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Enhanced External Counterpulsation Improves Endothelial Function in Patients With Symptomatic Coronary Artery Disease

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OBJECTIVES The goal of this study was to examine the effect of enhanced external counterpulsation (EECP) on endothelial function.

BACKGROUND Enhanced external counterpulsation improves symptoms and exercise tolerance in patients with symptomatic coronary artery disease (CAD). However, the exact mechanisms by which this technique exerts its clinical benefit are unclear.

METHODS Reactive hyperemia-peripheral arterial tonometry (RH-PAT), a noninvasive method to assess peripheral endothelial function by measuring reactive hyperemic response in the finger, was performed in 23 patients with refractory angina undergoing a 35-h course of EECP. In each patient RH-PAT measurements were performed before and after the first, at midcourse, and the last EECP session. In addition, RH-PAT response was assessed one month after completion of EECP therapy; RH-PAT index, a measure of reactive hyperemia, was calculated as the ratio of the digital pulse volume during reactive hyperemia divided by that at rest.

RESULTS Enhanced external counterpulsation led to symptomatic improvement (≥1 Canadian Cardiovascular Society class) in 17 (74%) patients; EECP was associated with a significant immediate increase in average RH-PAT index after each treatment ($p < 0.05$). In addition, average RH-PAT index at one-month follow-up was significantly higher than that before EECP therapy ($p < 0.05$). When patients were divided by their clinical response, RH-PAT index at one-month follow-up increased only in those patients who experienced clinical benefit.

CONCLUSIONS Enhanced external counterpulsation enhances peripheral endothelial function with beneficial effects persisting at one-month follow-up in patients with a positive clinical response. This suggests that improvement in endothelial function may contribute to the clinical benefit of EECP in patients with symptomatic CAD. (J Am Coll Cardiol 2003;41:1761–8) © 2003 by the American College of Cardiology Foundation

Enhanced external counterpulsation (EECP) is a noninvasive treatment for patients with stable symptomatic coronary artery disease (CAD) who are not amenable to standard revascularization procedures, such as percutaneous coronary intervention and coronary artery bypass graft surgery. Several trials have demonstrated that EECP reduces anginal symptoms in the majority of patients undergoing treatment. Aside from decreasing angina (1–4) and nitrate use (1,4), EECP was also shown to increase exercise tolerance (1,5–8), as well as to prolong the time to exercise-induced ST-segment depression (6,8,9) and to improve myocardial perfusion (1,5–8).

The inflation/deflation sequence of EECP leads to an increase in diastolic aortic pressure, with subsequent increase in coronary perfusion pressure, whereas systolic pressure is reduced, resulting in a diminution of cardiac workload (10). In addition, EECP also promotes venous return leading to an increase in cardiac output of up to 25% (11). However, little is known about the exact mechanisms by which these hemodynamic effects translate into clinical benefit. Improvement in endothelial function has been suggested as a potential mechanism contributing to the favorable clinical effect of EECP (11). However, although an increase in plasma levels of nitric oxide (NO) in response to EECP, suggesting an improvement in endothelial function, has been reported (6), little is currently known about the effect of EECP on endothelium-dependent vasodilatory capacity.

This study was designed to investigate the effect of EECP on peripheral endothelial function, as determined by reactive hyperemia-peripheral arterial tonometry (RH-PAT), a noninvasive plethysmographic technique to assess reactive hyperemic response in the finger (12–14), in patients with advanced symptomatic CAD.

