Vagal heart rate control in patients with a history of atrial fibrillation: Impact of tonic activation of peripheral chemosensory function in heart failure

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This work was supported by the European Community's Seventh Framework Program in the context of the Information Society Technologies Program Grant agreement FP7-216695 (HeartCycle) (JM, TD, CM). CM is also the owner of a research grant from the Hans-und-Gerti-Fischer Stiftung.
ABSTRACT

Background:
Heart failure (HF) and atrial fibrillation (AF), emerging as two epidemics of the 21st century, are commonly associated with each other. Both have been mechanistically linked to changes in cardiac vagal control. The importance of peripheral chemosensors, residing in the carotid body, within this relationship between AF and HF has not been elucidated so far. We therefore investigated whether tonic activation of excitatory chemoreceptor afferents contributes to the altered vagal control in HF patients with a history of AF.

Methods and results:
In 18 patients (72±9y, 7 male) with sinus rhythm and a history of AF (n=9, without any evidence of structural heart disease, AF group; n=9 with structural heart disease and clinical presentation of HF, AFHF group) we investigated the impact of chemosensory deactivation (by breathing 100% oxygen) on hemodynamics, oxygen saturation and breathing rate. 10 healthy individuals served as a control group. In addition, we performed a deep breathing test demonstrating an impaired heart rate variation in patients without and with HF as compared to controls (Expiration/Inspiration difference: 23.9±6.9 vs 6.9±6.1 bpm, and 23.9±6.9 vs 7.8±4.8 bpm; p<0.05). In the control as well as the AF group heart rate decreased during chemoreceptor deactivation (control: -4.8±3.4%; AF: -5.1±3.0%; p<0.05), whereas heart rate did not change in AFHF patients. This resulted in an impaired cardiac chemoreflex sensitivity in AFHF patients (1.9±1.6 vs 0.5±1.2 ms/mmHg; p<0.05).

Conclusions:
Our data suggest that tonic activation of excitatory chemoreceptor afferents contribute to a low vagal tone in heart failure patients with a history of AF. (Clinical Trials NCT01262508)

Key words: atrial fibrillation, heart failure, autonomic nervous system, deep breathing, hyperoxic chemoreflex sensitivity
ABBREVIATIONS

AF atrial fibrillation
ANOVA analysis of variance
AVR average
BMI body mass index
BPV blood pressure variability
BR breathing rate
CAD coronary artery disease
CHRS hyperoxic cardiac chemoreflexsensitivity
CO cardiac output
DBP diastolic blood pressure
ECG electrocardiogram
E/I inspiratory to expiratory
HF hear failure
HR heart rate
HRV hear rate variability
MAP mean arterial pressure
pCO2 carbon dioxide partial pressure
pO2 oxygen partial pressure
PPG photoplethysmogram
SBP systolic blood pressure
SpO2 peripheral oxygen saturation
SV stroke volume
TFM Task Force® monitor
TPR total peripheral resistance
INTRODUCTION

Heart failure (HF) and atrial fibrillation (AF), emerging as two epidemics of the 21st century, have been mechanistically linked to changes in cardiac vagal control (de Vos et al., 2008). The pathophysiological relationship between AF and HF has only been partially elucidated although both entities are commonly associated with each other. Experimental and clinical evidence demonstrated that a relative decrease of vagal tone is common in HF and can precede the onset of AF as characterized by heart rate variability (HRV) at rest and during respiratory maneuvers (deep breathing test). Noteworthy, peripheral chemoreceptors, residing in the carotid body, are well known to modulate vagal heart rate control. High arterial oxygen levels, as achieved by inhalation of pure oxygen, lead to a deactivation of these chemoreceptors with a following rise in vagal tone resulting in a decrease of heart rate (Seals et al., 1991). Impairment of this deactivation is supposed to be linked to vagal dysfunction (Ponikowski et al., 1997) and can be quantitated by hyperoxic cardiac chemoreflex sensitivity (CHRS) testing. Importantly, whether and how peripheral chemosensory function modulates efferent vagal activity within the interaction of both AF and HF is not known. Therefore, the aim of the present study was to investigate whether tonic activation of excitatory chemoreceptor afferents contributes to the altered vagal heart rate control in HF patients with a history of AF.
METHODS

