Correspondence

Mathematical Treatment of Autonomic Oscillations

To the Editor:

Montano et al[1] measured RR interval and muscle sympathetic nerve activity (MSNA) autoregressive spectral power before and after small- and large-dose atropine and drew inferences regarding human central autonomic mechanisms. I have several questions for the authors, as well as comments.

Your finding that low-dose atropine does not alter low-frequency RR-interval spectral power (Table 2) is at variance with results published by Ikuta et al,[2] which document significant increases. Your observation also is at variance with one of your principal conclusions (Abstract), that low-dose atropine decreases low-frequency RR-interval spectral power. In the absence of changes of measured low-frequency RR-interval spectral power, the reduction of normalized low-frequency RR-interval spectral power that you report simply signifies that low-dose atropine increases respiratory sinus arrhythmia.[3]

You report that low-dose atropine does not alter MSNA. This confirms an observation we made earlier.[4] You report also that high-dose atropine reduces muscle sympathetic nerve burst frequency, expressed as bursts/100 heart beats and bursts/min. Our study[4] also showed that large-dose atropine significantly reduces sympathetic activity expressed as bursts/100 heart beats. However, contrary to your observations, we found that large-dose atropine does not significantly alter sympathetic activity expressed as bursts/min. This finding was supported by a related observation that large-dose atropine does not alter antecubital vein plasma norepinephrine concentrations (which correlate well with MSNA).[5] Can you explain the disparity between your results and ours?

You present only "normalized" MSNA; therefore, it is impossible to determine whether measured MSNA frequency or amplitude spectral power changed in high or low ranges or both. I am aware of substantial uncertainty regarding what high- and low-frequency MSNA oscillations signify individually. My sense is that when you divide one by the other (and thereby "normalize" them), you enter largely uncharted territory. The notion that a change of this quotient documents central parasympathetic modulation of sympathetic oscillations is provocative. However, high-dose atropine is a complex intervention that profoundly alters autonomic function; there may be several alternative explanations for your results.

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To the Editor:

Recently, Montano et al[1] claimed a central vagotonic effect of high-dose atropine was evidenced in peroneal nerve muscle sympathetic outflow (MSNA). However, the authors' conclusions critically depend on "normalized units" to quantify low-frequency (LF) and high-frequency (HF) oscillations, a practice that can impart significance to the fluctuations beyond the regulatory mechanisms they subserve. This led to the conclusion that insight into parasympathetic nervous outflow can be gleaned from activity in a sympathetic nerve. We take issue with the interpretation of these data and believe that despite cautionary argument,[2] this approach subsumes the physiological meaning of cardiovascular oscillations to their spectral measures.

Heart period oscillations primarily derive from beat-by-beat autonomic control of systemic hemodynamics, ultimately buffering or augmenting arterial pressure fluctuations.[3] Vascular sympathetic rhythms have been identified also, although they may or may not be related directly to pressure fluctuations.[4,5] Spectral analysis conveniently quantifies these rhythms but in itself does not reveal their source. The findings of Montano et al rely solely on "normalizing" power spectral data, a technique that uncouples the oscillations from their physiological significance by measuring LF and HF relative to each other and making absolute amplitude irrelevant. In the present study, average heart period variance after atropine was <1% of control, representing almost complete elimination of beat-by-beat cardiac autonomic regulation. However, normalized units indicated that high-dose atropine reduced HF variability by only two thirds and increased LF variability by one third, divorcing spectral measures from the oscillations' minimal physiological significance. It is unclear how normalized units affected measures of MSNA variability, since absolute values were not provided.

The use of normalized units seems to presume that cardiovascular oscillations *are* rather than *derive from* autonomic outflows; that is, that HF *is* parasympathetic outflow and LF *is* sympathetic outflow. Furthermore, the authors apply this assumption to direct MSNA recordings, arriving at the curious conclusion that parasympathetic effects may be "revealed only by examination of the HF oscillation of MSNA."[1] Outflow from sympathetic nerves measured by peroneal microneurography is simply sympathetic outflow, regardless of the frequency at which it oscillates. However, "normalizing" HF and LF oscillations to one another and equating HF oscillations with parasympathetic outflow lead to a conclusion that ignores this simple fact.

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Response

We thank Dr Eckberg for his comments on our work.

