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Immediate Early Genes after Pulsed Radiofrequency Treatment: Neurobiology in Need of Clinical Trials

THE search for treatments that relieve chronic pain is expanding and includes biobehavioral techniques, the discovery of new drugs, novel routes of drug administration, neuroablative treatments, and innovative surgical procedures. The use of less invasive, interventional strategies for chronic pain relief has gained popularity since the publication of evidence from randomized controlled trials. Electrical stimulation techniques, such as transcutaneous nerve stimulation and spinal dorsal column stimulation, are attractive treatment options for chronic pain because the intervention can be somatotopically localized and can be removed if effectiveness declines, there are few side effects, and tolerance does not appear to be a problem. Recently, the technique of pulsed radiofrequency treatment, the application of brief, high frequency electrical stimulation adjacent to sensory ganglia, has been described for the relief of chronic, intractable pain. In this issue of ANESTHESIOLOGY, Van Zundert *et al.*[1] describe changes in the expression of c-*fos*, an immediate early gene, after pulsed radiofrequency treatment in laboratory rats.

Conventional radiofrequency treatment, using a constant output of high-frequency electric current, produces controllable tissue destruction surrounding the tip of the treatment cannula and, when placed at precise anatomic locations, has demonstrated success in reducing a number of different chronic pain states, including chronic neck pain after whiplash injury[2] and trigeminal neuralgia.[3] Pulsed radiofrequency utilizes brief "pulses" of high-voltage, radiofrequency range (~300 kHz) electrical current that produce the same voltage fluctuations in the region of treatment that occur during conventional radiofrequency treatment but without heating to a degree at which tissue coagulates. The idea arose from a chance meeting during a 1995 scientific conference in Austria between Dr. Menno Sluijter, M.D., Ph.D. (Professor Emeritis, Department of Anesthesia, Maastricht University, Maastricht, Netherlands), a physician who has pioneered the clinical application of radiofrequency treatment, and William Rittman, M.S. (Principal, RF Medical Devices, Middleton, MA), then an engineer with Radionics, the firm that developed the original radiofrequency treatment equipment (personal written communication, William Rittman, October, 2004). The two were discussing the mechanism behind radiofrequency treatment with a basic scientist from the former Soviet bloc who had been examining cellular changes induced by magnetic fields; this scientist challenged the conventional belief that pain relief after radiofrequency treatment was a result of tissue destruction, suggesting that the pain relief could result from the strong magnetic fields induced by voltage fluctuations in the area of treatment. Mr. Rittman returned to the bench and quickly devised a means of creating the same high-voltage fluctuations without any heating at the tip of the needle by using pulses of electrical current rather than continuous current. Dr. Sluijter immediately introduced the technique into clinical practice and within months had treated numerous patients with the new modality; based on this initial, uncontrolled clinical experience, the new technique has been aggressively promoted and its use has rapidly spread worldwide.

The conceptual appeal of a minimally invasive, nondestructive technique that is useful in treating chronic pain of any sort is compelling. In clinical practice, there has been a mass migration to the use of pulsed radiofrequency with few data to support efficacy of this new technique. The modality has great appeal, specifically because it is not neurodestructive. With conventional radiofrequency, the thermal lesion occasionally leads to worsening pain and even new onset of neuropathic pain.[4] A small retrospective case series[5] and the overwhelming "word on the street" among practitioners suggest that pulsed radiofrequency results in neither increased pain nor any risk of neuropathic pain, and it is very well tolerated by patients from treatment through recovery.

In the study by Van Zundert *et al.*,[1] experimental neurobiologic techniques are used to probe the effects of pulsed radiofrequency on spinal cord sensory neurons. The gene c-*fos* codes for the production of fos protein and is rapidly and transiently expressed in neurons after an excitatory stimulus. Using immunohistochemical techniques, Hunt *et al.*[6] first reported that Fos-like-immunoreactivity appears in neurons of the dorsal horn of the spinal cord in rats after noxious stimulation. Subsequently, Fos-like-immunoreactivity has been used as a marker for sensory neuron activation in preclinical animal studies allowing the investigator to determine the number of neurons activated and their segmen-

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tal and laminar (or depth) location in the dorsal horn.[7] In many cases, the number and location of Fos-expressing neurons relates to the intensity, modality, and location of the noxious stimulus. Treatments such as opioids and local anesthetic nerve blocks not only reduce pain responses but prevent the development and reduce the maintenance of Fos-like-immunoreactivity caused by a noxious stimulus.

