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Sympathetic cardiac influence and arterial blood pressure instability

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Abstract

Previous studies have suggested that sympathetic cardiac blockade enhances baroreflex function, whereas parasympathetic blockade diminishes baroreflex sensitivity and elicits arterial blood pressure (ABP) instability. The aim of this project was to test the hypothesis that sympathetic cardiac blockade was beneficial in maintaining ABP stability during orthostatic challenge. In 8 young healthy subjects, measurements were taken before and after sympathetic cardiac blockade (β_1-adrenoceptor blockade via metoprolol) in combination with or without parasympathetic blockade (atropine) at rest and during lower body negative pressure (LBNP). Arterial blood samples were obtained to evaluate plasma renin activity (PRA) and norepinephrine (NE). Power spectral analyses were performed on heart rate (HR) and ABP variability. LBNP −50 Torr significantly decreased systolic blood pressure (SBP, −6±3 mm Hg) and increased PRA (from 0.72±0.23 to 1.75±0.24 ng ml^{-1} h^{-1}) and NE (from 1.02±0.11 to 2.13±0.32 pg ml^{-1}). Low frequency (LF, 0.04–0.12 Hz) SBP and diastolic blood pressure (DBP) variability were significantly augmented by LBNP (4.1±1.6 vs. 10.8±3.0 mm Hg^2, and 3.1±1.0 vs. 7.9±1.9 mm Hg^2, respectively). Following metoprolol, arterial baroreflex sensitivity (assessed by the slope of HR interval to SBP during injection with 1 μg kg^{-1} phenylephrine) increased significantly (9.9±2.2 to 19.6±4.1 ms mm Hg^{-1}). With β_1-adrenoceptor blockade, LBNP still decreased SBP (−10±2 mm Hg) and increased NE, but did not significantly augment PRA (0.59±0.22 vs. 1.03±0.18 ng ml^{-1} h^{-1}), or LF SBP and DBP variability (3.3±0.6 vs. 5.7±1.3 mm Hg^2, and 3.1±0.7 vs. 5.4±1.1 mm Hg^2, respectively). The increased PRA during LBNP remained non-significant following metoprolol combined with atropine, whereas the augmented LF SBP (2.6±0.7 vs. 9.9±2.8 mm Hg^2) and DBP (2.5±0.7 vs. 11.1±3.0 mm Hg^2) variability were significantly accentuated compared to both metoprolol alone and control conditions, accompanied by a greater ΔSBP (−17±7 mm Hg) and significantly diminished baroreflex gain (0.91±0.05 ms/mm Hg). These data suggested that removal of sympathetic cardiac influence improved cardiovascular stability as indicated by a diminished LF ABP variability, which was related to an enhanced cardiac responsiveness.

Keywords: Power spectral analysis; Lower body negative pressure; Plasma renin activity; Metoprolol; Vasomotion

1. Introduction

Both sympathetic nerve fibers (mediated by β_1-adrenoceptors) and parasympathetic nerve fibers (mediated by muscarinic cholinergic receptors) innervate the heart. Metoprolol is a selective antagonist to β_1-adrenoceptors, which convey sympathetic nerve discharge to the heart and the kidneys, whereas atropine blocks parasympathetic influence to the heart. Beta-adrenoceptor blockade has been reported to enhance baroreflex gain in healthy young volunteers (Lucini et al., 1994) and hypertensive patients (Vesalainen et al., 1998; Ylitalo et al., 1999). As baroreflex function is mediated by both the sympathetic and parasympathetic nervous systems, these previous studies suggest that cardiac sympathetic nerve activity (SNA) may influence parasympathetically mediated baroreflex control of heart rate (HR) and vagal cardiac function (Munakata et al., 1994). While vagal cardiac function has been demonstrated to play an important role in maintaining cardiovascular homeostasis and arterial blood pressure (ABP) stability

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(Wray et al., 2001), the impact of sympathetic cardiac blockade and its combination with parasympathetic blockade on ABP variability remained largely unknown.

