Is Cardiac Shock Wave Therapy an Option for the Treatment of Myocardial Ischemia in Patients with Refractory Angina?

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Optimal medical therapy and percutaneous or surgical coronary revascularization are well-established tools for the treatment of patients with chronic coronary syndromes. However, as the population ages and mortality from coronary artery disease (CAD) decrease, a growing number of patients with severe CAD continue to experience angina which is not amenable to surgical or percutaneous coronary revascularization despite excellent medical therapy. Overall, the prevalence of this condition, defined as refractory angina,[1] is estimated to be 5% to 10% in stable CAD patients, possibly accounting for 50,000 to 100,000 new cases/year in the USA and 30,000 to 50,000 new cases/year in Europe.[2] The general definition of refractory angina includes patients with anatomic reasons precluding revascularization (severe diffuse disease, lack of graft conduits for surgical revascularization, multiple coronary restenoses, degenerated saphenous vein grafts), patients with severe comorbidities (advanced age, pulmonary obstructive chronic disease, high-risk procedure), or patients with coronary disorders other than obstructive CAD causing angina (microvascular dysfunction).[3,4] Currently, treatment option for this setting of patients is limited to implementation of traditional anti-anginal therapy with the inclusion of novel pharmacological agents (i.e., ranolazine) and secondary risk-factors modification. Thus, a variety of alternative treatment modalities of refractory angina are being investigated. These include transmyocardial laser revascularization,[5] enhanced external counterpulsation,[6] spinal cord stimulation,[7] transcutaneous electrical nerve stimulation,[8] stem cell therapy[9], and coronary sinus reducer.[10] Some studies showed that all these nonpharmacological treatments may reduce anginal symptoms and improve exercise capacity, myocardial perfusion, and function in patients with refractory angina. However, these benefits were not consistent across all studies and, currently, only transmyocardial laser revascularization, enhanced external counterpulsation, and spinal cord stimulation have a IIb/B class of recommendation in the ACC/AHA guidelines. Some characteristics of these alternative therapeutic technologies are shown in the Table 1.

Ultrasound-guided cardiac shock wave therapy (CSWT) is another promising non-invasive treatment modality in patients with stable CAD.[4] It has been developed based on the lithotripsy method; it uses application of low-intensity shock waves to stimulate angiogenesis.[11] Specifically, several experimental studies have demonstrated that the application of low-intensity shock waves might induce the release of angiogenic factors such as endothelial nitric oxide synthase, vascular endothelial growth factor, and proliferating cell antinuclear antigen.[11] CSWT is delivered using a generator accompanied by a cardiac ultrasound system to target the myocardial ischemic area of interest. Improvements in symptoms, cardiac function, and ischemic threshold have been reported with CSWT in small placebo-controlled trials and real-world registries.[4] Notably, a recent meta-analysis of 39 studies with 1,006 patients treated with CSWT showed moderate improvement in exercise capacity, thus suggesting that CSWT is a potentially effective non-invasive option

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Table 1. Alternative therapeutic technologies in refractory angina

Treatment	Mechanism of action	Efficacy	Potential complications
Transmyocardial laser revascularization	Laser-created intramyocardial transmural channels; angiogenesis; denervation	++	Major
Enhanced external counterpulsation	Improved diastolic coronary perfusion; reduced afterload	+++	Minor
Spinal cord stimulation	Pain signal neuromodulation	+++	Major
Transcutaneous electrical nerve stimulation	Pain signal neuromodulation	+	No
Stem cell therapy	Neovascularization; endothelial protection	+++	Minor
Coronary sinus reducer	Coronary flow redistribution	+++	Minor
Cardiac shock wave therapy	Neoangiogenesis; improved myocardial perfusion	++	No

