-1216.
44	571	Voss, A., Schroeder, R., Heitmann, A., Peters, A., & Perz, S. (2015). Short-Term Heart Rate
45	572	Variability—Influence of Gender and Age in Healthy Subjects. <i>PLoS One, 10</i> (3), e0118308.
46	573	doi: 10.1371/journal.pone.0118308
47		
48	574	
49	575	Yamada, A., Hayano, J., Sakata, S., Okada, A., Mukai, S., Ohte, N., & Kimura, G. (2000). Reduced
50	576	ventricular response irregularity is associated with increased mortality in patients with
51	577	chronic atrial fibrillation. <i>Circulation, 102</i> (3), 300-306.
52 52		
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54 55	579	
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	Atrial Fibrillation	Sinus Rhythm (n=69)	р
Age	(n=31) 74.3 (68.9, 83.8)	70.3 (62.9, 77.7)	0.056
Male	20 (64.5%)	46 (66.7%)	1.000
Diabetes	5 (16.1%)	5 (7.2%)	0.277
Hypertension	23 (74.2%)	11 (15.9%)	< 0.001
Heart Failure	2 (6.5%)	0 (0%)	0.094
Medications			
ACEi/ARB	15 (48.4%)	12 (17.4%)	0.002
Beta-blockers	10 (32.3%)	3 (4.3%)	< 0.001
ССВ	8 (25.8%)	3 (4.3%)	0.003
Digoxin	7 (22.6%)	0 (0%)	< 0.001
Diuretics	7 (22.6%)	6 (8.7%)	0.103
Median	2 (1, 2)	0 (0, 0)	< 0.001

Table 1: Demographics, past medical and medication history of the patients with atrial fibrillation and age matched sinus rhythm. Data are presented as median (quartile 1, quartile 3) or count (%). ACEi- angiotensin converting enzyme inhibitor; ARB- angiotensin receptor blocker; CCB- calcium channel blocker

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			Baseline		Change	e from baseline a	fter HUT
	Cohort	AF (n=31)	SR (n=81)	P (AF vs SR)	AF	SR	P (AF vs SR
		126.5	123.1				
		(112.0,	(112.7,		+5.2 (-2.5,	+6.6 (-1.7,	
	SBP (mmHg)	139.1)	134.9)	0.469	12.1)	16.6)**	0.431
			77.8				
		79.2	(70.6,		+4.8 (-0.6,	+10.4 (1.5,	
	DBP (mmHg)	(68.9, 83.5)	84.5)	0.871	13.1)*	16.1)**	0.100
			70.7				
		74.9	(60.9,		+3.8 (1.4,	+4.6 (1.7,	
	HR (beats/min)	(67.6, 87.5)	78.2)	0.018	7.1)**	8.2)**	0.776
			34.7				
	Stroke index	36.8	(29.9,		-5.2 (-8.1,	-5.7 (-10.0, -	
	(ml/m²)	(25.9, 42.2)	41.5)	0.729	1.0)*	1.1)**	0.417
			2.52		Z		
	Cardiac index	2.41	(2.17,		-0.13 (-0.44,	-0.26 (-0.54,	
	(L/[min.m ²])	(2.12, 2.94)	2.98)	0.663	0.26)	0.06)**	0.326
		3464	2930				
	TPR index	(2666,	(2585,		+612 (-168,	+628 (106,	
Haemodynamics	(dyne*s*m²/cm⁵)	3792)	3488)	0.252	1092)*	1028)**	0.515
							÷
		102.8	39.2				
		(28.3,	(25.3,		+0.9 (-13.9,	+3.4 (-6.7,	
	SDNN (ms)	160.4)	57.1)	0.003	18.4)	18.8)*	0.396
		139.2	26.9				
		(18.4,	(15.9,		-5.5 (-21.4,	-2.2 (-22.1,	
Time	RMSSD (ms)	208.1)	47.2)	0.001	4.2)	21.5)	0.291

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LF (ms²)	2075 (135, 5243)	254 (156, 612)	0.005	65.1 (-223, 320)	-21.6 (-151, 137)	
HF (ms²)	3921 (106, 10491)	209 (75, 539)	0.001	-92.5 (-2124, 119)*	-28.0 (-234, 36)*	
LF/HF	0.58 (0.46,	1.39 (0.80, 2.25)	<0.001	+0.10 (-0.12, 0.35)*	+0.61 (-0.32, 2.33)**	
LFnu (%)	36.4 (31.4, 50.4)	58.0 (44.3, 69.2)	<0.001	+4.4 (-4.0, 9.9)	+7.1 (-4.3 <i>,</i> 17.5)**	
	63 1 (49 6	41.8		-4 2 (-9 8	-7 1 (-17 2	

