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# Lack of Benefits of Endurance Training in Patients with Chronic Heart Failure: Role of Asymptomatic Peripheral Artery Disease

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## Abstract

**Purpose:** To evaluate the impact of asymptomatic peripheral artery disease (PAD) on exercise recovery in patients with heart failure (HF).

**Methods:** The study enrolled 204 HF patients in stable conditions, mean age 72 ± 12 years, M/F 138/66, consecutively admitted to our cardiac rehabilitation unit. Asymptomatic PAD was assessed by ankle/brachial index (ABI). Subjects with history of symptomatic PAD were excluded from the study. Exercise tolerance was evaluated by six minute walking test (6mwt). At admission patients were divided into three group according to their ABI index (ABI >0.9; ABI 0.6-0.9; ABI <0.6). All patients underwent an 8-weeks program of aerobic exercise training at 60-70% of heart rate reserve.

**Results:** Overall 52% of patients had ABI<0.9. At baseline patients with ABI <0.6 were older, had a higher rate of hypertension, diabetes, atrial fibrillation and a lower ejection fraction (EF) the other two groups. ABI resulted significantly related to EF, and it was inversely related to creatinine levels. After exercise training patients with ABI <0.6 and ABI 0.6-0.9 had a significantly lower recovery of exercise capacity (25.7% and 31.6% respectively) than patients with ABI >0.9 (41.9%). In a multivariate logistic regression model, including several covariates, asymptomatic PAD predicted a reduced performance at 6MWT in the overall population (adjusted OR 1.82; 95% CI 1.66-2.11; p=0.03).

**Conclusions:** Asymptomatic PAD is a marker of advanced HF and reduced physical performance. HF patients with asymptomatic PAD have lower functional recovery than subjects without asymptomatic PAD after exercise training. Asymptomatic PAD seems to be related to lack of benefit of exercise training in HF patients and a marker of frailty of these patients.

**Keywords:** Peripheral artery disease; Chronic heart failure

## Introduction

Exercise training has been established as an adjuvant therapy in patients with heart failure (HF) due its broad spectrum of effects including improvement of exercise tolerance, quality of life and survival [1,2]. However, some HF patients show limited improvement in exercise capacity after performing exercise training programs. This is an important point because lack of benefit to exercise training seems to be related to a poorer clinical outcome [3]. Despite some possible causes have been recently elucidated [4,5], mechanisms underlying the so called resistance to exercise training remain largely unknown.

Peripheral arterial disease (PAD) is a manifestation of systemic atherosclerosis and predicts adverse cardiovascular outcomes also in patients with HF [6]. The association of PAD with lower exercise capacity and lack of benefit to exercise training in HF subjects has been recently demonstrated in retrospective studies [6,7]. However most patients with PAD do not have classic intermittent claudication symptoms either because of their asymptomatic or because they have exertional leg symptoms other than intermittent claudication such as pain that does not cause the patient to stop walking or pain in different sites that not resolve early after rest [8]. Epidemiological studies have found that asymptomatic PAD is three to four times more common than symptomatic types in the general population [9,10]. Moreover PAD often coexists with HF [7] and can be masked by symptoms of HF such as reduced exercise tolerance. Studies now have demonstrated that PAD confers a markedly heightened risk of cardiovascular morbidity and mortality irrespective of the presence of claudication. The presence of asymptomatic PAD can be readily identified by the ankle-brachial index (ABI), a simple test comparing systolic blood pressure measured in the arm and in the ankle by Doppler [11]. The rate of asymptomatic PAD among HF patients is unknown. Moreover it is possible that PAD affects exercise tolerance in HF subjects beyond the presence of exertional pain.

In this study we hypothesized that asymptomatic PAD affects exercise tolerance and exercise recovery after exercise training, in patients with CHF undergoing cardiac rehabilitation.

