Respiratory Patterns and Chronic Heart Failure

To the Editor:

A primary rhythm in the central nervous system that entrains both heart rate, blood pressure, and ventilation is suggested by profound effects on angina through consciously focusing on breathing and intervening pauses; adaptation to stress manifested by slower, deeper breathing, contributing to a 5.5-fold reduction in mortality; and the role of a slower rate of living in a lifespan increased 5-fold. This hypothesis is supported by the association of the reduction of blood pressure with longer, less recurrent speech hesitation pauses 1 second or more in length, manifested by pauses averaging 1.18 seconds at >2 per minute and 1.93 seconds at 1 per minute, thus yielding a ratio of 0.611, approximating the golden section 0.618 (range, 0.534 to 0.833). It is also supported by the fact that even brief (1–5-second) spontaneous pauses in ongoing patterned behaviors are accompanied by an immediate reduction of 5-hydroxytryptamine neuronal activity to or below baseline levels, coordinatig autonomc, motor, and sensory functions and serotonergic modulation of dopamine lateralized to the right hemisphere, thereby preventing disruption of brain stem cardiovascular control and left hemisphere dominance associated with hazardous surges of sympathetic tone in abnormal awake respiratory patterns that are common in chronic heart failure manifested by cardiac dysrhythmia and vasoconstriction.1–2

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Clinical Significance of Obstruction of the First Major Septal Branch

To the Editor:

The first major septal branch of the left anterior descending coronary artery seems to be closely related to disorder of the conduction system. Blood supply to the anterosuperior fascicle of the left bundle branch originates exclusively from the septal branches. During myocardial ischemic attack due to stenosis of the proximal left anterior descending coronary artery, from the ostium of the left coronary artery to just before the first major septal branch, left-axis deviation often appears.2–4 Very recently, we reported that transient leftward QRS-axis shift during treadmill exercise testing or PTCA was a highly specific marker of proximal left anterior descending coronary artery disease. However, no one has confirmed that this left-axis deviation associated with myocardial ischemia is due to ischemia of the first septal branch.

Recently, Knight et al5 reported that nonsurgical septal reduction due to selective intracoronary alcohol injection into the first major septal branch reduced left ventricular outflow tract obstruction and improved symptoms in patients with hypertrophic obstructive cardiomyopathy. They also reported the ECG changes associated with this procedure. The most common ECG change was the development of right bundle-branch block (11 of 13 patients). Right bundle-branch block was accompanied by anterior ST-segment elevation in 3 patients and by development of anterior Q waves in another 2. Two patients developed ventricular arrhythmias and 4 experienced transient complete heart block after injection of alcohol. We are very interested in the occurrence of right bundle-branch block and transient complete heart block.

The procedure performed by Knight et al provides an ideal opportunity to confirm the influence of the first septal branch on the ECG. Thus, we would like to ask Knight et al whether or not left-axis deviation occurred during the administration of alcohol into the first septal branch, and if it occurred, did left-axis deviation continue or not. In addition, we would like to ask why right bundle-branch block occurs during obstruction of the first septal branch of the left anterior descending artery.

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Phentolamine and Preconditioning During Coronary Angioplasty

To the Editor:

We read with great interest the article by Tomai et al. on the role of α-adrenergic receptors in ischemic preconditioning during coronary angioplasty. They provide evidence that pretreatment with phentolamine, a nonselective α-adrenoceptor blocking agent, abolishes the adaptation to myocardial ischemia during sequential coronary balloon inflations. The authors conclude a role for α-adrenergic receptors in mediating ischemic preconditioning in this model. This work extends previous work by the same group implicating a role for adenosine A1 receptors and the ATP-sensitive potassium channels (K_{ATP}) in ischemic preconditioning using the same model.

What the authors fail to mention in their discussion is the fact that phentolamine, independent of its α-blocking properties, has been shown to block K_{ATP} channels in insulin-producing cells, in vascular and nonvascular smooth muscle cells, and more recently, in cardiac ventricular myocytes. The involvement of K_{ATP} channels in the mechanism of ischemic preconditioning has been demonstrated in a number of animal models, as well as in isolated human atrial trabeculae. Furthermore, Tomai et al. have previously shown that blockade of K_{ATP} channels abolishes the myocardial adaptation observed during sequential coronary balloon inflations. It is therefore not possible to draw any conclusions about the exact mode of action of phentolamine and consequently about the mechanisms of ischemic preconditioning during coronary angioplasty from the presented data. Although, as the authors suggest, the α-blocking properties of phentolamine may be responsible for the loss of adaptation to ischemia, their observations can also be explained by blockade of K_{ATP} channels by phentolamine. Thus, while the findings of this study can be appreciated, one has to bear in mind the confounding effect of the multiple actions of this agent.