Study design and patient selection

Hemodynamics, HRV, and blood pressure variability (BPV) at baseline and during chemosensor deactivation by inhalation of 100% oxygen over five minutes were studied in 18 patients with a history of AF and in 10 healthy controls. We included two different patient groups: The AF group consisted of nine individuals with a history of AF but without any evidence of structural heart disease as excluded by coronary angiography. The AFHF group included another nine AF patients with documented moderately impaired left ventricular systolic function. All patients were in stable sinus rhythm during our experiments. Ten healthy volunteers without any known history of cardiovascular disease served as a control group. AF was defined as recently proposed by the guidelines for the management of atrial fibrillation issued by the European Society of Cardiology (Camm et al., 2010). The diagnosis of HF was based on a documented structural heart disease, as well as clinical appraisal according to the classification of the New York Heart Association (Dickstein et al., 2008). Exclusion criteria were congestive heart failure with a cardiac ejection fraction of <30%, heart disease associated hypotension, severe cardiac arrhythmias, sleep apnoea syndrome, chronic obstructive pulmonary disease and acute inflammation (C-reactive protein >5 mg/l). The study protocol was approved by the institutional review board of the University of Duesseldorf and all patients gave written informed consent.

Experimental setup and autonomic reflex testing

All subjects rested in a supine position in a quiet examination room for at least 10 minutes before testing was commenced. In order to characterize autonomic cardiovascular reflex control we measured HRV and BPV at baseline over five minutes (Task Force of the European Society of Cardiology, 1996). In addition, we performed two interventions to investigate the characteristics of vagal tone and vagal reflex control: We analyzed (1.) heart rate (HR) characteristics during deep breathing and (2.) investigated the CHRS sensitivity by pure oxygen inhalation. Both tests were performed in a randomized order. The recovery period between both tests was at least 10 minutes.
Measurements of hemodynamics and standard clinical blood parameters

Hemodynamics, HRV and BPV were measured continuously. We recorded beat-to-beat HR by a two-channel electrocardiogram (ECG), stroke volume by an improved method of impedance cardiography (Gole et al., 2011, Gratze et al., 1998), and blood pressure by a finger cuff, which values were corrected automatically to the oscillometric blood pressure measured on the contralateral arm (Task Force Monitor (TFM), CNSystems, Graz). Additionally the TFM calculated HRV and BPV by using power spectral analysis, applying an autoregressive methodology (Gratze et al., 1998, Gratze et al., 2005, Task Force of the European Society of Cardiology, 1996). Main spectral components were low frequency (LF 0.04–0.15 Hz, HRV and BPV) and high frequency (HF 0.15–0.40 Hz, HRV and BPV) which were calculated in absolute values (HRV: LF-RRI and HF-RRI in ms²; BPV: LF-sBP and LF-dBP in mmHg²) and were in normalized units (HRV: LFnu-RRI and HFnu-RRI; BPV: LFnu-sBP and LFnu-dBP, %) (Task Force of the European Society of Cardiology, 1996).

A standard patient monitor (Philips Intellivue MP50) was used to additionally acquire the following signals: an electrocardiogram (at 504 Hz), two photoplethysmograms one from the ear and one from the finger (at 125Hz) as well as a respiration signal (at 62.5 Hz). This system provided HR, respiration rate, perfusion index and oxygen saturation level measured from the ear and finger locations. Signals and data coming from the TFM and the MP50 were synchronized via the detected R-R sequences from the ECG signals with an accuracy of less than 0.01 s. Standard clinical blood parameters were analyzed in a central laboratory using standard techniques (Meyer et al., 2010a).