## Methods

### Population

We prospectively studied 204 consecutive patients, mean age 72 ± 12 years, M/F 138/66, NYHA class II/III, referred to our cardiac rehabilitation centre between November 2009 and May 2010. Included in the study were those with established diagnosis of HF (history of HF at least 6 months), left ventricular ejection fraction (LVEF) <40%, stable clinical conditions without cardiac decompensation in the last two months. Exclusion criteria were inability to exercise, history of claudication, clinical instability, ventricular arrhythmias, severe aortic stenosis, congenital heart disease, hypertrophic or restrictive cardiomyopathy, acute coronary syndrome within the past 2 weeks, or patients with planned coronary revascularization or cardiac surgery, active myocarditis, severe COPD, and pericardial effusion.

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At entry baseline, anthropometric, clinical, morphological and biochemical variables were collected by the medical and non-medical staff. Body mass and stature were obtained at admission and measured using a standard physician's scale and meter and the BMI (kg/m$^2$) was calculated

### Asymptomatic PAD assessment

All patients underwent a functional evaluation of PAD at baseline. The diagnosis of PAD was confirmed at inclusion by an ABI <0.9 in at least one leg [12]. The ABI was calculated from Doppler derived measurements of the systolic pressure at the brachial and ankle arteries. The measurement of upper and lower extremities blood pressure was performed in a supine position after at least 10 min of rest. After placing the blood pressure cuffs over each brachial artery and above each malleolus, the cuff was inflated rapidly to 20 mmHg above the audible systolic pressure of each arm and deflated in 2 mmHg/s decrements. The arterial pulse was detected twice in both the dorsalis pedis and posterior tibial arteries and ABI was calculated as the ratio of the higher of the systolic blood pressures in the ankle (either the dorsalis pedis and posterior tibial artery) and the higher of the 2 brachial systolic blood pressures [13].

An ABI <0.9 was considered the threshold for confirming the diagnosis of lower-extremity PAD. Patients were divided into three groups according to the ABI value. ABI >0.9: subjects without PAD; ABI from 0.6 to 0.9: subject with mild-moderate disease; ABI <0.6: severe disease. The cut off of 0.6 for the lowest ABI category was chosen to maximize the number of patients in this group.

### Exercise tolerance evaluation

Exercise tolerance was evaluated by 6MWT and exercise test. 6MWT was performed at admission and before discharge. The test was performed according to the standardized procedure [14] and was supervised by a physical therapist. Patients were asked to walk at their own maximal pace a 100 m long hospital corridor with 10 meters signs on the floor. Every minute a standard phrase of encouragement was told. Patients were allowed to stop if signs or symptoms of significant distress occurred (dyspnoea, angina), through they were instructed to resume walking as soon as possible. Results of 6MWT were expressed as distance walked (metres). Functional recovery was defined as the percent increase of the distance walked at second 6MWT respect to the first 6MWT.

**Physical rehabilitation program:** It was performed according to the AHA guidelines [15]: Every exercise session included warm-up, cool-down and flexibility exercises and 30-60 minutes of aerobic exercise with cycling or treadmill. Patients underwent one exercise sessions every day for 6 days/week over an 8 weeks period. The intensity of exercise was planned at 60-70% of heart rate reserve.

**Statistical analysis:** Results are expressed as median ± standard deviation (SD) or percentages were appropriate. Chi-square tests for trend and ANOVA were used to compare performance on each functional measure between patients with ABI <0.60, patients with ABI 0.6 to 0.9, and participants with ABI >0.9. Multiple logistic regression and multiple linear regression analyses were performed to determine the independent relation between ABI and each functional measure, controlling for age, gender, current cigarette smoking, and comorbidities. The difference of distance walked at 6MWT between baseline and the end of the exercise training program (Δ6MWT) was dichotomized according to its median value (79.4 m). We considered as having a good exercise recovery subjects with Δ6MWT over 79.4 meters and weak exercise recovery those with Δ6MWT below 79.4 meters.

