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ORIGINAL PAPER

# Effect of Exercise Training on 24-Hour Ambulatory Blood Pressure Monitoring in Heart Failure Patients

*The effect of exercise training (ET) on 24-hour ambulatory blood pressure monitoring (ABPM) in heart failure (HF) patients is unknown. The aim of this study was to evaluate the 24-hour ABPM response to ET in HF patients. Twelve HF patients (32%±5% ejection fraction, New York Heart Association class 1.6±0.6, oxygen uptake ($VO_2$)=20±3 mL/kg/min, 52±9 years, body mass index = 22±3 kg/m$^2$) and 15 controls (sedentary healthy subjects, $VO_2$=30±5 mL/kg/min, 25±8 years, body mass index = 20±5 kg/m$^2$) underwent ET in a 20±1° controlled temperature room for 2 months (3 ×/wk in the afternoon, from 80% to 90% of the ventilatory threshold). Twenty-four-hour ABPM was measured before and 2 days after the last exercise season. Despite the fact that exercise training in HF patients was associated with significant improvements in peak oxygen consumption ($pVO_2$) (20±3–24.3±5 mL/kg/min, P=.016), there were no significant changes in systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate (HR). On the other hand, controls decreased 24-hour mean SBP (117±8–115±9 mm Hg, P=.019) and 24-hour mean DBP (73±6–71± 5 mm Hg, P=.016), mainly at nighttime SBP (107±8–103±9, P=.0004) and DBP (63±5–59±5 mm Hg, P<.0001) after $pVO_2$ improvement (33±5–40±3 mL/kg/min, P<.001). No changes in HR were found in controls. Twenty-four-hour blood pressure did not change with ET in HF patients. Controls had their blood pressures decreased mainly in the nighttime.*
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Heart failure (HF) can be considered the last stage of heart disease and a significant cause of mortality and morbidity in the world.[1] It is associated with a persistent activation of a circadian neurohormonal system and endothelial dysfunction.[2] This low endothelial function, as exercise capacity, is associated with an increase in mortality.[3,4] Aerobic exercise training (ET) is a well-established nonpharmacological method to increase exercise capacity and to improve endothelial function (vasodilatation) in HF patients.[5]

Patients can experience fatigue and dizziness that may relate to periods of hypotension exacerbated by vasodilator drug therapy. The 24-hour ambulatory blood pressure monitoring (ABPM) in HF may help to evaluate time-dependent pharmacodynamic drug effects, titrate angiotensin-converting enzyme (ACE) inhibitors and other drugs to optimization.[6]

Auscultation of the Korotkoff sounds is fraught with potential sources of error.[7] Arterial blood pressure (BP) has a daily variation characterized by reductions during sleep, a rapid rise upon awakening, and increased variability during the awake period.[8] The timing and amplitude of the rhythm of BP is influenced by intrinsic and extrinsic factors, such as neurohormonal regulation, ET, and dietary sodium.[8] The 24-hour ABPM is reproducible and allows registration of the BP in subjects engaged in their usual activities, avoiding the white-coat effect.[7] We hypothesized that ET could decrease 24-hour BP in HF patients and in healthy subjects by the attenuation of the sympathetic system. The aim of this study was to evaluate the effect of ET on 24-hour BP in sedentary HF patients.

## Methods

**Population.** Nineteen sedentary HF patients were recruited from a Heart Failure Ambulatory (March 2006–2007). Twelve HF patients (10 male and 2 female) 52±9 years with left ventricle ejection fraction 32%±5% (echocardiography), New York Heart Association (NYHA) functional class 1.7±0.7, peak oxygen consumption ($pVO_2$) 20±3 mL/kg/min, body mass index (BMI) 22±3 kg/m$^2$ (Table I) completed the protocol.

All patients were in stable clinical condition without changes on medication and free from any kind of ET for 3 months. Patients with atrial fibrillation, pacemaker, noncardiovascular functional limitations such as osteoarthritis, and chronic obstructive pulmonary disease (proven by baseline pulmonary function test) were excluded from the study.