Deep breathing test

The test routine consisted of an initial resting phase in which the patients remained recumbent for a period of 10 minutes in a quite environment. Starting the test they performed six breathing cycles during one minute synchronized to a acoustical signal to obtain reproducible results. The expiratory – inspiratory difference (E/I difference) was calculated by subtracting the maximum HR during inspiration from the minimum HR during expiration for each cycle of breathing, and then determining the mean of these differences. The expiratory–inspiratory ratio (E/I ratio) assesses the ratio of the mean of the maximum heart rates and the mean of the minimum heart rates (Hilz and Dutsch, 2006).
Hyperoxic cardiac chemoreflexsensitivity testing

Hyperoxic CHRS testing was performed following an established protocol (Hennersdorf et al., 2001). Patients were recumbent for a period of 10 minutes in a quite environment before testing was commenced. Then, the patients received five litre O2/min via a nasal mask over a period of five minutes. No conversation was allowed during this period for minimization of mental influences. A capillary blood sample was taken from the earlap at rest and after oxygen inhalation and the partial oxygen and carbondioxide pressure (pO$_2$ and pCO$_2$) were determined using a standardized blood gas analyzer (Radiometer Copenhagen, Denmark). Furthermore, the mean R–R interval out of 10 consecutive R–R intervals (R–R interval preoxygen) was calculated using a two-channel electrocardiogram (TFM) at baseline and after oxygen inhalation. The difference of the R–R intervals before and after oxygen inhalation divided by the difference of capillary oxygen pressure was calculated as the CHRS (ms/mmHg). A CHRS below 3.0 ms/mmHg was defined as pathological (Meyer et al., 2010b, Hennersdorf et al., 2002).

Statistical analysis

Continuous variables are presented as mean ± standard deviation (SD). Univariate correlations were Spearman rank correlations. Analysis of variance and student t-test were employed for calculation of significance. P values of less than 0.05 were considered to be statistically significant. Statistical analysis was performed using Graphpad Prism 5® (Graphpad Inc., La Jolla, USA).
RESULTS

Patient characteristics

The clinical baseline characteristics are shown in Table 1. Age, gender and cardiovascular risk factors including smoking, arterial hypertension, dyslipidemia and diabetes did not differ between the AF and the AFHF group. All patients received optimal medication according to current guidelines, resulting in a homogenous pharmaceutical profile of our study groups. Most patients were on a combination of beta blockers, ACE-Inhibitors / AT-II antagonists, diuretics and statines.

Impaired heart rate variation during deep breathing in AF and AFHF patients

The response to deep breathing was depressed in both groups compared to the healthy controls (Figure 1a). Heart rate variation expressed by the E/I difference was lower in the AF group and in the AFHF group compared to healthy controls (6.9±6.1 bpm, 7.8 ± 4.8 bpm, 23.9 ± 6.9 bpm, respectively; p<0.05) but did not differ between AF and AFHF patients. The E/I ratio was lower in the AF group and in the AFHF group compared to healthy controls (E/I ratio: 1.15 ± 0.15, 1.14±0.09, 2.26±1.16, respectively; p<0.05, Figure 1b). E/I ratio did not differ between AF and AFHF patients (Figure 1c).

No change in heart rate during deactivation of peripheral chemoreceptors in AFHF patients

No significant changes in systolic blood pressure (SBP), stroke volume (SV) and cardiac output (CO) could be observed. Diastolic blood pressure (DBP) and total peripheral resistance (TPR) increased. Hemodynamic changes during oxygen administration are shown in Table 2. Inhalation of pure oxygen led to a lower breathing rate in every group. However the dimension of this effect differed between both patient groups as compared to healthy controls. The AF group and the AFHF group had a lower decrease in breathing rate compared to healthy controls (change in breathing rate: -10%, -9%, -23%, respectively; p<0.05) and did not differ significantly among each other.