A value of p <0.05 was considered significant. All analyses were performed using a commercially available statistical package (SPSS for Windows 12.0, Chicago, III).

## Results

Overall 107 (52.4%) patients had ABI <0.9 and 36 (17.6) had severe PAD with ABI <0.6. Baseline characters of the population study according to the ABI value are summarized in Table 1. The most common cause of HF was coronary artery disease followed by hypertension. Most of the patients were on beta-blockers, ACE-inhibitors or angiotensin receptor blockers, and medications were not altered throughout the study.

Patients with HF secondary to coronary artery disease had a lower ABI compared to HF with other causes. 36.2% of patient with ABI <0.9 and 23.6% of those with ABI >0.9 were in NYHA class III. Patients with ABI <0.6 were older and had the worst prognostic profile having lower EF, higher rate of comorbidities such as diabetes and atrial fibrillation, higher levels of creatinine and NT-proBNP than patients of the other two groups. ABI was directly related to ejection fraction (r=0.25; p=0.007) and inversely related to creatinine (r=-0.31; p 0.002).

The proportion of patients with NYHA class III was inversely

| Parameters | **ABI <0.6** N=36 | **ABI 0.6-0.9** N=71 | **ABI >0.9** N=97 |
|---|---|---|---|
| **Age, y** | 73 ± 13* | 71 ± 11 | 71 ± 14 |
| **M/F** | 23/13 | 44/27 | 71/26 |
| **NYHA class II/III** | 21/15 * | 48/23 | 75/22 |
| **Ethiology** | | | |
| **CAD** | 27 (75) | 49 (69) | 57 (59) |
| **Hypertension** | 4 (11) | 14 (20) | 28 (29) |
| **Valvular disease** | 4 (11) | 6 (8) | 12 (12) |
| **Dilated cardiomiopaty** | 1 (3) | 2 (3) | - |
| **BMI ( kg/m2)** | 29 ± 8 | 28 ± 4 | 27 ± 5 |
| **Resting heart rate, bpm** | 88 ± 7 | 76 ± 7 | 74 ± 8 |
| **Systolic BP, mmHg** | 108 ± 19 | 107 ± 21 | 113 ± 17 |
| **Diastolic BP, mmHg** | 82 ± 10 | 80 ± 14 | 80 ± 12 |
| **Echocardiography** | | | |
| **LVEF, %** | 27 ± 7* | 34 6 | 37 ± 9 |
| **LVDD, mm** | 63.1 ± 11 | 62.6 ± 8 | 58 ± 7 |
| **E/A ratio** | 1.4 ± 0.7 | 1.4 ± 0.8 | 1.6 ± 0.8 |
| **E deceleration time** | 171 ± 23 | 180 ± 17 | 181 ± 14 |
| **Comorbidities** | | | |
| **Hypertension** | 21 (58) | 43 (60) | 58 (59) |
| **Diabetes** | 16 (44) * | 25 (35) | 31 (28) |
| **Dislipidemia** | 22 (61 ) | 42 (59) | 59 (51) |
| **COPD** | 14 (38) | 27 (39) | 33 (34) |
| **Atrial fibrillation** | 15 (41 ) * | 18 (25) | 22 (23) |
| **History of smoke** | 24 (66) | 37 (52) | 47(48) |
| **Laboratory** | | | |
| **Creatinine, mg/dl** | 1.7 ± 0.2 * | 1.4 ± 0.2 | 1.3 ± 0.2 |
| **Hemoglobin, g/dl** | 10.4 ± 2 | 11.1 ± 4 | 11.7 ± 2 |
| **NT-proBNP** | 823.6 ± 31* | 432.3 ± 47 | 357 ± 38 |
| **Therapy** | | | |
| **Beta-blockers** | 29 (80) | 64 (90) | 81 (84) |
| **ACE-i/ARBs** | 32 (88) | 62 (87) | 88 (91) |
| **Diuretics** | 26 (72) | 58 (81) | 64 (66) |
| **Digoxin** | 11(30) | 20 (28) | 34 (35) |

*= p<0.05 ABI <0.6 vs. ABI >0.9

**Table 1:** Baseline characters of the population study according to the ABI value.

related to the ABI value ranging from 22.6% in the group with ABI >0.9 to 41.4% in the group with ABI <0.6. The proportion of female patients was similar in ABI <0.6 and ABI 0.6-0.9 (38.3% and 36.1% respectively) and was lower in the group with ABI >0.9.

