

Resistive Exercise in the Evaluation of Endothelial Dysfunction in Heart Failure

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OBJECTIVE

To evaluate the use of resistive exercise in the study of endothelial dysfunction in heart failure (HF) comparatively to reactive hyperemia (RH).

METHODS

Eighteen patients with heart failure and 15 normal volunteers were submitted to intermittent handgrip exercise in a pneumatic bag, at an intensity that corresponds to 75% of the previously assessed maximum load. Patients underwent high-resolution vascular ultrasonography for brachial artery diameter and flow evaluation as well as cardiac output determination at rest, RH and after exercise. The systolic flow index in the brachial artery and cardiac index were calculated.

RESULTS

Systolic flow index increase in the brachial artery was observed after RH and physical exercise, with the latter presenting the highest increase. There was an increase in the cardiac index after the study conditions in comparison to resting conditions.

CONCLUSION

Resistive exercise, performed at the assessed load, increases blood flow more intensively than RH, constituting a physiological option for the evaluation of endothelial function in HF.

KEY WORDS

Endothelial dysfunction, heart failure, exercise.

Heart failure (HF) is characterized by the impairment of the ventricular function, with progressive physical limitation of affected individuals as the disease advances. However, one of the most remarkable facts regarding this syndrome is that the severity of ventricular dysfunction is not related to the functional capacity assessed by exercise tolerance¹⁻³. Although the central (cardiac) alterations start and perpetuate the HF, the main limitation to exercise is of peripheral origin, involving alterations in oxygen transportation and consumption⁴.

The physiopathological basis of this fact consists in the presence of histological and metabolic modifications in the skeletal muscle fibers^{5,6}, as well as alterations in the capacity of the vessels to distribute flow to muscles.

The characteristics of peripheral vessels are important determinants of left ventricular function in HF and are subject to the action of substances released by the endothelium in response to local flow⁷. Among these substances, nitric oxide (NO) is particularly relevant. Additionally, the endothelial-independent vascular response can also be altered in such patients⁸⁻¹⁰.

Endothelial dysfunction is a systemic phenomenon and can be assessed by cellular and molecular methods¹¹⁻¹² in animals. In humans, it is noteworthy the assessment of flow-mediated vasodilation in peripheral sites¹³.

With the description of RH utilization as an assessment method of flow-dependent endothelial dysfunction¹⁴, this technique started to be extensively employed; however, only recently this assessment method has been standardized¹⁵.

Physical exercise can also be utilized for endothelial function assessment. The basis of this observation is in the increase of blood flow in active muscular sites^{16,17}.

Daily exercise sessions has shown to be beneficial for the increase of NO expression in normal individuals and for endothelial-dependent vasodilation increase in HF patients^{18,19}. A review of randomized and controlled studies corroborates the beneficial effect of physical exercise in HF²⁰. The cardiac output increase that occurs during the exercise would augment shear stress, and thus, NO expression. It is not a consensus that the relative ischemia produced during localized muscular activity is enough stimulation to cause vasodilation.

Therefore, we tested the hypothesis that resistive exercise can be effective in assessing endothelial dysfunction in HF and it is comparable to reactive hyperemia.

METHODS

Thirty-three individuals aged between 18 and 65 yrs were studied. They were divided in two groups: 18 patients with congestive heart failure (CHF group) and 15 normal volunteers (NL group) (Table 1).

Table 1 - Characteristics of the groups

	CHF GROUP (N=18)	NL GROUP (N=15)	P
Age (yrs)	50 ± 12	46 ± 11	p= NS
Gender M	14	09	p= NS
Gender F	04	06	p= NS
Weight (Kg)	64.7 ± 11.95	71.5 ± 10.08	p= NS
Height (m)	1.6 ± 0.11	1.7 ± 0.08	p= NS
BMI (Kg/m ²)	23.7 ± 2.6	25.9 ± 2.6	p= NS

CHF=congestive heart failure; NL=normal

In the CHF group, left ventricular ejection fraction < 40% at the echocardiogram was the inclusion criterion for the study. Patients with coronary insufficiency, hypertension, permanent pacemaker, cardiac arrhythmias including frequent ventricular and supraventricular extrasystoles, atrial flutter and fibrillation and II-III degree atrioventricular block were excluded from the study.

The usual medication was withdrawn in all patients before the study for at least twelve hours. Patients were clinically stable with no peripheral edema.