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Response

In the setting of coronary angioplasty, ATP-sensitive potassium (KATP) channels play a pivotal role in ischemic preconditioning and probably represent the final mediator of this phenomenon. Because phentolamine has been shown to act directly on KATP channels in experimental models, Dr Yellon and colleagues correctly suggest that in our study phentolamine might have abolished the adaptation to ischemia observed during sequential coronary balloon inflations not only by blockade of α-adrenergic receptors but also via blockade of KATP channels. This hypothesis is attractive; however, we have some concerns about this possible interpretation of our results. First, all studies showing blockade of KATP channels by phentolamine independently of its α-blocking properties were performed in vitro. To the best of our knowledge, an in vivo demonstration of such a mechanism is still lacking. Second, the doses of phentolamine able to block KATP channels in vitro are far higher than those used in our study. In fact, in the majority of in vitro studies, phentolamine concentration needed to block KATP channels was ≈0.1% mol/L, whereas in our study the estimated plasma concentration was ≈0.2 to 0.4% mol/L. Indeed, we used the lowest phentolamine dose able to reduce systolic arterial pressure by 10 mm Hg or to increase heart rate by 10 bpm (effects obviously mediated by α-adrenergic receptor blockade and not by KATP channel blockade, which would have had an opposite effect), in the absence of any significant coronary blood flow velocity changes. Thus, it is likely that the loss of adaptation to ischemia observed in our study was mainly accounted for by α-adrenergic receptor blockade by phentolamine.

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Cardiac Risk of Noncardiac Surgery

To the Editor:

I would like to compliment Dr Eagle and colleagues on an excellent article regarding cardiovascular risk of patients with coronary artery disease undergoing noncardiac surgery, published recently in Circulation. I do take issue, however, with the general statement that coronary revascularization done before the planned procedure is effective in reducing the risk of postoperative myocardial infarction and/or death.

Although retrospective studies, including the CASS registry patients used in Dr Eagle’s study, have shown a low mortality rate after noncardiac surgical procedures in patients who have undergone coronary bypass surgery, I do not believe that percutaneous revascularization procedures have been shown to be similarly effective. Again, retrospective studies have been done, such as the one by Huber et al from Mayo Clinic, that have not clearly shown whether PTCA is also “protective”.

It has been my perception that many angioplasty procedures are being performed, especially now with the widespread use of stenting, on patients who have been found by intensive preoperative testing and screening to have obstructive coronary disease, with the belief that the risk of surgery will be reduced. The article by Eagle et al may unintentionally foster behavior that is possibly inappropriate by not making a more clear distinction between surgical and percutaneous revascularization.

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Response

As Dr Miller points out, the prophylactic application of coronary angiography and related procedures for the expressed purpose of lowering coronary risk for noncardiac surgery remains ill defined. There have been at least 3 nonrandomized trials that suggest, on average, that patients who have successfully undergone coronary angioplasty without untoward complications are at relatively low risk for cardiac events after noncardiac surgery. However, these studies had no comparison group, and it is impossible to gauge whether any protection was conferred as a result of the angioplasty. Contrariwise, the evidence that suggests that prior successful coronary artery bypass surgery reduces the cardiac risk of noncardiac surgery is somewhat more compelling, but again no randomized trial is available with this specific question in mind. Since the management of patients with coronary heart disease with medical, interventional, and surgical treatments is rapidly evolving, it is difficult to know which strategy or strategies will be most effective for reducing perioperative complications without prospective studies.

Because of these uncertainties, the recently published guideline line on the evaluation and management of the patient with cardiac disease undergoing noncardiac surgery indicated that the justification to perform coronary artery angioplasty or coronary bypass surgery in such patients should be identical to the indications for these procedures in general. At this point, there is no compelling evidence that one should create special indications for these procedures in individuals just because they are being considered for noncardiac surgery. However, it certainly is true that the presentation for noncardiac surgery may represent...
the first opportunity to identify a patient in need of further therapy, and a noncardiac procedure may influence the timing surrounding a decision to perform coronary intervention or bypass surgery for appropriate indications.

It was not the intent of our article on the CASS database to promote routine preoperative testing and indiscriminate coronary interventions in patients being considered for noncardiac surgery. In fact, the national guideline on this topic specifically argues for a very selected use of noninvasive testing and interventional procedures in subsets of patients where current evidence supports their value.

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ACE Inhibition and Heart Failure

To the Editor:

The 2 articles by Spinale et al. and Brundage et al. represent an important contribution by demonstrating that combination therapy with both ACE inhibitors (ACEI) and AT1 angiotensin II (Ang II) receptor blockers provided greater improvement of left ventricular function and isolated myocyte contractile processes than either therapy used alone. Although further studies are necessary, they provided experimental data that may serve as an impetus to modify the clinical therapy of congestive heart failure. There are a few points that require clarification. The authors stated on page 2400 that “There was no significant difference in steady-state myocardial contractile function between the ACEI-alone group and the combined ACEI and AT1 Ang II blockade group.” This statement is contradicted by Table 1 (page 2401), which notes that both time to peak contraction and total contraction duration were significantly shorter in the combination treatment group than in the ACEI-alone group. It is also stated on page 2400, “In the AT1 Ang II receptor blockade and rapid pacing group, the absolute change in myocyte velocity of shortening with β-receptor stimulation was unchanged from rapid pacing–only values.” However, Figure 2 (page 2402) seems to indicate that the AT1 Ang II receptor blockade and rapid pacing group had a significantly slower shortening velocity than the rapid pacing–alone group.

