Relief of Chronic Pain May Be Accompanied by an Increase in a Measure of Heart Rate Variability

R. J. Storella, PhD, Y. Shi, MD, D. M. O’Connor, RN, G. H. Pharo, DO, J. T. Abrams, MD, and J. Levitt, MD
Department of Anesthesiology, Allegheny University of the Health Sciences, Philadelphia, Pennsylvania

Decreased heart rate variability (HRV) is generally associated with compromise of cardiovascular feedback systems (1,2). Changes in HRV can be caused by congestive heart failure (1), myocardial infarction (3,4), diabetic autonomic dysfunction (5), aging (6), anesthesia (7,8), and surgery (9–12). We report initial findings using new techniques to measure HRV that we believe warrant additional investigation in a broad range of conditions involving pain.

The acute effect of pain to increase heart rate is well known. We hypothesized that there may be adaptive effects of chronic pain on the autonomic regulation of the cardiovascular system that could be reversed by analgesia, and we examined whether the acute relief of chronic pain affects HRV. We monitored several measures of HRV because these can differ in their ability to detect different conditions affecting the cardiovascular system (4,6,9,12–15). Traditional measures of HRV include sd(1,2). More recent measures estimate dimension (8,13,15,16) and entropy (6,8,9,15,17,18).

Methods
After institutional review board approval and informed consent, electrocardiograms were recorded from 16 patients scheduled for first or second treatment of lower back or leg pain. Patients had experienced pain for 3 mo to 1 yr and had a history and physical examination consistent with nerve root compression secondary to a herniated disk, which was confirmed by imaging (magnetic resonance imaging or computerized tomography scan). Treatment was a caudal epidural injection of a local anesthetic (5 mL of 0.25% bupivacaine) and a corticosteroid (methylprednisolone 80 mg). Pain and heart rate were measured just before and after treatment. Pain was assessed using a standard 10-point visual analog scale.

Based on their pain levels before and after treatment, patients were categorized into two groups: relief or control. Relief patients had substantial pretreatment pain (pain scale score ≥6) and experienced substantial pain relief (≥50% decrease in pain scale) after treatment (n = 9). Control patients had little pretreatment pain (pain scale score ≤5) and thus little pain relief (n = 7). Control patients were usually receiving a repeat treatment and were used to assess the effect of treatment on HRV in the absence of substantial pain relief.

Electrocardiograms were digitized (1000 Hz) and interbeat (R-R) intervals were calculated by using HRView software (Boston Medical Technologies, Brighton, MA). HRV was analyzed for a series of 500 normal R-R intervals. The mean ± sd of each series of 500 R-R intervals was calculated using standard software.

Point correlation dimension (PD2) is a measure of dimension (13,16) that is an estimate of the number of independent variables needed to describe a system. PD2 is calculated by reconstructing the series of R-R intervals as a series of vectors. In the present case, we start creating a series of vectors with two elements, the first pair of R-R intervals, the second pair, the third pair, etc. For any given reference vector, the number of vectors that are similar to it (i.e., vectors that do not differ by more than a specified amount r) is then counted (C). When log C is plotted against log r, the slope of the linear portion of the relationship can be calculated. As one recalculates the slopes of log C versus log r for vectors with increasing numbers of elements (pairs, triplets, etc.), the slopes converge on a value defined as the dimension. PD2 uses special constraints (most particularly on the portion of the curves used to calculate the slopes) so that the dimension for individual points in the time series is estimated accurately even if the dimension changes over time (13,16). The ability of PD2 to be measured for individual heart beats and its robustness to nonstationarity (i.e., change over the measurement period) are special advantages.
of PD2 compared with other measures of HRV. PD2 (13, 16) was determined for individual points in the R-R series by using PD2–02 software (Enhanced Cardiology, Lubbock, TX) using default criteria (tau = 1, interval = 4, linearity = 0.30, convergence = 0.40, plot length = 0.15) that have previously been found useful in HRV analysis (8, 15). For each series, the mean of the PD2 values determined for that series characterized the entire series.