A marked decrease in HR during oxygen administration occurred in controls (-4.8%, p<0.05) and in the AF group (-5.0%, p<0.05), as opposed to the AFHF group where no significant HR change was present (Figure 2).
Change in heart rate variability during peripheral chemosensor deactivation

In the control group high frequency bands in normalized and absolute values increased during oxygen administration compared to baseline (HFnu-RRI +18.3%, HF-RRI +96.7%, p<0.05) whereas the LF/HF ratio decreased (-20.8%±29, p<0.05). By contrast, in both AF (+3.1%) and AFHF (+5.26%) patients no significant change in high frequency bands and in LF/HF ratio was observed. Peripheral chemosensor deactivation did not change the low frequency bands of BPV (LF-sBP, LF-dBP) neither in healthy controls nor in AF or AFHF patients.

Dysturbance of chemoreflex sensitivity is advanced in atrial fibrillation patients with heart failure

None of the patients were hypoxemic at baseline with oxygen saturation values ranging from 94% to 100%. Every subject reached an oxygen saturation value more than 99% during inhalation of pure oxygen (controls: 100±0%; AF group: 99.9%±0.02%; AFHF group: 99.8%±0.3%, p=ns). Baseline oxygen saturation and HR did not differ in AF and AFHF patients as compared to healthy controls. Baseline pO2 values were lower in both AF and AFHF patients as compared to healthy controls, whereas pO2 values during oxygen inhalation did not differ between both patient groups (Table 3). During inhalation of 100% oxygen the pO2 of all subjects increased (controls: +35%, AF: +65%, AFHF: +60%, p<0.05). In healthy controls the increase in pO2 correlated with the decrease in HR during inhalation of pure oxygen (r=0.9; p<0.05), while in the AF and AFHF groups this could not be observed. Corresponding to the changes in HR the RR-interval increased in AF patients (+4.9%, p<0.05) and in healthy controls (+5.2%, p<0.05) but not in AFHF patients. This resulted in an impaired CHRS in both AF and AFHF patients. CHRS was lower in AFHF patients than in AF patients (Figure 3).
DISCUSSION

To the best of our knowledge, this is the first study to assess the impact of heart failure on peripheral chemoreflex control in patients with a history of atrial fibrillation. The key findings of the present study are as follows: 1) AF patients with and without HF manifest a comparably low heart rate variation during deep breathing. 2) The disturbance of chemoreflex sensitivity in AF patients is advanced in patients with heart failure. Our findings indicate that tonic activation of peripheral chemoreceptors in AF patients contributes to a lower vagal tone in patients with heart failure that might be influenced by spontaneous breathing characteristics.

The role of autonomic dysregulations in patients with atrial fibrillation has been discussed for several years (Bettoni and Zimmermann, 2002, Chen et al., 1998). Deep breathing is an established test in clinical measurement of autonomic nervous function and therefore numerous studies propose deep breathing for early detection of cardiovagal dysfunction (Blumenthal et al., 2005, Shields, 2009, van den Berg et al., 2001, Wheeler and Watkins, 1973). In our study we found lower values in deep breathing indexes in AF patients compared to healthy subjects. Corresponding to these results we suspect a lower vagal tone in AF patients which is in line with previous reports (Chen et al., 1998, de Vos et al., 2008).

Importantly, this might be partly explained by a decrease of sinus arrhythmia with increasing age (Low et al., 1997, O'Brien et al., 1986). Van den Berg et al. assess an E/I difference more than 15 bpm as normal (van den Berg et al., 2001) and claims a marginal decrease in heart rate variation, whereas Hilz and Dutsch defined a cut off below five beats per minute as abnormal in persons older than 50 years (Hilz and Dutsch, 2006). Therefore the interpretation of heart rate variation during deep breathing has to be done with caution. However, in our population there were no differences in deep breathing measurements between AF patients with and without HF. Consequently we suppose that the two groups do not vary in basal vagal tone of efferent fibres innervating the sinus node.

