The role of enhanced external counterpulsation in the treatment of angina and heart failure

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As the incidence of angina and heart failure continue to rise, new therapeutic options will be needed to treat patients who remain symptomatic or who are intolerant to current treatment. Enhanced external counterpulsation (EECP) is a noninvasive modality being investigated in both angina and congestive heart failure patients. It has been proven to provide symptomatic benefit in angina patients, but has not been proven to show an increase in life expectancy or decrease in cardiovascular events. EECP in heart failure has been proven to be safe, but its efficacy is still uncertain. The present paper summarizes the current literature on the clinical use of EECP in angina and heart failure.

Key Words: Angina; Congestive heart failure; EECP; Prognosis

Heart disease is the leading cause of morbidity and mortality in the United States. As the incidence of angina and heart failure has increased, so has our understanding and treatment. Despite these advances, many patients continue to be symptomatic; any intervention that can improve symptoms or outcomes is eagerly anticipated. Enhanced external counterpulsation (EECP) has received much recent attention, but the precise role that this noninvasive technique will play in these disease states is unclear.

Much of the uncertainty stems from the unknown mechanisms by which EECP delivers its beneficial effects. Similar to the intra-aortic balloon pump, EECP is based on the principle of diastolic augmentation to increase coronary flow while simultaneously decreasing systolic afterload (1). The direct pressure from diastolic augmentation can cause an increase in shear stress to open or form collaterals. The increase in shear stress itself, either through direct or indirect mechanisms, can increase angiogenesis factors such as hepatocyte growth factor, vascular endothelial growth factor, fibroblast growth factor and nitric oxide (2-4). Improved endothelial function, possibly by increased shear stress and nitric oxide levels, is another postulate (2,3). Indeed, increased endothelial reactivity, as measured by noninvasive tonometry testing, has been shown to be associated with significant symptomatic improvement in patients (5). Improvement in central cardiac function may also contribute to the results, because studies have shown increases in both resting and stress ejection fraction (EF) (6), as well as improvements in pump function with associated bradycardia (7). Neurohormonal regulation via production of nitric oxide and B-type natriuretic peptide has

Le rôle de la contre pulsation externe à haut rendement dans le traitement de l'angine et de l'insuffisance cardiaque

À mesure que l'incidence d'angine et d'insuffisance cardiaque continuera d'augmenter, il faudra de nouvelles options thérapeutiques pour traiter les patients qui demeurent symptomatiques ou qui ne tolèrent pas leur traitement courant. La contre pulsation externe à haut rendement (CEHR) est une modalité non effractive qui fait l'objet d'études auprès de patients atteints autant d'angine que d'insuffisance cardiaque. Il est démontré que cette modalité a des effets bénéfiques chez les patients angineux, mais pas qu'elle accroît l'espérance de vie ou qu'elle diminue les événements cardiaques. La sécurité de la CEHR est établie en cas d'insuffisance cardiaque, mais son efficacité n'est pas certaine. Le présent article résume les publications scientifiques actuelles sur l'utilité clinique de la CEHR en cas d'angine et d'insuffisance cardiaque.

also been implicated as a factor (2,8). However, the two important considerations are the placebo and peripheral training effects.

EECP IN ANGINA

EECP is not novel. Its use has been documented for more than four decades, but its use in the treatment of heart failure is incipient. Numerous small clinical studies of patients with stable chronic angina pectoris have shown improved cardiac perfusion imaging (2,8-13), reduction of angina class (2,9,10,12,13), increases in exercise tolerance (2,8-11), decreased use of nitroglycerine (10,12,13) and increased time to ST segment depression on stress testing with the use of EECP (2,8). Some of these studies have shown a sustained improvement for as long as five years after treatment (13).

However, these were nonrandomized trials conducted with a limited number of patients and institutions, thus introducing bias and not excluding the possibility of a placebo effect. The landmark trial that attempted to address these concerns was the Multi-center Study of Enhanced External CounterPulsation (MUST-EECP). This was a multicentre, blinded study conducted in seven university hospitals that randomly assigned 139 patients to either full-dose EECP or a sham method with minimal pressures. At one month post-treatment, treated patients had a significant increase in time to ST segment depression on stress testing and significant decreases in angina frequency compared with non-treated patients. Although nitroglycerine use did decrease in both groups, there was no significant difference between the two groups (14). No objective follow-up in angina frequency or ischemic testing after more than one month was reported, but a substudy

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analysis at one year post-treatment demonstrated significant improvement in quality of life parameters (15).

These results, however, need to be considered with caution. Both groups had increases in exercise duration and decreases in nitroglycerine use, and while the decrease in angina frequency was statistically significant, a similar number of patients in each group showed a 0% to 25% level of improvement. Thus, the placebo effect may still have contributed to the results. Furthermore, cardiac perfusion imaging was not performed, precluding correlation of the clinical results to radiographic evidence of improved ischemia. Coupled with the fact that the double product (a measure of heart rate $\times$ blood pressure) at the level of stress testing was not reported, the benefits of EECP may have been transmitted via a peripheral effect (similar to exercise training). Both may explain the results of a recent prospective, blinded study that failed to show quantitative improvement using myocardial single-photon emission computed tomography imaging, even though patients showed a significant decrease in angina class and increased exercise duration (16).

