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LETTERS TO THE EDITOR

Dimensionality of Flow Data

Use of "three dimensional" in the title of the report on flow patterns in the left ventricle by Kim et al. (1) raises an issue of terminology. "Three dimensional," as used in that title, denoted acquisition of three directional components of velocity and not, as readers may initially have assumed, data representing a three-dimensional volume.

As acquisition of anatomic and flow data becomes more comprehensive, either by magnetic resonance or by advanced ultrasound techniques, concise and unambiguous terminology relating to dimensionality becomes necessary. In accordance with echocardiographic usage, I would propose the following conventions: *Two dimensional* or *cross sectional* = acquisition in two *spatial* dimensions of a plane. *Three dimensional* = acquisition in all three *spatial* dimensions of a volume. *Cine* = acquisition of a temporal sequence of data sets. In echocardiography, "real-time" may be used, except when sequential images are reconstructed from data acquired over longer periods of time, when "cine" is more appropriate. *Two* or *three directional* = acquisition of two or three orthogonal components of velocity (2). Either may also be called multidirectional in that correlation of two or three components may reveal vectors in many directions.

According to this terminology, Kim et al. acquired two-dimensional, *three-directional* cine velocity data. For comprehensive investigation of flow in the heart, three-dimensional, three-directional cine acquisition would be required. To refer to this type of acquisition, "seven dimensional" has been used (3), but it is questionable whether measurement of a directional component of velocity is equivalent to determination of location in the dimensions of space–time. Flow velocity components are measured in relation to points or regions located in space–time, but the converse is not true.

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Reply

Kilner has raised an important issue of terminology in relation to dimensionality of flow data. He suggests that *three dimensional* be used for spacial dimensions or volumes only and should not be used to describe vectorial velocity data. He also suggests that these data be described as *two* or *three directional* instead. In our opinion there is no need for this distinction because "three dimensional" can be used for both spacial (volume) as well as vectorial data. For instance, in the report to which Kilner refers (1), the title contains the words "three-dimensional magnetic resonance velocity." In this case "three-dimensional" clearly refers to the nature of the velocity, not to its spacial variation. In a more recent report (2) the title "Three-dimensional reconstruction of the flow in a human left heart using magnetic resonance phase velocity encoding" is used. In this case, "three-dimensional" clearly refers to the spacial variation in the velocity, not to its vectorial nature. For decades, a velocity field has been referred to by its dimensionality. For instance, fully developed laminar flow in a pipe (Poiseuille flow) is one-dimensional flow. That is, the velocity varies in the radial direction only, not in the axial or circumferential directions. Flow in a curved tube by comparison is three dimensional because it varies in the radial, axial and circumferential directions. The important point is that these statements refer to the flow field, not to the nature in which the flow field (velocity) is measured. Therefore, even if the velocity vector is measured at a single point (e.g., by laser Doppler anemometry), the three-dimentional velocity is still obtained.

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Zatebradine and Exercise Tolerance

We read with interest the report by Frishman et al. (1) in a recent issue of the Journal. The authors concluded that sinus node inhibition with the bradycardic agent zatebradine does not provide sufficient antianginal and anti-ischemic effects to be useful for long-term treatment in patients with chronic angina who are taking nifedipine.

The authors offered two possible explanations for their findings: 1) The Bruce protocol used in the exercise might not be sufficiently sensitive to the reduction in cardiac ischemia expected to result from a decrease in heart rate of 12 to 14 beats/min. 2) The reduction in heart rate might offset an increase in other determinants of myocardial oxygen consumption, such as ventricular preload or myocardial contractility.

Myocardial ischemia is a result of an imbalance between myocardial oxygen supply and demand. Thus, in addition to factors determining myocardial oxygen demand, factors determining myocardial oxygen supply must also be taken into consideration. Heart rate is an important determinant, not only of myocardial oxygen demand, but also of myocardial oxygen supply. Kjekshus (2) in a meta-analysis of all prospective randomized studies of beta-blockade therapy in postmyocardial infarction patients, concluded that heart rate reduction after therapy was the best predictor of survival.

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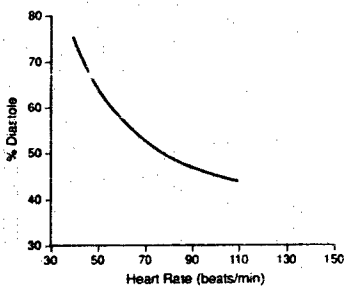

Figure 1. Relation between heart rate and percent diastole. Because of the nonlinear relation, small changes in heart rate produce dramatic changes in percent diastole, especially at a slower heart rate. Reprinted with permission from Boudoulas et al. (4).