It is well known, that inhalation of pure oxygen leads to a decrease of HR in healthy subjects (Gole et al., 2011). This can be an expression of the physiological mechanisms of peripheral chemoreceptors. These receptors respond primarily to changes in the partial oxygen pressure. High arterial oxygen levels lead to a deactivation of the peripheral chemoreceptors. Consequently excitatory receptor afferents evoke a rise of vagal tone resulting in a decrease of heart rate (Thoren, 1979). We could underline all these postulations with the results of our healthy controls: they showed an obvious decrease in HR and thus no pathological CHRS
values. In addition the high frequency band of HRV, representing parasympathetic activity rose during administration of oxygen.

Corroborating a previous study we found a decreased CHRS in AF patients (Budeus et al., 2003). Furthermore Hennersdorf et al. demonstrated that patients with HF have a reduced CHRS as well (Hennersdorf et al., 2001). Though there exists no study that investigated the effect of inhalation of pure oxygen in patients with a combined history of AF and HF. Here we could demonstrate unchanged HR during administration of oxygen in AF patients with HF, indicating a lower CHRS compared to the AF patients without HF. According to these results we assume that tonic activation of chemoreceptors contributes to a lower vagal tone in AF patients with HF.

Considering critically our assumption other underlying mechanisms could have played an important role or influenced the measurements. HF is characterized by an increased sympathetic activity (Schwartz and De Ferrari, 2011). Esler and Kaye detected higher levels in plasma catecholamines in HF patients (Esler and Kaye, 2000). This might have influenced the increased vagal activity during deactivation of chemoreceptors (“accentuated antagonism”). Nevertheless, the fact that all patients were on highest tolerable beta-blocker dosis should have kept this influencing parameter low. Furthermore unchanged values in the low frequency bands of BPV (LF-dBP and LF-sBP) in AF patients substantiates our suspicion that the observed effects were predominantly modulated by parasympathetic and not sympathetic activity which is in line with previous reports (Gole et al., 2011, Seals et al., 1991).

Next, the inhalation of oxygen produced a reduction of respiration rate and therefore a prolongation of expiratory time. This leads to a reduced activation of the pulmonary stretch receptors resulting in an increased vagal tone (Zuperku et al., 1982, Schelegle and Green, 2001). It is possible, that this respiratory phenomenon contributes to the decrease in heart rate. This limits the interpretation of our data because decreasing HR might not only reflect the dysfunction of one reflex arch, but the interaction of two mechanisms: deactivation of peripheral chemoreceptors and diminution of the respiration rate with reduced activation of pulmonary stretch receptors. Despite this possibility we preclude an essential role of respiratory mechanisms. In all subjects breathing rate decreased. Despite this decreasing respiration rate the HR did not change in AF patients with HF whereas in healthy controls and in AF patients without HF the HR clearly decreased. This fact underlines a low contribution of decreased respiration rate to heart rate changes.
Schwartz et al. highlight the clinical relevance of our results: whenever vagal activity (tonic or reflex) is decreased, cardiac mortality increases (Schwartz and De Ferrari, 2011). According to this fact we suppose that quantification of peripheral chemosensor function might be a useful tool to improve the evaluation of vagal heart rate control in some patients. The combination of different non invasive autonomic function tests (e.g. cold pressure, cold face or handgrip test) might additionally be useful for specifying autonomic dysfunction in AF patients with heart failure.
CONCLUSION

Our data suggest that tonic activation of excitatory chemoreceptor afferents contribute to a low vagal tone in heart failure patients with a history of AF. Quantification of deactivation characteristics of peripheral chemoreceptor function might be useful to characterize cardiac vagal control in patients with a history of atrial fibrillation during the development and progression of heart failure. This might improve heart failure management in the future.
REFERENCES


