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Abnormal muscle vascular responses during exercise in myocardial infarction patients

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Neurovascular alteration has been described in patients with coronary artery disease (CAD). Muscle sympathetic nerve activity (MSNA) is increased in patients with myocardial infarction (MI) [1] and some investigators have reported that flow-mediated dilatation is lower in MI patients when compared with healthy subjects and patients with cardiovascular risk factors [2]. Previous studies show that acetylcholine infusion into the left coronary artery causes paradoxical coronary vasoconstriction in patients with CAD [3]. This vasoconstrictor status has been associated with augmented sympathetic outflow and reduced endothelial function. In addition, this endothelial dysfunction has clinical implication, because it is an independent predictor of recurrence of cardiovascular events in patients with acute coronary syndromes [4]

Accumulated evidence shows that physiological maneuvers, including exercise, provoke sympathetic nerve activation, which, in turn, increases cardiac output and blood pressure (BP) and reduces visceral blood flow (BF). These hemodynamic adjustment works in concert to increase muscle BF and, in consequence, energy production in the skeletal muscle [5,6]. More recently, it has become evident that the increase in muscle BF during exercise depends not only on the

Table 1
Clinical characteristic in the case and the control groups. Type of myocardial infarction, left ventricular systolic function and medications utilized in the infarcted population.

	MI (N = 32)	NC (N = 11)	P
Age (years)	51 ± 1	49 ± 2	0.33
Weight (kg)	76.3 ± 2.3	69.7 ± 2.6	0.13
Height (m)	1.68 ± 0.02	1.67 ± 0.03	0.79
BMI (kg/m^2)	27 ± 1	25 ± 1	0.08
MBP (mmHg)	86 ± 3	83 ± 3	0.68
Heart rate (bpm)	56 ± 1	63 ± 2	0.01
LVEF (%)	57 ± 1	–	–
STEMI (N)	17	–	–
NSTEMI (N)	15	–	–
Coronary angiography (N)	32	–	–
No PCI	4	–	–
PCI			
Balloon	1	–	–
1 stent	22	–	–
2 stents	4	–	–
3 stents	1	–	–
Medications			
β-adrenergic blocker	28	–	–
ACE/AT1 Inhibitor	28	–	–
Antiplatelet therapy	32	–	–
Statin	32	–	–

Values are mean ± SE. MI, myocardial infarction; NC, normal control; BMI, body mass index; MBP, mean blood pressure; LVEF, left ventricular ejection fraction; STEMI, ST-segment elevation myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; ACE, angiotensin-converting enzyme; AT1, angiotensin receptor.

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Table 2
Absolute values of hemodynamics and muscle sympathetic nerve activity at rest and during handgrip exercise at 10 and 30% of maximal voluntary contraction in the myocardial infarction patients and the normal controls.

	10% MVC				30% MVC			
	Exercise				Exercise			
	Baseline	1 min	2 min	3 min	Baseline	1 min	2 min	3 min
MBP, mmHg								
MI	95 ± 3	95 ± 3	99 ± 3	97 ± 3†	96 ± 2	105 ± 2†	111 ± 3†	116 ± 3†
NC	94 ± 2	97 ± 2	97 ± 2	101 ± 2†	97 ± 2	100 ± 4†	107 ± 4†	109 ± 4†
Heart rate, bpm								
MI	55 ± 1*	55 ± 2*	56 ± 2†*	57 ± 2†*	55 ± 1*	57 ± 1†*	60 ± 1†*	61 ± 2†*
NC	62 ± 2*	64 ± 2*	64 ± 2†*	64 ± 2†*	63 ± 2*	66 ± 2†*	69 ± 2†*	69 ± 2†*
FBF, ml/min/100 ml								
MI	1.41 ± 0.08*	1.40 ± 0.09*	1.62 ± 0.12*	1.62 ± 0.12*	1.49 ± 0.08*	1.58 ± 0.11*	1.75 ± 0.12*	1.91 ± 0.14*
NC	2.30 ± 0.20*	2.65 ± 0.27*	2.85 ± 0.28*†	2.92 ± 0.30*†	2.29 ± 0.23*	2.72 ± 0.33*	3.07 ± 0.34*	4.25 ± 0.68*†
MSNA, bursts/min								
MI	32 ± 2*	32 ± 2*	33 ± 2*	34 ± 2*†	31 ± 2*	34 ± 2*†	37 ± 2*†	41 ± 2*†
NC	22 ± 2*	22 ± 2*	23 ± 2*	24 ± 2*†	22 ± 2*	26 ± 2*†	28 ± 2*†	30 ± 2*†