			41.8				
		63.1 (49.6,	(30.7,		-4.2 (-9.8,	-7.1 (-17.2,	
Frequency	HFnu (%)	68.2)	55.6)	<0.001	3.8)	4.3)**	0.331
			19.0				
		98.5 (13.0,	(11.3,		-3.9 (-15.2,	-1.4 (-10.9,	
	SD1 (ms)	147.4)	33.4)	0.001	3.0)	5.8)	0.393
		110.6	49.3				
		(34.9,	(33.6,		+1.9 (-14.4,	+4.7 (-6.4,	
	SD2 (ms)	163.9)	66.4)	0.006	29.3)	26.7)**	0.669
			1.06		· · ·		
		0.70 (0.61,	(0.84,		+0.01 (-0.11,	+0.07 (-0.14,	
	DFA-α1	1.01)	1.22)	<0.001	0.09)	0.45)*	0.179
			0.94				
		0.69 (0.54,	(0.80,		+0.14 (-0.03,	+0.14 (-0.03,	
	DFA-α2	0.86)	1.11)	<0.001	0.32)**	0.36)**	0.806
			1.26				
		1.78 (1.26,	(0.94,		-0.17 (-0.50, -	-0.25 (-0.55,	
Non linear	Sample Entropy	2.05)	1.55)	<0.001	0.01)**	0.04)**	0.887

Table 2: Baseline and change with HUT of haemodynamic and HRV data. *= p≤0.05 (within group delta from baseline, paired t-test) **=p≤0.005 (within group delta from baseline, paired t-test). DFA1, DFA2 and Sample Entropy are dimensionless.

0.364

0.149

0.216

0.341

SBP- systolic blood pressure; DBP- diastolic blood pressure; HR- heart rate; TPR- total peripheral resistance; SDNN- standard deviation of the RR interval; RMSSD- root of the mean squared differences of successive RR intervals; LFnu- low frequency power in normalized units; HFnu- high frequency power in normalized units; SD1- minor axis on Poincaré plots; SD2- major axis on Poincaré plots, DFA- detrended fluctuation analysis

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Tertiles of age	0-30 (n=50)	30-60 (n=69)	60+ (n=57)	р
Age	22.0 (18.5, 24.9)	47.1 (38.4, 52.4)	72.7 (66.2, 79.4)	< 0.001
Male	20 (40.0%)	34 (49.3%)	38 (66.7%)	0.018
Diabetes	9 (18.0%)	5 (7.2%)	4 (7.0%)	0.131
Hypertension	10 (20.0%)	14 (20.3%)	9 (15.8%)	0.807
Heart Failure	1 (2.0%)	0 (0%)	0 (0%)	0.284
Medications				
ACEi/ARB	6 (12.0%)	10 (14.5%)	10 (17.5%)	0.65
Beta-blockers	4 (8.0%)	6 (8.7%)	2 (3.5%)	0.52
ССВ	5 (10.0%)	6 (8.7%)	3 (5.3%)	0.64
Diuretics	4 (8.0%)	3 (4.3%)	5 (8.8%)	0.56
Total	0.0 (0.0, 0.3)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.94

Table 3: Demographics, past medical and medication history of the patients in sinus rhythm across tertiles of age. Data are presented as median (quartile 1, quartile 3) or count (%). Abbreviations as per Table 1

