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Inspiratory Muscle Training Improves Blood Flow to Resting and Exercising Limbs in Patients With Chronic Heart Failure

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Objectives We tested the hypothesis that inspiratory muscle loading could result in exaggerated peripheral vasoconstriction in resting and exercising limbs and that inspiratory muscle training (IMT) could attenuate this effect in patients with chronic heart failure (CHF) and inspiratory muscle weakness.

Background Inspiratory muscle training improves functional capacity of patients with CHF, but the mechanisms of this effect are unknown.

Methods Eighteen patients with CHF and inspiratory muscle weakness (maximal inspiratory pressure <70% of predicted) and 10 healthy volunteers participated in the study. Inspiratory muscle loading was induced by the addition of inspiratory resistance of 60% of maximal inspiratory pressure, while blood flow to the resting calf (CBF) and exercising forearm (FBF) were measured by venous occlusion plethysmography. For the patients with CHF, blood flow measurements as well as ultrasound determination of diaphragm thickness were made before and after a 4-week program of IMT.

Results With inspiratory muscle loading, CHF patients demonstrated a more marked reduction in resting CBF and showed an attenuated rise in exercising FBF when compared with control subjects. After 4 weeks of IMT, CHF patients presented hypertrophy of the diaphragm and improved resting CBF and exercise FBF with inspiratory muscle loading.

Conclusions In patients with CHF and inspiratory muscle weakness, inspiratory muscle loading results in marked reduction of blood flow to resting and exercising limbs. Inspiratory muscle training improves limb blood flow under inspiratory loading in these patients. (J Am Coll Cardiol 2008;51:1663–71) © 2008 by the American College of Cardiology Foundation

Patients with chronic heart failure (CHF) might present decreased strength and endurance of the inspiratory muscles, which are currently recognized as factors implicated in their limited exercise response and quality of life as well as in their poor prognosis (1). We and others have shown that inspiratory muscle training (IMT) results in improvement in inspiratory muscle strength, functional capacity, ventilatory response to exercise, recovery oxygen uptake kinetics, and quality of life of patients with CHF and inspiratory muscle weakness (2–4). The mechanisms responsible for these effects, however, have not been elucidated.

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In a series of experiments conducted in healthy individuals, Dempsey et al. (5–7) demonstrated that fatiguing contractions of the inspiratory muscles and the consequent accumulation of metabolic products activate type IV phrenic afferents, resulting in pronounced increase in sympathetic vasoconstrictor activity (8–11). This mechanism, named inspiratory muscle metaboreflex, is thought to be particularly important during sustained heavy intensity exercise in healthy humans, where it modulates the competition for blood flow between the respiratory and working locomotor muscles (5,9–11). In accordance with this hypothesis, Miller et al. (12) demonstrated, in a canine model of pacing-induced

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Abbreviations and Acronyms

CBF = calf blood flow
CHF = chronic heart failure
CVR = calf vascular resistance
f_b = breathing frequency
FBF = forearm blood flow
FVR = forearm vascular resistance
HR = heart rate
IMT = inspiratory muscle training
MAP = mean arterial pressure
$P_{ET}Co_2$ = resting end-tidal partial pressure of carbon dioxide
PI_{max} = maximal static inspiratory pressure
Spo_2 = pulse % oxygen saturation

heart failure, that respiratory muscle metaboreflex is tonically active during submaximal exercise, persistently stealing blood from locomotor muscles. In humans, however, there is still no information concerning the activity of the inspiratory muscle metaboreflex in CHF.

Patients with CHF might present abnormalities of peripheral circulatory control and regulation that might contribute to their limited functional capacity (13,14). Accordingly, 1 potential explanation for the observed benefits of IMT could be an attenuated activity of the inspiratory muscle metaboreflex in patients with CHF, which would improve blood flow to peripheral muscles, as has been previously demonstrated in healthy individuals (15,16). Therefore, the present study was conducted to evaluate the effects of inspiratory loading on blood flow of resting and exercising limbs in patients with CHF and inspiratory muscle weakness. We also tested the hypothesis that selective IMT could attenuate peripheral vasoconstriction during inspiratory loading to resting and exercising limbs.

Methods

Patients and control subjects. Eighteen patients with a previous history of stable symptomatic heart failure due to left ventricular systolic dysfunction (left ventricular ejection fraction <40%), with inspiratory muscle weakness (maximal static inspiratory pressure [PI_{max}] <70% of the predicted [2]) and without history of pulmonary disease or angina, were recruited for the study. In our outpatient clinic of patients with CHF due to left ventricular systolic dysfunction, the prevalence of inspiratory muscle weakness is approximately 30% (2). A group of 10 individuals with normal medical history and physical examination as well as with normal resting and exercise electrocardiograms served as the control group. The protocol was approved by the Committee for Ethics in Research of the Hospital de Clínicas de Porto Alegre, and all individuals signed an informed consent form.