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**Table I.** Characteristics of Patients With Heart Failure

| Characteristics of the Heart Failure Patients | Number of Patients (%), Dose (mg/d) |
|---|---|
| Etiology | |
| Ischemic | 42 |
| Idiopathic dilated cardiomyopathy | 42 |
| Hypertensive | 16 |
| New York Heart Association functional class | |
| I | 42 |
| II | 42 |
| III | 16 |
| Current medications | |
| Diuretics | 84 |
| Furosemide | 67, 33±10 |
| Hydrochlorothiazide | 17, 25±0 |
| ACE inhibitor (enalapril) | 75, 37±18 |
| Angiotensin II AT1 receptor antagonists (losartan) | 16, 100±0 |
| β-Adrenergic receptor blocker (carvedilol) | 100, 52±32 |
| Spironolactone | 33, 25±0 |
| Digoxin | 41, 0.25±0 |
| Isosorbide 5-mononitrate | 16, 120±0 |

Abbreviation: ACE, angiotensin-converting enzyme.

Fifteen sedentary healthy subjects without cardiovascular risk factors (13 male and 12 female), 25±8 years, BMI 20±5 kg/m$^2$, $pVO_2$ 33±5 mL/kg/min completed the exercise training protocol as a control. An ethical committee approved this protocol and all patients provided informed consent before participation.

**Study Design.** This clinical trial was designed to evaluate the 24 hour BP change after ET in HF patients. All patients and controls first underwent 24-hour ABPM. The day after, when 24-hour ABPM was over, subjects underwent a cardiopulmonary exercise test to determine the exercise capacity and the ventilatory threshold. Two days after the cardiopulmonary exercise test, all subjects began the ET protocol. In the second day after the last exercise session, HF patients and controls performed a 24-hour ABPM. When ABPM was over a cardiopulmonary exercise test was performed to evaluate the effect of ET.

**Cardiopulmonary Exercise Test Protocol.** HF patients and controls underwent a cardiopulmonary exercise test (Naughton and Balke 4.0 protocol, respectively) on a programmable treadmill in a temperature-controlled room (21–23°C) with standard 12 lead continuous electrocardiogram monitoring and BP monitoring by auscultation method. Minute ventilation (VE, L), oxygen uptake ($VO_2$, STPD), carbon dioxide output ($VCO_2$, STPD) and other cardiopulmonary variables were acquired breath-by-breath by a computerized system. All exercise tests were performed in the afternoon. The V-slope method was used to calculate ventilatory threshold.

**Exercise Training Protocol.** All HF patients and controls performed the ET protocol in a 20±1°C controlled temperature room during 2 months, 3 ×/wk in the afternoon. Supervised exercise sessions consisted of 5 minutes of warm up stretching exercises, 30 minutes of exercise training on a treadmill, and 5 minutes of cool down exercises. All subjects trained from 80% to 90% of the ventilatory threshold, calculated by the cardiopulmonary exercise test.

**Ambulatory BP.** The 24-hour ambulatory BP was measured on the nondominant arm using an oscillometric ambulatory BP device. The device was set to take readings every 15 minutes for daytime and 20 minutes for nighttime, a repeated measurement was obtained if the first one was unsuccessful. The analysis software automatically edited values outside of normal physiologic ranges. Spurious readings, due to factors such as movement artifact, were also automatically edited by the software. Awake and asleep periods were determined by the patient before the exam. All subjects were instructed to maintain their usual activities and medications. The ambulatory BP monitor was set a day before each maximal cardiopulmonary exercise test. Data were only accepted if at least 75% of the measurements were taken successfully.