Values are mean ± SE. MI, myocardial infarction; NC, normal control; MBP, mean blood pressure; FBF, forearm blood flow; MSNA, muscle sympathetic nervous activity, MVC, maximal voluntary contraction. † $p<0.05$, within-group comparisons vs. baseline. * $p<0.05$, between-group comparisons.

sympathetic-mediated cardiac output redistribution, but also on the local endothelial-mediated vasodilatation [7]. However, the neural and vascular controls during exercise in patients with MI remains poorly understood. We tested the hypotheses that MSNA response would be increased and muscle vasodilatation would be reduced during exercise in patients with MI and that this neurovascular dysregulation would be more pronounced during more intense exercise.

After a written informed consent, 32 patients with MI (mean 39 ± 2 days after the acute event, 23 men) and 11 age-matched healthy normal controls individuals (NC, 6 men) were included in the study. The type of MI and medications are displayed in Table 1. All the patients underwent percutaneous coronary intervention with success during hospitalization. This protocol was approved by the Scientific Committee of the Heart Institute (InCor) HCFMUSP and the Ethics Committee of the Clinical Hospital, University of São Paulo Medical School.

MSNA was directly measured from the peroneal nerve by microneurography and forearm BF (FBF) was measured by venous occlusion plethysmography [8,9]. At baseline, BP was non-invasively measured (beat-to-beat basis) and during exercise BP was intermittently monitored from an oscillometric cuff. Forearm vascular conductance (FVC) was calculated by dividing FBF by the mean BP times 100 and expressed in arbitrary units. Heart rate (HR) was measured by