Protocol. Patients and control subjects came to the laboratory on separate days for maximal inspiratory pressure assessment, performance of cardiopulmonary exercise testing, ultrasonographic determination of diaphragm thickness, and induction inspiratory muscle metaboreflex to resting calf and to exercising forearm. The CHF patients also repeated maximal inspiratory pressure assessment, determination of diaphragm thickness, and induction inspiratory muscle metaboreflex to resting calf and to exercising forearm after 4 weeks of IMT. After training, all testing was performed with the same absolute inspiratory pressure used in the pre-training protocols.

Maximal inspiratory pressure. The PI_{max} was obtained with a pressure transducer (MVD-500 V.1.1 Microhard System, Globalmed, Porto Alegre, Brazil) connected to a system with 2 unidirectional valves (DHD Inspiratory Muscle Trainer, Chicago, Illinois), as previously described (2).

Cardiopulmonary exercise testing. The maximal incremental exercise test was performed on an electrically braked cycle ergometer (ER-900, Ergoline, Jaeger, Würzburg, Germany) with minute increments of 10 W for CHF patients and 15 W for healthy individuals. Subjects were instructed to maintain a pedaling frequency of 60 rpm. During the test, gas exchange variables were measured breath-by-breath by a previously validated system (Metalyzer 3B, CPX System, Cortex, Leipzig, Germany [17]). Heart rate (HR) was determined from a 12-lead electrocardiogram.

Diaphragm thickness. In patients and control subjects, B-mode ultrasonography (EnVisor C, Philips, Bothell, Washington) with a 12.0-MHz ultrasound probe (L12-3, Philips) was used to image the diaphragm in the zone of apposition, the vertical section that lies against the lateral portion of the right ribcage, with the method described by Wait et al. (18). Measurements were obtained at end-inspiration (T_{di}) and end-expiration (T_{de}) to calculate relative fractional thickness ($TF_{rel} = [T_{di} - T_{de}]/T_{di}$) at functional residual capacity.

Induction of the inspiratory muscle metaboreflex. To induce the inspiratory muscle metaboreflex, patients had a nose clip in place (PK Morgan, Ltd., Gillingham, United Kingdom) and breathed continuously into a 2-way Lloyd valve (Warren E. Collins, Inc., Braintree, Massachusetts) with low resistance (<1.5 cmH_2O at 3 l/s) connected to an inspiratory resistance obtained by a Threshold Inspiratory Muscle Trainer (Healthscan Products Inc., Cedar Grove, New Jersey) for loads of 7 to 41 cmH_2O or to a POWERbreathe Inspiratory Muscle Trainer (Southam, United Kingdom) for higher inspiratory pressures. Throughout each protocol, inspiratory pressure was continuously measured by a temperature-compensated and calibrated electronic pressure transducer (Silicon Pressor Sensor, MPX5050, Motorola, Denver, Colorado) and displayed on a computer monitor to the patient and investigator. The 10-point Borg scale (19) was used to access inspiratory effort at task failure.

Each patient and control subject participated in 2 experiments separated by a 30-min interval. Initially, inspiratory muscle metaboreflex was induced to evaluate blood flow responses to the resting calf and, subsequently, to the exercising forearm. For each of these experiments, individuals were assigned to inspiratory muscle loading (60% of PI_{max}) or to placebo inspiratory muscle loading (2% of

PI_{max}), in random order. Throughout protocols, all individuals maintained a breathing frequency (f_b) of 15 breaths/min^{-1} and duty cycle (T_I/T_{TOT}) of 0.7, by listening to a computer-generated audio signal with distinct inspiratory and expiratory tones. After baseline measures, individuals started breathing against the pre-defined inspiratory resistance of 60% of PI_{max} and continued until task failure, defined as a reduction of PI to <80% of the prescribed during 3 consecutive breaths (20). For the experiments with inspiratory resistance of 2% of PI_{max}, measures were interrupted at 3 min.

For the experiments on resting calf blood flow (CBF), hemodynamic measures were performed while the individuals were breathing against the inspiratory resistances. For the experiments on exercising forearm blood flow (FBF), hemodynamic measures were obtained after task failure, while individuals were performing the handgrip exercise protocol. Maximum voluntary contraction of the dominant forearm was initially measured with a hand dynamometer (Kratos, DLC, Cotia, Brazil). Forearm exercise consisted of repetitive maximal voluntary contractions on the hand dynamometer maintained for 10 s and released for 30 s until task failure or for 12 repetitions. Task failure was defined as the time at which the subject could no longer sustain the force within 5% of the target level for more than 2 s. During the relaxation phase, FBF was measured (21) and all patients were provided verbal encouragement throughout the isometric contraction in order to maintain handgrip force at target.