### Table 1. Baseline characteristics

<table>
<thead>
<tr>
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<th>AF group</th>
<th>AFHF group</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n</strong></td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td><strong>Age [years]</strong></td>
<td>71±10</td>
<td>72±9</td>
</tr>
<tr>
<td><strong>Sex [male]</strong></td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td><strong>Height [cm]</strong></td>
<td>167±5</td>
<td>166±10</td>
</tr>
<tr>
<td><strong>BMI [kg/m²]</strong></td>
<td>28±4</td>
<td>27±5</td>
</tr>
<tr>
<td><strong>Current smokers, n</strong></td>
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<td>0</td>
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<tr>
<td><strong>Past smokers, n</strong></td>
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<td>3</td>
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<tr>
<td><strong>Diabetes mellitus, n</strong></td>
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<tr>
<td><strong>Hypertension, n</strong></td>
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</tr>
<tr>
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<td>4</td>
</tr>
<tr>
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<td>7</td>
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<tr>
<td><strong>CVD, n</strong></td>
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<td>0</td>
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<tr>
<td><strong>Vitium</strong></td>
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<td>6</td>
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<tr>
<td><strong>NYHA class I/II/III/IV, n</strong></td>
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<td>0/4/5/0</td>
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<tr>
<td><strong>CHADS2 - Score</strong></td>
<td>1±1.2</td>
<td>2±1.3</td>
</tr>
<tr>
<td><strong>CHA2DS2-VASc - Score</strong></td>
<td>3±1.9</td>
<td>4.1±2.1</td>
</tr>
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**Medication**

- Propafenon, n
- Amiodaron, n
- Dronedaron, n
- Beta blockers, n
- ACE inhibitors/ AT-II-antagonists, n
- Ca antagonists, n
- Digitalis, n
- Diuretics, n
- Statins, n
- Oral antidiabetics, n
- Insulin, n
- Phenprocoumon

**Blood parameters**

- Serum protein [g/l]
- Serum creatinin [mg/dl]
- Erythrocyts [mio/µl]
- Haemoglobin [g/dl]
- Haematocrit [%]
- Total cholesterol [mg/dl]
- HDL cholesterol [mg/dl]
- LDL cholesterol [mg/dl]
- Triglycerides [mg/dl]
- Plasma glucose [mg/dl]

BMI: body mass index; CAD: coronary artery disease; CVD: cerebrovascular disease;

All values are mean±SD
### Table 2. Hemodynamics at baseline and after chemosensor deactivation (oxygen)

<table>
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<th>AF group</th>
<th>AFHF group</th>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate [bpm]</td>
<td>63±10</td>
<td>68±12</td>
<td>63±9</td>
</tr>
<tr>
<td>SBP [mmHg]</td>
<td>128±29</td>
<td>120±27</td>
<td>124±18</td>
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<tr>
<td>DBP [mmHg]</td>
<td>73±13</td>
<td>72±16</td>
<td>76±11</td>
</tr>
<tr>
<td>MAP [mmHg]</td>
<td>86±17</td>
<td>85±20</td>
<td>91±13</td>
</tr>
<tr>
<td>Rate pressure product [mmHg/min]</td>
<td>7.7±1.3</td>
<td>8.0±1.6</td>
<td>7.7±1.3</td>
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<tr>
<td>Stroke volume [ml]</td>
<td>83±20</td>
<td>68±16</td>
<td>119±21</td>
</tr>
<tr>
<td>Cardiac output [l/min]</td>
<td>5.2±1.6</td>
<td>4.5±0.8</td>
<td>7.4±1.2</td>
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<tr>
<td>TPR [dyne*s/cm^5]</td>
<td>1432±622</td>
<td>1630±517</td>
<td>992±237</td>
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<tr>
<td>Breathing rate [1/min]</td>
<td>16±6</td>
<td>19±3</td>
<td>18±2</td>
</tr>
<tr>
<td><strong>Oxygen (5l/min)</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate [bpm]</td>
<td>59±9 *</td>
<td>67±12</td>
<td>59±9 *</td>
</tr>
<tr>
<td>SBP [mmHg]</td>
<td>135±24</td>
<td>129±21 *</td>
<td>126±18</td>
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<tr>
<td>DBP [mmHg]</td>
<td>76±12</td>
<td>77±13 *</td>
<td>78±11 *</td>
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<tr>
<td>MBP [mmHg]</td>
<td>91±16</td>
<td>92±16 *</td>
<td>94±14 *</td>
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<tr>
<td>Rate pressure product [mmHg/min]</td>
<td>7.7±1.4</td>
<td>8.5±1.2</td>
<td>7.5±1.2 *</td>
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<tr>
<td>Stroke volume [ml]</td>
<td>84±21</td>
<td>66±15</td>
<td>120±21</td>
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<tr>
<td>Cardiac output [l/min]</td>
<td>5.0±1.6</td>
<td>4.3±0.7</td>
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<tr>
<td>TPR [dyne*s/cm^5]</td>
<td>1547±671 *</td>
<td>1835±508 *</td>
<td>1073±277 *</td>
</tr>
<tr>
<td>Breathing rate [1/min]</td>
<td>15±6 *</td>
<td>17±4</td>
<td>14±4 *</td>
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</table>