Normalization of burst amplitudes and normalization of spectral power: Low-dose atropine did not cause a significant change in MSNA ($-15\pm14\%$). High-dose atropine decreased MSNA by $62\pm7\%$ ($P<0.03$). Dr Eckberg correctly refers to potential effects of "uncontrollable differences" in burst amplitude between subjects. These bursts are arbitrary measures and are best understood when they are normalized, an approach clearly favored by Dr Eckberg. Later in his comments, however, he suggests that our normalization of LF and HF powers of MSNA may not be appropriate. Since absolute LF and HF spectral measures are derived from absolute and arbitrary measures of MSNA, we believe that normalization helps mitigate the problem of variability between individuals and is consistent with the principles inherent in normalization of burst amplitudes.

Comparisons of our data with those of Ikuta et al[1]: They found a slight increase in LF RR spectral power after low-dose atropine, whereas we found no change. This difference in our studies needs to be kept in perspective. First, all subjects in our study were male. Ikuta et al studied only females. Second, we used a bolus dose of atropine; Ikuta et al used steady-state infusions increasing every 4 to 5 minutes to a total duration of 24 minutes. Third, we used an autoregressive algorithm, whereas Ikuta et al used a fast Fourier transform with an LF band between 0.05 and 0.15 Hz.

"Your observation is at variance with one of your principal conclusions": There is no conflict between the results and the conclusions in our Abstract. The Abstract refers exclusively to normalized data. It would then seem logical that the conclusion would also refer to normalized data.

Reduced normalized LF RR power simply signifies increased sinus arrhythmia: This suggestion highlights the importance of simultaneous measurements of both RR and MSNA spectral powers. Sinus arrhythmia (breathing-related changes in RR interval) occurs in the HF range. During low-dose atropine, the decrease in normalized LF RR in our study was accompanied by a decreased normalized LF of MSNA, and as described later, a decreased absolute LF power of MSNA. Thus, the similar effects of low-dose atropine not only on heart rate but also on MSNA demonstrate very clearly that effects of low-dose atropine on RR interval and on other measures of cardiovascular variability involve mechanisms other than sinus arrhythmia alone.

"Can you explain the disparity between your results and ours?": Our data are consistent with human studies by others[2] demonstrating that atropine increases blood pressure and decreases norepinephrine, which is also at odds with Dr Eckberg's findings. In Dr Eckberg's study, only descriptive information of the qualitative absence of changes in blood pressure, MSNA (in bursts per minute), and norepinephrine was provided. No actual measurements of these variables were reported. It is surprising that blood pressure did not increase after high-dose atropine.

Blood pressure in his study was measured noninvasively by use of an intermittent blood pressure monitor. By contrast, we report actual measures of continuous recordings of intra-arterial blood pressure and MSNA. We are very comfortable with our data showing that tachycardia after high-dose atropine is associated with an increase in intra-arterial systolic pressure and that this increase in systolic pressure is associated with an unequivocal reduction in MSNA, whether expressed as bursts per minute, bursts per 100 heart beats, arbitrary units, or normalized units. In view of the unreported data and qualitative descriptions of changes in blood pressure and MSNA referred to by Dr Eckberg, we are not comfortable speculating on theoretical reasons for inconsistencies in the findings in his study compared with more explicit data from our and other investigators' studies.[2]

"You present only 'normalized' MSNA": The following are the absolute values, in arbitrary units squared (au^2): MSNA LF: baseline 277 ± 179, low-dose atropine 107 ± 80 ($P<0.05$ versus baseline), and high-dose atropine 117 ± 103. MSNA HF: baseline 189 ± 124, low-dose atropine 108 ± 66, and high-dose atropine 161 ± 153. Thus, the decrease in normalized LF of MSNA after low-dose atropine is accompanied by a decrease in absolute LF of MSNA, demonstrating that the effect of low-dose atropine on the variability profile of MSNA is not simply a function of normalization.

"When you divide one by the other . . . , you enter largely uncharted territory": We are in uncharted territory whether we refer to ratios or absolute values, since we do not know the precise mechanism of the oscillations. By looking at simultaneous oscillatory characteristics of 2 different autonomic outflows, RR and MSNA, we may arrive at more reasonable interpretations. The only certainty is that methodological and conceptual paradigms will change as new experimental knowledge is gleaned.