Ventilatory and hemodynamic measures. During each of the protocols, f_b, arterial oxygen saturation via finger oximetry (Spo_2), and resting end-tidal partial pressure of carbon dioxide ($P_{ET}Co_2$) were measured with oxycapnography (Takaoka Oxicap, São Paulo, Brazil). The HR was monitored by lead II of the electrocardiogram. Mean arterial blood pressure (MAP) was measured on the nondominant arm with an automated sphygmomanometer (Dinamap 1846 SX/P, Critikon, Tampa, Florida), at 1-min intervals. The CBF and FBF were measured by venous occlusion plethysmography (Hokanson, TL-400, Bellevue, Washington) as previously described (21,22). During forearm exercise, the venous cuff was inflated for 25 to 30 s for each flow measurement and then released during handgrip contraction (21). Calf vascular resistance (CVR) and forearm vascular resistance (FVR) were calculated as MAP/CBF and MAP/FVR (21,22).

IMT. The CHF patients received IMT for 30 min, 7 times/week, for 4 weeks with the Threshold Inspiratory Muscle Trainer (Healthscan Products Inc.) according to the protocol that has been previously shown to induce marked improvement in inspiratory muscle strength in 4 weeks (2).

Statistical analysis. Values are reported as mean ± SD. Two-tailed unpaired *t* tests were used to compare differences in patient characteristics and baseline values between the groups, whereas paired *t* tests were used to compare values before and after IMT in the CHF group. The CHF patients and control subjects had their mean values for respiratory variables, HR, and hemodynamic measures during each of the protocols compared across time with 2-way analysis of variance (ANOVA) with repeated measures on 2 factors (group and time). Two-way ANOVAs with repeated measures on both factors were used to compare these measures across time before versus after IMT in the CHF group. The Pearson correlation coefficient was used to evaluate associations between changes in variables. Significance was accepted when the probability was <0.05.

Results

Patients. Characteristics and baseline values for control subjects as well as characteristics and baseline values for CHF patients before and after IMT are shown in Table 1. Etiology of CHF was predominantly nonischemic, and patients had severe left ventricular systolic dysfunction as well as mild to moderate impairment in functional capacity. Sixty seven percent of the patients were taking digoxin, 89% were taking angiotensin-converting enzyme inhibitors, 56% were taking beta-blocker drugs, and 50% were taking diuretic drugs. There were no changes in medications throughout the experiments, and responses and adaptations of CHF patients were similar regardless of the use of beta-blocker drugs or diuretic drugs. The CHF patients were older, had lower peak HR and peak oxygen uptake (Vo_2 peak), and higher ventilation-carbon dioxide output (V_E/Vco_2) slope than healthy subjects. The PI_{max} was significantly lower in CHF patients, as by protocol, and they had significantly smaller diaphragm thickness. There were no differences between the groups for baseline MAP, HR, SpO_2, and $P_{ET}Co_2$. The CHF patients had lower baseline CBF and increased CVR. For CHF patients, the 4-week program of IMT resulted in significant increments in PI_{max} as well as in diaphragm thickness, with no changes in resting CBF. There was a significant correlation between the change in PI_{max} and the change in diaphragm thickness (T_{di}) after IMT ($r = 0.88$; $p < 0.001$).

Induction of the inspiratory muscle metaboreflex. For CHF patients and control subjects, Borg scale ratings for inspiratory effort at task failure during induction inspiratory muscle metaboreflex protocol were of 8.5 ± 0.5 for the inspiratory load at 60% of PI_{max} compared with 2.5 ± 0.6 ($p < 0.05$) for the inspiratory load at 2% of PI_{max}. The CHF patients reached task failure of inspiratory effort earlier for the 60% of PI_{max} inspiratory load (333 ± 117 s) than control subjects (410 ± 125 s, $p < 0.05$). After IMT, CHF patients increased time to task failure at 60% of PI_{max} by 30%.