It has been reported that metoprolol administration diminishes plasma renin activity (PRA) in hypertension (von Bahr et al., 1976) and heart failure (Jansson et al., 1999). These studies indicate that PRA responds to the β_1-adrenoceptor mediated renal SNA in addition to the changes in renal blood flow and tubular sodium chloride delivery (Laragh and Sealey, 1992). It has been established that lower-body negative pressure (LBNP) simulated orthostatic challenge stimulates PRA (Cleroux et al., 1989; Tidgren et al., 1990) and activates the renin–angiotensin system (RAS) (Tidgren et al., 1990). This activated PRA has been related to augmentation of ABP variability during orthostatic challenge (Schmedtje et al., 1996). However, it was not evaluated whether PRA response would be attenuated by β_1-adrenoceptor blockade during sympathoexcitation and subsequent RAS activation. Furthermore, the interaction of ABP stability and β_1-adrenoceptor blockade in relation to the activation of the RAS or PRA response remained unknown.

The main purpose of this study was to address the sympathetic and parasympathetic cardiac influence on baroreflex control of HR and its contribution to ABP stability. To address these relationships, we elicited orthostatic stress (using LBNP) before and during β_1-adrenoceptor blockade (metoprolol) alone or in combination with vagal cardiac blockade (atropine). We hypothesized that selective β_1-adrenoceptor blockade with metoprolol would improve ABP stability during orthostatic challenge through 1) improved vagal cardiac responsiveness and baroreflex sensitivity, and 2) attenuated PRA. However, during double cardiac autonomic nerve blockade (metoprolol+atropine) we expected the vagal dysfunction would counteract any beneficial effects from β_1-adrenoceptor blockade alone and provoke ABP instability during LBNP.

2. Materials and methods

2.1. Subjects

Eight healthy young (29±2 years of age) men (n=6) and women (n=2) volunteers (group mean body weight: 71±5 kg and height: 170±4 cm) participated in this study. All subjects passed a physical screening that consisted of completing a health and physical activity questionnaire form and a resting 12-lead ECG. Female volunteers completed a urine pregnancy test verifying that they were not pregnant. The aerobic fitness of these volunteers was not evaluated, but physical activity questionnaire answers revealed that all subjects were physically active, but none of them was athlete. Volunteers who passed the screening test and agreed to be the subjects received both oral and written explanation of the experimental protocol, and signed a written consent form that was approved by the Institutional Review Board for the Protection of Human Subjects at the University of North Texas Health Science Center at Fort Worth.

2.2. Measurements

During the experiment, beat-to-beat HR interval (from standard lead electrocardiogram), thoracic impedance (TI), LBNP, and intra-radial arterial blood pressure (ABP) were continuously recorded for mean, systolic and diastolic blood pressure (SBP and DBP) as described previously (Wray et al., 2001). Stroke volume (SV) and cardiac output (CO) were estimated using electrical impedance measurements (Minnesota Impedance Cardiography) from four tetra polar electrodes (3/4 in. wide Mylar tape strip) placed around the neck and lower chest. This method has been previously validated in our lab for monitoring SV and CO during supine rest with or without LBNP in healthy individuals (Wray et al., 2001). LBNP was performed with a custom designed box equipped with motors that create negative pressure inside the box. CO and SV were estimated before LBNP and at the 2nd, 5th, 8th, 10th, 13th, and 16th minutes of the LBNP application (i.e., −40 Torr for 8 min, minute 0 to 8, and −50 Torr for 8 min, minute 8 to 16). Total peripheral resistance (TPR) was calculated from the ratio of mean arterial pressure (MAP) to CO.

In addition, arterial blood samples were collected in pre-chilled syringes. Arterial blood gas, pH value, hematocrit level, [Na^+] and [K^+] were measured immediately after collection using a blood gas analyzer (NOVA IL synthesis 35). Blood samples for the determination of catecholamines and PRA were centrifuged in a 4 °C centrifuge (Beckman model TJ-6) at 2700 rpms, 1500×g for 15 min. Test tubes used for determination of catecholamine were pretreated with 100 μl of glutathione and 10 μl of heparin, and test tubes used for PRA were pre-chilled and contained ethylene diamine tetraacetic acid. After centrifuge, the plasma portion of samples was transferred into disposable tubes and stored in a −80 °C refrigerator (Puffer Hubbard) for subsequent analyses within 2 weeks. Catecholamine levels from arterial blood plasma were determined by high performance liquid chromatography. Plasma renin activity was analyzed by radioimmunoassay (Angiotesnsin $I^{[125]}$ Radioimmunoassay kit). All assays were processed in duplicate.

2.3. Procedure

Subjects reported to the laboratory for a total of two visits. During the first visit, the subjects were familiarized with LBNP, experimental measurements, and procedure that were to be used during the study. The experiment was conducted on the second visit. All experiments were