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Abbreviations and Acronyms

CAD	= coronary artery disease
CCS	= Canadian Cardiovascular Society
DASI	= Duke Activity Status Index
EECP	= enhanced external counterpulsation
eNOS	= endothelial nitric oxide synthase
L-NAME	= N^{ω}-nitro-L-arginine methyl ester
NO	= nitric oxide
NTG	= nitroglycerin
PAT	= peripheral arterial tonometry
RH	= reactive hyperemia

METHODS

Patients and study protocol. This study was approved by the Mayo Clinic Institutional Review Board. All consecutive patients who were referred for EECP treatment because of refractory angina and agreed to participate were prospectively enrolled in the study after informed consent was obtained. As per institutional practice, all patients had established ischemic CAD and were not amenable to standard forms of revascularization after review by at least two cardiologists. Digital deformities and an allergy to latex were the only exclusion criteria for participation in the study. All patients underwent a standard 35-h course of EECP (1 h daily, 5 days a week, over 7 weeks). Acute hemodynamic effects of EECP, measured as the peak diastolic-to-systolic pressure ratio (EECP effectiveness ratio), were monitored using conventional finger plethysmography (15). Cardiovascular medications remained unchanged during the duration of the study. For each patient, all EECP sessions were scheduled at the same time of day in order to prevent possible effects of circadian variability of vascular reactivity; RH-PAT measurements were performed immediately before and after EECP treatment on the first (session 1), a midcourse (session 17), and the last (session 35) EECP session. In addition, RH-PAT response was measured at a follow-up visit one month after completion of the EECP course. Patient demographics were obtained at baseline. In addition, on all study days, severity of angina was assessed using the Canadian Cardiovascular Society (CCS) grading system (16), and cardiovascular functional status was determined by using the Duke Activity Status Index (DASI), a self-administered questionnaire assessing functional capacity that correlates well with objective measures of maximal exercise capacity (17).

To further document the severity of endothelial dysfunction in patients undergoing EECP, single RH-PAT measurements were also performed in a control group of seven healthy individuals without evidence for CAD (mean age, 63 ± 2 years).

RH-PAT. The principle of PAT, a finger plethysmographic device that allows the isolated detection of pulsatile arterial volume changes, has been recently described (12,18,19). This device (Itamar Medical Ltd., Caesarea, Israel) consists of two finger-mounted probes, which include a system of inflatable latex air-cushions within a rigid external case. The probe design allows the application of a constant and evenly distributed near-diastolic counterpressure within the entire probe, which increases sensitivity by unloading arterial wall tension, and prevents venous blood pooling to avoid venoarteriolar reflex vasoconstriction. Pulsatile volume changes of the fingertip are sensed by a pressure transducer and transferred to a personal computer where the signal is band pass-filtered (0.3 to 30 Hz), amplified, displayed, and stored.

The RH-PAT studies were performed with the patient in the supine position and both hands on the same level in a comfortable, thermoneutral environment. A blood pressure cuff was placed on one upper arm (study arm), while the contralateral arm served as a control (control arm); RH-PAT probes were placed on one finger (finger II, III, or IV) of each hand (same finger on both hands). The fingers on either side of the one with the probe were separated using soft sponge rings, and continuous recording of pulsatile blood volume responses from both hands was initiated. After a 10-min equilibration period, the blood pressure cuff on the study arm was inflated to 60 mm Hg above systolic pressure for 5 min. The cuff was then deflated to induce RH, whereas PAT recording was continued. Ten minutes later, the patients were given a single dose of nitroglycerin (NTG) (0.4 mg, sublingual) to assess endothelium-independent PAT response, and, after another 10 min, PAT recording was stopped.

The RH-PAT data were analyzed by a computer in an operator-independent manner. As a measure of the extent of RH, the RH-PAT index was calculated as the ratio of the average amplitude of the PAT signal over a 1-min time interval starting 1 min after cuff deflation divided by the average amplitude of the PAT signal of a 3.5-min time period before cuff inflation (baseline); RH-PAT index values from the study arm were then normalized to the control arm to compensate for potential systemic changes. Hyperemic response to NTG was assessed in a similar manner. At first, average PAT signal amplitude of four consecutive 1-min periods starting at 5 min after administration of sublingual NTG (5- to 6-min, 6- to 7-min, 7- to 8-min, and 8- to 9-min interval) was calculated; PAT response to NTG was then calculated as the ratio of the PAT amplitude of the 1-min interval during which peak average PAT signal was recorded divided by the amplitude of the PAT signal at baseline (NTG-PAT index).