Effects of inspiratory muscle metaboreflex activation on ventilatory and resting calf hemodynamic responses. Table 2 and Figure 1 present ventilatory and hemodynamic responses for CHF patients and control subjects as well as adaptations to IMT for CHF patients in the experiments on the induction of inspiratory muscle metaboreflex to the

Table 1 Clinical Characteristics and Results for Patients With CHF Before and After IMT and Baseline Values for Normal Control Subjects

	CHF_{pre} (n = 18)	CHF_{post} (n = 18)	Normal Control Subjects (n = 10)
General			
Male/female	12/6	—	8/2
Age, yrs	57 ± 11	—	38 ± 12*
Body mass index, kg/m^2	25 ± 1.5	—	22 ± 1
LVEF, %	24 ± 3	—	—
Ischemic/nonischemic	7/11	—	—
Peak exercise			
HR, beats/min	127 ± 8	—	188 ± 12*
Vo_2 peak, $ml/kg^{-1} \cdot min$	15 ± 2	—	38 ± 10*
V_E/VCo_2 slope	39 ± 2	—	30 ± 3
NYHA functional class	I–II (10) III–IV (8)	—	
Pulmonary function			
PI_{max}, cmH_2O	60 ± 8	103 ± 16†	153 ± 26*
PI_{max}, % predicted	60 ± 3	82 ± 8†	95 ± 12*
Diaphragm thickness			
Tdi, cm	0.42 ± 0.02	0.65 ± 0.14†	0.85 ± 0.1*
Tde, cm	0.25 ± 0.05	0.26 ± 0.06	0.26 ± 0.02
TF_{rel}	0.73 ± 0.55	1.68 ± 0.7†	2.1 ± 0.3*
Dif, cm	0.17 ± 0.12	0.38 ± 0.12†	0.54 ± 0.08*
Resting hemodynamics			
MAP, mm Hg	93.6 ± 19	91.6 ± 17	86 ± 11
CBF, ml/min · 100 ml	2.84 ± 1.6	2.95 ± 1	4.00 ± 2*
CVR, U	40 ± 17	34 ± 11	26 ± 10*
HR, beats/min	66 ± 11	68 ± 9	76 ± 12
Spo_2, %	97.4 ± 1.5	97.3 ± 1.4	98 ± 0.5
$P_{ET}Co_2$, mm Hg	33 ± 5	33 ± 4	32 ± 6
f_b, resp/min	15.3 ± 1.5	14.6 ± 1.3	15 ± 2

Values are presented as mean ± SD. Diaphragm thickness measurements were taken under 2 conditions: end-inspiration (T_{di}) and end-expiratory (T_{de}). *$p < 0.05$ by unpaired *t* test control versus CHF_{pre}; †$p < 0.05$ by paired *t* test CHF_{pre} versus CHF_{post}.

CBF = calf blood flow; CHF_{post} = chronic heart failure after inspiratory muscle training; CHF_{pre} = chronic heart failure before inspiratory muscle training; CVR = calf vascular resistance; Dif = difference between end-inspiration and end-expiration; f_b = breathing frequency; HR = heart rate; LVEF = echocardiographically determined left ventricular ejection fraction; MAP = mean arterial pressure; NYHA = New York Heart Association; $P_{ET}Co_2$ = resting end-tidal partial pressure of carbon dioxide; PI_{max} = maximal inspiratory pressure; Spo_2 = pulse % oxygen saturation; TF_{rel} = diaphragm thickness fractional at functional residual capacity; Vo_2peak = peak oxygen uptake; V_Epeak = peak minute ventilation; V_E/VCo_2 slope = relationship between change in ventilation and carbon dioxide output during incremental testing.

resting calf. Inspiratory loading at 60% of PI_{max} resulted in similar increments of HR, f_b, and MAP, with reduction in Spo_2 and maintenance of constant $P_{ET}Co_2$ in both groups. The IMT had no significant effects on these variables. The CBF decreased significantly more in CHF patients, and this effect was attenuated after IMT (Fig. 1). This was due to larger increment in CVR in CHF patients, which was also attenuated after IMT.

Effects of inspiratory muscle metaboreflex activation on ventilatory and exercising forearm hemodynamic responses. Time to fatigue during forearm exercise was reduced with inspiratory loading in control subjects (from 304 ± 132 s to 180 ± 60 s, p = 0.02) as well as in CHF patients (from 402 ± 112 s to 280 ± 151 s, p = 0.01). The IMT improved time to fatigue during forearm exercise with inspiratory loading (from 280 ± 151 s to 437 ± 77 s, p = 0.01) in CHF. Table 3 and Figure 2 present ventilatory and hemodynamic responses for CHF patients and control subjects as well as adaptations to IMT for CHF patients in the experiments on the induction of inspiratory muscle metaboreflex to the exercising forearm. Intermittent static handgrip exercise with inspiratory loading after 60% of PI_{max} resulted in similar reduction of HR, whereas $P_{ET}CO_2$ was stable (Table 3). The FBF increased during exercise in both groups, but CHF patients showed an attenuated rise, which was partially corrected after IMT (Fig. 2). In contrast, FVR response to exercise was increased in CHF patients but also improved after IMT (Fig. 2).