Many studies have used c-*fos* expression as a tool in pain research, and within the last 10 yr our understanding of the role of Fos protein and persistent pain has been clarified.[7] Fos is an indicator of neuron activation; its value as a marker for plasticity and central sensitization is less well accepted. C-*fos* is expressed in some but not all dorsal horn neurons after noxious stimulation[8,9] and at least a few neurons express c-*fos* protein in the absence of noxious stimulation. Some treatments that reduce pain responses do not affect c-*fos* expression, so the link between c-*fos* expression and nociception is evident, but other studies demonstrate that the association between pain-related behaviors, analgesia, and c-*fos* is not absolute. For instance, it is hypothesized that fos-expressing neurons may be inhibitory interneurons activated by noxious stimuli because many spinal neurons with Fos-like-immunoreactivity contain inhibitory neurotransmitters that reduce nociception: gamma aminobutyric acid, glycine, and dynorphin.[7]

In the study by Van Zundert *et al.*,[1] c-*fos* expression induced by two pulsed radiofrequency paradigms was compared to c-*fos* expression induced by continuous (heated) radiofrequency and a sham (surgical exposure only) control. Both pulsed and continuous radiofrequency induced similar increases in the number of cells expressing c-*fos*, and the expression was present for 7 days after radiofrequency treatment. The observation that c-*fos* was present 7 days after stimulation suggests sustained activation of a pain-inhibiting process. The duration of Fos-like-immunoreactivity exceeded the expected length of time for c-*fos* expression caused by the acute effects of surgery and electrical stimulation of sensory nerves. The authors suggest that their clinical and experimental observations may be similar to those described by Sandkuhler *et al.*,[10] who demonstrated in spinal cord recordings that repetitive burst-like stimulation of A-delta fibers caused depression of synaptic activation by C-fibers for several hours. The concept that pulsed radiofrequency may produce inhibition of excitatory C-fiber responses using a phenomenon such as long-term depression is indeed an attractive hypothesis.

As appealing as the concept behind pulsed radiofrequency may be, we must be honest with ourselves and our patients regarding how much clinical evidence supports the efficacy of this new technique. Even the current report[1] references only a scant collection of uncontrolled, retrospective studies, many appearing only as preliminary reports during scientific symposia. Without controlled studies, we must remain keenly aware of the magnitude and duration of the placebo effect in patients undergoing diagnostic blocks as well as those going on to receive radiofrequency treatment for chronic pain. Lord *et al.*[11] have emphasized how important it is to include placebo controls among the panel of diagnostic blocks used to identify those who should go on to active radiofrequency treatment, as many will report prolonged pain relief after saline injection. In a series of patients receiving conventional radiofrequency treatment for chronic whiplash injury, those receiving sham radiofrequency treatment (needle placement without an active, thermal lesion) had 50% pain reduction for an average duration of 8 days *versus* an average of 263 days in the active treatment group.[2] More than 20% of patients receiving sham treatment had 50% pain reduction that lasted more than 3 months, the average duration of pain relief reported after pulsed radiofrequency treatment.[5]

Scientifically, it might be suggested that we move forward to examine pulsed radiofrequency in validated models of persistent pain and examine new neurobiologic markers in pain-transmitting neurons after pulsed radiofrequency treatment. However, basic scientific studies in the neurobiology of pain models and analgesic techniques are not a substitute for randomized controlled clinical trials, and studies such as that of Van Zundert *et al.* do not justify using the technique clinically. We have not a single randomized trial that compares the efficacy of pulsed radiofrequency to any type of control treatment or to conventional radiofrequency treatment. We urge practitioners using these techniques to conduct the randomized trials we need to demonstrate the effectiveness (or lack thereof) of pulsed radiofrequency treatment and hold hope that the evidence will soon appear to support the enthusiasm of practitioners for this new treatment. If and when it is established that particular groups of patients (*e.g.*, chronic cervicobrachialgia) exhibit long-term pain relief from a treatment such as pulsed radiofrequency, then demonstrating its mechanisms using basic science neurobiology and persistent pain models will provide important fundamental information to understand and advance the technique.