Repeatability of RH-PAT results. Repeatability of RH-PAT measurements was assessed in 28 volunteers (mean age, 31 ± 1 year; 10 men) on two consecutive days. These data were analyzed according to the method by Bland and Altman (20) (Fig. 1).

Statistical analysis. Results are expressed as mean ± SEM. Repeated-measures analysis of variance followed by the Bonferroni *t* procedure (all pairwise comparison), if indicated, was used to compare continuous data at different points in time, and Student *t* test was used to compare

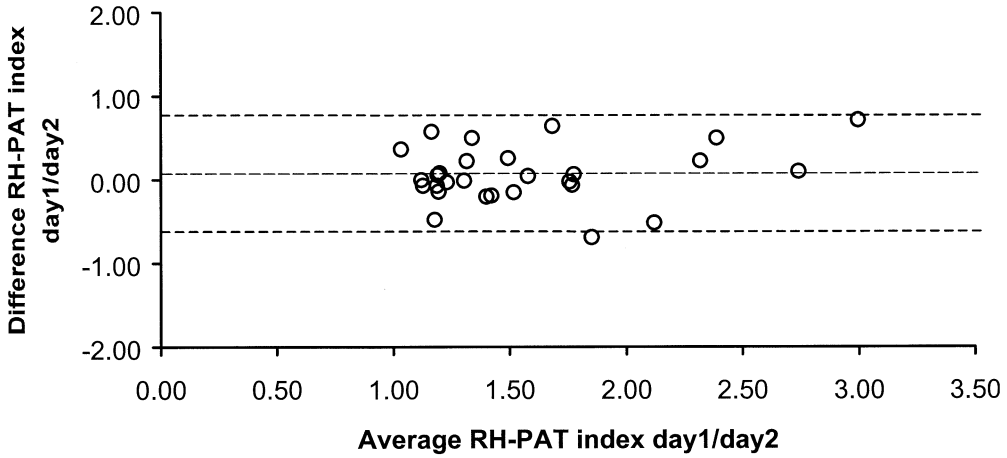

Figure 1. Bland-Altman plot of reactive hyperemia-peripheral arterial tonometry (RH-PAT) repeatability data; RH-PAT index was determined on two consecutive days among 28 volunteers. The difference between the two paired readings is plotted against their average. The average difference and the upper and lower limits of agreement (2 SDs of the differences) are indicated.

continuous data between different groups. All analyses were performed using SigmaStat statistical software, version 2.03 (SPSS Inc., Chicago, Illinois). Statistical significance was accepted for $p < 0.05$.

RESULTS

Patients. Twenty-three patients with advanced symptomatic CAD were prospectively studied. The baseline characteristics of these patients are shown in Table 1. All patients completed their 35-h course of EECP, and 18 patients returned for a one-month follow-up visit. No major adverse cardiovascular events were noted during the study period.

EECP and functional class. Thirty-five EECP sessions led to an improvement by one CCS class in 12 (52%) patients and by two CCS classes in 5 (22%) patients, whereas 6 (26%) patients showed no change in CCS class at the end of EECP treatment. Average CCS class decreased significantly in response to EECP, an effect that was maintained at one month after termination of treatment (Fig. 2). Similarly, 17 (74%) patients reported an improvement in their functional status, as measured by the DASI score, during the course of treatment. Moreover, average DASI score improved significantly in response to EECP and remained stable at the one-month follow-up visit (Fig. 2).

Hemodynamic effects of EECP. Average EECP effectiveness ratio achieved at the end of the EECP course did not differ from that at the beginning of treatment (EECP day 1: 0.89; EECP day 35: 1.02; $p < 0.42$), and EECP had no acute or chronic effect on heart rate or blood pressure in the patients studied.