The cause of heart failure was defined as dilated cardiomyopathy in 7 cases, Chagas' cardiomyopathy in 9 cases, alcoholic cardiomyopathy in 1 case and cardiomyopathy secondary to chemotherapy in 1 case. Left ventricular ejection fraction assessed by echocardiogram at rest was 0.31±0.05. Based on the NYHA functional classification, nine patients were class II, five were class III and 4 patients were class IV.

Study Protocol - Each subject was asked out with patients in the supine position and it was started after at least a 20- minute resting period in a quiet, dimly illuminated and temperature-controlled environment (21°C).

Before the study was started, the maximum left hand grip strength was measured using a kilogram (kg) scale dynamometer and afterward a pneumatic bag coupled to a pressure scale in millimeters of mercury (mmHg). Each individual was asked to perform three maximum handgrip movements. The value considered as maximum handgrip strength was the arithmetical mean of the strength obtained at the three gripping movements performed with the pneumatic bag²¹. This value was used for the calculation of the exercise load to be applied.

The correlation between the two measurements was carried out ($r = 0.90$, $p < 0.01$, $n = 33$). Only the measurements carried out with the pneumatic bag were utilized in the study, as this was the only way for the individual to control the strength to be applied, according to what had been previously established.

Cardiac rhythm was monitored by electrocardiogram for the echocardiogram to be performed.

High-definition vascular ultrasonography was carried out in order to acquire blood flow velocity curves, by Doppler, in the brachial artery, as well as longitudinal-cut images of this vessel simultaneously to the electrocardiogram

recording, for arterial diameter measurement.

In the study protocol, the arterial diameter and flow velocity curve were initially evaluated at rest (B1 condition). Afterward, the vascular reactivity was evaluated by reactive hyperemia after a 5-minute cuff occlusion in the left forearm, insufflated with a 200 mmHg pressure (HR condition). After a 30-minute rest, brachial artery diameter and flow velocity parameters were reassessed under a new basal condition (B2 condition). After that, each subject received the same pneumatic bag which was utilized to assess maximum handgrip strength capacity and they were asked to performed repeated gripping and relaxation movements with the left hand, with 75% of the maximum load (EX75 condition), in a protocol adaptation developed for this purpose²¹. After the first minute of exercise, the aforementioned parameters in brachial territory were assessed.

Cardiac output was evaluated by echocardiogram, using bidimensional mode, during each phase of the study immediately after the analysis of the peripheral parameters. This was performed to verify whether there was a correlation between the increase of local flow and the output increase that could take place because of exercise.

Acquisition of arterial diameters - An ultrasonography device (Apogee 800 plus, ATL Inc., Bothell WA, USA) equipped with a high-resolution vascular plane transducer of 5-10 MHz with automatic focus adjustment was utilized to acquire the bidimensional images at longitudinal cuts of the brachial artery, at approximately 5 cm distal to the elbow fold. The transducer was positioned at 90° to the vessel, so the vessel walls could be visualized. The image acquisition of the vascular diameter under reactive hyperemia was carried out one minute after cuff-occlusion release, and under the exercise conditions, one minute after exercise beginning. The acquisition of arterial images was carried out by the same observer, coupled to the simultaneous recording of the electrocardiographic signal. They were recorded in VHS tapes for posterior determination of the arterial diameter.

The VHS recording was utilized so that, based on the electrocardiographic recording, the images could be selected at the moment of systolic expansion, which corresponds to the first 60 milliseconds of the T wave. A computer software, which was specially developed for this purpose, was utilized to determine the arterial diameter²² (Fig. 1).

Peripheral arterial flow - An ultrasonography device (Apogee.-800 plus, ATL Inc, Bothell Wa, USA), equipped with a high-resolution vascular plane transducer of 5-10 MHz was utilized for the evaluation of the brachial artery blood flow velocity, using a pulsatile Doppler.

The arterial flow velocity images, coupled to the simultaneous electrocardiogram recording, were always

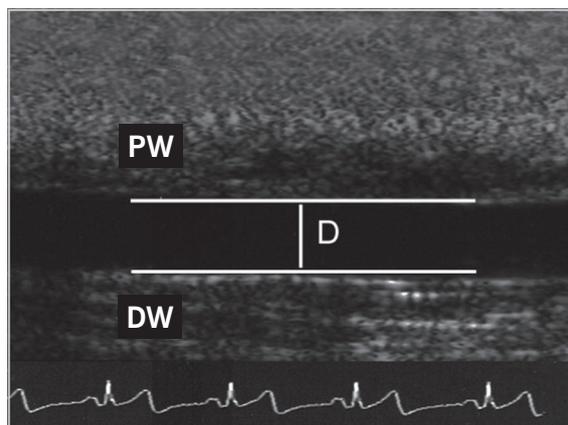


Fig. 1 - Brachial artery longitudinal section delimitating limits for the vascular diameter measurement. PW: proximal wall; DW: distal wall; D: diameter