Discussion

The primary findings of the present study were as follows: 1) repeated voluntary efforts against a resistive inspiratory load to the point of task failure caused an exaggerated vasoconstriction of the resting calf in patients with CHF and inspiratory muscle weakness when compared with healthy control subjects; 2) prior fatigue of the inspiratory muscles reduces forearm hyperemic responses to handgrip exercise in patients with CHF and inspiratory muscle weakness; and 3) 4 weeks of IMT attenuates calf vasocon-

Table 2 Mean Group Data for Resting Calf Experiment During Respiratory Exercise at 2% of PI_{max} and 60% of PI_{max} in CHF Patients Before and After IMT and Normal Control Subjects

	Resting Calf			
	Baseline	1 min	2 min	End
2% PI_{max} HR (beats/min)				
CHF_{pre}	64 ± 8	65 ± 8	65 ± 8	66 ± 10
CHF_{post}	68 ± 9	68 ± 10	69 ± 9	69 ± 8
Control	72 ± 8	71 ± 8	73 ± 10	73 ± 9
f_b (resp/min)				
CHF_{pre}	15 ± 0.9	15 ± 2.3	15.1 ± 1.5	15.2 ± 2
CHF_{post}	15 ± 1.3	15 ± 2	14.6 ± 2	14.6 ± 1.8
Control	14.8 ± 2	13.3 ± 3	13.8 ± 2	14.7 ± 3
$P_{ET}Co_2$ (mm Hg)				
CHF_{pre}	33 ± 6	32 ± 5	32 ± 5	32 ± 6
CHF_{post}	33 ± 5	33 ± 5	32 ± 5	32 ± 5
Control	33 ± 4	32 ± 6	31 ± 6	31 ± 6
Spo_2 (%)				
CHF_{pre}	98 ± 1.5	97 ± 1.6	97.8 ± 1	97.8 ± 1.3
CHF_{post}	98 ± 1.5	97.4 ± 2	97.6 ± 1.6	97 ± 1.5
Control	98 ± 0.9	98 ± 0.9	97 ± 1	97 ± 2
60% PI_{max} HR (beats/min)				
CHF_{pre}	66 ± 11	70 ± 10	75 ± 12	89 ± 15*
CHF_{post}	68 ± 9	72 ± 8	73 ± 9	82 ± 10*
Control	76 ± 12	82 ± 9	88 ± 12	89 ± 13*
f_b (resp/min)				
CHF_{pre}	15 ± 1	14.8 ± 2.5	14.8 ± 1.6	15.5 ± 1.3
CHF_{post}	14.6 ± 1.3	14.7 ± 1.7	14.5 ± 2.4	15 ± 1.8
Control	15 ± 2	14.6 ± 4	14.8 ± 2	15.2 ± 2
$P_{ET}Co_2$ (mm Hg)				
CHF_{pre}	33 ± 5	31 ± 5	31 ± 4.5	33 ± 5
CHF_{post}	33.5 ± 4	32 ± 5	33 ± 6	33 ± 4
Control	32 ± 6	31 ± 6	32.2 ± 7	33 ± 7
Spo_2 (%)				
CHF_{pre}	98 ± 1.5	97 ± 1.5	98 ± 1	94 ± 3*
CHF_{post}	97.3 ± 1.4	97 ± 1.6	97 ± 2	95 ± 3
Control	98 ± 0.9	98 ± 0.9	96 ± 3	93 ± 4*

Values are presented as mean ± SD. Results of 2-way analysis of variance for repeated measures ($p < 0.05$): *time effect; group (CHF_{pre} vs. control), training status (CHF_{pre} vs. CHF_{post}), and interaction effects were not significant.

Abbreviations as in Table 1.

striction response to inspiratory loading and improves forearm hemodynamic responses to handgrip exercise after inspiratory muscle fatigue in patients with CHF and inspiratory muscle weakness. Overall, this study provides the first evidence of an abnormal activity of the inspiratory muscle metaboreflex in patients with CHF and inspiratory muscle weakness.

Inspiratory muscle loading and peripheral vasoconstriction in CHF. To evaluate the effects of inspiratory loading to the point of task failure on calf hemodynamic responses, we employed a protocol similar to that described by Sheel et al. (6). According to these authors, the fatigue trial would cause prolonged ischemia of the diaphragm, thus evoking the respiratory muscle metaboreflex and a consequent sympathetic mediated vasoconstriction in the resting limbs (6,7). In agreement with this concept, healthy subjects demonstrated a small reduction in CBF during loading condition (6,13,23). In contrast, CHF patients exhibited a distinct response, characterized by a premature and greater reduction in blood flow during the fatiguing trial, compatible with an abnormal activity of the inspiratory muscle metaboreflex.