Effect of EECP on vascular function. Before therapy, patients undergoing EECP had a significantly lower average RH-PAT index than healthy control individuals (1.03 ± 0.04 vs. 1.77 ± 0.18, $p < 0.001$); EECP led to an acute and significant increase in average RH-PAT index on all three EECP study days. Moreover, average RH-PAT index was significantly higher one month after completion of treatment than before initiation of EECP therapy (1.29 ± 0.09 vs. 1.03 ± 0.04; $p < 0.05$) (Fig. 3). In contrast, average peak PAT response to the nonendothelium-dependent vasodilator NTG was not altered by EECP (Fig. 4).

When the patients were divided into two groups based on

Table 1. Baseline Characteristics of 23 Patients Undergoing EECP and RH-PAT Testing

Age, yrs	66 ± 2
Male gender, n (%)	22 (96)
BMI, kg/m^2	31.9 ± 0.8
Cardiovascular risk factors	
Family history of premature CAD, n (%)	17 (74)
Hypertension, n (%)	16 (69)
Hyperlipidemia, n (%)	20 (87)
Smoking history, n (%)	11 (48)
Diabetes, n (%)	9 (39)
Average total risk factors, n	3.1 ± 0.2
Medication	
Beta-blocker, n (%)	23 (100)
Calcium-antagonist, n (%)	13 (57)
ACE inhibitor, n (%)	17 (74)
Nitroglycerin, n (%)	22 (96)
Statin, n (%)	22 (96)
Platelet inhibitor, n (%)	23 (100)
Cardiac history and status	
Prior MI, n (%)	17 (74)
Prior coronary revascularization, n (%)	22 (96)
Prior PCI, n (%)	17 (74)
Prior CABG, n (%)	21 (91)
Prior TMR, n (%)	4 (17)
One-vessel disease, n (%)	2 (9)
Two-vessel disease, n (%)	5 (22)
Three-vessel disease, n (%)	16 (69)
Left mainstem disease, n (%)	4 (17)
Prior CHF, n (%)	5 (22)
LVEF, %	47 ± 3

Values are mean ± SEM or n (%).

ACE = angiotensin-converting enzyme; BMI = body mass index; CABG = coronary artery bypass graft surgery; CAD = coronary artery disease; CHF = congestive heart failure; EECP = enhanced external counterpulsation; LVEF = left ventricular ejection fraction; MI = myocardial infarction; PCI = percutaneous coronary intervention; RH-PAT = reactive hyperemia-peripheral arterial tonometry; TMR = transmyocardial revascularization.