acquired by the same observer and recorded in VHS tapes. Five images were selected and recorded in a computer equipped with video-frame grabber (Willow Publishers VGA, Willow Peripherals, Inc., Bronx, NY, USA), for posterior analysis. Afterward, the curve point that represented the peak systolic velocity (*) was enhanced (Fig. 2). The quantification of the peak systolic velocity of the arterial flow was carried out through the use of a software developed for this purpose.

In the reactive hyperemia condition, the flow velocity curve of the first heartbeat after cuff-occlusion release was always analyzed (Fig. 3). In the exercise condition, the velocity curves of the fifth heartbeat of the muscle relaxation phase were analyzed (Fig. 4).

After the flow velocity and arterial diameters during systole are measured, the systolic flow index (SFI) is calculated using the following formula:

$$SFI = \frac{TSA \cdot V_{si} \cdot 0.06}{BS} \text{ (L/min/m}^2\text{)}$$

where TSA (transverse sectional area of the vessel) = $\pi \cdot \text{radius}^2$, V_{si} = peak systolic velocity (m/s), BS = body surface area (m^2) and 0.06 is the correction factor necessary for the conversion of the units to l/min.

Cardiac assessment - Cardiac assessment was carried out using an ultrasonography device (Apogee-800 plus, ATL Inc, Bothell Wa., USA), with a setorial 3 MHz mechanical transducer. The M-mode echocardiogram and the bidimensional echocardiogram were always performed by the same observer, as well as the study of intracardiac flow using pulsatile Doppler device. The Doppler echocardiogram was recorded in VHS tapes. All quantifications were carried out based on the images recorded in 3 to five heartbeats, and the mean value of the measurements was considered for the analysis.

The bidimensional echocardiogram images were acquired according to the guidelines of the American Society of Echocardiography²³.

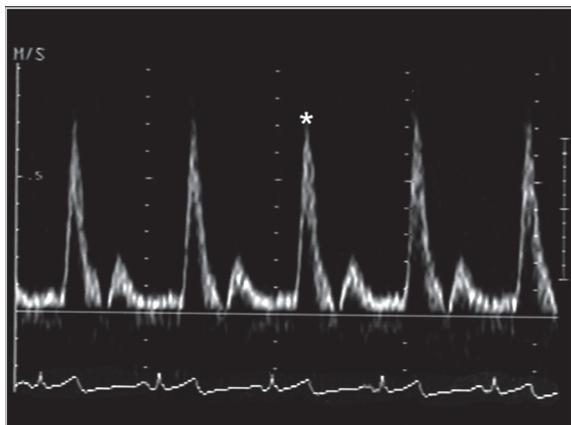


Fig. 2 - Flow velocity variation curve in the brachial artery showing the reference point for analysis of the systolic peak velocity (V_{sy}); * Systolic peak

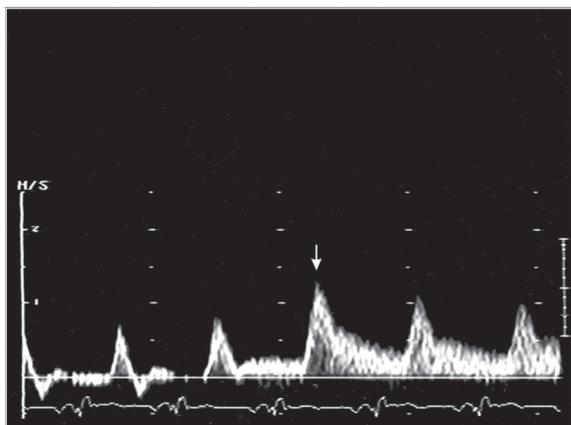


Fig. 3 - Curve of flow velocity variation in the brachial artery for reactive hyperemia analysis. The arrow indicates the velocity curve of the first heartbeat after cuff-occlusion release