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			Baselii	Change from baseline after HUT					
	Age Tertiles (years)	0-30 (n=50)	30-60 (n=69)	60+ (n=57)	P (between groups)	0-30	30-60	60+	P (betweer groups)
	SBP (mmHg)	114.5 (108.4, 122.6)	124.9 (112.8, 135.1)	123.3 (113.2, 135.0)	0.004	+9.3 (3.7, 11.0)**	+6.6 (0.3 <i>,</i> 17.0)**	+6.7 (-1.4, 14.7) **	0.419
	DBP (mmHg)	73.8 (67.7. 81.5)	83.6 (76.5 <i>,</i> 88.6)	75.9 (69.8 <i>,</i> 81.6)	<0.001	+14.3 (6.2, 19.3) **	+10.6 (2.2, 10.6) **	+10.3 (2.5, 15.7) **	0.102
	HR (beats/min)	72.5 (64.8 <i>,</i> 79.7)	72.2 (61.9, 80.6)	71.4 (61.9 <i>,</i> 78.5)	0.800	+8.8 (5.6, 14.9) **	+6.1 (2.8, 11.2) **	+4.4 (1.1, 7.3) **	<0.001
	Stroke index (ml/m²)	50.2 (42.1 <i>,</i> 57.3)	38.2 (31.3, 44.6)	34.8 (29.2, 40.5)	<0.001	-9.8 (-15.6 <i>,</i> -4.5) **	-7.8 (-13.0, -1.7) **	-5.1 (-9.0 <i>,</i> - 1.5) **	0.004
	Cardiac index (L/[min.m²])	3.39 (3.06, 4.08)	2.68 (2.16, 3.15)	2.52 (2.20, 3.05)	<0.001	-0.35 (- 0.78, 0.06) **	-0.33 (- 0.65, 0.02) **	-0.25 (- 0.59, 0.09) **	0.582
Haemodynamic s	TPR index (dyne*s*m²/cm⁵	1985 (1714, 2479)	2960 (2450, 3675)	2925 (2516, 3305)	<0.001	+532 (162, 750) **	+661 (328, 1224) **	+617 (7.7 <i>,</i> 1030) **	0.218
	,	21737	30737	55057	.0.001	1507		10007	0.210
	SDRR (ms)	70.2 (48.9, 88.5)	43.7 (29.6, 62.4)	40.2 (26.3, 58.3)	<0.001	+0.2 (-9.5, 8.6) **	+7.0 (-7.0 <i>,</i> 19.6)*	+1.8 (-7.8, 18.7)	0.144
Time-domain	RMSSD (ms)	47.8 (37.0, 82.2)	30.2 (17.4 <i>,</i> 55.20	27.9 (16.7, 52.7)	<0.001	-19.3 (- 49.9, -4.2) **	-4.0 (-18.5 <i>,</i> 14.5)	+0.6 (-26.8, 19.0)	0.001
Frequency- domain	LF (ms ²)	1092 (651, 2381)	492 (235, 806)	251 (142, 600)	<0.001	-14.8 (-350, -15) **	+24.2 (- 150, 430)	-52.6 (-155, 126)	0.357

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	LIE (ma ²)	1085 (456,	210 (108, 020)	100 (76 504)	-0.001	1651, -592) **	-71.9 (-392,	-23.6 (-227,	-0.001
	HF (ms²)	2485)	310 (108, 926)	189 (76, 584)	<0.001		21) **	62)	<0.001
		1 12 /0 00	1 60 /0 02	1 25 (0 60		1 56 (0.02	1 22 (0 40	+0.33 (-	
	15/115	1.13 (0.68,	1.69 (0.93,	1.25 (0.68,	0.027	+1.56 (0.82,	+1.23 (0.40,	0.25,	0.005
	LF/HF	1.85)	2.37)	2.13)	0.037	3.15)**	3.57)**	2.33)**	0.005
		53.0 (40.3,	62.7 (48.0,	55.6 (40.4,		+20.3 (12.5,	+12.2 (3.6,	+6.3 (-4.8,	
	LFnu (%)	64.8)	70.3)	67.9)	0.037	26.3) **	23.5) **	19.4)*	<0.001
						-20.2 (-	-12.1 (-		
		46.9 (35.1,	37.2 (29.6,	44.4 (32.0,		26.2, -	23.4, -	-6.3 (-19.1,	
	HFnu (%)	59.6)	51.8)	59.1)	0.037	12.3)**	3.58)**	4.8)*	< 0.001
			2			-14.5 (-			
		33.9 (26.2,	21.4 (12.3,	19.8 (11.8,		24.7, -2.8)	-3.3 (-14.0,	-1.4 (-10.4,	
	SD1 (ms)	58.2)	39.1)	37.3)	<0.001	**	1.9) **	7.9)	<0.001
		84.9 (62.7,	55.7 (38.8,	49.3 (34.1,		+5.2 (-8.5,	+9.4 (-6.2,	+3.5 (-7.3,	
	SD2 (ms)	108.8)	81.3)	66.4)	<0.001	14.3)	28.4) **	27.2)	0.406
							+0.24 (-		
		1.00 (0.84,	1.13 (0.92,	1.04 (0.77,		+0.28 (0.11,	0.06, 0.42)	+0.06 (-	
	DFA-α1	1.26)	1.33)	1.19)	0.082	0.48)**	**	0.21, 0.49)	0.010
						+0.13 (-	+0.12 (-		
		0.84 (0.78,	0.87 (0.77,	0.94 (0.80,		0.04, 0.28)	0.03, 0.25)	+0.18 (-0.3,	
	DFA-α2	0.94)	1.05)	1.06)	0.142	**	**	0.37) **	0.260
						-0.45 (-	-0.30 (-	-0.20 (-	
		1.58 (1.36,	1.42 (1.19,	1.20 (0.86,		0.66, -0.18)	0.60, -0.05)	0.55, 0.13)	
Non linear	Sample Entropy	1.77)	1.63)	1.49)	<0.001	**	**	**	0.070
ahle 4. Raseline	and change with	HUT of baem	odynamic and	HRV data acro	uss the terti	les of age in 1	nationts with	sinus rhythr	n Data 🗌

Table 4: Baseline and change with HUT of haemodynamic and HRV data across the tertiles of age in patients with sinus rhythm. Data are presented as median (quartile 1, quartile 3). *= p≤0.05 (within group delta from baseline) **=p≤0.005 (within group delta from baseline). Abbreviations as per Table 2.