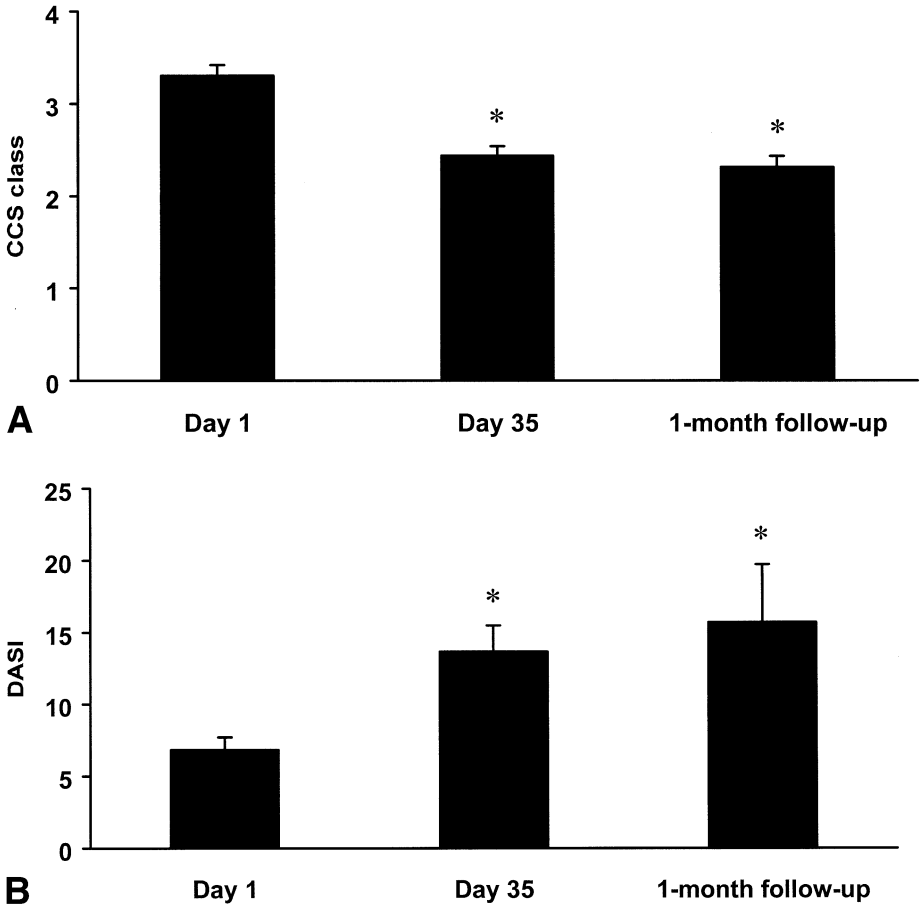

Figure 2. Effect of enhanced external counterpulsation on average Canadian Cardiovascular Society (CCS) class **(A)** and average Duke Activity Status Index (DASI) score **(B).** *$p < 0.05$ vs. day 1.

their clinical response to EECP, RH-PAT index at one-month follow-up was significantly higher in those patients who experienced a decrease in CCS class or an increase in DASI score (Fig. 5).

DISCUSSION

The present study demonstrates that EECP acutely improves peripheral endothelial function, as measured by RH-PAT, in patients with advanced CAD. Moreover, it is shown that patients who experience clinical improvement during EECP show an additional enhancement of their RH-PAT response one month after completion of therapy. These data support a role for an improvement in endothelial function as a mechanism underlying the clinical benefit associated with EECP.

Clinical benefit of EECP. As a result of recent improvements in cardiovascular care, life expectancy of patients with

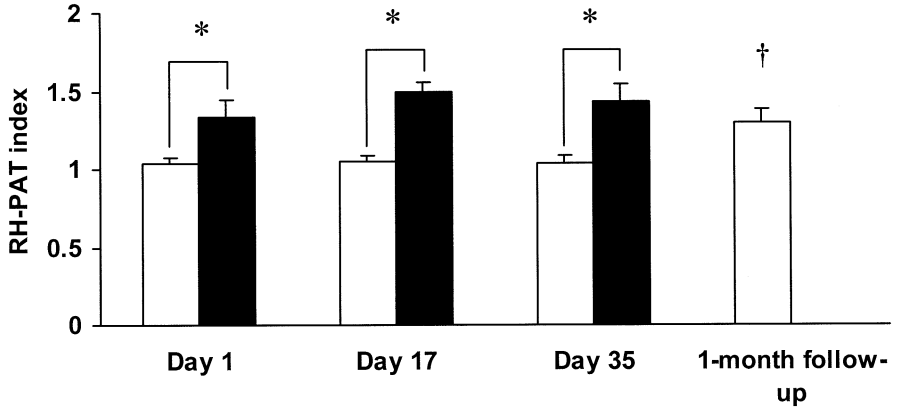

Figure 3. Average peripheral arterial tonometry response to reactive hyperemia (RH-PAT index) on the four study days. *$p < 0.05$; †$p < 0.05$ vs. pre-enhanced external counterpulsation (EECP) RH-PAT indexes on day 1, day 17, and day 35. **Open bars** = pre-EECP; **solid bars** = post-EECP.