The present data extend prior observations of Miller et al. (12) in a canine model of CHF by showing that the ability of inspiratory muscles to "steal" blood flow from locomotor muscles is overactive in animals with CHF. Our results are in agreement with the concept that impaired oxygen delivery to the diaphragm, along with augmented inspiratory muscle work in CHF, would favor the accumulation of local muscle metabolites, such as lactic acid, which activates type IV nerve endings (12), leading to an exaggerated sympathetic mediated vasoconstriction (5,6). Indeed, Mancini et al. (24) had previously shown that patients with CHF present respiratory muscle deoxygenation during maximal exercise on the cycle ergometer.

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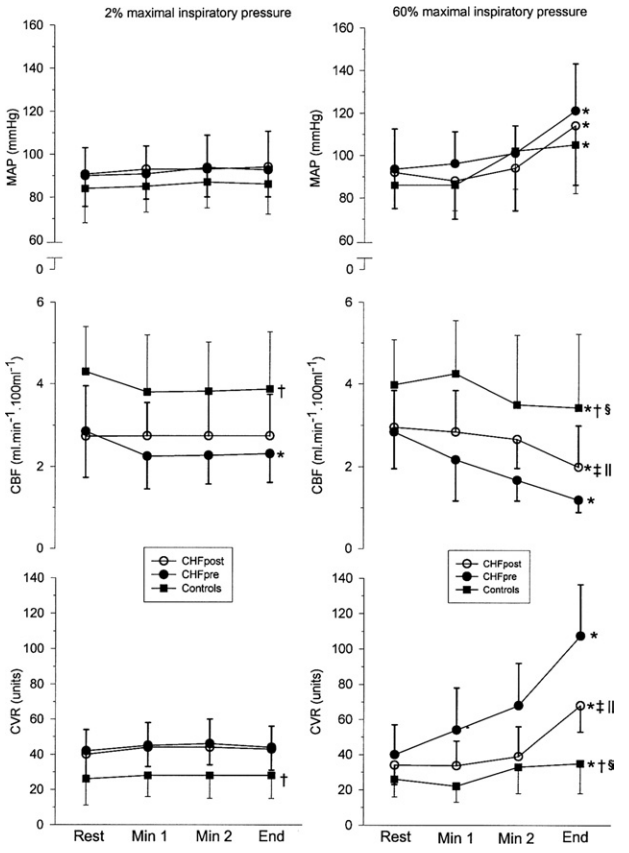

Figure 1 **Hemodynamic Responses of the Resting Calf to Inspiratory Loading**

Mean (±SD) responses mean arterial pressure (MAP) **(upper panels)**, calf blood flow (CBF) **(middle panels)**, and calf vascular resistance (CVR) **(lower panels)** obtained at rest, 1 min, 2 min, and at the end of inspiratory loading protocol, with "placebo loading" (**left panels** with 2% of maximal inspiratory pressure) and with inspiratory muscle loading (**right panels** with 60% of maximal inspiratory pressure). Results of 2-way analysis of variance for repeated measures ($p < 0.05$): *time effect; †group effect control versus CHF pre; ‡training status effect CHF pre versus CHF post; §interaction control versus CHF pre; ‖interaction CHF pre versus CHF post. CHF pre = chronic heart failure patients with inspiratory muscle weakness before inspiratory muscle training; CHF post = chronic heart failure patients with inspiratory muscle weakness after inspiratory muscle training; Control = healthy individuals.

Effect of inspiratory muscle loading on limb hemodynamic response to exercise. Previous work has shown that prior fatigue of the inspiratory muscles influences limb performance during subsequent exercise in healthy individuals (15). In agreement with these findings, time to fatigue during handgrip exercise was significantly reduced in healthy individuals and CHF patients after inspiratory loading when compared with the control task. Of note, however, forearm hemodynamic responses were similar after loaded and control conditions (Fig. 2) in healthy individuals but not in CHF patients. These findings suggest that a reduced time to fatigue after inspiratory muscle loading is less dependent on blood flow responses in healthy individuals than in patients with heart failure, and future studies should address the possible mechanisms responsible for these differential responses.

In patients with CHF and inspiratory muscle weakness, prior fatigue of the inspiratory muscles importantly modified forearm hyperemic response to handgrip exercise (Fig. 2). Specifically, FBF remained unchanged during the first minutes of handgrip exercise after inspiratory fatigue, whereas after the control task FBF increased immediately at the beginning of exercise. Thus, possibly inspiratory muscle metaboreflex activation after fatiguing trial and the consequent elevated sympathetic vasoconstrictor activity restricted forearm hyperemic responses to handgrip exercise in these patients (13).

