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Increased muscle sympathetic nerve activity predicts mortality in heart failure patients ☆

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Abstract

Background: Previous studies have associated neurohumoral excitation, as estimated by plasma norepinephrine levels, with increased mortality in heart failure. However, the prognostic value of neurovascular interplay in heart failure (HF) is unknown. We tested the hypothesis that the muscle sympathetic nerve activity (MSNA) and forearm blood flow would predict mortality in chronic heart failure patients.
Methods: One hundred and twenty two heart failure patients, NYHA II–IV, age 50±1 ys, LVEF 33±1%, and LVDD 7.1±0.2 mm, were followed up for one year. MSNA was directly measured from the peroneal nerve by microneurography. Forearm blood flow was obtained by venous occlusion plethysmography. The variables were analyzed by using univariate, stepwise multivariate Cox proportional hazards analysis, and Kaplan–Meier analysis.
Results: After one year, 34 pts died from cardiac death. The univariate analysis showed that MSNA, forearm blood flow, LVDD, LVEF, and heart rate were significant predictors of mortality. The multivariate analysis showed that only MSNA ($P=0.001$) and forearm blood flow ($P=0.003$) were significant independent predictors of mortality. On the basis of median levels of MSNA, survival rate was significantly lower in pts with >49 bursts/min. Similarly, survival rate was significantly lower in pts with forearm blood flow <1.87 ml/min/100 ml ($P=0.002$).
Conclusion: MSNA and forearm blood flow predict mortality rate in patients with heart failure. It remains unknown whether therapies that specifically target these abnormalities will improve survival in heart failure.

Keywords: Heart failure; Muscle sympathetic nerve activity; Forearm blood flow; Mortality rate

1. Introduction

Despite improvement in the treatment of heart failure in the last decades, the heart failure syndrome is one of the major causes of death in industrialized countries. Thus, the development of new strategies for prognostication and treatment of heart failure are the greatest challenges in medicine today.

It is well established that sympathetic activation is typical of heart failure [1–5]. Plasma norepinephrine levels are

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significantly increased in heart failure patients [1,4,5]. Muscle sympathetic nerve activity (MSNA) progressively increases from normal controls to moderate and severe heart failure patients [6]. Cardiac norepinephrine spillover is greater in heart failure patients when compared with healthy individuals [7]. Further studies demonstrate that sympathetic activation is associated with poor prognosis in humans with heart failure. In a classical study, Cohn et al. [8] elegantly reported that plasma norepinephrine concentration was related to poor prognosis in heart failure patients. Brouwer et al. [9] found that heart rate variability has prognostic value not only for identification of patients at high risk for all-cause cardiac mortality, but also for sudden cardiac death. More recently, Kinugawa et al. [10] observed that patients with supramedian level of exercise plasma norepinephrine concentration had a significantly lower survival rate than those with inframedian level. Although plasma norepinephrine levels and heart rate variability are important markers of prognosis in heart failure, they have some limitations. Plasma norepinephrine depends on removal of the neurotransmitter from plasma, which can be slowed in heart failure in consequence of lower cardiac output [11,12]. Thus, plasma norepinephrine levels may over estimate the degree of central sympathetic outflow. In this regard, a unique technique described by Wallin et al. [13] allows a direct measure of the efferent sympathetic nerve traffic, and hence, the sympathetic outflow directly from central sympathetic activity. Although this technique stratifies the severity of cardiac dysfunction [6], its usefulness in the prognosis of patients with heart failure is unknown.

The increase in sympathetic outflow in heart failure patients contributes to vasoconstriction and, in consequence, a reduction in regional blood flow [14–16]. Previous studies have shown that renal cortical blood flow and muscle blood flow are reduced in patients with moderate or severe cardiac dysfunction [14,17]. The severity of peripheral vasoconstriction may be directly dependent on central sympathetic outflow, or more likely, is the result of an imbalance of several overactive vasoconstrictor influences, and inadequate vasodilator influences. Recent studies demonstrated that impairment in forearm vasodilatation in response intra-arterial infusion of acetylcholine and reduced flow-endothelium-mediated vasodilatation after reactive hyperemia are predictors of poor prognosis in patients with chronic heart failure [18,19]. Although these studies provide important information regarding the prognosis in heart failure, they would be cumbersome to perform in clinical practice. In the present study, we studied the value of a single noninvasive measure of forearm blood flow by venous occlusion plethysmography in the prognosis of heart failure patients.

In the present investigation, we sought whether MSNA directly measured by microneurography would predict mortality rate in patients with heart failure. In addition, whether resting forearm blood flow assessed by venous occlusion plethysmography would independently predict prognosis in patients with heart failure.

2. Material and methods

2.1. Study population

After written informed consent was obtained and the Ethical Committee for Human Research Protocols of the University of São Paulo Medical School approved this study, a total of 122 patients with heart failure (New York Heart Association [NYHA] functional class II–IV) were enrolled in the study. The characteristics of the study patients are displayed on Table 1. Patients abstained from the caffeine before initiation of the study. These studies were performed in the post absorptive state. All the patients were followed prospectively for 12 months.

2.2. Measurements and procedures

2.2.1. Muscle sympathetic nerve activity

Resting MSNA was recorded directly from the peroneal nerve using the technique of microneurography [20,21]. Multiunit post-ganglionic muscle sympathetic nerve recordings were made using a tungsten microelectrode. Signals were amplified by a factor of 50,000 to 100,000 and bandpassed filtered (700 to 2000 Hz) Nerve activity was rectified and integrated (time constant 0.1 s) to obtain a mean voltage display of sympathetic nerve activity that was recorded on paper. All recordings of MSNA met previously

Table 1
Clinical baseline characteristics.

N	122
Age, yrs	50±1
Gender, M/F	84/38
BMI, kg/m^2	24±0.3
Etiology:	
Idiopathic	52%
Ischemic	13%
Hypertension	13%
Chagas' disease	22%
Medications:	
ACEI/ARB	92%
Digoxin	89%
Diuretics	88%
Spironalactone	35%
Beta blockers	15%
LVEF, %	33±1
LVDD, cm	7.1±0.2
NYHA Class:	
II	35%
III	39%
IV	26%
Serum sodium, mEq/l	138±0.4
Creatinine	1.2±0.03
Urea, mg/dl	55±3
Hematocrit, %	42±1

Values are mean±SE. BMI, Body mass index; ACEI, Angiotensin converting enzyme inhibitors; ARB, Angiotensin receptor blocker; LVEF, Left ventricle ejection fraction; LVDD, Left ventricle diastolic diameter; NYHA, New York Heart Association.