EDITORIAL COMMENT

Enhanced External Counterpulsation

What Can We Learn From the Treatment of Neurasthenia?*

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Neurasthenia is defined by the Columbia Encyclopedia as “a condition characterized by general lassitude, irritability, lack of concentration, worry, and hypochondria.” The term was introduced into psychiatry in 1869 by G. M. Beard, an American neurologist. Used by Freud to describe a “fundamental disorder in mental functioning,” the term was applied to people with a large constellation of symptoms and is now rarely used.

In 1910, when neurasthenia was considered an actual disorder, Howard Kelly from Johns Hopkins University published a series on 78 patients with neurasthenia who were treated for mobile kidneys (1). Mobile right kidney (nephroptosis) was said to be found in one-fourth of all women and to be the cause of discomfort or pain in many. Symptoms of a moveable kidney could be confirmed by inducing pain by hydrodistention of the renal pelvis through a ureteral catheter. The appropriate treatment was surgery to suspend the kidney in place (nephropexy). Although Dr. Kelly acknowledged that mobile kidneys were not the cause of all neurasthenia, his findings suggested major benefit of surgery for those women with neurasthenia. Local symptoms of nephroptosis were relieved in most patients, and “in a surprisingly large number of cases the neurasthenic symptoms also disappeared.” Of the worst cases, 60% were relieved of both “pain in the side and the nervousness.” Case reports provided examples of increased weight, elimination of chronic headaches, and resolution of cough after surgery.

In 2006, Feldman et al. (2) provide evidence that patients with heart failure can benefit from enhanced external counterpulsation (EECP). The evidence that the authors present is a small rise in the percentage of patients with an increase in exercise time of 60 s (10% more than that observed in the control group). In this PEECH (Prospective Evaluation of EECP in Congestive Heart Failure) trial, subjective questionnaires also improved, but there was no significant increase in peak oxygen uptake ($\text{VO}_2$). The authors admit that the failure to increase peak $\text{VO}_2$ could, in fact, mean that the increase in exercise time is due to a placebo effect. To counter this hypothesis, Feldman et al. refer us to work by Metra evaluating metoprolol and carvedilol. Metra et al. (3) showed no changes in peak $\text{VO}_2$ in the carvedilol group, despite better cardiac performance. It should be noted, however, that ventilatory threshold (VT) did not change with either drug. Lack of a change in VT implies that true exercise capacity did not change with either drug, because exercise duration is a poor measure of functional capacity and functional capacity does not correlate with hemodynamics (4). Therefore, Metra’s study does not support the notion that the findings in PEECH demonstrate improved exercise capacity or cardiac function with EECP.

The beneficial effects of EECP in ischemic disease have been attributed to diastolic augmentation of arterial pressure with enhanced venous return to the heart. The extracardiac effects of EECP, however, are less well studied. Additional possible targets for EECP in heart failure would include elevated peripheral vascular resistance and endothelial dysfunction. One could speculate that the “training effects” of repetitive inflations and deflations of compressive cuffs with shear stress could improve peripheral resistance and enhance endothelial function similar to that of exercise training (5,6). Should a “training effect” be occurring with peripheral improvements in vascular resistance and endothelial function, one should expect a change in peak $\text{VO}_2$ as well. The literature reporting drops in vascular resistance and improvements in endothelial function have all been accompanied by substantial increases in peak $\text{VO}_2$ (7–11). Therefore, we must return to the placebo theory once more.

The connection between the neurasthenia and the PEECH reports published almost a century apart should be the realization that improvement after an intervention might be caused by the belief that the treatment will work; the mechanisms by which an aggressive intervention can cause benefit are manifold.

We usually think of the placebo effect as a subjective response to an inert ingredient. When evaluating interventions, however, the response to a placebo or a medically inefficacious intervention might depend upon true physiologic changes. For example, placebo-induced activation of $\mu$-opioid receptor-mediated neurotransmission has been demonstrated and could lead to the pain relief seen with placebos or acupuncture (12).

Frequent patient visits (the EECP protocol led to patients being seen daily for 7 weeks) might not only improve attitude and psychological status but might have more tangible benefits as well. The ability to adjust medications or address problems early could promote improved medical care—the state of enhanced surveillance.
Device trials are particularly susceptible to improvement in symptoms unrelated to the direct effects of the intervention. It is difficult to design a study to prove that devices exert more of an effect than ordinary placebos, but there are publications which suggest the more aggressive an intervention, the greater the response (13,14). Supporting this hypothesis are the findings that intravenous placebo is more effective for hypertension than a pill (15). Similarly, sham surgery seems to markedly decrease angina; in an investigation of the effects of internal mammary artery ligation, 80% of both the active and the sham groups responded (16).

Many studies show increased exercise time when patients with heart failure perform stress tests while receiving placebo. However, it has also been demonstrated that those receiving placebo increased exercise time more than a control group receiving no intervention. In one study, placebo therapy resulted in a mean 81-s improvement in exercise duration. This was statistically significant when compared with pretreatment baseline and to the duration achieved in the non-placebo control group (17).

The authors acknowledge that a placebo effect is possible, and we must agree that it is often difficult to devise an appropriate control for a device. Patient and doctor unblinding in a device study is usually easy, and ethical concerns prohibit risky controls. Some controls even have the potential of direct positive or negative consequences. However, it is obligatory for designers of any study to eliminate as many non-medical effects of an intervention as possible so that the true medical outcome can be assessed.

In the PEECH trial, the non-medical effects of the intervention were not controlled. Furthermore, only slight benefit was seen, there was a large dropout rate (which will probably inflate the percentage of patients categorized as responders), and the subgroup analyses are post hoc and based on few patients.

In 2004, Medicare received 410,862 billing claims for EECP for a total of over $54 million in charges (personal communication by Centers for Medicare and Medicaid Services). Angina as an indication accounted for 94.9% of claims with approximately 10% having been denied. Because Medicare pays for only 80% of the charges and if all denials remained, then the cost to Medicare was $29,530,476, leaving $8,427,224 to be paid by secondary insurance or patients. This amount is surprising in light of the newness of this therapy for angina. With the growing number of heart failure patients in the U.S. and the even more important increase in the Medicare population, the use of EECP in heart failure merits a very close look. Although costs such as these are acceptable for therapies with proven benefits, they are a reason for even greater scrutiny for a therapy with more modest or perhaps placebo-attributed effects.

Better-controlled studies are needed before we can ascribe a benefit to EECP for patients with heart failure. Only then could we place it in the already extensive treatment algorithm for this complex syndrome.

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REFERENCES