enthusiasm for the stentless porcine valve was not supported by the available data.

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REPLY

In Dr. Bloomfield’s letter discussing the Viewpoint (1) and Commentary (2) recently published in the Journal, Dr. Bloomfield notes that, in long-term follow-up of the Edinburgh Heart Valve Trial (3), mortality at 20 years did not differ between mechanical and tissue prostheses; 2) owing to differences in rates of re-operation, freedom from all valve-related complications was superior after mechanical mitral (but not aortic) valve replacement; and 3) over time, an increasing use of anticoagulant therapy was seen after tissue valve replacement. Dr. Bloomfield concludes that long-term follow-up of patients in randomized trials is the only means by which differences between prostheses can be elucidated.

Equivalence of mortality at 20 years supports that, using this end point, existing data (including those from the Edinburgh Heart Valve Trial) do not favor one prosthesis type over another. Freedom from all valve-related complications favors neither prosthesis type following aortic valve replacement, which comprises a preponderance of valve replacement surgeries in the United States; for both mitral and aortic valves, higher rates of re-operation after tissue compared with mechanical valve replacement exemplifies an inherent difference between prostheses. However, re-operation may be an end point more universally feared by cardiologists than by patients. Operative mortality for elective “re-do” valve replacement is not substantially different from that for initial surgery. Whereas some patients may wish to avoid re-operation at all costs, others are clearly willing, if given the option, to face the near-certainty of additional surgery in order to avoid daily anticoagulation. This argument is not obviated by an early experience showing increasing requirement over time for anticoagulation due to atrial fibrillation. Atrial fibrillation carries a lower thromboembolic risk (and therefore requires less aggressive anticoagulation) compared with mechanical mitral valve replacement. Moreover, earlier intervention as well as newer medical therapies and surgical and percutaneous procedures presently available for the treatment of atrial arrhythmias can be expected to lower the need for additional long-term anticoagulation compared with the cohort studied from the 1970s.

The tenet of the previously published Viewpoint (1) is not that long-term data are not desirable, but that for prosthetic valve choices that are made today, pertinent long-term, randomized data do not (and will never) exist. Although Dr. Bloomfield and his co-investigators (3) are to be commended for their study, the data as they relate to current decisions in prosthetic valve surgery are moot. In 2004, neither the Bjork-Shiley nor the original Hancock valve is available for implantation. Future randomized studies are unrealistic, and even if performed, valve technology would again have evolved by the time long-term data became available. Rather than attempting to extrapolate to current practice “tissue versus mechanical” data from valves that are obsolete and in some cases known to be poorly representative of currently available prostheses, this author asks the clinician to understand the limitations of these data, and to recognize that the gradual and continuing advances made in heart valve prostheses make a demand for only long-term, randomized data unrealistic and therefore unwise.

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Increased Randomness of Heart Rate Could Explain Increased Heart Rate Variability Preceding Onset of Atrial Fibrillation

The recent study in JACC by Amar et al. (1) describes significant increases in heart rate variability (HRV) in the period preceding the onset of atrial fibrillation (AF) in postoperative patients. This increase in HRV is interpreted by the investigators as reflecting increased parasympathetic and sympathetic activity. Whereas this is a possible explanation, another equally plausible explanation requires testing. We propose that the increase in HRV is due to an increase in the randomness of the heart-period signal, associated with a marked increase in sympathetic activation. This would be
consistent with a study in normals in which increasing doses of norepinephrine produced increased randomness of heart rate patterns (2). This hypothesis could easily be tested using multiple methods. One would be to plot the HRV power spectrum. If there were, indeed, an increase in vagal modulation of heart rate, there would be a clear increase in the size of a clearly seen peak in the high-frequency band. If an increase in randomness occurred, any increase in high-frequency power would be associated with an increasingly broad and abnormal-looking peak.

Alternatively, the Poincaré plot (a plot of each normal-to-normal interval vs. the next) could be generated. Increased randomness would be associated with an increasingly complex-looking plot (3). Finally, nonlinear HRV indices could be calculated. The calculation of the short-term fractal scaling exponent (4) would normally require about 1,000 beat-segments of data. The ratio of the axes of an ellipse fitted to the Poincaré plot (SD12) could be calculated for the same 5-min segments that were used for HRV. Increasing values of SD12, or decreasing values of the short-term scaling exponent, would be consistent with increasing randomness, rather than increased levels of autonomic modulation of the heart. Indeed, this technique has previously been applied to ventricular tachycardias, and increased SD12 was found to precede arrhythmic events (5).

Dr. Stein suggests that postoperative patients behave similarly to healthy volunteers in whom increased randomness of the heart-period signal was attributed to increasing doses of norepinephrine (1) and that the increases in both time- and frequency-domain parameters of heart rate variability (HRV) observed in our study do not represent vagal resurgence (2). We disagree with this hypothesis for several reasons.

First, in a study of patients undergoing major thoracic or abdominal surgery, we showed persistent downregulation and desensitization of the lymphocyte beta-adrenergic receptor/adenylyl cyclase system, which correlated with decrements in time- and frequency-domain indices of HRV throughout the first week after surgery (3). These changes occurred in the absence of change in perioperative epinephrine or norepinephrine levels.

Second, to suggest that our atrial fibrillation (AF) patients (n = 48) had a significantly different perioperative neurohumoral response than did that of controls (n = 48) matched for age, gender, and identical operation, appears unlikely. Finally, the HRV response seen in our control group was very similar to that seen in other patients undergoing major thoracic surgery, supporting the presence of parasympathetic withdrawal and not resurgence (4).

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Measurement of Circulating Vascular Endothelial Growth Factor in Obese Subjects

I read with interest the report by Rehman et al. (1) evaluating the circulating levels of hepatocyte growth factor (HGF) and vascular endothelial growth factor (VEGF) in obese subjects. Although the investigators should be congratulated by their results on the study of HGF, I would like to underline some methodological concerns regarding the measurement of VEGF levels.

Serum VEGF is not a suitable indicator of circulating extracellular VEGF levels at the time of sampling; VEGF is stored in the α-granules of platelets and is released during blood clotting. As a consequence, VEGF level in the serum is several-fold higher than that in matched plasma samples (2,3). In plasma, platelet degranulation is minimized by adding anticoagulants to the blood samples; in particular, CTAD (citrate, theophylline, adenosine, dipyridamole) plasma is recommended for the measurement of VEGF.