The data from the International EECP Patient Registry (IEPR) show the efficacy of EECP in the general population. Outcomes for 1097 patients (approximately 86% of patients were not candidates for further revascularization procedures) who were mostly in Canadian Cardiovascular Society classes III or IV showed a sustained, significant decrease in weekly angina episodes and a dramatic reduction in angina class immediately post-treatment, in addition to a significant improvement in quality of life parameters after two years. Approximately 41% of patients remained event-free during this two-year period, and nitroglycerine use remained significantly decreased compared with baseline (17). The only predictors of death, myocardial infarction or heart failure during EECP treatment were age older than 80 years, history of stroke or transient ischemic attack, diabetes and prior heart failure (18).

However, the optimal medical management of patients from these nonrandomized uncontrolled studies is unknown. Secondary to hemodynamic effects or intolerance, patients were often not titrated to optimal doses of nitrates or beta-blockers, especially those on triple antianginal therapy. Furthermore, only 70% of patients from the IEPR were taking statins after two years, and similarly, only 72% were taking acetylsalicylic acid. Given that most of these patients were at high risk for coronary events, these percentages are relatively low. With optimal medical management, would EECP still have such an impact? The data from the IEPR also do not exclude the placebo effect; in patients who did not have an acute decrease in angina class, the angina frequency per week was still significantly decreased. Despite these improvements, the major adverse cardiac event (MACE) rate after 12 months was approximately 16% in those who showed an initial response to therapy, while those who did not show an initial response had a significantly higher MACE rate of 28% (19). Thus, although one can infer that the nonresponders had more clinically advanced cardiac disease, it cannot be excluded that EECP did not directly or indirectly cause an increase in the MACE rate in the nonresponders. The data imply that although these patients had decreased symptoms, they continued to have clinical events, and thus, EECP did not seem to greatly alter their disease process.

Increasing the hours or repeat courses of EECP may possibly increase benefits. The only data on patients with repeat EECP are from the IEPR; 18% of patients repeated EECP, most of them within one year of initial treatment. However, only 70% of these repeat users improved in angina class, and they did not sustain their symptomatic improvement (20). If the rate of repeat EECP is compared with the revascularization rate of stents, then the 18%

repeat EECP rate is significantly higher than the 4% rate of revascularization with drug-eluting stents observed in other interventional trials.

EECP IN LEFT VENTRICULAR DYSFUNCTION

In heart failure patients with left ventricular dysfunction, the increase in cardiac output and cardiac index by the hemodynamic effects of EECP can also be associated with an acute increase in right atrial mean pressure and pulmonary capillary wedge pressure, possibly precipitating an exacerbation (21). Data from the IEPR reveal that after six months, there was a significant increase in MACEs, death, congestive heart failure and cardiac hospitalization in patients with a history of heart failure, with an EF of 35% or less portending a worse outcome (22). This was markedly evident in patients not able to complete the full course of EECP (23); after two years, there was a significant decrease in survival rate in those patients who did not complete treatment (24). On the other hand, in IEPR patients with an EF of 35% or less, 81% had no occurrence of congestive heart failure two years post-treatment. The MACE rate was similar between the group that showed improvement in angina class and the group that showed no initial improvement, but the rate of unstable angina was significantly increased in those who did not show initial improvement (24).

In patients with a left ventricular EF of 35% or less, a small, nonrandomized prospective study showed a significant increase in maximal oxygen uptake and exercise duration after six months (25). The randomized controlled Prospective Evaluation of EECP in Congestive Heart failure (PEECH) trial (26) enrolled 187 patients with ischemic or nonischemic cardiomyopathy to either EECP treatment or to the control group. The results showed significant improvements in exercise duration and New York Heart Association classification, but no significant change in maximal oxygen uptake or quality of life after six months, although there was an acute increase in maximal oxygen uptake one week post-treatment. Consistent with previous studies, the discontinuation rate was higher in the treated group, but it is unclear whether this was secondary to the acute hemodynamic effects of EECP or other circumstances.

Although the results are promising, these results are not conclusive. The IEPR is a registry, and like all registries, there was no control for comparison or screening of the patients. Again, the optimization of the IEPR patients with heart failure is not ideal; little more than one-half were taking angiotensin-converting enzyme inhibitors and 11% were taking angiotensin II receptor blockers at follow-up. There are less data on patients with heart failure without chronic angina. The PEECH trial results could be due to the placebo effect or a training effect; 25% of patients in the control group had increased exercise duration. There were no reported data on the rate-pressure product during exercise training, thus not excluding a peripheral effect. The awaited neurohormonal results will address the issue of whether EECP affects neurohormonal regulation, especially noradrenaline levels; however, only a small, limited number of studies to date have shown such hormonal changes.

CONCLUSIONS

In both heart failure and angina, patients have been shown to have symptomatic improvement, but this does not imply longer life expectancy or decreased cardiovascular events. As of yet, the true effects of EECP have not been fully elucidated. Currently, in patients with angina who have exhausted other interventions or do not tolerate certain medications, EECP may be useful in

improving symptoms; EECP is a Food and Drug Administration-approved, class IIb-recommended treatment for refractory angina. However, results of the newer antiangina medication ranolazine have shown increased exercise duration and time to ST segment depression, and decreased angina frequency (27-29) versus placebo; thus, it is even more difficult to refer patients. EECP appears to be

relatively safe in heart failure patients, but its efficacy is more nebulous; it is not recommended that patients undergo treatment only for heart failure. Until a well-controlled, randomized clinical trial of optimally managed patients can demonstrate a decrease in clinical end points or can exclude the placebo effect, EECP remains a second-line, alternative treatment for refractory angina.

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