**Current Medication Intake.** All HF patients were using β-blocker (carvedilol) associated to ACE inhibitors (enalapril) or angiotensin II AT1 receptor antagonists (losartan). The medication profile is in Table I. Patients took β-blockers, ACE inhibitors, Angiotensin II AT1 receptor antagonists, and isosorbide 5-mononitrate 2 times in the day—half of the daily dose in the morning (9:00 AM) and the other half at night (9:00 PM). Diuretics, digoxin, and spironolactone were taken in the morning (9:00 AM).

**Statistical Analysis.** The descriptive analysis was presented as mean and standard deviation. Paired Student's *t* test was used to compare means before and after ET for each group. Data were analyzed using Statistical Package for Social Sciences (SPSS) for Windows, v 11.5 (SPSS Inc, Chicago, IL). Statistical significance was $P<.05$.

## Results

Nineteen HF patients were recruited, 12 satisfactorily completed the protocol (25±1 sessions). Six patients gave up the exercise training for personal reasons and 1 was excluded due to atrial fibrillation. The control increased $pVO_2$ (33±5–40±3 mL/kg/min, $P<.001$) and the HF group (20±3–24.3±5 mL/kg/min, $P=.016$), showing the efficiency of our ET protocol.

The 24-hour ABPM method and ET protocol were well tolerated by all subjects. There were no significant changes

in HF patients' 24-hour mean systolic blood pressure (SBP), 24-hour mean diastolic blood pressure (DBP) (Figure 1), and heart rate (HR) (Table II). On the other hand, controls decreased 24-hour mean SBP (117±8–115±9 mm Hg, *P*=.019) and 24-hour mean DBP (73±6–71±5 mm Hg, *P*=.016) (Figure 1), mainly with nighttime SBP (107±8–103±9 mm Hg, *P*=.0004) and DBP (63±5–59±5 mm Hg, *P*<.0001) (Figure 2). No changes in HR were found in controls (Table III).

## Discussion

We hypothesized that ET could decrease 24-hour BP in HF patients and in healthy subjects by the attenuation of the sympathetic system. Our data showed that our ET protocol did not change HF 24-hour BP, but in normal subjects it decreased mainly at night.

Physical exercise is an important well-established technique in HF patients to increase $pVO_2$ and to restore quality of life.[9] ET is considered to augment blood flow and shear stress, resulting in increased nitric oxide (NO) production and upregulation of endothelial NO synthase activity.[10] Short periods of regular localized exercise training has been shown to restore flow-dependent dilatation of the systemic arteries of patients with chronic HF[11] but, in healthy subjects it remains uncertain. The shear-stress-mediated effects of exercise and consequent production and bioactivity of NO differ qualitatively and quantitatively according to the exercise involved.[12] Higashi et al.[13] concluded that BP, HR and forearm blood flow were not affected by 12 months of aerobic ET in normal subjects. However, Clarkson et al.[14] found that flow-mediated vasodilatation improved with ET without effects on BP or HR. In both studies, BP was measured only once in the daytime. These data agree partially with our study because no change in daytime BP in normal controls was found. It seems that, even if endothelium-dependent dilatation could improve, it is not enough to decrease BP in the daytime. The effect of ET on 24-hour BP and circadian flow-dependent dilatation is unknown. Our study suggests that the BP in the nighttime after an ET protocol is decreased, probably because at this period the endothelium-dependent dilatation can influence BP, mediated by neurohormonal circadian attenuation and a better improvement on dilatation.[2]

