Antioxidants and Nitrate Tolerance

To the Editor:

We read with interest the recent report of Watanabe et al.1 demonstrating that nitrate tolerance, as shown by reduced vasodilating and platelet cGMP responses after sublingual 0.3-mg nitroglycerin tablets, develops quickly in both normal subjects and patients with ischemic heart disease; a 3-day application of a 10-mg/24-hour nitroglycerin tape is sufficient to induce these effects. Concomitant treatment with vitamin E (200 mg TID) for 3 days prevented the development of nitrate tolerance during continuous nitrate therapy, pointing to the potential usefulness of this antioxidant approach. Although vitamin E may have vascular effects of its own linked to its interaction with specific endothelial receptors,2 the conclusions of the authors seem supported by the data presented.

The development of nitrate tolerance represents a major therapeutic limitation inherent to the use of organic nitrates. Recent experimental data demonstrated that continuous nitroglycerin treatment is associated with increased vascular superoxide anion production and consequent inhibition of nitric oxide–mediated vasodilation induced by both endogenous and exogenous nitrates.3 If enhanced steady-state concentration of vascular superoxide anion is inherent in nitrate tolerance, one would expect reduced vascular effects of nitrates in any condition associated with an increased production of free radicals. Diabetes mellitus is a state of oxidative stress resulting from enhanced free radical formation and/or defects in antioxidants defenses.4 Impaired forearm vasodilatory response to nitroglycerin treatment is associated with increased vascular superoxide anion production and consequent inhibition of nitric oxide–mediated vasodilation induced by both endogenous and exogenous nitrates.5 If enhanced steady-state concentration of vascular superoxide anion is inherent in nitrate tolerance, one would expect reduced vascular effects of nitrates in any condition associated with an increased production of free radicals. Diabetes mellitus is a state of oxidative stress resulting from increased vascular superoxide anion production and consequent inhibition of nitric oxide–mediated vasodilation induced by both endogenous and exogenous nitrates.6

In addition to its hemodynamic effects, nitroglycerin improves some rheological properties of the normal blood because it reduces blood viscosity and increases blood filterability.6 None of these effects is seen in type 2 diabetic patients, in whom a paradoxical deterioration occurs after sublingual or transdermal nitroglycerin administration. Both vitamin E (300 mg/d) and glutathione (600 mg/d) for 7 days normalize the vascular responses to nitroglycerin in diabetic patients.5 Taken together, the data of Watanabe et al.1 and our previous results6 suggest that tolerance to the vascular effects of nitrates may be prevented by high doses of vitamin E (300 to 600 mg/d).

The evidence that 2 structurally unrelated antioxidants, vitamin E and glutathione, can normalize nitrate tolerance suggests a reduced vascular level of superoxide anion as a likely mechanism of action.

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Response

We appreciate the interest shown by Drs Giugliano and Marfella in our article1 and their supportive comments regarding our findings.

They reported in their articles2–3 that the beneficial rheological effects of nitroglycerin were impaired in patients with type 2 diabetes mellitus and that vitamin E and glutathione normalized the vascular responses to nitroglycerin. We reported in our recent article4 that intracellular production of cGMP was impaired in normal volunteers and patients with ischemic heart disease and that vitamin E normalized the response of cGMP production to nitroglycerin.

We recently reported that ascorbate, as well as vitamin E, normalized the response to nitroglycerin in normal volunteers and patients with ischemic heart disease.5 In another report,6 we showed that concomitant administration of ascorbate with nitroglycerin prevented the development of nitrate tolerance on hemodynamics and cGMP production in patients with congestive heart failure. Moreover, hydralazine,6–8 and carvedilol,10 both of which have antioxidant properties, have been reported to similarly prevent the development of nitrate tolerance. These data support the finding that oxidative stress caused by increased superoxide is an important mechanism of nitrate tolerance. We agree that supplementation with antioxidants is potentially useful for prevention of nitrate tolerance.

We again thank Drs Giugliano and Marfella for comments supporting our findings.