Approximate entropy (ApEn) is derived from concepts of informational entropy (17, 18), which are concerned with the extent to which increasing knowledge about a series increases its predictability. It measures regularity (17). Similar to dimensional calculations, ApEn calculation reconstructs the R-R series into a series of vectors and determines the number of vectors that are the same within a tolerance r. However, whereas dimensional calculations use many r values and vector lengths (i.e., the number of R-R intervals in the vector), ApEn is calculated with one value of r and only two vector lengths. ApEn is calculated from the conditional likelihood that should two vectors differ by less than r at length m, they continue to differ by less than r at length m + 1. The use of r in this fashion is designed to allow ApEn to be robust with respect to the types of noise found in biomedical data. We calculated ApEn as described by Pincus et al. (17) and Pincus and Goldberger (18) using all 500 R-R intervals and calculation variables previously found (8, 9, 15, 17, 18) to be useful for heart rate applications: m = 2 (i.e., set the initial vector length at 2) and r (the tolerance level) set at 15% of the sd of the individual series being analyzed.

The HRV values before and after treatment were compared by using paired t-tests, with P < 0.05 considered significant.

### Results

In the control group, the mean ± sd pain score before treatment was 8.2 ± 1.1, and the mean pain score after treatment was 1.4 ± 1.9. In the relief group, the pain score before treatment was 3.1 ± 1.8, and the mean pain score after treatment was 1.0 ± 1.5.

Treatment had no significant effect (P > 0.05) on any heart rate variable measured for the control group of patients with little pain relief (Table 1).

In the relief group of patients with substantial pain relief (Table 2), the mean RR interval, sd, or ApEn did not differ before and after treatment. However, PD2 was significantly increased after treatment in the relief group (Table 2). Moreover, PD2 increased in eight of nine patients in the relief group, ≥5% in seven of nine patients. In contrast, PD2 increased after treatment by ≥5% in only two of the seven control patients.

### Discussion

Because patients in both the control and relief groups received the same treatment, the increase in PD2 in the relief group was due to pain reduction, not to the medication per se. This supports our hypothesis that there are effects of chronic pain that can be reversed by acute pain relief. Among the measures examined, PD2 seems best at detecting the effects of pain relief on heart rate, because the other measures did not change after treatment in either the relief or control groups. However, the small scope of this investigation limits the power of the analysis to detect significant effects of pain relief on the various measures of HRV, as well as the ability to relate the significant finding with PD2 to the wide variety of patients with chronic pain.

Different measures of HRV are designed to reflect different aspects of HRV and thus do not always provide the same information about the cardiovascular system (4, 6, 13–15). Thus, some measures of HRV (e.g., PD2) may be more attuned to the effects of chronic pain on the cardiovascular system than others (e.g., sd).

Another implication is that chronic pain itself may be detrimental to the cardiovascular system. Thus, increased HRV with pain relief may reflect a restoration of cardiovascular health. This follows from the argument that depressed levels of PD2 are associated with conditions of cardiovascular compromise (8, 13, 16) and that the increase with analgesia observed in the present study is a return from depressed levels of PD2. However, the extent to which poor PD2 can be used as an indicator of cardiovascular fitness under these conditions (particularly in the absence of unimpaired HRV according to other measures) must be determined.
Unlike power spectral measures of HRV, nonlinear measures of HRV are not clearly related to aspects of autonomic regulation of the cardiovascular system. Thus, there would be no standard physiological interpretation to the change of PD2 with pain relief.

Most importantly, the present results suggest that acute pain relief may be assessed by PD2 monitoring. Therefore, a broad range of continued investigation into the circumstances under which acute pain relief is accompanied by an increase in PD2 is warranted. Reliable software for the measurement of R-R intervals is commercially available from Boston Medical Technologies (Wakefield, MA), and executable computer code for PD2 can be obtained for research purposes from DE Water Gap Science Institute (Bangor, PA). If our finding that PD2 increases with pain relief is generally applicable, this could be an important objective adjunct to pain assessment in patients unable to self-report, such as children or adults with incapacitating neurologic deficits, e.g., from stroke or Alzheimer’s disease.

In conclusion, based on the present data, we hypothesize that acute relief of chronic pain is accompanied by an analgesia-specific increase in PD2 in many patients. We encourage others to test this hypothesis.

References