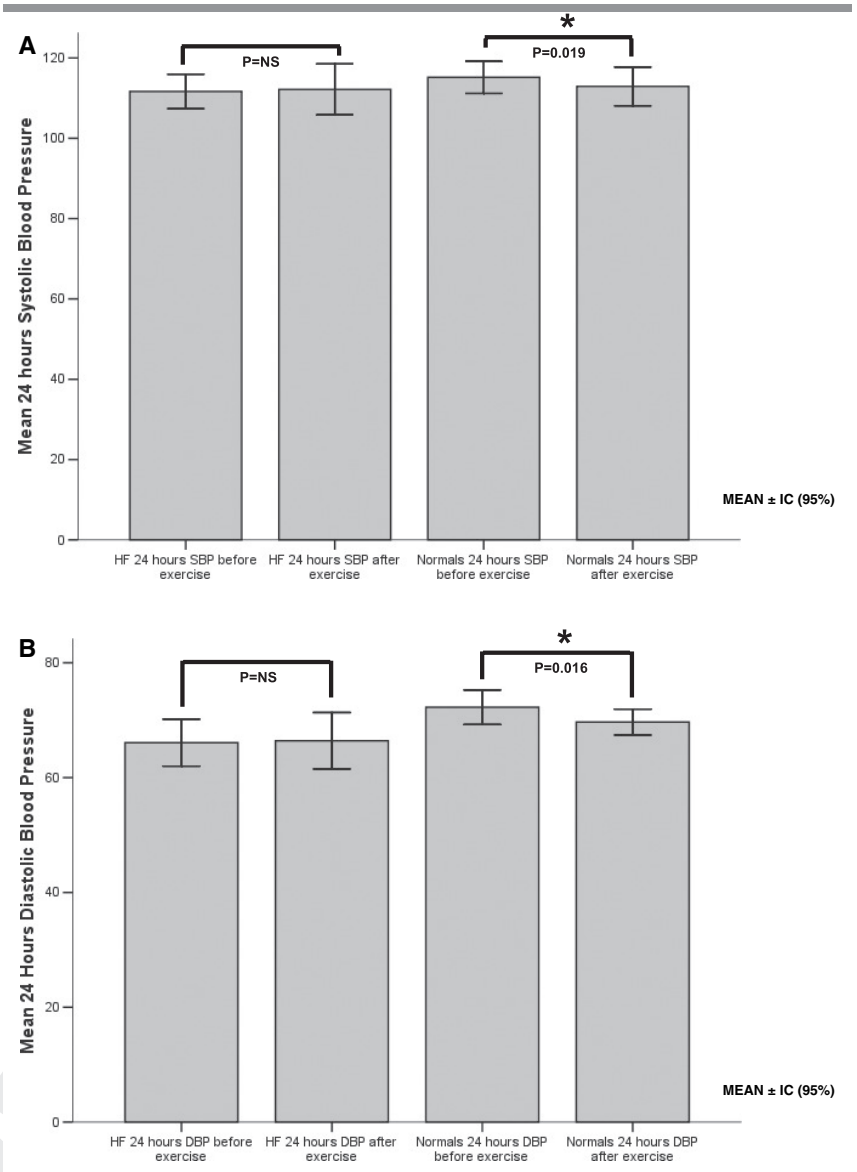


**Figure 1. (A) Mean 24-hour systolic blood pressure (SBP) of heart failure patients and controls before and after exercise training. (B) Mean 24-hour diastolic blood pressure (DBP) of heart failure patients and normals before and after exercise training (ET). IC indicates; NS, not significant.**

The HF syndrome is characterized by a persistent activation of the neurohormonal system and by impairment of endothelial function that can be explained by a reduction in NO production, increased NO degradation and increased endothelin-1 production.[15] This impairment is described to have a circadian variation in idiopathic HF. Patients with NYHA functional classes I and II had lowest flow-mediated vasodilatation in the morning and highest at night, whereas the vasodilatation in severe HF was depressed throughout the day.[2] Moreover, endothelium-mediated vasodilation represents an independent predictor of cardiac death and hospitalization in HF patients.[16]

Treatment with ACE inhibitors, angiotensin, aldosterone, and endothelin-antagonists has been shown to