Results of 6MWT at baseline and 8 weeks are summarized in Table 2. Baseline distance walked at 6MWT was significantly lower in the group with ABI <0.6 compared to patients with ABI >0.9. (254.3 ± 89 vs. 315.8 ± 72; p=0.0001). At the end of the exercise training program, overall distance walked at 6MWT increased significantly (+34.0%, p 0.0003). Patients with ABI <0.6 had the lowest a increase of distance walked at 6MWT after exercise training (+25.7%) compared to the other two groups (ABI 0.6-0.9=+31.6%; ABI >0.9=+41.9%).

The independent prediction power of asymptomatic PAD on exercise recovery was evaluated through a logistic regression analysis in which we included as covariates some confounding variables such as age, diabetes, atrial fibrillation, and gender and ejection fraction. After adjusting for these covariates the presence of asymptomatic PAD resulted significantly related to a lower functional recovery in the overall population (adjusted OR 1.82; 95% CI 1.66–2.11; p 0.03).

## Discussion

This study shows two main results. At first we found a very high prevalence of asymptomatic PAD in our population of HF patients, 52% of whom had ABI <0.9. We think that this very high prevalence is related to the characters of our patients who are elderly and with cardiovascular disease at an advanced stage. It has been demonstrated that the prevalence of ABI <0.9 is directly related to the patients age and to the stage of cardiac disease and ranges from 28% in subjects under 62 years to 52% in those over 81 years [16]. Our results are in agreement with those of Mourad et al. [17] who studied a population of 2146 patients at high cardiovascular risk and found that 41% of them had ABI<0.9. Conversely, previous studies, which found lower PAD rates (30%), were performed in lower risk subjects such as patients hospitalized for nonvascular diseases or cardiovascular outpatients followed by general practitioners [10,18]. Our data show that asymptomatic PAD is widely diffuse in HF patients and highlight the utility of ABI as screening tool in such population.

The second result, that is also the aim of this study, is the demonstration that asymptomatic PAD is associated to lower performance at 6MWT and to lower response after exercise training compared to patients without PAD in our population. The association between PAD and low exercise capacity in HF subjects has been recently described by several authors [6,7,19]. In a large population of non-institutionalized HF subjects, including those with and without claudication, Adesunloye et al., using a multivariate model and adjusting for multiple covariates, found that ABI<0.9 was independently associated to low exercise capacity [7]. In a post hoc analysis, Jones et al. [6] observed that the presence of PAD in HF subjects was related to limited functional benefit after exercise training as well as to higher mortality rate. While these studies included in the PAD-HF groups mostly patients with a clinical history of claudication, the prevalence of asymptomatic PAD among elderly HF patients and its impact on their exercise capacity remained until now underestimated. Our study is the first specifically focusing asymptomatic PAD on HF patients. We think that the importance of this condition arises from several observations: the prevalence of asymptomatic PAD in the general population is higher compared to intermittent claudication [10]; on the other hand it is well known that several subjects with PAD do not have classic intermittent claudication symptoms [20]. At least, PAD, long before the onset of claudication, is also associated with measures of impaired lower extremity functioning, such as lower walking velocity, as demonstrated by McDermott et al. [21,22].

| | Overall population | ABI >0.9 | ABI 0.6-0.9 | ABI <0.6 |
|---|---|---|---|---|
| Baseline | 282.3 ± 55 | 315.8 ± 72 | 278.4 ± 62 | 254.3 ± 89* |
| 8 weeks | 378.6 ± 67 | 447.8 ± 95 | 366.3 ± 84† | 329.5 ± 92* |