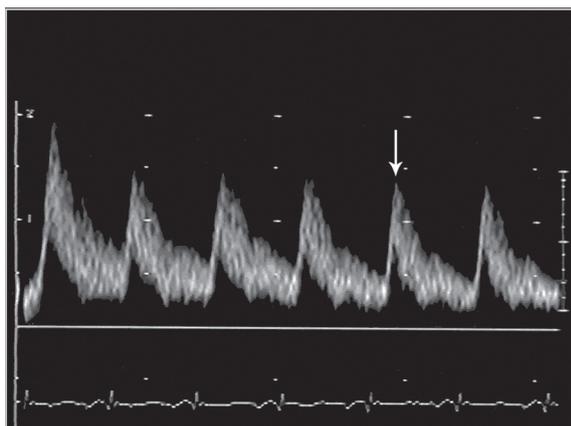


Fig. 4 - Curve of brachial flow velocity variation in the relaxation phase of the exercise condition with 75% of maximum load (EX75). The arrow indicates the fifth heartbeat, used for the analysis

The bidimensional left parasternal longitudinal cut was utilized for the measurement of left ventricular outflow diameter, necessary for the calculation of the systolic volume. The systolic flow of the left ventricle outflow tract was obtained from the apical cut, with the integral of the flow velocity being determined through the use of an adequate software for the ultrasound equipment. The

systolic volume (SV) was then calculated based on the following formula:

$$SV = FVI \cdot TSA$$

where: FVI=flow velocity integral and TSA = transverse sectional area of the aortic ring.

Heart rate was obtained based on the RR interval of the electrocardiogram. Cardiac output was calculated as the product of the systolic volume and heart rate. The cardiac index was obtained dividing the cardiac output by the body surface area.

Statistical analysis - To analyze the behavior of the groups considering the studied conditions, repeated measures analysis of variance was utilized (TIMM, 1975). The use of this technique presumes normal distribution of data. Significance level was set at 5%. The calculations were carried out with the SAS system (Statistical Analysis System) (SAS, 1989).

RESULTS

For the normal group, the systolic flow index mean values in brachial artery were 0.25 ± 0.08 l/min/m² for reactive hyperemia; 0.20 ± 0.06 l/min/m²; 0.48 ± 0.17 l/min/m² and 0.60 ± 0.24 l/min/m², for basal conditions (B1 and B2), for post-reactive hyperemia (RH) and exercise with 75% of the maximum load (EX75), respectively.

For the CHF group, the systolic flow index mean values in brachial territory were 0.19 ± 0.08 l/min/m² and 0.21 ± 0.09 l/min/m² for basal conditions (B1 and B2), respectively and 0.43 ± 0.14 l/min/m² and 0.45 ± 0.18 l/min/m² for post-reactive hyperemia (RH) and exercise with 75% of the maximum load (EX75), respectively.

There was a positive and significant correlation between the systolic flow indexes in RH and EX75 conditions ($r=0.66$, $p=0.005$).

The groups did not present a statistically significant difference regarding behavior during the evaluations performed ($p=NS$). The groups did not present a significant difference regarding their mean values at each evaluation moment ($p=NS$). There was an alteration of this parameter during the evaluations ($p<0.001$) for both groups.

When analyzing the means of the systolic flow index under the stimulation conditions (RH and EX75), no significant difference was observed between them.

The comparison between basal conditions and those that came subsequently (B1XRH and B2EX75) showed a significant difference in all evaluations performed for both groups ($p<0.001$) (Fig.5).

For the CHF group, the means of the cardiac index values under basal conditions and after exercise with 75% of the maximum load were, respectively, 1.93 ± 0.35 L/min/m² and 2.01 ± 0.39 L/min/m² ($p < 0.001$).

The analysis of percentage variations was carried out by assessing the value at a post-stimulation condition, and relatively taking into account its respective basal value. Thus, we call delta 1 ($\Delta 1$) that value observed between the B1 and RH conditions, and delta 2 ($\Delta 2$) the one observed between B2 and EX75 conditions.

The percentage variations of the brachial artery systolic flow index means ($\Delta 1$ and $\Delta 2$) for the CHF group were, respectively: $134.1 \pm 48.5\%$ and $208.3 \pm 96.5\%$. For the normal group, the same parameters were, respectively: $94.5 \pm 56.8\%$ and $193.3 \pm 90.1\%$. The groups did not present differences regarding either behavior ($p=NS$) or difference between the means in $\Delta 1$ as well as in $\Delta 2$ ($p=NS$). There was a difference between the conditions 1 (B1 and RH) and 2 (B2 and EX75) for both groups ($p < 0.001$). $\Delta 1$ showed a significant difference compared to $\Delta 2$ ($p < 0.001$) (Fig. 6).

DISCUSSION

This study proposes a new methodology in the assessment of the endothelium-dependent vascular reactivity. Physical exercises have been increasingly considered in HF^{24,25}. Despite that, few studies have associated this practice to the peripheral hemodynamic response in HF patients^{18,26}.