The final problem is the omission in all of the figures and tables of any statistical comparison among the different groups versus the rapid pacing and AT1 Ang II receptor blocker group. For example, pacing produced a statistically significant increase in pulmonary capillary wedge pressure compared with control (29 versus 8 mm Hg) (see Table 1, page 2389). This increase was significantly attenuated by ACEI therapy alone and in the combined ACEI and Ang II receptor blocker group. However, comparisons between monotherapy with the AT1 Ang II receptor blocker and the other treatment groups are not reported. It is unclear if a difference, statistically significant or otherwise, exists with respect to the hemodynamic parameters in question.

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Response

In the 2-part series, we attempted to address the potential basis by which combined treatment with ACE inhibition and Ang-II receptor blockade may have beneficial effects compared with monotherapy treatment in a pig model of pacing-induced congestive heart failure (CHF). Dr Stein has raised several specific and important points regarding these studies that warrant clarification.

In order to more carefully examine the intrinsic effects of the specific treatment interventions on contractility, isolated left ventricular myocyte function was examined in a large number of cells from each group. Myocyte percent and velocity of shortening, which reflect the relative number and rate of cross-bridge formation, respectively, were improved in the ACE inhibition group and the combined treatment group compared with untreated CHF values. As indicated in the myocyte function summary table (page 2401), specific temporal characteristics of the contractile process, such as time to peak and duration of contraction, were shorter in the combined treatment group than with ACE inhibition alone. Temporal characteristics of the contractile process are influenced by a number of factors that include myofilament Ca2+ sensitivity, phosphorylation states, and Ca2+ release and sequestration. With combined ACE and AT1 Ang-II receptor blockade, L-type Ca2+ channel and sarcoplasmic reticulum Ca2+-ATPase density were increased from untreated CHF values. Thus, the shortened time to peak contraction and contraction duration in the combined treatment group was probably due, at least in part, to improved Ca2+ homeostatic processes. In these studies, the capacity of the left ventricular myocyte to respond to an inotropic stimulus was examined through β-adrenergic receptor stimulation. Left ventricular myocyte contractile response to 25 mmol/L isoproterenol was reduced in all rapid pacing groups compared with control myocytes. Combination therapy improved myocyte β-adrenergic response to a greater degree than ACE inhibition alone, whereas AT1 Ang-II receptor blockade with chronic rapid pacing did not result in a positive effect on β-receptor response. Indeed, as correctly pointed out by Dr Stein and indicated in Figure 2 (page 2402),
the absolute change in myocyte velocity of shortening after β-receptor stimulation was lower in the AT₁–Ang-II receptor blockade group compared with untreated CHF values. Extrapolation of these isolated myocyte contractile function data to in vivo myocardial performance can be problematic. Nevertheless, we have recently demonstrated that isolated myocyte contractile performance behaves in a predictable fashion with increased loading conditions. Thus, the improved capacity of left ventricular myocytes to respond to an inotropic stimulus in the combined ACE inhibition and AT₁–Ang-II receptor blockade group would suggest an improved capacity of these cells to respond to an external load.

The final query raised by Dr Stein was that of specific hemodynamic comparisons with monotherapy and combined therapy. Pairwise comparisons were performed using Bonferroni bounds, a fairly conservative statistical test. On the basis of this analysis, mean pulmonary artery pressure was not different between the untreated CHF group and the AT₁–Ang-II receptor blockade group but was lower in the ACE inhibition and combination treatment groups. From this analysis, mean pulmonary artery pressure was higher in the AT₁–Ang-II receptor blockade–treated group than in the ACE inhibition or combination therapy groups. Pulmonary vascular resistance was reduced in all treatment groups compared with untreated CHF values (Figure 2, page 2390). However, pulmonary vascular resistance was highest in the AT₁–Ang-II receptor blockade group compared with ACE inhibition monotherapy or combination treatment. It is important to point out that all of these measurements were performed in the anesthetized and ventilated animal. Future studies in the intact, conscious CHF preparation will be necessary to more carefully examine the potential differential hemodynamic effects of ACE inhibition and AT₁–Ang-II receptor blockade.

In closing, we wish to thank Dr Stein for his comments and hope that our studies will serve as a catalyst for future basic and clinical investigations regarding the utility of combined ACE inhibition and AT₁–Ang-II receptor blockade in the treatment of heart failure.

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