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Cardiorenal anemia syndrome in chronic heart failure contributes to increased sympathetic nerve activity ☆

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ABSTRACT

Background: We sought to assess whether cardiorenal anemia syndrome (CRAS) in chronic heart failure (CHF) patients contributes to sympathetic overactivity through modulation of sympathetic reflexes.
Methods and results: We prospectively studied 15 patients with CRAS and CHF and 15 control CHF patients, matched for age, gender distribution, type of cardiomyopathy, left ventricular ejection fraction (LVEF) and BMI. We compared muscle sympathetic nerve activity (MSNA) and the effect of peripheral chemoreflex deactivation on MSNA in both groups. We also compared sympathetic baroreflex function, assessed by the slope of the relationship between MSNA and diastolic blood pressure in both groups and while peripheral chemoreflexes were (by breathing 100% oxygen for 15 min) or not deactivated. Baseline MSNA was significantly elevated in CHF patients with CRAS compared with control CHF patients (83.1 ± 4.6 versus 64.9 ± 2.9 bursts/100 heart beats; $P<0.05$) and sympathetic baroreflex impaired (2.69 ± 0.44 vs 5.25 ± 0.60% bursts/mm Hg; $P<0.01$). Chemoreflex deactivation with administration of 100% oxygen led to a significant decrease in muscle sympathetic nerve activity (77.8 ± 4.7 versus 82.1 ± 4.9 bursts/100 heart beats; $P<0.01$) and to an increase in sympathetic baroreflex function (2.77 ± 0.45 vs 5.63 ± 0.73% bursts/mm Hg; $P<0.01$) in patients with CRAS and CHF. In contrast, neither room air nor 100% oxygen changed MSNA, hemodynamic or sympathetic baroreflex function in control CHF patients.
Conclusions: CRAS in CHF patients is associated with elevated sympathetic activity mediated by both tonic activation of peripheral chemoreflex and baroreflex impairment.

1. Introduction

The prevalence and impact of chronic kidney disease and anemia in CHF patients have been emphasized by observational studies in the past years, and both are directly implicated in the increase in sympathetic tone of heart failure patients [1,2]. This activation triggers initiation and progression of heart failure (HF) that could partly explain the poor prognosis and outcome of patients with HF associated to anemia and chronic kidney disease [3,4]. While renal dysfunction and anemia have been extensively studied separately in CHF [5–8], recent epidemiological data also suggest that renal dysfunction may coexist with anemia in CHF patients. Silverberg et al. called the association of CHF, renal dysfunction, and anemia the "cardiorenal anemia syndrome (CRAS)", where CHF may cause progressive renal dysfunction and both may lead to anemia, which in turn can worsen CHF and renal dysfunction [9]. More recently, this syndrome has been requalified by a consensus conference as anemia associated with type 2 or type 4 cardio-renal syndromes [10]. Epidemiological evidence demonstrates that CRAS is prevalent in patients with CHF and significantly worsen patient's prognosis [11]. While sympathetic activation has been identified in CHF patients with anemia or CKD separately, it remains unknown if sympathetic tone is increased in CHF patients with CRAS, and if so, what mechanisms are involved. This question is clinically relevant because identification of elevated sympathetic tone in these patients could explain the progression of this particular type of HF, and its significant bad prognosis [11–13].

The present study was undertaken to determine if CHF complicated by CRAS was associated with an increase in sympathetic nerve activity as assessed by microneurographic nerve traffic recording. We further planned to investigate the role of autonomic reflexes in the genesis of this elevated sympathetic tone. We first tested the

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hypothesis that tonic activation of excitatory chemoreceptor afferents contributes to elevated sympathetic activity in patients with CRAS and CHF and that chemoreflex deactivation with 100% oxygen would, therefore, cause a reduction in sympathetic nerve traffic in these patients. Using a double-blind, randomized, placebo-controlled design, we examined the effects of chemoreflex deactivation on sympathetic activity in patients with both CRAS and CHF and in CHF patients matched for age, sex, blood pressure (BP), and body mass index. Since tonic chemoreflex activation cannot explain by itself sympathetic overactivity and knowing that chemoreceptors interact with baroreceptors we further looked at sympathetic baroreflex function in both groups.

2. Material and methods

2.1. Study population

This prospective study was conducted at the Intensive Cardiac Care Unit, Rangueil University Hospital, Toulouse, France. We studied 15 patients (13 men and 2 women) with CRA syndrome (age: 66.5 ± 3.1 years; mean BMI: 24.1 ± 0.9 kg/m^2) and 15 control patients with CHF alone (14 men and 1 woman) matched for age, gender distribution, type of cardiomyopathy, left ventricular ejection fraction (LVEF) and BMI. We used the World Health Organization definition of anemia (hemoglobin concentration less than 13.0 g/dl in men and 12.0 g/dl in women), which takes into account gender differences in distribution of hemoglobin values. Estimated glomerular filtration rate (eGRF) was evaluated with the use of the 4-variable simplified Modification of Diet in Renal Disease equation [14]. None of the participants was receiving erythropoietin, and none had diabetes. No individual had any pre-existing lung disease history. All patients were free of any symptoms or signs of respiratory dysfunction on clinical examination. Furthermore, there was no suggestion of sleep apnoea as assessed by a sleep questionnaire (Epworth test) [15].

The investigation complies with the principles outlined in the Declaration of Helsinki. Informed written consent was obtained from all participants. Institutional Human Subjects Review Committee approved the study.