We studied clinically compensated patients, especially regarding the presence of peripheral edema. This factor can interfere in the vasodilating response due to the increase of vascular stiffness²⁷, related to the increase amount of sodium levels in the vessel wall. In addition, the edema can lead to an increase in tissue pressure with mechanical compression of the capillaries²⁸.

In EX75 condition, the choice of the fifth heartbeat in the relaxation phase was carried out in order to facilitate the standardization of the analysis of flow velocity curves, as there is a rapid and progressive decrease until their normalization, with time (Fig. 4).

The choice of manual stress involving a small muscle mass, instead of exercise utilizing the lower limbs, seemed a more interesting physiologic. The evaluation of the vascular response to a submaximum stress would be more compatible with the reality of patients who present limitations to physical activity and who perform household tasks that demand more muscular resistance than aerobic conditioning.

It was not possible to observe a difference in local blood flow in our study, even under elevated load, between reactive hyperemia and localized exercise. However, in terms of percentage, the variation of post-exercise flow was more intense than post-reactive hyperemia, especially when considering that the post-exercise analysis was carried out at the fifth heartbeat after exercise interruption, and not in the first heartbeat as under the reactive hyperemia condition.

At the evaluation of flow in calf and forearm muscles,

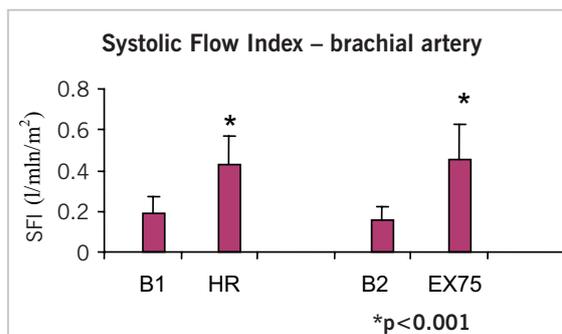


Fig. 5 - Systolic flow index in the brachial artery. Comparison between basal conditions (B₁ and B₂) and the subsequent stimulations. RH: reactive hyperemia; EX75: exercise with 75% of maximum load

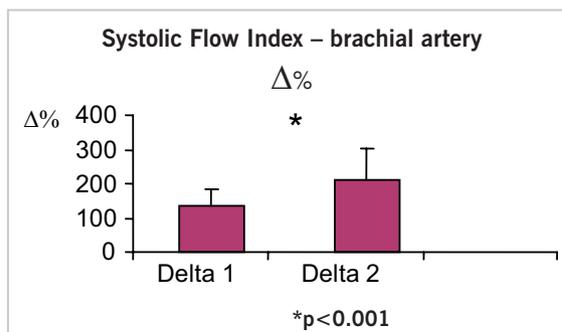


Fig. 6 - Percentage variation between the systolic flow indexes in the brachial artery between B₁ and RH ($\Delta 1$) and B₂ and EX75 ($\Delta 2$)

after five minutes of local ischemia in patients with compensated HF and no edema, and in normal age-matched individuals, a decrease in blood flow was observed, compared to normal volunteers, only in the calf²⁹. In this study, there was also no difference regarding the blood flow in the forearm between the two groups.

Therefore, it is suggested that vascular abnormalities in CHF are regionally specific not only for the flow differences observed in distinct territories but also for the flow distribution inside the muscle itself, favoring oxidative fibers³⁰.

Additionally, it is possible that, as HF advances, the alterations that were initially evident in lower limbs also start to occur in the upper limbs. Thus, it seems that the disparity among the results that assess vascular reactivity in the presence of exercise in heart failure is due to differentiation regarding disease severity, to the state of clinical compensation of the studied population and the type of stimulation employed (aerobic exercise, resistive exercise, distinct loads and muscular site territory evaluated).

It is noteworthy that, from a methodological point of view, the non-invasive studies utilizing arterial ultrasound are more appropriate and accurate for the analysis in the upper limbs than in the lower limbs.

We conclude that the study of a smaller muscular site that imitates daily activities regarding the type of work as well as the load, demonstrated that the exercise with 75% of the maximum load increased the peripheral

flow more intensively than the reactive hyperemia, in percentage terms.

Thus, it is possible that the assessment of vascular reactivity, using resistive exercise, is a physiological, more comfortable and easy to perform option, and that it is comparable to reactive hyperemia in the study of endothelium-mediated vasodilation.

Potencial Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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