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Metabolism of Fatty Acids and Glucose

To the Editor:

Apstein and Taegtmeyer\(^1\) note that increased glycolytic substrate from glucose-insulin-potassium treatment has been shown to improve outcome in acute ischemic conditions and that this treatment attenuates the ischemia-induced decrease in ATP. One mechanism for this improvement should be due to the fact that in the metabolism of glucose, energy stored in the high-energy phosphate bonds requires relatively less oxygen than does an equivalent energy storage from metabolism of fatty acids. For example, oxidation of 1 mol of glucose yields a net gain of 38 high-energy phosphate bonds\(^2\) while utilizing 6 mol of O\(_2\), or 6.3 high-energy phosphate bonds per mole of O\(_2\). Metabolism of the fatty acid palmitate, on the other hand, yields 129 high-energy phosphate bonds\(^3\) while utilizing 31 mol of O\(_2\), or 4.1 high-energy phosphate bonds per mole of O\(_2\). Therefore, for each mole of O\(_2\) consumed, there is a 53.7% higher energy production in the form of high-energy phosphate bonds from the metabolism of glucose than from the metabolism of palmitate.

Nevertheless, each gram of palmitate produces significantly more high-energy bonds than a gram of glucose, and the caloric value of the stored high-energy phosphate bonds derived from the oxidation of a gram of palmitate is 2.4 times greater than that derived from a gram of glucose, albeit at a greater relative cost in oxygen. Hence, when oxygen is abundant and food is scarce, there is an advantage in utilizing fatty acids for fuel as opposed to using glucose. The reverse, however, would occur when food is plentiful and oxygen is scarce.

The above indicates that for the heart to work efficiently, it must be able to switch rapidly from the metabolism of fatty acids to the metabolism of glucose. Evidence shows that this indeed occurs and that with increased epinephrine,\(^4\) as in stress, or with hypoxia,\(^4\) the heart switches from fatty acid metabolism to glucose metabolism. Increasing the concentration of glucose and insulin would facilitate this switch\(^1\) and in so doing would decrease an ischemic burden. The decreased ability to make this switch could help explain the more devastating effects of ischemia in patients with diabetes mellitus and/or insulin resistance.

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Viability Assessment Before CABG

To the Editor:

In a recent edition of your journal, Kron et al\(^1\) presented their outcome data on patients with significantly impaired left ventricular (LV) function, presumably due to chronic ischemic cardiomyopathy, undergoing repeat revascularization via coronary bypass surgery. Surgical mortality was 9.3% among patients with an ejection fraction (EF) <25% and 12.0% for patients with an EF <36%, with the latter group’s mortality rate being statistically different compared with primary CABG.

I certainly agree with the authors that outcome is much worse for patients after redo bypass surgery with impaired ventricular function preoperatively but wonder why some assessment of myocardial viability was not undertaken before surgery in an attempt to select those patients most likely to benefit from the procedure. Although perhaps not universally accepted as a important variable in determining outcome during the early years of the trial (Rahimtoola’s original article on hibernation was published in 1989\(^2\)), the patients who underwent redo surgery in the later years may have benefited from an assessment of myocardial viability.

The benefit of assessing myocardial viability before surgery in patients with LV dysfunction has been shown with a number of different imaging modalities, including dobutamine echocardiography, myocardial perfusion scintigraphy with thallium and technetium agents, and PET. Eitzman et al\(^3\) showed in a study of 82 patients with advanced coronary artery disease and impaired LV function that PET imaging with \(^11\)N and \(^18\)fluorodeoxyglucose to assess blood flow and tissue metabolism could identify both patients at high risk for a cardiac event on medical therapy and patients with jeopardized myocardium who were most likely to benefit from revascularization. These results from Eitzman’s study were so compelling that Dr K.L. Gould wrote in the accompanying editorial,\(^4\) “I myself would consider revascularization only after cardiac positron emission tomography should I ever develop coronary artery disease.”
Although a surgical mortality rate as high as 12% in a population such as this may not be inordinately high, when the procedure is not emergent and viability is in question, a noninvasive assessment of tissue viability and therefore likelihood of functional improvement after surgery would likely prove to be cost-effective and possibly ethically correct, although still in need of improvements to increase specificity.