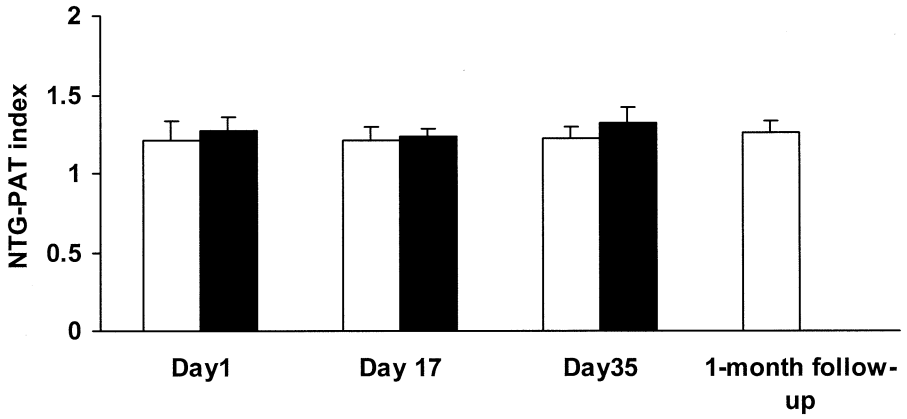

Figure 4. Average peripheral arterial tonometry response to the nonendothelium-dependent vasodilator nitroglycerin (NTG-PAT index) on the four study days, p = 0.594 (repeated measures analysis of variance). **Open bars** = pre-enhanced external counterpulsation (EECP); **solid bars** = post-EECP.

CAD will probably continue to increase in the near future. As a consequence, the cohort of patients who remain symptomatic despite optimal medical therapy and who are not amenable to standard revascularization techniques will likely continue to grow as well (21); EECP represents a valuable treatment option for these patients. Several trials have demonstrated that EECP is associated with a positive clinical response in the majority of CAD patients with refractory angina undergoing treatment (1–9). Despite significant cardiac risk profiles and advanced CAD among patients included in the present study, 74% experienced an improvement in their functional status in response to EECP, further supporting the role of EECP as an effective therapeutic strategy for patients with symptomatic CAD.

EECP and endothelial function. Enhanced external counterpulsation has been shown to acutely increase blood flow in various vascular beds, including the coronary arteries (10,22–25). In the absence of significant arterial obstructions (26,27), increased blood flow theoretically translates into enhanced shear stress, which represents a key factor for endothelial homeostasis (28,29). Thus, given the significance of endothelial dysfunction for the development and