Effects of IMT. In a prior report (2), we demonstrated that CHF patients with inspiratory muscle weakness presented major improvements in inspiratory muscle strength after the first 4 weeks of IMT. The present results confirm that this short training protocol is effective, as evidenced by the increment of 72% in the inspiratory muscle strength, but we also demonstrate that this protocol induces marked diaphragmatic hypertrophy, similar to that previously found in healthy subjects (25). Moreover, there was a significant correlation between the change in inspiratory muscle strength and the change in diaphragmatic thickness after IMT.

The IMT importantly increased the ventilatory load required to elicit the inspiratory muscle metaboreflex mediated peripheral vasoconstriction in CHF patients, confirming our original hypothesis. These findings are quite similar of those reported by other investigators in healthy subjects (15,16) and underscore the notion that IMT might be associated with reduced accumulation of muscle metabolites during the fatiguing trial, which would explain the attenuated vasoconstriction observed. Moreover, IMT also improved FBF response to intermittent handgrip exercise, with improvement in limb performance in CHF patients, suggesting that inspiratory muscle fatigue is also important for blood flow response to exercise, which might be a determinant in exercise performance in CHF (26).

Study limitations. In a previous placebo-controlled clinical trial (2), we have shown the efficacy of IMT in improving functional capacity and quality of life of patients with CHF and inspiratory muscle weakness. In the present mechanistic study, we chose not to include a placebo group, because we had previously demonstrated that there is no placebo effect (2). With this simpler design, and adding a control group of healthy individuals, we showed that IMT attenuated inspiratory muscle metaboreflex and reduced the influence of diaphragmatic fatigue on peripheral blood flow of resting and exercising limbs in patients with CHF and inspiratory muscle weakness. We did not measure V_{O_2} peak after IMT, but in our previous study we have shown that there is a significant correlation between the improvement in PI_{max} and the improvement in V_{O_2} peak after IMT in this patient population (2). However, these findings cannot be

Table 3 Mean Group Data for the Forearm Exercise Experiment During Respiratory Exercise at 2% of PI_{max} and 60% of PI_{max} in CHF Patients Before and After IMT and Normal Control Subjects

	Forearm Exercise			
	End-Inspiratory Load	1 min	2 min	End
2% PI_{max} HR (beats/min)				
CHF_{pre}	66 ± 10	69 ± 14	68 ± 15	68 ± 15
CHF_{post}	69 ± 8	69 ± 14	66 ± 12	69 ± 13
Control	73 ± 9	84 ± 9	84 ± 10	81 ± 12
f_b (resp/min)				
CHF_{pre}	15 ± 1.6	16 ± 3	15 ± 2	17 ± 2
CHF_{post}	15 ± 2	15 ± 2	15 ± 2	17 ± 2
Control	14 ± 3	20 ± 6	18 ± 5	19 ± 5
$P_{ET}Co_2$ (mm Hg)				
CHF_{pre}	32 ± 6	31 ± 2	32 ± 2	31 ± 3
CHF_{post}	32 ± 5	30 ± 5	32 ± 5	34 ± 6
Control	30 ± 6	29 ± 6	31 ± 8	33 ± 5
Spo_2 (%)				
CHF_{pre}	98 ± 1.3	97 ± 2	96 ± 1.6	96 ± 1.5
CHF_{post}	98 ± 2	98 ± 1.5	97.4 ± 2.6	97 ± 2
Control	97 ± 1	97 ± 2	97 ± 1.6	97 ± 1
60% PI_{max} HR (beats/min)				
CHF_{pre}	89 ± 15	68 ± 10	70 ± 7	75 ± 9
CHF_{post}	88 ± 14	69 ± 9	72 ± 11	75 ± 16
Control	89 ± 11	77 ± 26	77 ± 25	84 ± 14
f_b (resp/min)				
CHF_{pre}	15.5 ± 1.3	16 ± 3	16 ± 4	15 ± 2
CHF_{post}	15 ± 1.8	16 ± 3	15 ± 1.5	16 ± 3
Control	15 ± 2	17 ± 4	19 ± 4	19 ± 6
$P_{ET}Co_2$ (mm Hg)				
CHF_{pre}	32 ± 5	31 ± 2	33 ± 3	34 ± 3
CHF_{post}	33 ± 4	30 ± 2	30 ± 7	31 ± 3
Normal	32 ± 6	30 ± 6	30 ± 7	31 ± 9
Spo_2 (%)				
CHF_{pre}	94 ± 3	97 ± 2	96 ± 2	96 ± 3
CHF_{post}	94 ± 3	95 ± 3	97 ± 2	96 ± 2
Control	93 ± 4	97 ± 2	98 ± 1	98 ± 1

Values are presented as mean ± SD. Results of 2-way analysis of variance for repeated measures ($p < 0.05$): time effect; group (CHF_{pre} vs. control), training status (CHF_{pre} vs. CHF_{post}), and interaction effects were not significant.