We also appreciate Drs Taylor and Myers' interest in our findings:

"Heart period oscillations primarily derive from beat-by-beat autonomic control of systemic hemodynamics": This thesis is flawed for several reasons. First, LF oscillations have been demonstrated in the discharge of single brain stem neurons recorded in sinoaortic denervated cats; furthermore, this LF oscillation was present even in the absence of similar blood pressure fluctuations.[3] Second, in patients with heart failure studied before and after implantation of a left ventricular assist device, there is a striking, newly evident LF oscillation in RR interval of the native heart after device implantation.[4] This LF oscillation is manifest in the absence of any similar oscillation in blood pressure (which is dependent on the artificial heart output and independent of RR characteristics of the native heart). Third, in our study of atropine, low-dose atropine induced significant changes in the spectral patterns of both RR and MSNA in the absence of any changes in absolute or spectral components of intra-arterial blood pressure. Fourth, Dr Taylor himself concludes in one of his recent studies[5] that "respiratory sinus arrhythmia does not represent simple baroreflex buffering of arterial pressure."

"HF is parasympathetic outflow and LF is sympathetic outflow": Drs Taylor and Myers have misinterpreted and misrepresented our Results and Discussion in their last paragraph. We refer them to our extensive experimental evidence showing, for example, that despite high sympathetic drive, patients with heart failure have decreased or absent LF powers of RR and MSNA variability.[6] We also refer them to our unequivocal statements that "our data do not imply that the frequency composition of an oscillatory signal can be equated with the strength of that signal"[7] and "[our] findings should not be misinterpreted as implying that power spectral variability can be equated to direct measurements of sympathetic or other autonomic function."[8]

"*Outflow from sympathetic nerves . . . is simply sympathetic outflow, regardless of the frequency at which it oscillates*": It is not clear why Drs Taylor and Myers presume that central effects of low-dose atropine would affect heart rate exclusively and that sympathetic and parasympathetic outflows are mutually exclusive and devoid of interaction. Cholinergic muscarinic receptor blockade modulates adrenergic neurotransmission and norepinephrine release. Parasympathetic mechanisms therefore exert inhibitory effects on both cardiac[9] and vascular[10] sympathetic activity.

"*The authors . . . [arrive] at the curious conclusion that parasympathetic effects 'may be revealed only by examination of the HF oscillation of MSNA.'*" Any central parasympathetic muscarinic influence of high-dose atropine on RR variability would be masked by the peripheral (sinoatrial nodal) muscarinic blockade by atropine and the ensuing tachycardia. Changes in the MSNA oscillatory profile are consistent with central vagotonic effects of atropine, are evident whether one considers normalized or absolute measures, and occur even in the absence of any change in overall MSNA. These effects cannot be ignored. We welcome a better strategy for assessing in humans the influence of central muscarinic modulation of cardiovascular oscillations.

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C-Reactive Protein, Serum Amyloid A Protein, and Coronary Events

To the Editor:

Ridker et al[1] examined C-reactive protein (CRP) and serum amyloid A protein (SAA) in patients from CARE, a secondary-prevention study of pravastatin after myocardial infarction. They observed that the median plasma concentrations of CRP (0.31 versus 0.28 mg/dL; $P=0.05$) and SAA (0.34 versus 0.28 mg/dL; $P=0.006$) were significantly higher among those in whom coronary events occurred than in age- and sex matched controls. They concluded that the plasma concentrations of CRP and SAA predict the risk of recurrent coronary events among patients with prior myocardial infarction.

However, the matching of the subjects and controls was not complete. The group in whom events occurred contained a significantly higher proportion of diabetic patients (22.3% versus 9.7%; $P=0.001$), who are known to be at high risk of coronary events.[2]

We investigated 23 diabetic patients (mean age 62.0 years, SD 10.3, range 42 to 76; 18 men, 5 women) and 33 nondiabetic controls (61.3 years, SD 9.2, range 39 to 86; 31 men, 2 women), all with similar symptoms of stable angina and angiographically confirmed coronary disease. There were no significant differences between the groups in the mean number of affected coronary vessels (2.47 in diabetic and 2.21 in controls) or in history of hypertension, smoking, total cholesterol, cholesterol subfractions, or use of statins and aspirin. However, we found that the diabetic patients had significantly higher plasma concentrations of both CRP (mean, SD of log values 2.78, −0.60, +0.77 versus 1.52, −1.00, +2.92 mg/L, $P=0.05$) and SAA (mean, SD of log values 2.33, −1.52, +4.38 versus 1.15, −0.86, +3.38 mg/L, $P=0.042$). The values of these analytes were highly skewed, as usual, but were normalized by log transformation and were then subjected to a 1-way ANOVA.