**Table II.** Twenty-Four-Hour Ambulatory Blood Pressure Measurement Values Before and After Exercise Training Protocol for Heart Failure Patients

| | Before Exercise Training | After Exercise Training | *P* Value | IC (95%) |
|---|---|---|---|---|
| 24-Hour SBP | 111±6 | 112±10 | .74 | −3.768–2.768 |
| 24-Hour DBP | 66±6 | 66±7 | .81 | −3.402–2.736 |
| 24-Hour HR | 68±6 | 67±7 | .35 | −1.985–5.151 |
| Daytime SBP | 114±10 | 113±11 | .37 | −4.241–6.908 |
| Daytime DBP | 70±10 | 68±9 | .56 | −4.349–7.516 |
| Daytime HR | 70±10 | 68±8 | .31 | −2.006–5.673 |
| Nighttime SBP | 108±11 | 109±12 | .57 | −6.029–3.529 |
| Nighttime DBP | 62±8 | 62±10 | .97 | −5.464–5.297 |
| Nighttime HR | 63±5 | 63±7 | .92 | −2.083–1.916 |

Abbreviations: DBP, diastolic blood pressure; HR, heart rate; IC,; SBP, systolic blood pressure.

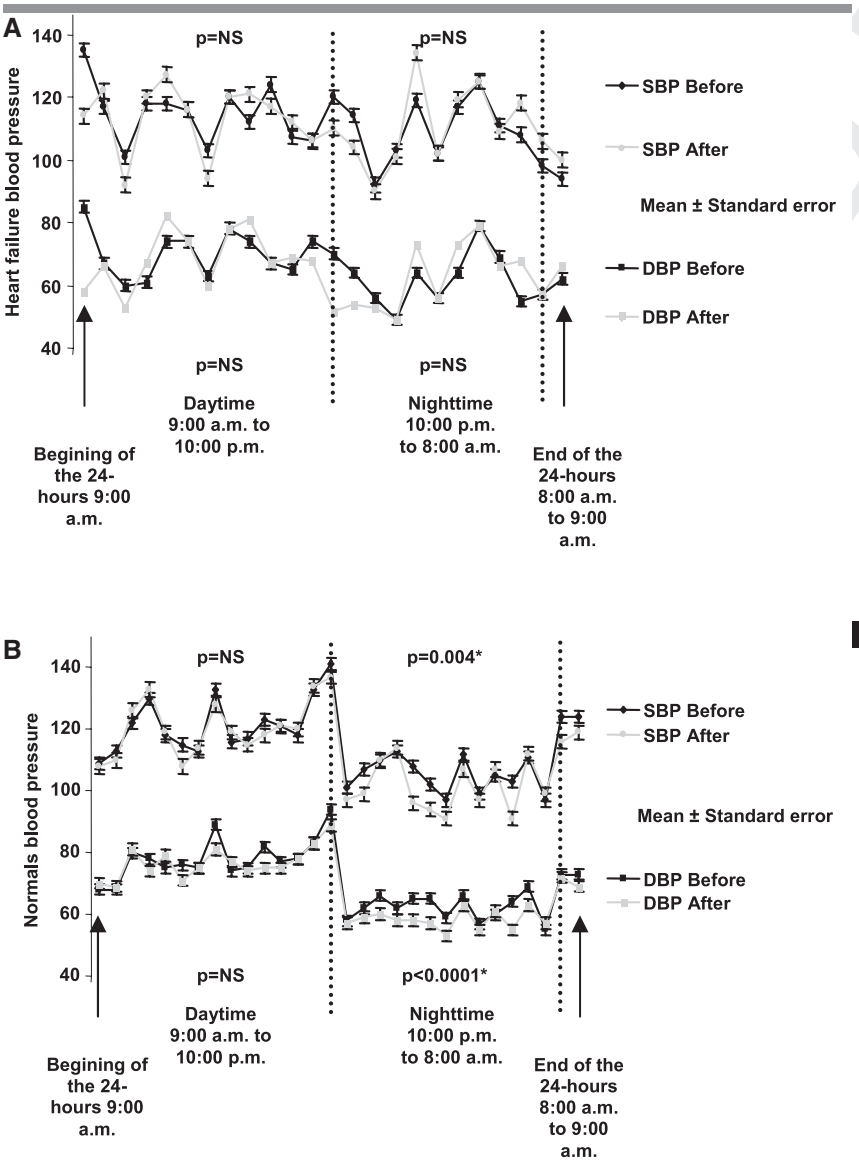


**Figure 2. (A) Hourly average of systolic blood pressure (SBP) and diastolic blood pressure (DBP) over the daytime and nighttime to heart failure patients before and after exercise training. (B) Hourly average of SBP and DBP over the daytime and nighttime to normals before and after exercise training. NS indicates not significant.**

beneficially modulate endothelial dysfunction in HF.[17] These current medications have a vasodilator effect such as others commonly used like phosphodiesterase type 5 inhibitor (sildenafil) that can provide a decrease on BP.[18] That is why the 24-hour ABPM is important to evaluate time-dependent pharmacodynamic drug effects, such as peak and end-of-dose phenomena, tolerance, rebound, titrate ACE inhibitors, and other drugs to highest-tolerated doses and correlate circadian BP profiles with symptoms.

Regular ET in HF patients can also partially restore the endothelial function (vasodilatation).[19,20] Despite this, no BP changes were mentioned before. Fraga et al.[21] studied the influence of ET on sympathetic nerve activity and vascular resistance in HF patients. They found that, even treated with carvedilol, the endothelial function and the sympathetic nerve activity improved, but BP and HR did not. This result agrees with our study. The daytime BP, as nighttime and 24-hour BP mean did not change after ET in HF patients. It seems that the improvement in the endothelial function by the ET is not significant to decrease BP in the daytime, nighttime, and the 24-hour mean.