2.2. Experimental protocol

Participants were studied in the supine position under carefully standardized conditions. Baseline recording of all parameters was done for 15 min (MSNA and sympathetic baroreflex function). The experimental protocol is depicted in Fig. 1. To study peripheral tonic chemoreflex activation we used the transient hyperoxic method as described previously [1,2]. Briefly, we studied the effect of chemoreflex deactivation with 100% oxygen, by using a randomized, double blind, placebo-controlled crossover design. The placebo consisted of breathing room air. In random order, 100% oxygen or room air was administered via a nonrebreathing mask for 15 min. Following a 30-min recovery period, the other gas (room air or 100% oxygen) was administered via a nonrebreathing mask for 15 min. Finally, to study the baroreflex and chemoreflex interaction, MSNA and sympathetic baroreflex function were analyzed during both study time periods of the randomized procedure used to assess chemoreflex function.

2.3. Measurements

Heart rate (HR) was measured continuously by electrocardiogram (AD Instruments, Castle Hill, New South Wales, Australia). Blood pressure (BP) was measured continuously by the Finometer system (Finapress Medical System BV, Amsterdam, The Netherlands). Oxygen saturation was monitored with a pulse oximeter (AD Instruments, Castle Hill, New South Wales, Australia). Multiunit postganglionic sympathetic nerve activity was recorded as previously described [1,2]. Briefly, a tungsten microelectrode (shaft diameter 200 μm, tapering to an uninsulated tip of 1–5 mm) was inserted selectively into muscle or skin fascicles of the peroneal nerve. A subcutaneous reference electrode was first inserted 2–3 cm away from the recording electrode, which was itself inserted into the nerve fascicle. The neural signals were amplified, filtered, rectified and integrated to obtain a voltage display of sympathetic nerve activity. The intralaboratory reproducibility of microneurography has been assessed previously. In stable heart failure patients, muscle sympathetic nerve activity (MSNA) was measured twice at a 2-week interval. We observed a high and significant correlation between sessions ($r = 0.88$, $P = 0.001$).

Assessment of spontaneous arterial baroreflex control of MSNA was performed as described previously [1,2]. Briefly, over a 3 to 5 min resting period, diastolic pressures of individual heart beats were grouped in intervals of 2 mm Hg and, for each interval, the percentage of diastoles associated with a sympathetic burst was plotted against the mean of the pressure interval (threshold diagram). Muscle sympathetic bursts were advanced by 1.3 s to compensate for baroreflex delay. The sensitivity or reflex gain was defined as the slope of the regression line (Fig. 2).

All patients underwent standard transthoracic echocardiography with measurement of conventional parameters, including left ventricular end-diastolic and systolic diameter, septum and posterior wall thickness during both systole and diastole, and calculation of left ventricular mass index with the Penn method [16]. Standard laboratory tests were performed to determine hemoglobin levels, red blood cell volume, serum creatinine, plasmatic sodium, and levels of brain natriuretic peptide (ADVIA Centaur BNP reagent and Bayer Diagnostic, Domont, France). Samples were not frozen and the time between blood sampling and analysis was less than 20 min.

2.4. Statistical analysis

The amplitude of each burst was determined and sympathetic activity was calculated as bursts per minute, bursts for 100 heart beats (which allows comparison of sympathetic discharge between individuals). MSNA-related data were collected by NF, FD and ML, sampled by a research assistant and analyzed blindly by investigators. Demographic data and baseline characteristics of the two groups (CHF with CRA syndrome and CHF patients alone) were compared by use of an unpaired Mann Whitney test. The responses to administration of 100% oxygen and room air were assessed as comparisons between measurements taken during the last 5 min of each period of

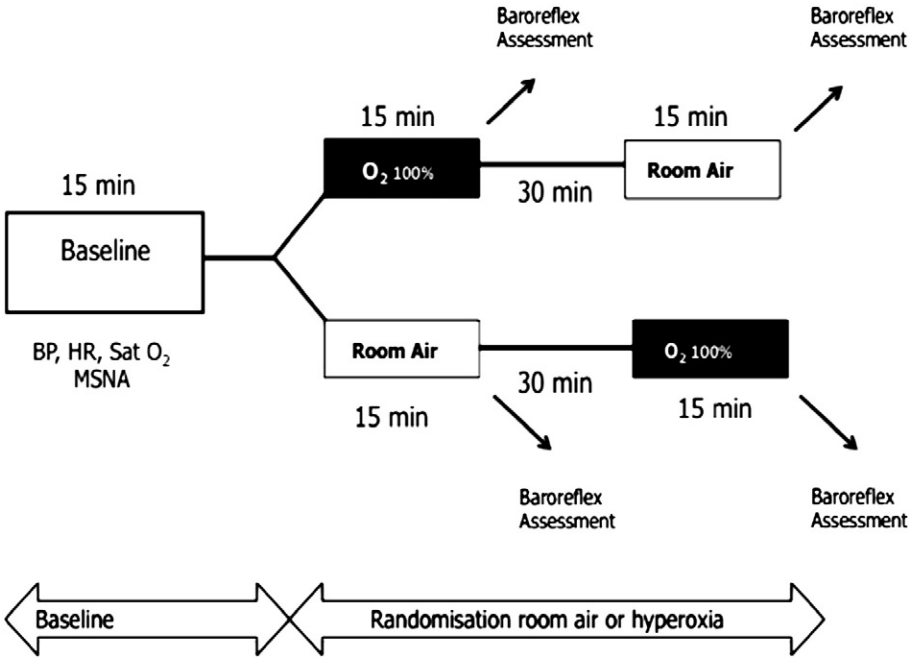

Fig. 1. Experimental protocol. During all sessions the following measurements were released: blood pressure, heart rate, O2 saturation, respiratory rate and muscle sympathetic nerve activity (MSNA) activity.