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Off-pump Coronary Artery Bypass and the Hypothesis from Which It Grew: Is It Yet to Be Tested? What Are the Downsides of the Lingering Questions?

CME This editorial accompanies the article selected for this month's *Anesthesiology* CME Program. After reading the article and editorial, go to http://www.asahq.org/journal-cme to take the test and apply for Category 1 credit. Complete instructions may be found in the CME section at the back of this issue.

WITH the rising costs of health care and the desire to demonstrate best outcomes, there is increasing interest in demonstrating that surgical procedures are both efficacious and cost effective. There is now sufficient justification to perform randomized trials to evaluate the appropriateness of procedures for specific indications.[1] Coronary artery bypass grafting (CABG) continues to be one of the most commonly performed procedures that has a significant impact on overall health care resources. In this issue of the Journal, Cheng *et al.* report on their meta-analysis of the randomized literature comparing off-pump (OPCAB) and conventional approaches to coronary revascularization.[2] They utilized a comprehensive search strategy to identify the relevant randomized studies and therefore their work should represent the best evidence on which to base future treatment decisions and research directions. In an analysis of 37 trials involving 3,369 patients, they found no difference in their primary outcomes of 30-day and 2-yr mortality rates. For their secondary nonfatal outcomes, results were mixed, but with no significant difference in the incidence of major adverse clinical outcomes such as myocardial infarction, renal failure, or stroke.

There are significant limitations in how best to generalize their findings to current clinical practice and whether they have been able to effectively address the original hypotheses that drove the development of OPCAB. As this article documents, there are incidental benefits to OPCAB that may be important, such as decreased transfusion, lower incidence of atrial fibrillation, and even important economic benefits. However, we must not forget that the push to develop techniques for OPCAB can be traced to the plethora of reports documenting that CABG with cardiopulmonary bypass results in an alarmingly high incidence of postoperative cognitive dysfunction (POCD) and a lesser but important occurrence of stroke. These sequelae are the major adverse clinical outcomes that OPCAB was developed to ameliorate. Testing the hypothesis that these outcomes are diminished by OPCAB should be a priority in any randomized study. Furthermore, anyone who has witnessed the challenge of sewing coronary grafts on a beating heart would agree that one other primary outcome should test the hypothesis that OPCAB results in poorer graft survival, given the increased degree of difficulty.

Reports of the complication of POCD after CABG have reached the mainstream media[3] and have been the focus of hospital advertising campaigns promoting OPCAB. The public has been convinced that coronary revascularization with cardiopulmonary bypass will likely lead to the syndrome known colloquially as "pump head." As a result, many surgeons are faced with patients who present for CABG demanding OPCAB, thus compelling many surgery programs to offer OPCAB as an alternative or, in many cases, as the primary approach for CABG. This has resulted in a steady increase in the number of

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OPCAB procedures performed over the past several years; it has plateaued at approximately 20–30%. There is general agreement that the incidence of POCD early after cardiac surgery is high but that cognitive function probably returns nearly to baseline in 6–12 weeks.[4,5] However, some studies have suggested that although patients may improve dramatically during the 6–12 weeks after cardiac surgery, a significant deficit remains which may last for years.[6] Some suggest that POCD may herald further long-term decline,[5] and still others deny the existence of any long-term evidence of POCD.[7]

Despite the high level of interest in POCD, another, better, reason to support the development of OPCAB may be to prevent strokes. Although stroke after cardiac surgery occurs in only 2–3% of all patients, the rate may approach 35–70% in aged patients with multiple risk factors such as hypertension, diabetes mellitus, and previous stroke.[8,9] Furthermore, although the overall incidence of stroke is much less than that of POCD, the consequences of stroke after cardiac surgery, including a fivefold to 10-fold increase in early mortality,[10] are far more devastating than any sequelae of POCD.