Differently from HF, in hypertensive patients, ET plays a different hole in BP. Studies have been shown that ET is a powerful nonpharmacological strategy to reduce BP levels in never-treated[22] and treated hypertensive patients.[23]

Depressed endothelial function is more amenable to improvement by exercise than is a "normal" endothelial function in the young and healthy, who might need a higher intensity or volume of exercise training for benefit to be apparent. Despite this, BP did not change probably because our HF patients had current medication intake optimized, reflected by low basal 24-hour BP.

## Study limitations

This study is limited by the number of patients and the difference of age between control and HF groups, so it is

difficult to make generalizations. We did not evaluate the endothelial dysfunction before and after ET to correlate with BP changes. Sleep-Wake Cycle of the control and HF groups were not evaluated, but it could have affected our results.

## Conclusion

In HF patients, ET did not change 24-hour BP, but it decreased in healthy subjects, mainly at night.

**Disclosure:** *This study was supported by* 11 *CAPES.*

**Table III.** Twenty-Four-Hours Ambulatory Blood Pressure Measurement Values Before and After Exercise Training Protocol for Controls

| | Before Exercise Training | After Exercise Training | *P* Value | IC (95%) |
|---|---|---|---|---|
| 24-Hour SBP | 117±8 | 115±9 | .019[a] | 0.409–3.857 |
| 24-Hour DBP | 73±6 | 71±5 | .016[a] | 0.512–4.154 |
| 24-Hour HR | 80±6 | 79±7 | .81 | –2.639–3.305 |
| Daytime SBP | 121±9 | 120±9 | .37 | –1.074–2.674 |
| Daytime DBP | 78±7 | 76±5 | .15 | –0.616–3.416 |
| Daytime HR | 84±7 | 83±8 | .54 | –2.312–4.179 |
| Nighttime SBP | 107±8 | 103±9 | .004[a] | 1.606–6.926 |
| Nighttime DBP | 63±5 | 59±5 | *P*<.0001[a] | 2.009–5.590 |
| Nighttime HR | 70±5 | 71±6 | .30 | –5.238–1.772 |

Abbreviations: DBP, diastolic blood pressure; HR, Heart rate; IC,; SBP, systolic blood pressure. [a]Significant values (<.05).

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