AF	SDNN	RMSSD										Sample
SR	(ms)	(ms)	LF (ms ²)	HF (ms ²)	LF/HF	LFnu (%)	HFnu (%)	SD1 (ms)	SD2 (ms)	DFA-α1	DFA-α2	Entropy
SDNN		0.992	0.926	0.943	-0.476	-0.614	0.613	0.992	0.996	-0.572	-0.737	0.703
(ms)		P<0.001	P<0.001	P<0.001	P=0.007	P<0.001	P<0.001	P<0.001	P<0.001	P=0.001	P<0.001	P<0.001
RMSSD	0.892		0.908	0.935	-0.514	-0.664	0.663	1.000	0.976	-0.637	-0.762	0.735
(ms)	P<0.001		P<0.001	P<0.001	P=0.003	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001
	0.871	0.740	1	0.970	-0.366	-0.474	0.474	0.908	0.930	-0.461	-0.676	0.663
LF (ms ²)	P<0.001	P<0.001		P<0.001	P=0.043	P=0.007	P=0.007	P<0.001	P<0.001	P=0.009	P<0.001	P<0.001
	0.841	0.878	0.765		-0.399	-0.530	0.529	0.935	0.939	-0.506	-0.659	0.696
HF (ms ²)	P<0.001	P<0.001	P<0.001		P=0.26	P=0.002	P=0.002	P<0.001	P<0.001	P=0.004	P<0.001	P<0.001
	-0.227	-0.444	-0.106	-0.327		0.904	-0.905	-0.514	-0.453	0.886	0.393	-0.448
LF/HF	P=0.002	P<0.001	P=0.160	P<0.001		P<0.001	P<0.001	P=0.003	P=0.010	P<0.001	P=0.029	P=0.012
	-0.274	-0.553	-0.063	-0.444	0.823		-1.000	-0.664	-0.580	0.956	0.595	-0.555
LFnu (%)	P<0.001	P<0.001	P=0.403	P<0.001	P<0.001	_	P<0.001	P<0.001	P=0.001	P<0.001	P<0.001	P=0.001
	0.275	0.553	0.065	0.446	-0.823	-1.000		0.663	0.579	-0.955	-0.595	0.555
HFnu (%)	P<0.001	P<0.001	P=0.389	P<0.001	P<0.001	P<0.001		P<0.001	P=0.001	P<0.001	P<0.001	P=0.001
	0.892	1.000	0.740	0.879	-0.444	-0.553	0.553		0.976	-0.637	-0.762	0.735
SD1 (ms)	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001		P<0.001	P<0.001	P<0.001	P<0.001
	0.986	0.807	0.880	0.785	-0.150	-0.163	0.164	0.807		-0.538	-0.713	0.678
SD2 (ms)	P<0.001	P<0.001	P<0.001	P<0.001	P=0.047	P=0.031	P=0.029	P<0.001		P=0.002	P<0.001	P<0.001
	-0.242	-0.539	-0.066	-0.375	0.731	0.907	-0.904	-0.539	-0.123		0.551	-0.598
DFA-α1	P=0.001	P<0.001	P=0.381	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001	P=0.103	0.001	P=0.001	P<0.001
	-0.081	-0.227	-0.189	-0.100	0.187	0.156	-0.154	-0.227	-0.032	0.231		-0.698
DFA-α2	P=0.287	P=0.002	P=0.012	P=0.188	P=0.013	P=0.039	P=0.041	P=0.002	P=0.674	P=0.002	0.4.00	P<0.001
Sample	-0.024 P=0.754	0.111 P=0.141	0.096 P=0.204	0.175 P=0.020	-0.279 P<0.001	-0.162 P=0.032	0.164 P=0.029	-0.111 P=0.141	-0.057 P=0.453	-0.178 P=0.018	-0.189 P=0.012	
Entropy			P=0.204									

Table 5: Correlations (r) between heart rate variability parameters in the sinus rhythm (SR- in white) population (N=176) and atrial fibrillation (AF- in grey) population (N=31). Abbreviations as per Table 2.