In view of these findings, it is possible that higher levels of CRP and SAA observed by Ridker et al may have been due to an excess of diabetic patients in the event group. Larger studies will establish the role of CRP and SAA as predictors of future events in diabetic patients. The inflammatory response may be an important factor in the predisposition to atherothrombotic events in diabetes. The stimuli responsible for the acute-phase response in higher-risk atherosclerosis patients may arise from more severe, extensive, or unstable arterial lesions and/or from inflammation or low-grade infection elsewhere.

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C-Reactive Protein After First-Ever Ischemic Stroke

To the Editor:

We would like to compliment Paul Ridker and colleagues on the interesting study published in *Circulation*[1] regarding the role of inflammation in secondary prevention after myocardial infarction and add further observations. In their study, Ridker and colleagues[1] found an intriguing association between evidence of inflammation after myocardial infarction and an increased risk of recurrent coronary events. Though the mechanism responsible for this increased risk was unclear, the authors' recommendation to stratify postinfarction patients into relatively high- and low-risk groups according to inflammation levels sounds appropriate considering that the relevance of inflammation in cardiovascular disease is not completely established,[2] and it encourages us to study the role of C-reactive protein (CRP) levels in short-term prognosis after first-ever ischemic stroke.

We studied 30 ischemic stroke patients (10 men and 20 women) between 49 and 90 years of age (mean±SD 72±10 years) within 4 weeks of their qualifying event who were prospectively included in the Villa Pini Stroke Data Bank, Chieti, Italy. To avoid confounding factors, no patients with evidence of acute infection were included in the series. CRP samples were collected a median of 14 days from stroke event. The mean±SD Canadian Neurological Stroke Scale score was 9.0±2.7.

Increased CRP levels were detected in all examined patients. There was a notable difference in the mean level of CRP between patients and our healthy control subjects (3.8 mg/dL [95% CI 1.4 to 6.1] versus 0.3 mg/dL [95% CI 0 to 0.5]). Higher CRP levels also correlated with a significant neurological deficit ($P=0.01$) and a relevant disability ($P=0.05$), assessed with the Canadian Neurological Scale (Pearson correlation coefficient, $r=-0.6$) and the Barthel Index ($r=-0.4$), respectively. Patients with the highest CRP levels (>5.0 mg/dL) at study entry died (n=2), had severe complications after stroke (n=1; pulmonary embolism), or had no evidence of recovery (n=3) during the 2-month follow-up.

In conclusion, CRP was increased in patients with cerebral ischemia and appears to provide additional information regarding prognosis after ischemic stroke, as it appears to do after myocardial infarction. We believe that the role of CRP after ischemic stroke is far more complicated than perhaps we realize. CRP may be primarily an indicator of other vascular risk factors that are themselves related to prognosis. In our patients, CRP levels were correlated with serum ferritin levels ($r=0.7$; $P=0.002$), suggesting that the effect of CRP may rely on a positive association with serum ferritin. Iron overload may elevate the risk of atherosclerotic disease and has been identified as a risk factor and an outcome predictor in recent studies.[3,4]

The overall benefit of a preliminary study of CRP levels in all patients with cerebral ischemia is still undetermined, but this marker appears to provide additional information and should be included in future investigations of prognostic factors in stroke.

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Response

Inflammatory parameters may be elevated among individuals with diabetes mellitus, and Drs Choudhury and Leyva hypothesize on this basis that the elevations of C-reactive protein (CRP) and serum amyloid A (SAA) we observed among post–myocardial infarction (MI) patients in the CARE trial might be confounded by this factor. However, as described in our original article,[1] adjustment for diabetes had minimal impact on risk estimates. Specifically, in logistic regression analyses, the crude relative risk (RR) of recurrent coronary events for those with SAA levels above the 90th percentile was 1.61 ($P=0.03$), whereas the RR after adjustment for diabetes was 1.54 ($P=0.04$). Similarly, the crude RR associated with baseline CRP levels above the 90th percentile was 1.62 ($P=0.03$), whereas the RR after adjustment for diabetes was 1.58 ($P=0.04$). Thus, at least among the 782 participants evaluated, we found no important differences between diabetic and nondiabetic subjects with regard to either SAA (0.29 versus 0.30 mg/dL) or CRP (0.36 versus 0.38 mg/dL). Our data do not, however, address whether or not diabetes has an important effect on inflammatory parameters among those without a prior history of MI.