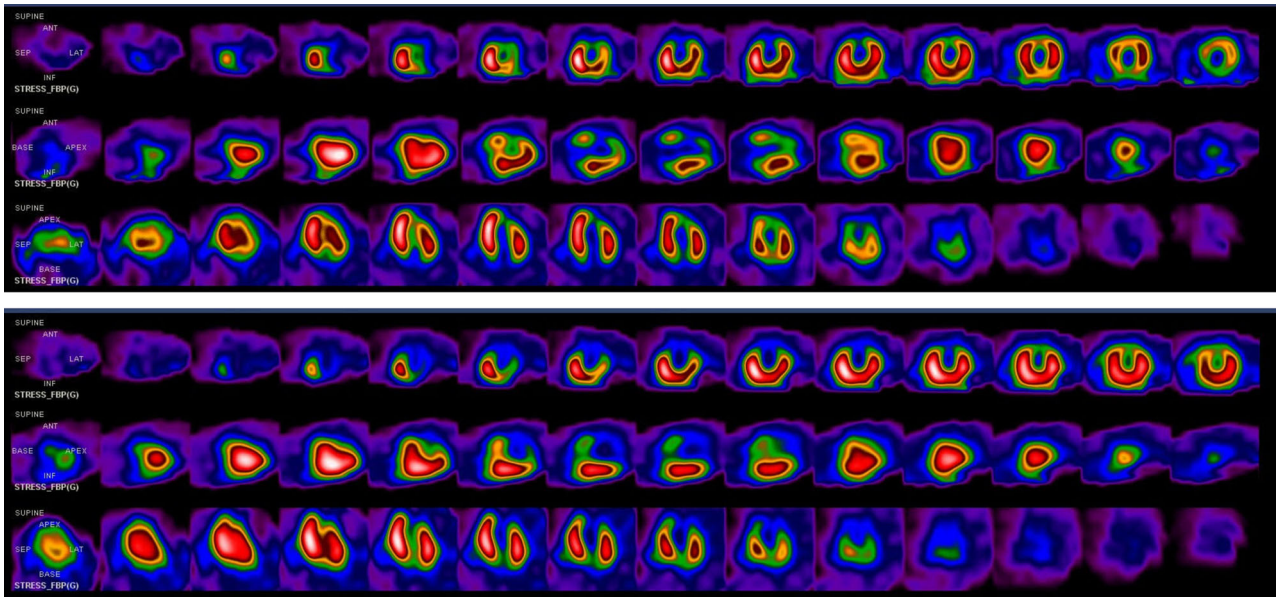

Figure 1. Myocardial perfusion imaging with dipyridamole (up) and with bicycle exercise test (down), in the same patient with LAD coronary artery stenosis. A perfusion defect is present in the anterior wall and apex with dipyridamole stress; the size and severity of the defect is greater after exercise stress.

for patients with CAD, but evidence is limited to small low/moderate quality single-center studies.[12]

In this issue of the *Journal of Nuclear Cardiology*, Jia et al[13] report the results of another randomized, double-blind control study, aimed at assessing efficacy and safety of CSWT in patients with severe CAD unsuitable for coronary revascularization, with more than two ischemic segments at myocardial perfusion imaging, refractory angina, and left ventricular (LV) ejection fraction $\geq$ 30%. Stress perfusion imaging was used to identify the two LV segments with the most severe reversible perfusion defect, which were the segments targeted during treatment.

They found a statistically significant improvement of global and regional (segments targeted) myocardial perfusion in CSWT-treated patients, without significant difference in clinical symptom, quality of life, and exercise tolerance between groups. No procedural complications or adverse effects were noted, confirming the safety of CSWT.

The evaluation of myocardial perfusion as primary endpoint (i.e., total perfusion score) seems to be

adequate, being angiogenesis with improved coronary perfusion the proposed anti-ischemic (antianginal) pathophysiological target of CSWT. It should be noted, however, that the possibility of quantitative measurements, using positron emission tomography or cadmium zinc telluride technology, would allow a more precise estimate of the quantification of global perfusion, that could be partially underestimated with the SPECT, especially in the presence of balanced ischemia, frequently found in these patients. In this regard, the most accurate estimation of the extension and severity of the ischemic area to be targeted during treatment would optimize the efficacy of CSWT in terms of ischemia reduction and relief of angina. Furthermore, although the authors utilized a dynamic or a pharmacological stress test depending on the patient's condition, it would have been more appropriate in these patients the use of a dynamic exercise test, as the alteration of perfusion associated with anginal symptoms accurately represents the ischemic area to be treated. Of note, with pharmacological testing, the extent and severity of a perfusion defect may be underestimated, making less accurate the evaluation of the possible reduction of ischemia after treatment[14] (Figure 1). Finally, the authors enrolled patients with normal LV geometry and function, despite more than 50% were revascularized, and around 30% had previous myocardial infarction or a NYHA class 3. It would be interesting to evaluate the efficacy of CSWT also in patients with LV dysfunction, in whom the reduction of ischemic burden may have a prognostic benefit.

In conclusion, CSWT seems to improve myocardial perfusion in patients with severe CAD, but it remains unanswered its efficacy in the reduction of anginal symptoms, which should be the most important goal in this specific clinical setting. Similarly to previous studies, it is likely that the small sample size, the improvements in the placebo group, and the limited period of follow-up of this trial preclude definitive conclusions on the efficacy of CSWT. Thus, 20 years after its introduction, CSWT cannot yet be considered a further therapeutic option in patients with refractory angina. Larger multicenter, adequately powered, randomized double-blind studies are required to define the role of CSWT in this setting of patients, to decrease nonresponder rates and ascertain benefit beyond potential placebo effects.

Disclosure

All authors disclose no potential conflict of interest.

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