Abbreviations as in Table 1.

generalized to patients who do not have inspiratory muscle weakness, and future studies are needed to evaluate other patient populations. Likewise, because we studied the hemodynamic responses to forearm exercise, our findings might not necessarily explain the mechanisms responsible for the improvement in functional capacity that is dependent on large locomotor muscles. However, on the basis of experiments in healthy individuals (27), it is likely that the effects might be even more marked when maximal exercise is performed with large muscle groups.

Because individuals in the control group were significantly younger than CHF patients, it can be argued that age per se could be a potential confounding factor for the interpretation of the present results. Of note, however, a number of recent studies (28,29) have demonstrated that age does not affect FBF and forearm vascular conductance responses to steady-state dynamic handgrip exercise. Furthermore, as pointed out previously (30), when corrected by the higher baseline levels, older individuals have similar muscle sympathetic nerve activity responses to handgrip exercise as well as preserved sympathetic mediated vasoconstriction in the inactive limbs when compared with young subjects (31). Nevertheless, the effects of age on the respiratory muscle metaboreflex remain to be determined.

We did not evaluate muscle sympathetic nerve activity in our patients, but other investigators have demonstrated that exercise-induced diaphragmatic fatigue caused important peripheral vasoconstriction secondary to sympathetic activation (6,8). Finally, in our protocol for induction of inspiratory muscle metaboreflex we did not add CO_2 to inspiration, as has been done by others (16), but we found no significant $P_{ET}Co_2$ reduction. Acute severe

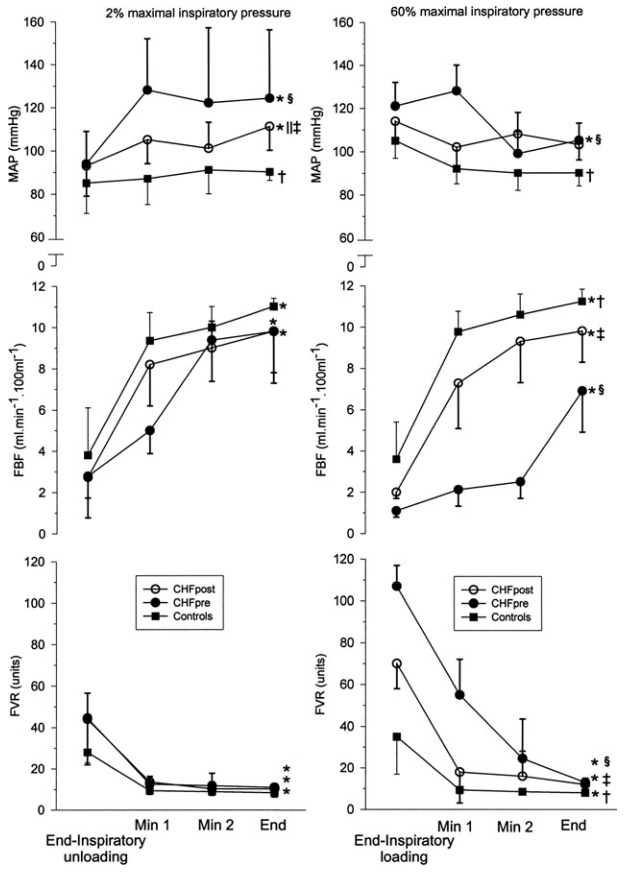

Figure 2 **Hemodynamic Responses to Forearm Exercise After Inspiratory Loading**

Mean (±SD) responses MAP **(upper panels)**, FBF **(middle panels)**, and FVR **(lower panels)** obtained at rest, minute 1, minute 2, and at the end of handgrip exercise after inspiratory loading protocol, with "placebo loading" (**left panels** with 2% of maximal inspiratory pressure) and with inspiratory muscle loading (**right panels** with 60% of maximal inspiratory pressure). Results of 2-way analysis of variance for repeated measures ($p < 0.05$): *time effect; †group effect control versus CHF pre; ‡training status effect CHF pre versus CHF post; §interaction control versus CHF pre; ‖interaction CHF pre versus CHF post. Abbreviations as in Figure 1.

hyperventilation elicits a decrease in CVR and an increase in blood flow (32,33). However, McConnell and Lomax (15) suggested that mild hypocapnia (approximately 30 mm Hg) of the magnitude observed after our inspiratory loading task fails to elicit changes in either FVR or blood pressure.

Conclusions

In patients with CHF and inspiratory muscle weakness, the induction of inspiratory muscle fatigue results in marked reduction of blood flow to resting and exercising limbs. Inspiratory muscle training improves limb blood flow under inspiratory loading in these patients, with possible consequences to exercise performance.

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