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Firing patterns of muscle sympathetic neurons during short-term use of continuous positive airway pressure in healthy subjects and in chronic heart failure patients

Petra Zubin Maslov[a], Toni Breskovic[a], J. Kevin Shoemaker[b,c], Thomas P. Olson[d], Bruce D. Johnson[d], Davor Eterovic[e,f], Zeljko Dujic[a,*]

[a] Department of Physiology, University of Split School of Medicine, Soltanska 2, 21 000 Split, Croatia
[b] Neurovascular Research Laboratory, School of Kinesiology, Western University, London, Ontario, Canada
[c] Department of Physiology and Pharmacology, Western University, London, Ontario, Canada
[d] Division of Cardiovascular Diseases, Department of Internal Medicine, Mayo Clinic and Foundation, Rochester, MN, United States
[e] Department of Nuclear Medicine, University Hospital Split and University of Split School of Medicine, Croatia
[f] Department of Biophysics, University Hospital Split and University of Split School of Medicine, Croatia

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ABSTRACT

The current study tested the hypothesis that modification in central hemodynamics during short-term continuous positive airway pressure (CPAP) application was accompanied by altered firing patterns of sympathetic nerve activity in CHF patients and healthy subjects.

Muscle sympathetic nerve activity (MSNA), hemodynamic and ventilatory parameters were obtained from 8 healthy middle aged subjects and 7 CHF patients. Action potentials (APs) were extracted from MSNA neurograms, quantified as AP frequency and classified into different sized clusters. While on CPAP at 10 cm H_2O, multi-unit MSNA, AP frequency and mean burst area/min increased in healthy middle aged subjects ($p < 0.05$) whereas CPAP had no effect on these variables in CHF patients. In conclusion, the impact of CPAP on central hemodynamics in healthy individuals elicited a moderate activation of sympathetic neurons through increased AP firing frequency, whereas in CHF patients both hemodynamics and MSNA remained unaltered.

1. Introduction

The long-term use of continuous positive airway pressure (CPAP) has been associated with clinical benefit in patients with chronic heart failure (CHF) and is recognized as a novel non-pharmacological therapeutic option in this condition, which is characterized by a high mortality rate and limited treatment options (Usui et al., 2005; Naughton et al., 1995a). The improvement in left ventricular function with CPAP in CHF patients has been ascribed to increased intrathoracic pressure and associated reduction in left ventricular transmural pressure (Naughton et al., 1995b; Baratz et al., 1992; Bradley et al., 1992). However, data on short-term hemodynamic effects of CPAP in CHF patients as well as in healthy subjects are still controversial and inconsistent. Improvement of cardiac index (CI) and stroke volume index (SVI) was found in CHF patients with increased pulmonary capillary wedge pressure (PCWP) after 10 min of CPAP; however, CHF patients with normal PCWP exhibited an opposite effect (De et al., 1995). Naughton et al. (1995b) reported that acute CPAP produced a reduction in CI and SVI in healthy subjects but no change in CHF patients. Several other studies found no beneficial effects of short-term use of CPAP in CHF (Buckle et al., 1992; Davies et al., 1993).

The responses of the autonomic nervous system after short-term application of the CPAP appear to be different between CHF patients and healthy individuals. In young subjects with normal cardiac filling pressures, a positive end-expiratory pressure induced by CPAP causes reduced venous return, followed by a decrease in cardiac output (CO) in accordance with Frank-Starling mechanism. Diminished CO leads to unloading of aortic baroreceptors and a reflexive increase in the muscle sympathetic nerve activity (MSNA) (Naughton et al., 1998; Tanaka et al., 1994). Contrary to healthy subjects, the short-term effects of CPAP in CHF are less consistent. Positive end-expiratory pressure in CHF patients

* Corresponding author at: Department of Integrative Physiology, University of Split School of Medicine, Soltanska 2, 21000 Split, Croatia. Tel.: +385 21 557 906; fax: +385 21 465 304.
E-mail addresses: petra.zubin@mefst.hr (P. Zubin Maslov), toni.breskovic@mefst.hr (T. Breskovic), kshoemak@uwo.ca (J.K. Shoemaker), Olson.Thomas2@mayo.edu (T.P. Olson), johnson.bruce@mayo.edu (B.D. Johnson), davor.eterovic@mefst.hr (D. Eterovic), zeljko.dujic@mefst.hr (Z. Dujic).

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with increased cardiac filling pressures may cause a reduction in afterload (due to lowering of the left ventricular transmural pressure) and result in increased CO without the need for sympathetic outflow augmentation (Naughton et al., 1995b).

However, sympathetic neural firing patterns and activation strategies of the sympathetic nervous system during CPAP are not completely understood. In contrast to the idea that sympathoinhibition should occur if CPAP enhances cardiac index (as above), Heindl et al. (2001) found a modest increase in multi-unit MSNA burst frequency in both CHF patients and healthy control subjects. Recently, our studies have explored the potential importance of quantifying actual action potential (AP) patterns in the postganglionic sympathetic nerve activity as an indicator of sympathetic patterns, rather than just the frequency of integrated bursts (Steinback et al., 2010; Salmanpour et al., 2010, 2011; Breskovic et al., 2011; Maslov et al., 2012).Specifically, multi-unit MSNA bursts are composed of several sympathetic neurons firing at the same time with burst-by-burst variations in the numbers of APs recruited (Salmanpour et al., 2010). Traditional quantification of MSNA as bursts frequency or burst incidence provides only general impression about sympathetic nerve activity without insight into neural firing patterns of sympathetic neurons contributing to sympathetic burst.