Given this historical and clinical perspective on the origins of OPCAB, readers are left to question whether the data in this report are sufficient to adequately address the major hypotheses outlined above.

Cheng *et al*. reported no consistent differences in the occurrence of POCD at the timepoints measured and, most importantly, demonstrated no benefits of OPCAB at 1 yr. The authors state that the lack of consistency in testing approaches, as well as the small number of studies meeting criteria, underpower this meta-analysis to draw conclusions regarding important clinical differences in the incidence of POCD.

This report also concludes that there is no significant difference in the incidence of stroke between OPCAB and conventional coronary artery bypass. This conclusion should also be a cautious one, as the quoted aggregate risk of stroke from this meta-analysis is only 1% (lower than the average of 2–3% quoted in most studies), and the mean age was only 63 yr (younger than the national average undergoing CABG).‡ As the authors suggest, this indicates that the subjects selected for these studies were at low risk of stroke to begin with. This report includes only one study[11] that focused on 65 high-risk subjects. Furthermore, the authors of this meta-analysis note that "most studies stated that they excluded high risk subjects."

To illustrate the difficulty in assessing the benefit, or lack thereof, of OPCAB *versus* conventional coronary artery bypass in affecting the occurrence of stroke among a population such as that presented in this meta-analysis, we offer the following. In a population having an average risk of stroke is 1% and in which one was interested in demonstrating a 20% reduction in the rate of stroke, you would need 35,994 subjects in each study group, or a total of 71,988 subjects in the randomized study with 80% power. A total of 16,554 subjects would be needed to demonstrate a reduction of 40% in the rate of stroke. It is clear that this meta-analysis, which includes slightly more than 3,000 subjects, could not appropriately evaluate arguably the most important potential clinical benefit, reduction in the likelihood of stroke.

The OPCAB technique is more technically demanding, and long-term graft patency using this technique *versus* CABG on a still heart has yet to be determined. Although Cheng *et al.* report that all-cause mortality at 2 yr was not different, their conclusions regarding graft patency are not substitutes for a quantitative analysis of graft patency, nor can we be sure that 2 yr is an adequate period of follow-up to understand the potential impact of poor revascularization.

One should be aware that most reports of nonrandomized comparisons between OPCAB and conventional coronary artery bypass document less complete revascularization, as fewer average grafts are completed in the OPCAB series,[12] and complete revascularization of the lateral wall of the left ventricle in the circumflex artery distribution is especially challenging. Two recent randomized trials have produced conflicting results.[13,14] Using data from real-world experience rather than randomized trials, the 3-yr outcomes for survival, death, or revascularization slightly benefited the OPCAB approach in a large (>9,000 off-pump and 59,000 on-pump cases) analysis of the Cardiac Surgery Reporting System in New York State.[15]

How does the current report help define where research efforts should be directed to give surgeons better direction as to when and where to use the OPCAB approach? The work by Cheng *et al.* helps to frame the important questions that have yet to be answered, which is one of the goals of any good meta-analysis.

Given the disparate reports on graft patency, it is not hard to believe that success depends on the experience and innate ability of a surgeon, and it is far more likely that many cardiac surgeons have practice patterns with less robust results than the best groups.[13] Therefore, it is crucial that graft patency be studied in a cross-section of centers with different practice patterns. It is also likely that any neurologic benefit of OPCAB in decreasing stroke in a group of patients without elevated risk for stroke would be small and difficult to prove. However, to dismiss the potential neurologic benefit of the OPCAB approach may also miss the mark. Any compromise in coronary outcome may be a reasonable trade-off in a group at high risk for stroke.[8] Therefore, the hypothesis that stroke can be decreased in a high-risk population can and should be tested with appropriate controls for

‡ American Heart Association: Heart disease and stroke statistics—2004 update. Dallas, American Heart Association, 2003. Available at: http://www.americanheart.org. Accessed September 13, 2004.

important confounders. Cheng *et al.* have helped to define these questions.

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