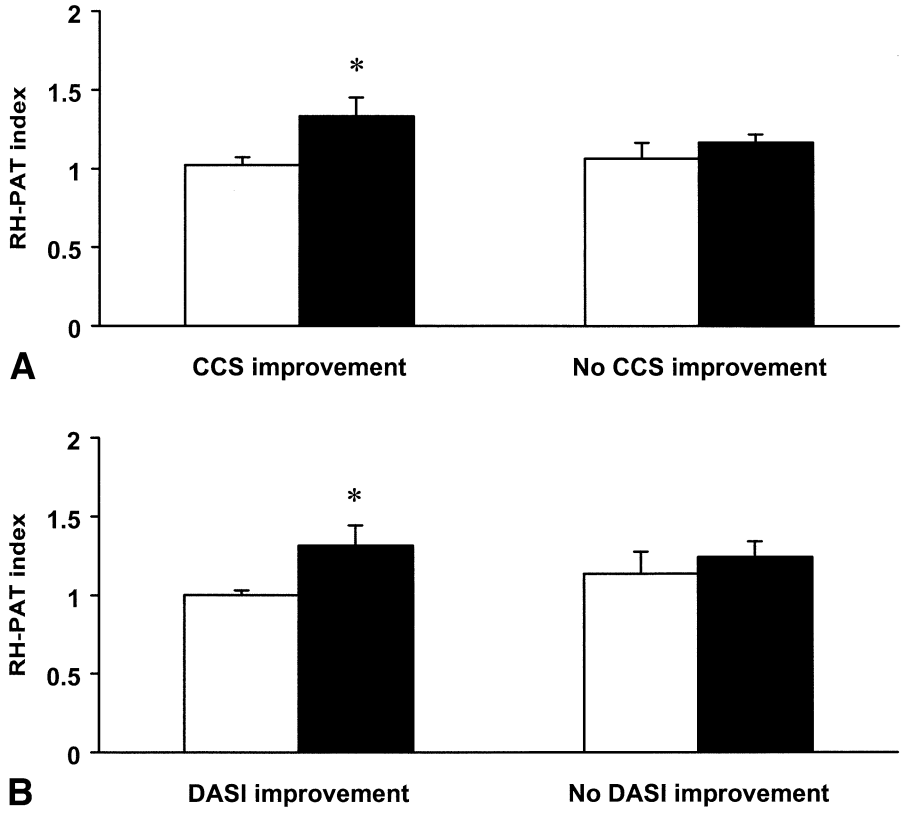

Figure 5. Average peripheral arterial tonometry response to reactive hyperemia (RH-PAT index) before initiation and one month after completion of enhanced external counterpulsation (EECP) therapy in patients with or without improvement in functional status. **(A)** Canadian Cardiovascular Society (CCS) class; **(B)** Duke Activity Status Index (DASI) score. *p < 0.05 vs. day 1. **Open bars** = day 1; **solid bars** = 1-month follow-up.

manifestation of CAD (30), improvement in endothelial function is an important mechanism by which EECP may exert its clinical benefit. The fact that patients undergoing EECP had a significantly lower baseline RH-PAT index than healthy control individuals, indicating the presence of endothelial dysfunction, together with the observed enhancement in the reactive hyperemic response in EECP-treated patients in our study, further supports this notion.

Reactive hyperemia, which is due to dilation of small resistance vessels, is partly mediated by endothelium-derived NO and, therefore, the magnitude of the hyperemic response serves as an indicator for the status of endothelial function (31,32). Moreover, using strain-gauge plethysmography, an excellent correlation between peak forearm blood flow response during RH and that to intra-arterial infusion of the endothelium-dependent vasodilator acetylcholine has been demonstrated, indicating that the magnitude of RH may serve as an index of peripheral endothelial function (33); RH-PAT permits the noninvasive assessment of peripheral vascular reactivity by measuring digital pulse volume at rest and during RH. Notably, although local, systemic, and environmental factors may modulate digital pulse volume, this parameter also depends on the bioavailability of NO (34). Moreover, endothelium-derived NO has been shown to be particularly important for the regulation of vascular tone in areas rich in arteriovenous anastomoses, such as the finger tip (35). The effect of NO synthesis inhibition by N^{ω}-nitro-L-arginine methyl ester (L-NAME) on the PAT response to reactive hyperemia was investigated recently (14). In this study, 19 healthy volunteers underwent RH-PAT testing, according to the same protocol as was used in the present study, before and after administration of L-NAME into the brachial artery. Importantly, L-NAME administration was associated with a significant 61% reduction ($p < 0.05$) in the RH-PAT index values, indicating that this index depends on endothelium-derived NO and, therefore, represents a marker of peripheral endothelial function. In accordance with these findings, it was demonstrated that factors known to affect endothelial function, including various cardiovascular risk factors and the presence of CAD, influence RH-PAT index values in a similar manner as flow-mediated dilation of the brachial artery, a widely-used method to evaluate peripheral endothelial function (12). Furthermore, a significant relationship between the PAT response to reactive hyperemia and flow-mediated dilation of the brachial artery has been shown, suggesting that vascular reactivity of the digital vasculature, as measured by the RH-PAT index, is influenced by endothelial function in a magnitude and direction similar to that of the brachial artery (12).