The purpose of the present study was to investigate short-term effects of CPAP on the firing strategies of sympathetic neurons measured by microneurography in CHF patients and in healthy, gender and age matched controls. We hypothesized that modification in the sympathetic nerve firing during short-term CPAP would reflect a response to altered central hemodynamics.

2. Methods

2.1. Subjects

Seven patients with moderate CHF and eight healthy age and gender-matched control subjects were included in the study. Patients were recruited from the Department of Cardiology, University Hospital of Split and from the Croatian Register of Heart Failure Patients (Croatian Cardiology Society). Eligibility was determined using the following criteria: age 20–75 years, left ventricular ejection fraction (LVEF) < 40%, New York Heart Association classes I–III, stable condition (no rales on auscultation or tibial edema) with no recent (1 month) history of decompensation or hospitalization, and stable pharmacotherapy (3 months). Exclusion criteria were: atrial fibrillation, pace maker dependence, history of smoking or alcoholism and history of comorbidities (kidney disease, obstructive lung disease, cerebrovascular insult, severe anemia Hgb < 90 g/l). Health volunteers free of cardiovascular disease were matched for age and gender and recruited as control subjects. All subjects gave written informed consent to participate in the study that was conducted in accordance with the Declaration of Helsinki and was approved by the research ethics board at The University of Split, School of Medicine.

2.2. Measurements

All blood tests were done in Biochemical laboratory at University Hospital Split. ECLIA (Electrochemiluminescence immunoassay; analyzer Cobas E601; Roche Diagnostics GMBH, Mannheim; Germany) was used to obtain pro-BNP.

Blood pressure was measured with the use of photoplethysmography (Finometer, Finapress Medical Systems, Arnhem, Netherlands). From the continuous blood pressure measurement, the arterial pulse wave was analyzed by an improved method of Wesseling (Modelflow program) which computes changes in left ventricular stroke volume (SV) from the pulsatile systolic area (Jellema et al., 1999). The values of systolic (SBP) and diastolic (DBP) blood pressures obtained by the photoplethysmographic method were gauged using the mercury sphygmomanometer. The heart rate (HR) was obtained by electrocardiogram (ECG, Bioamp, ADInstruments, Castle Hill, Australia) and CO was computed as SV times HR. Arterial oxygen saturation (SaO_2) was monitored continuously by pulse oximetry (Poet II, Criticare Systems,Waukesha, WI, USA), with the probe placed on the middle finger. A pneumatic respiratory belt, located around the chest at the level of the xiphoid process, was coupled to a differential pressure transducer (Prignitz Mikrosystemtechnik, Wittenberge, Germany) and was used to monitor thoracic movements. Respiratory parameters including tidal volume (V_T) and breathing frequency (Bf) were measured continuously with a breath-by-breath analyzer (AMIS2000, Innovision A/S, Odense, Denmark). Ventilatory volume (V_E) was computed as V_T times Bf.

Multi-unit MSNA of postganglionic sympathetic neurons was recorded using microneurography. A tungsten microelectrode was inserted percutaneously into the peroneal nerve while the reference electrode was inserted 1–3 cm from the recording site. Small adjustments of the active electrode were made until multi-unit bursts occurred. Confirmation that the recorded signal represented MSNA was determined by the absence of skin paresthesia and presence of a signal that increased in response to voluntary apnea but not during arousal to a loud noise (Vallbo et al., 2004). The nerve signal was amplified (100 000 times), bandpass filtered (band pass 700–2000 Hz), rectified, integrated using 0.1 s time constant and sampled at 10 000 Hz (Powerlab/16SP; ADInstruments) and stored for subsequent analysis using Chart software (version 5.5.6.7).

2.3. Protocol

The study was conducted in two consecutive days. On the 1st day of the study, upon arrival to the laboratory, subjects were informed about procedures and potential risks. A brief history, physical examination and ECG were obtained from each subject. All participants underwent anthropometric measurements and performed a dynamic spirometry test (Quark PFT; Cosmed, Rome, Italy). LVEF was determined using two-dimensional echocardiography (Vivid Q, GE, Milwaukee, WI USA). Blood samples were withdrawn from the antecubital vein to measure levels of pro- brain natriuretic peptide (pro-BNP). Additionally, all subjects were instructed in the use of CPAP (BiPAP Vision, Respironics, Pittsburg, PA, USA) to familiarize them with the device and minimize potential hemodynamic effects of anxiety. To maximize generalizability of data, the CHF patients continued on standard pharmacotherapy during the protocol. On the 2nd day of the study, subjects were placed in supine position and after instrumentation they were given 10 min of quite rest. After stabilization of hemodynamic parameters, subjects began breathing through a mouthpiece with a pneumatic one-way valve connected to a breath-by-breath respiratory gas analyzer with nose clip in place. All subjects breathed room air for 10 min to obtain baseline values prior to administering CPAP for 5 min at each of two levels of positive pressure (5 and 10 cm H_2O), followed by 10 min of recovery on room air.

2.4. Data acquisition and analysis

Hemodynamic, ventilatory and MSNA parameters were analyzed and averaged during the last minute of baseline, during the first minute (start) and last minute (end) of each CPAP level (5 and 10 cm H_2O) and during the last 1 min of recovery. Integrated bursts of MSNA were identified as exhibiting pulse-synchrony, having a signal-to-noise ratio (SNR) of at least 2:1 with respect to a previous period of neural silence and having characteristic rising and falling