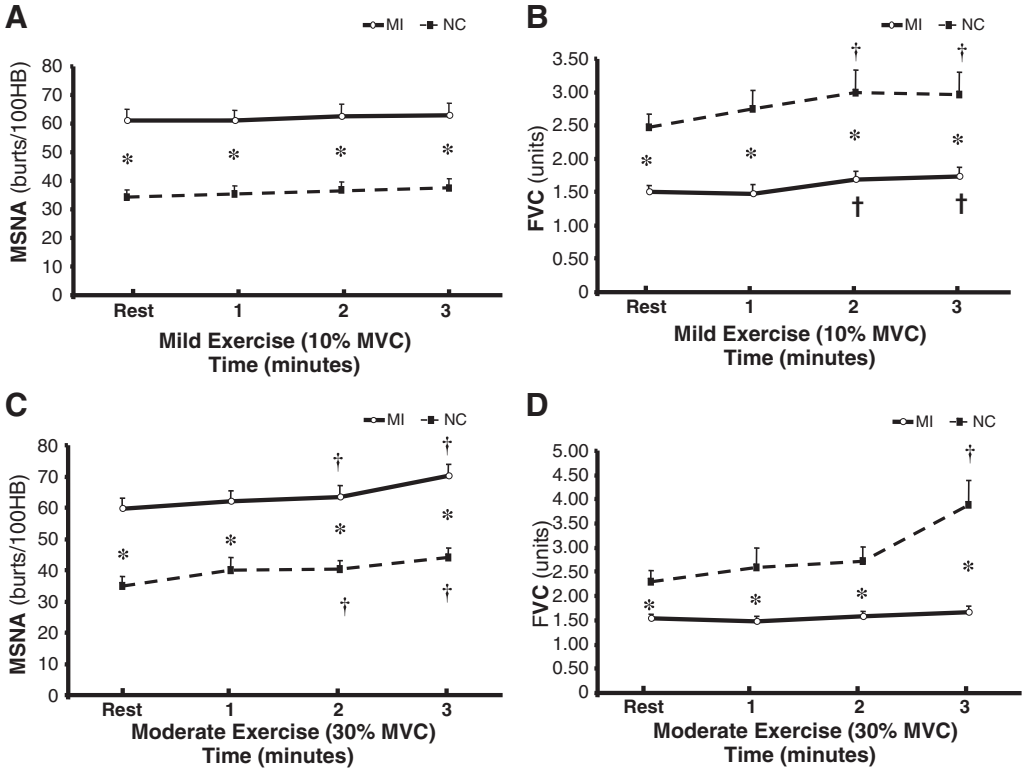

Fig. 1. Muscle sympathetic nerve activity (MSNA, bursts/100HB) and forearm vascular conductance (FVC, units) responses during mild (10% MVC, Panel A and B, respectively) and moderate handgrip exercise (30% MVC, Panel C and D, respectively) in myocardial infarction group (MI) and normal control group (NC). Note that MSNA increased during exercise in both groups during moderate exercise, but their levels are higher in MI group. And, the FVC increased during exercise in the NC group but were not expressively changed in MI group. In addition, the levels of FVC in MI group were significantly lower than NC during all experimental protocols. † = Difference vs. rest. $P<0.05$ and * = Difference vs. group. $P<0.05$.

electrocardiogram. Baseline MSNA, FBF, mean BP and HR were recorded for 10 min and during exercise protocol, these variables were recorded for 3 min at rest and 3 min during handgrip exercise at 10% (mild) and 30% (moderate) of maximal voluntary contraction (MVC).

The comparisons of baseline data between groups were subjected to unpaired *t*-tests. Two-way ANOVA with repeated measures was used for between-group comparisons during exercise. When significance was found, Scheffé's post hoc comparison test was performed. $P<0.05$ was considered statistically significant.

There were no significant differences in the physical characteristics and the mean BP values between patients with MI and NC (Table 1). HR was lower in patients with MI when compared with NC (Table 1).

MSNA burst frequency significantly increased during mild and moderate exercise in both groups (Table 2). And, MSNA burst incidence (corrected by 100 heart beats) progressively increased in both groups during moderate exercise (Fig. 1C) but not during mild exercise (Fig. 1A). And, the absolute levels of MSNA burst frequency and burst incidence during mild and moderate exercise protocols were higher in patients with MI than in NC (Table 2 and Fig. 1A, and C). FBF and FVC significantly increased during mild and moderate exercise in NC, but not in patients with MI (Table 2 and Fig. 1B and D, respectively). In addition, the FBF and FVC levels during mild and moderate exercise were significantly lower in patients with MI (Table 2 and Fig. 1B and D, respectively). Mean BP significantly and similarly increased during mild and moderate exercise in patients with MI and NC (Table 2). HR significantly increased during mild and moderate exercise in both groups (Table 2). And, the HR was significantly lower in MI patients during both mild and moderate exercise protocols (Table 2).

Sympathetic nerve activity during exercise is coordinated by both central command and neural afferent reflexes arising from mechanoreceptors and metaboreceptors in the exercising muscle [5,6]. Our study extends this knowledge to patients with MI, since mild and moderate exercise that selectively activates mechanoreceptors and metaboreceptors significantly increased MSNA in our study. In addition, the present study provides evidence that MSNA responses to exercise are preserved in patients with MI. However, it should be emphasized that the levels of MSNA are substantially augmented in patients with MI at rest and during mild and moderate handgrip exercise. In addition, this sympathetic activation occurred despite of beta-blocker treatment, which has been shown to significantly decrease MSNA [8]. Another interesting observation in our study is the blunted muscle vasodilatation in patients with MI. The mechanisms involved in the reduced muscle vasodilatory responses during mild and moderate exercise in patients with MI are out the scope of the present study. However, it is possible to think that the augmented sympathetic nerve activity restrains endothelial-mediated vasodilation. In fact, in a previous study, we found that intra-arterial infusion of phentolamine significantly increased forearm blood flow responses during exercise in heart failure patients [9]. However, we cannot rule out that the blunted vasodilatory response in patients with MI is mediated by endothelial dysfunction. Accumulated evidence shows that nitric oxide (NO) plays an important role in muscle vasodilatation during exercise [10].

The present findings have clinical implications. Firstly, MI causes increase in sympathetic nerve activity at rest and during exercise. Secondly, MI provokes reduction in resting FBF and muscle vasodilatory responses during exercise. These neurovascular abnormalities may increase the risk for cardiovascular events in patients with MI.

In conclusion, the increased MSNA in response to mild and moderate exercise in patients with MI is a consequence of elevated resting MSNA. Patients suffering of MI have blunted muscle vasodilatory responses during exercise, which may be associated with increased sympathetic nerve activity, endothelial dysfunction or both. All together, these findings may explain the exercise intolerance and poor prognosis in patients with MI.

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