The following is the abstract of the article discussed in the subsequent letter:

**DiBona, Gerald F., and Linda L. Sawin.** Functional significance of the pattern of renal sympathetic nerve activation. Am J Physiol Regulatory Integrative Comp Physiol 277: R346–R353, 2000.—To assess the renal functional significance of the pattern of renal sympathetic nerve activation, computer-generated stimulus patterns (delivered at constant integrated voltage) were applied to the decentralized renal sympathetic nerve bundle and renal hemodynamic and excretory responses determined in anesthetized rats. When delivered at the same integrated voltage, stimulus patterns resembling those observed in in vivo multifiber recordings of renal sympathetic nerve activity (diamond-wave patterns) produced greater renal vasoconstrictor responses than conventional square-wave patterns. Within diamond-wave patterns, increasing integrated voltage by increasing amplitude produced twofold greater renal vasoconstrictor response than by increasing duration. With similar integrated voltages that were subthreshold for renal vasoconstriction, neither diamond- nor square-wave pattern altered glomerular filtration rate, whereas diamond- but not square-wave pattern reversibly decreased urinary sodium excretion by 25 ± 3%. At the same number of pulses per second, intermittent stimulation produced faster and greater renal vasoconstriction than continuous stimulation. At the same number of pulses per second, increases in rest period during intermittent stimulation proportionally augmented the renal vasoconstrictor response compared with that observed with continuous stimulation; the maximum augmentation of 55% occurred at a rest period of 500 ms. These results indicate that the pattern of renal sympathetic nerve stimulation (activity) significantly influences the rapidity, magnitude, and selectivity of the renal vascular and tubular responses.

**Electrical stimulation of the renal nerve neither replicates its natural burst pattern nor proves the importance of that pattern for renal function.**

**To the Editor:** DiBona and Sawin (1) recently assessed the renal functional significance of the pattern of renal sympathetic nerve activity (RSNA). They propose that, independently of its mean activity, the pattern of RSNA is able to influence the rapidity, magnitude, and selectivity of renal vascular and tubular responses. It is an attractive proposition that the central nervous system produces bursts of sympathetic nerve activity not simply as a by-product of its generation and control but also because this may be functionally important. We applaud the effort to take this question seriously, but we take issue with two aspects of the paper.

DiBona and Sawin applied different computer-generated stimulus patterns to the distal end of the renal nerve and observed their effects on end organ function. They compared the effects of “square-wave noise” stimuli with those of “diamond-shaped noise,” a waveform of similar appearance to that seen in mass activity recordings of the renal nerve. They achieved these stimulus shapes by imposing different envelopes upon a basic “noise” template, consisting of multiple, rapid voltage fluctuations. In the two cases, the duration of each burst and the burst repetition rate were the same, but the amplitude of the “diamond noise” waveform was adjusted to give it the same voltage-time product (area) as the square-wave noise. The diamond-noise stimulus was then found to be more effective at reducing sodium excretion and causing renal vasoconstriction than the square-wave noise.

When one records mass activity from the renal nerve, the bursts of activity that one sees are caused by the relatively synchronous occurrence of (usually) a single action potential in each of a large number of individual fibers. The crescendo-diminuendo pattern of each burst reflects the statistical spread of spike initiation times and conduction times within the fiber population. Now, when one applies an electrical stimulus to a nerve, each pulse (or rapid voltage swing) of the appropriate polarity will give rise to a single action potential in all fibers for which it is above threshold and which are not refractory. So every “burst equivalent” applied as a stimulus by DiBona and Sawin, consisting of multiple voltage swings (>30 in 150 ms), would have produced multiple action potentials in each of an unknown number of renal nerve fibers. Thus, despite a superficial resemblance to the recorded signal, such stimuli would have produced an activity pattern in the renal nerve with no basis in physiology. Be that as it may, has this unconventional stimulus waveform nevertheless uncovered a pattern coding that is significant for determining different renal effector responses? We believe not. The reason is that DiBona and Sawin chose to match the integrated voltage (area), rather than peak voltage, of their diamond- and square-wave noise patterns. As a result, for the same integrated voltage the diamond pattern achieved twice the peak voltage amplitude of the square wave. Because the voltages used for this part of the study were all submaximal (sometimes near threshold), the greater amplitude of the diamond waveform would undoubtedly have exceeded threshold for larger numbers of renal nerve fibers than the square waveform with which it was compared. Like has not been compared with like. A selective action of weak diamond noise stimuli on sodium excretion—the renal response with the lowest threshold of those studied—may also be explained on this basis.

In summary, all the actions of diamond noise stimuli reported in this study may be explained on the basis of their amplitude rather than their pattern. The burst-
The pattern of renal sympathetic nerve activity (RSNA) is a population phenomenon, depending on grouping of impulses between, not within, individual fibers. Different experiments will be needed to establish whether this pattern encodes information important for renal function.

REFERENCES


Simon Malpas
Department of Physiology
University of Auckland
Auckland, New Zealand
E-mail: s.malpas@auckland.ac.nz

Robin McAllen
Howard Florey Institute
University of Melbourne
Parkville, Victoria, Australia
E-mail: r.mcallen@hfi.unimelb.edu.au

REPLY

To the Editor: Our study was designed to draw attention to the differences between the pattern of recorded renal sympathetic nerve activity and the pattern of electrical stimulation of the renal nerves used experimentally.

The patterns of stimuli used were chosen to produce multiple action potentials in those renal nerve fibers in which the voltage threshold was exceeded by the voltage profiles contained within either the square-wave or diamond-wave patterns. This served to test whether the voltage profile inherent in the square-wave pattern (uniform amplitude throughout the stimulus duration) would produce renal functional responses that were different from those obtained with the diamond-wave pattern (nonuniform increasing-decreasing amplitude throughout the stimulus duration).

Renal sympathetic nerve activity is commonly measured as integrated voltage over short time intervals, i.e., amplitude × duration or area. Measurements of integrated voltage of renal sympathetic nerve activity have been widely used to evaluate responses to interventions within the same animal (absolute values) or compare responses to an intervention between animals (fractional change). It is increasingly recognized that such measurements do not provide quantitative data on potentially informative characteristics such as the amplitude, duration, and frequency of the contained multispike discharge. Therefore, in this initial study, in view of the widespread use of the integrated voltage measurement, we chose to match the square- and diamond-wave patterns for integrated voltage. Given the mathematics of the calculation of the area for a square- versus a diamond-wave pattern, we clearly stated in METHODS: "For the same integrated voltage, either the amplitude or the duration of the diamond wave will be twice that of the square wave." Furthermore, the results clearly showed that, at matched integrated voltage, increasing the amplitude but not the duration of the diamond-wave pattern produced a greater renal vasoconstrictor response.

It remains to be seen if the square- and diamond-wave patterns, when matched for amplitude rather than integrated voltage, produce different renal functional responses.

Gerald F. DiBona
Professor and Vice Chairman
Departments of Internal Medicine & Physiology
University of Iowa College of Medicine
Iowa City, Iowa 52242