The role of CRP and other inflammatory markers as risk factors for ischemic stroke is less well established. However, in the prospective Physicians' Health Study of apparently healthy men, those with elevated baseline levels of CRP had a 2-fold increase in the risk of developing thromboembolic stroke over an 8-year follow-up period (RR=1.9, 95% CI 1.1 to 3.3).[2] Similar risk estimates have been reported for apparently healthy women.[3] Thus, the data provided from Drs Di Napoli, Di Gianfilippo, and Bocola regarding CRP levels among patients with acute stroke syndromes add to our understanding of the role of inflammation in cerebral thrombosis.

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Cardiac Neural Changes Before Vasovagal Syncope

To the Editor:

Furlan and colleagues[1] present 2 scenarios leading to orthostatically induced syncope in healthy young subjects: "progressive sympathetic activation" and "progressive sympathetic inhibition." Their physiological characterization of the scenarios is based in large part on the observed changes in heart rate variability (HRV).

HRV interpretation is complex. Muscle sympathetic nerve recordings show that sympathetic firing fluctuates on a beat-to-beat basis (see, for example, Reference 2).However, due to the time constants involved, the sinoatrial pacemaker can only follow the low-frequency fluctuations in sympathetic firing (10-second rhythm and slower), whereas faster-changing sympathetic activity is integrated and becomes apparent only in the average heart rate (HR). There is more uncertainty as to the interpretation of low-frequency (LF) HRV, and the Task Force on Heart Rate Variability disagrees as to whether it is sympathetic or sympathetic-plus-vagal modulations that are represented in LF.[3]

If the sympathovagal balance changes, HR changes too.[4] The LF dips and HF peaks that occur several times before the fainting episode in the sudden syncope case depicted in Figure 1 of the article by Furlan et al[1] are not reflected in HR itself. In their study, Furlan and colleagues present control subjects and fainting subjects categorized according to the 2 above-mentioned scenarios. HR increases in all groups, no matter the HRV responses (see Tables 2 and 3). The strongest increase is seen in the sudden fainters, the smallest in the control subjects. Therefore, progressive sympathetic inhibition is unlikely in any of the studied groups. An increase in HR while the sympathetic tone is lessening can only be conceived in the setting of simultaneously withdrawing vagal activity, for which the presented data bear no evidence. The assessment of vagal tone, sympathetic tone, or the sympathovagal balance from HRV remains speculative, especially in less common conditions.[5]

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Response

Swenne and colleagues raise the question of the lack of concomitant fluctuations in heart rate (HR) and in the oscillatory components of its variability (HRV) in subjects before tilt-induced syncope.[1]

In broad terms, HR depends on pacemaker intrinsic discharge, sympathetic and vagal neural activity, and circulatory neurohormones. Conversely, HRV reflects autonomic modulation of sinoatrial node activity. Thus, HR and HRV cannot be equated.

At least 3 variables (RR, low-frequency RR [LF_{RR}], and high-frequency RR [HF_{RR}]) are necessary to define the individual autonomic profile corresponding to a given posture,[2] which suggests that LF_{RR} and HF_{RR} contain information that is not simply inherent in the HR value. In addition, we found that a group of patients with syncope was characterized during tilt by a blunted increase of peroneal sympathetic nerve discharge (MSNA) and plasma norepinephrine levels but an exaggerated enhancement of epinephrine compared with controls.[3] Accordingly, HR increased to a similar level in both groups.[3]

Thus, under certain circumstances (eg, in the presence of an increased concentration of circulating catecholamines before syncope), HR may not parallel the changes of the spectral components of HRV. This seems to also apply to the other statement by Swenne and colleagues that vagal withdrawal is necessary to explain tachycardia while sympathetic tone is lessening.

The time-variant spectral approach enabled us to assess the time course of the changes in the oscillatory components of HRV (ie, the cardiac neural modulation) preceding the onset of syncope that would be otherwise undetectable by simple perusal of HR values. In the example shown in Figure 1,[1] the trends of HF_{RR} and LF_{RR} suggest a progressive rise in cardiac vagal modulation and decrease in sympathetic modulation in the case of "syncope with latency" before the onset of bradycardia. Clinical observation of these subjects also detected signs and symptoms of vagal progressive activation, such as increasing nausea, dizziness, and yawning that preceded the loss of consciousness.

Only after a "critical level" is reached, overwhelming the residual neurohormonal adrenergic activation, might vagal excitation and sympathetic inhibition silence the intrinsic sinoatrial node discharge.

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