* = p<0.05 ABI <0.6 vs. ABI >0.9
† = p<0.05 ABI <0.6-0.9 vs. ABI >0.9

**Table 2:** Results of 6MWT in the overall population and in groups according to ABI values.

We observed that, among subjects with asymptomatic PAD, exercise capacity decline with the decrease of ABI value. Patients with severe disease (ABI <0.6) showed the highest degree of physical disability having significantly lower baseline 6MWT and lower increase of distance walked at 6MWT after training compared to those with ABI >0.9. It has been already demonstrated that both cardiovascular risk and degree of functional limitation widely change across the ABI spectrum. Our study confirms results of other studies in different population, in which subjects with PAD and ABI <0.6 were at higher risk of having impaired walking abilities [23] and had increased mortality and cardiovascular events [24].

Taken together, our results and previous studies suggest that HF and PAD have additive effects on functional limitation leading to a higher degree of physical disability of patients. Because we ruled out symptomatic patients, according to our data we can speculate that, also when asymptomatic, PAD impacts exercise capacity and hasten physical decline in HF patients, as previously reported in other populations [22,25].

In the absence of exertional pain, the mechanism underlying the association between PAD and limited improvement after exercise training in our population is unknown. Functional limitation in PAD traditionally has been ascribed to diminished blood flow induced by arterial obstruction from atherosclerotic stenoses. However others factors, not directly related to the degree of arterial stenosis, seem to contribute. Among them, endothelial dysfunction, inflammatory activation and altered muscle phenotype including reduced overall area, increased fat content, increased apoptosis and reduced type I fibers have been described [26,27].

Regardless of local mechanisms, however, we think that the worst physical performance observed in patients with asymptomatic PAD is a consequence of their clinical complexity and frailty. Our results clearly show that patients with severe PAD are a group of more frail subjects being older and with a greater number of comorbidities, such as diabetes and atrial fibrillation, compared to patients without PAD. Severe PAD patients had also a more advanced stage of heart disease as demonstrated by the higher NYHA stage, lower LVEF, higher levels of NT-proBNP and higher creatinine blood levels than those without PAD. Our study is consistent with a previous study performed by our group who attempted to identify factors related to limited benefit after exercise training in HF patients. In that study we demonstrated that cognitive impairment contemporaneously was an independent predictor of lower exercise recovery after exercise training programs and a marker of advanced HF and clinical frailty [5].

Given the high prevalence of asymptomatic PAD and its impact on exercise capacity, we suggest that ABI assessment should be part of the baseline evaluation of HF patients undergoing exercise training as part of cardiac rehabilitation programs. In this contest ABI assessment, together with other measures, could help to identify HF patients with higher degree of physical disability, worst prognostic profile and that are

less likely to improve their exercise capacity after exercise training. The identification of such particularly frail patients could help physician to stratify their risk and to select appropriate modality of interventions as observed by other authors in elderly patients with HF [28] and patients undergoing cardiac surgery [29].

## Limitations

The most important limitation of this study is the small sample size and our data need further confirmation in larger prospective studies. Patients with typical leg pain during effort were ruled out from the study; however it is extremely difficult for some HF patients to discern claudicating symptoms from fatigue due to chronic low output state and deconditioning. This could generate a potential bias in our study. Another limitation is the lack of data on skeletal muscle changes and hemodynamic changes with exercise in this study.

## Conclusions

Asymptomatic PAD is a condition with a very high prevalence among patients with HF and seems to affect the functional recovery of these patients. Our results extend those obtained by Jones et al. [6] in HF patients with symptoms of PAD. Because of its potential role as a marker of frailty in HF subject, ABI should be assessed at the time of admission. This, together with other baseline measures, could help physicians in order to determine patients' risk profile, to predict the response to exercise training, and to plan an individual tailored rehabilitative intervention.

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