Taken together, we conclude that EECP is associated with an acute improvement in peripheral endothelial function, as is demonstrated by the acute increase in RH-PAT index observed in response to EECP on the first three study days. Moreover, the significant difference between RH-PAT indices before the course of EECP and at one-month follow-up suggests that EECP also exerts a beneficial medium-term effect on endothelial function, although enhanced mobility due to improved functional status in response to EECP could have contributed to this late effect. The existence of a beneficial effect on endothelial function is pointed out further by the observation that the PAT response to the nonendothelium-dependent vasodilator NTG was not altered by EECP. Moreover, in line with the medium-term effect of EECP on endothelial function observed in the present study are the findings by Masuda et al. (6), who reported no difference between plasma NO levels before initiation and one day after completion of a 35-h course of EECP, whereas plasma NO levels were significantly increased one month after completion of therapy in patients with chronic stable angina. The reason for the delayed improvement in parameters of endothelial function may be speculated upon. One possible explanation is the effect of increased shear stress on the activity and expression of the enzyme endothelial nitric oxide synthase (eNOS), the major source of endothelium-derived NO. An increase in shear stress enhances endothelial NO release via activation of eNOS through phosphorylation by the serine/threonine protein kinase Akt (36,37), which represents a likely mechanism for the acute increase in RH-PAT index observed in response to EECP. On the other hand, chronic-intermittent enhancement of shear stress, as generated by a standard course of EECP, may upregulate eNOS protein expression (28), which may translate into a delayed, but prolonged, improvement in endothelial function.

Peripheral effect of EECP. One of the mechanisms by which EECP may exert its clinical benefit is by increasing exercise capacity. It may be speculated that EECP may provide hemodynamic stimuli similar to those of physical exercise that contribute to the improvement in endothelial function (38). In line with this concept are the results of studies showing an enhancement of exercise tolerance, whereas peak exercise double product is maintained due to a decrease in maximal blood pressure in some patients after a course of EECP (5). These results indicate that EECP, similar to physical training, may promote an exercise-induced decrease in peripheral vascular resistance. Given the importance of endothelial function for the regulation of vascular tone and peripheral vascular resistance, our results support the notion of the existence of such a peripheral "training" effect of EECP.

Study limitations. Interventional procedures or the use of medical devices may be associated with enhanced placebo effects (39,40). Thus, given the therapeutic principle of EECP and the lack of an effective (e.g., sham EECP-treated) control group, the possibility that nonspecific placebo effects might have contributed to the clinical benefit observed in the present study cannot definitely be ruled out. However, the results of the randomized, placebo-controlled Multicenter Study of Enhanced External Counterpulsation (MUST-EECP) trial indicated no major role for nonspecific placebo effects as mediators of the clinical benefit

associated with EECP in patients with angina (9). In addition, our finding that the delayed increase in reactive hyperemic response observed during follow-up is restricted to patients who experience a symptomatic or functional benefit from EECP therapy supports the hypothesis that improvement in endothelial function may be an important mechanism contributing to the clinical benefit associated with this therapeutic strategy.

The lack of an effective control group also raises the question as to whether EECP-unrelated factors might have affected the RH-PAT results. However, on the basis of the study protocol, patients served as their own controls. Given that RH-PAT measurements were performed within about 1 h immediately before and after EECP therapy and without administration of drugs between these paired measurements, an effect of non–EECP-related factors on the RH-PAT results is rather unlikely. Also, the consistent effect of EECP on RH-PAT index during the course of treatment supports the existence of a direct effect of EECP on digital vasoreactivity.

Conclusions. In summary, the present study suggests that EECP may improve endothelial function. Aside from an acute beneficial effect, which occurs immediately after a therapeutic session, a standard 35-h EECP treatment also exerts a prolonged favorable effect on endothelial function that becomes apparent one month after completion of treatment and is restricted to patients who experience symptomatic improvement. These results support the notion that improvement in endothelial function may be an important mechanism by which EECP exerts its clinical benefit.

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