The majority of coronary blood flow in normal humans occurs in diastole (3). In patients with coronary artery disease, systolic coronary flow is most likely lost because the perfusion pressure distal to the obstructive lesions is less than the ventricular systolic and intramural systolic pressure. In diastole, coronary artery pressure distal to a significant obstruction is low and probably does not change significantly with aortic pressure changes. When coronary perfusion pressure drops below a certain level, maximal vasodilation takes place. At this point, flow in the comprised coronary artery becomes dependent on diastolic perfusion time as well as on its perfusion pressure (3,4).

Ferro et al. (5) determined diastolic time, heart rate and rate-pressure product in patients with stable angina pectoris at 0.1-mV ST segment depression using supine and upright exercise and transesophageal pacing with and without therapy. They demonstrated that heart rate, exercise time and rate-pressure product varied considerably at ischemic threshold (0.1 mV), whereas diastolic time was similar regardless of the type of stress or status of therapy. The authors concluded that stress-induced myocardial ischemia occurs at "fixed" diastolic time for each individual patient.

Two factors determine the duration of diastolic perfusion time: 1) heart rate and 2) duration of systole. A decrease in heart rate or a shortening of systole, or both, will result in a prolongation of diastolic perfusion time and vice versa. Because of the nonlinear relation between heart rate and diastolic myocardial perfusion time, small changes in heart rate produce significant changes in diastolic time (Fig. 1). A decrease in heart rate <75 beats/min produces a dramatic increase in diastolic time (4).

Pharmacologic agents can have a significant effect on diastolic time. Thus, the effect of drugs on diastolic time, with consequent implications for myocardial perfusion, should be considered along with the effects of such agents on myocardial oxygen consumption. The effect of zatebradine on diastolic time was not evaluated in the present report (1).

Elastic properties of the aorta have also been shown to be important determinants of myocardial, especially subendocardial, blood flow (6). Aortic distensibility is significantly decreased in patients with coronary atherosclerosis compared with that in normal subjects (7). The effect of zatebradine on the elastic properties of the aorta has not been studied. A further deterioration of aortic compliance after therapy with zatebradine may result in a reduction of subendocardial blood flow, an effect that would offset the benefit of reducing heart rate.

Another plausible explanation for the results of the study by Frishman et al. is that the combined therapy of the two drugs (nifedipine plus zatebradine) may produce a "steal phenomenon." In

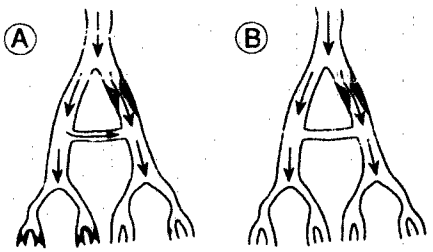

Figure 2. **A,** Schematic of coronary artery resistance in normal coronary artery and distal to a significant obstruction. Note that coronary artery resistance distal to a significant obstruction is decreased compared to that in a normal coronary artery; flow through collateral channels goes to the area perfused by the stenotic coronary artery. **B,** A potent arteriolar vasodilator will decrease significantly the resistance in the normal coronary artery but not the already low resistance, distal to coronary artery stenosis. Thus, the resistance in the normal coronary artery and distal to significant stenosis will become almost equal, with resulting cessation of flow through collateral channels from the normal to the stenotic coronary artery. This phenomenon is known as the *steal phenomenon*, and this pharmacologic effect can be considered an ischemic one. Reprinted with permission from Boudoulas et al. (8).

significant coronary artery stenosis, coronary artery resistance distal to a significant obstruction is low compared with that of a normal coronary artery, and thus blood tends to flow through collateral channels from a normal coronary distribution to that of the stenotic coronary artery (8) (Fig. 2). Potent arteriolar vasodilators decrease the coronary artery resistance in normal coronary vasculature but have much less effect on the vascular resistance distal to the obstruction. This may result in a reduction in collateral flow or in an actual shift of coronary blood flow through collateral channels from the region of the stenotic artery to that of a normal coronary artery. Collateral flow is a diastolic phenomenon. Thus, a reduction in heart rate, which increases diastolic time, may in the presence of maximal arteriolar vasodilation be accompanied by a steal phenomenon and be proischemic.