HF: heart failure; AF: atrial fibrillation; bpm: beats per minute; SBP: systolic blood pressure; DBP: diastolic blood pressure; MBP: mean blood pressure; TPR: total peripheral resistance; * significant difference from baseline (p<0.05).
Table 3. Blood gas analysis at baseline and after chemosensor deactivation (Oxygen)

<table>
<thead>
<tr>
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<th>AF group</th>
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<tr>
<td><strong>RRI [ms]</strong></td>
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<td></td>
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<tr>
<td>Baseline</td>
<td>988±157</td>
<td>954±146</td>
<td>984±162</td>
</tr>
<tr>
<td>Oxygen (5l/min)</td>
<td>1041±147 *</td>
<td>970±146</td>
<td>1037±175 *</td>
</tr>
<tr>
<td><strong>pO2 [mmHg]</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>72±8</td>
<td>65±3 #</td>
<td>91±10</td>
</tr>
<tr>
<td>Oxygen (5l/min)</td>
<td>115±40 *</td>
<td>104±28 *</td>
<td>123±20 *</td>
</tr>
<tr>
<td><strong>pCO2 [mmHg]</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>35.07±4.11</td>
<td>37.38±3.80</td>
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<tr>
<td>Oxygen (5l/min)</td>
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<td>39.16±3.64</td>
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<td><strong>pH</strong></td>
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<tr>
<td>Baseline</td>
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<tr>
<td>Oxygen (5l/min)</td>
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<td>7.47±0.03</td>
<td>7.43±0.02</td>
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</tbody>
</table>

HF: heart failure; AF: atrial fibrillation; RRI: RR-interval; pO2: partial pressure of oxygen; pCO2: partial pressure of carbon dioxide; * significant difference from baseline (p<0.05); # significant difference between AF and AFHF group
Figure 1. Change in heart rate (HR) during deep breathing. (A.) Example demonstrating the typical pattern of HR variation during deep breathing in controls, AF group, and AFHF group. (B.) HR variation indexed by expiration to inspiration (E/I) difference. E/I difference was lower in the AF group (6.9±6.1 bpm) and in the AFHF group (7.8±4.8 bpm) compared to healthy controls (23.9±6.9 bpm); *p<0.05) but did not differ between AF and AFHF patients. (C.) HR variation indexed by E/I ratio. The E/I ratio was lower in the AF group (1.15±0.15) and in the AFHF group (1.14±0.09) compared to healthy controls (2.26±1.16; *p<0.05). E/I ratio did not differ between AF and AFHF patients.
Figure 1B.
Figure 1C.
Figure 2. Change in heart rate (HR) after chemosensor deactivation. A marked decrease in HR during inhalation of 100% oxygen occurred in controls (-4.8%) and in the AF group (-5.0%, *p<0.05), as opposed to the AFHF group where no change in HR was seen.
Figure 3. Hyperoxic cardiac chemoreflex sensitivity (CHRS) is impaired in AF and AFHF patients. CHRS was lower in AFHF patients than in AF patients (*, #p<0.05).