The recent study (1) showed that the administration of zatebradine in patients treated with nifedipine does not increase exercise tolerance. However, it is not known whether administration of nifedipine in patients treated with zatebradine will augment exercise tolerance. Studies have shown that combination therapy with calcium channel and beta-blockers increases exercise tolerance in patients with coronary artery disease. However, beta-blockers may prevent the steal phenomenon induced by nifedipine. Because studies have suggested that increased survival in coronary artery disease is related to a decrease in heart rate (2), a detrimental effect of nifedipine in patients with coronary artery disease and a reduced heart rate cannot be excluded (9).

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Reply

In response to Boudoulas and Leier, our findings with zatebradine do not just relate to a lack of an additive effect on exercise tolerance when the drug is administered to patients with angina pectoris already receiving nifedipine (1). There are reports showing that zatebradine is less effective than long-acting diltiazem on exercise tolerance when used as monotherapy (2) in patients with angina pectoris and no different from placebo in double-blind randomized trials (3). There are also data suggesting that zatebradine is less effective than propranolol in patients with angina pectoris despite similar reductions in heart rate. It is the combination of these clinical experiences that made us propose that negative inotropy or some metabolic protective action, or both, may be more important than heart rate reduction in the antianginal effects of rate-lowering calcium-entry and beta-adrenergic blocking agents (4). This is also suggested by the successful experience of Moss et al. (5) in using internal pacing to increase heart rate when using high dose beta-blockade to relieve symptoms in patients with refractory angina pectoris and bradycardia.

We did not evaluate diastolic time, systolic ejection time, collateral function or indexes of left ventricular function in our study and cannot respond to some of the specific remarks raised by Boudoulas and Leier.

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Dobutamine Stress Echocardiography in Orthotopic Heart Transplant Recipients

We read with great interest the report by Derumeaux et al. (1) on the evaluation of transplant coronary artery disease by dobutamine stress echocardiography. The authors deserve to be commended for using quantitative coronary angiography as the reference standard to compare the dobutamine stress echocardiographic findings. However, we would like to comment on the methods utilized to calculate sensitivity, specificity and positive and negative predictive values, which may have important implications on their findings. In their study (1), the authors used quantitative coronary angiography as the reference standard to evaluate the diagnostic accuracy of dobutamine stress echocardiography in 37 patients. They report a sensitivity and specificity of 86% and 91%, respectively. The problem is that these values (sensitivity, specificity, positive and negative predictive values) are not based on the comparative analysis of the results of dobutamine stress echocardiography versus those of quantitative coronary angiography. To derive the values the authors made two major assumptions: 1) Any inducible wall motion abnormality observed was attributable to the mere presence of focal epicardial coronary angiographic lesions rather than significant (>50%) lesions. 2) All focal epicardial coronary lesions were considered physiologically significant regardless of degree of stenosis. For example, in their study, seven patients with mild angiographic lesions (<40%) were considered to have true positive results solely on the basis of the positive results by dobutamine stress echocardiography. Obviously, this creates major problems in the analysis of sensitivity, specificity and positive and negative predictive accuracy. It is inconsistent to first use a test (quantitative coronary angiography in this case) as a reference standard to assess the accuracy of dobutamine stress test results and then later to incorporate insignificant coronary lesions as angiographically abnormal. For instance, when stress echocardiography results were positive in the presence of angiographic lesions as minimal as 15% stenosis, they were considered "true positive" in the calculation of sensitivity, specificity and positive and negative predictive values.

Without adhering to strict criteria based on quantitative angiography (reference standard), it may be difficult to know the false positive rate of dobutamine stress echocardiography in heart transplant recipients. Most investigators consider ≥50% stenosis angiographically significant stenosis (2–5). The authors correctly point out the limitations of coronary angiography in assessing lesion severity in heart transplant recipients. Coronary angiography is known to underestimate the severity of underlying coronary artery disease in heart transplant recipients (6). However, at present, it is premature to consider dobutamine stress echocardiography the diagnostic test of choice for transplant coronary artery disease and as a substitute for coronary angiography as the reference standard.

Using standard criteria for defining significant coronary disease by nonquantitative coronary angiography, we derived the sensitivity and specificity in 41 transplant recipients (2). The sensitivity and specificity were 95% and 55%, respectively, and the negative and positive predictive values were 92% and 76%, respectively (2). In the current