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**Response**

The principal objective of our study was to test the hypothesis that among patients with severe preoperative left ventricular (LV) dysfunction, those individuals undergoing reoperative CABG would have significantly worse outcomes than those undergoing primary CABG. Hence, preoperative assessment of myocardial viability was not a focus of our current investigation. It is possible, however, that future studies from the CABB Patch Trial will feature such data. Evaluation of tissue viability varied between institutions participating in the CABB Patch Trial, but in our study we made the assumption that at any single institution, the preoperative myocardial evaluation of patients undergoing reoperative CABG was similar to those referred for the primary operation.

We are aware of the positive results with such techniques as PET and $^{201}$TI scanning in predicting favorable outcomes after coronary revascularization in patients with severe preoperative LV dysfunction. However, routine and widespread application of PET scanning for this purpose is limited by both its cost and lack of availability. Although an earlier study from our institution questioned the validity of preoperative thallium scanning in predicting outcomes after CABG in patients with a severely reduced ejection fraction, more recent data suggest that this modality is actually quite reliable in this setting.

It deserves mention that variables other than an estimation of the degree of myocardial viability might also be reliable in predicting post-CABG morbidity and mortality in the setting of severely diminished LV function. For example, poor quality of the distal vessels on preoperative coronary arteriography had a 100% predictive value for early death after CABG in patients with an ejection fraction of $\leq 25%$. Perhaps assessment of a combination of preoperative factors might prove most effective and more reliable than any single criterion in selecting these high-risk patients for surgery.

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**Effect of Age Adjustment in Predicting Outcome**

**To the Editor:**

We read with interest the report of Ling et al that examined long-term outcome in a cohort of patients in whom pure mitral regurgitation due to flail leaflet was first diagnosed by echocardiography between 1980 and 1989.

In the introduction, the authors correctly state that it is uncertain whether early surgery or conservative management should be the preferred approach in these patients, irrespective of symptoms. Accordingly, they analyzed their cohort on an “intention-to-treat” basis, comparing follow-up events among patients who underwent surgery within 1 month after the diagnosis (the early-surgery group) with those who did not (the conservative-treatment group). Because this was not a randomized trial, the validity of the study is threatened by incomparability of prognosis of both treatment groups at baseline (ie, confounding).

Age is always an extremely important potential confounder. When the baseline characteristics of the patients at the time of diagnosis are compared (Table 1 in the article), there is an important difference in mean age between the early-surgery group and the conservative-treatment group (61.1 versus 66.5 years), which is called “slight” by the authors. The estimated probability of 10-year survival for 61- and 67-year-old men (at approximately 1990 in The Netherlands) was 77.7% and 63.7% respectively, a difference of 14%. The same difference (14% in 10-year survival) was found between early surgery and conservative treatment in the present study. The horizontal distance between the 2 groups in Figure 1 in the article is $\approx 4$ years; this means that patients in the early-surgery group lived $\approx 4$ years longer. If we look again at the Dutch general population in 1990, 61-year-olds lived 4 years longer than 67-year-olds. Thus, the expected impact of the age factor alone is of the same magnitude as the survival difference presented here as a result of treatment. It is unlikely that all age-related confounding is eliminated by including age as a linear covariate in a multivariate Cox model, if the data originate from an elderly population followed up over a long period of time. After all, the use of a linear component in the Cox model fails to correct for the extremely nonlinear (almost exponential) increase of “background mortality” (ie, the expected mortality in the source population) in higher-age groups. Thus, the baseline characteristic of age was biased in favor of survival in the early-surgery group, and it is doubtful whether this bias has been sufficiently removed.

Although there are more effective ways to deal with differences in age and associated expected mortality between 2 groups of patients, we agree with the authors that the only way to solve the issue of timing of surgery in asymptomatic patients with pure mitral regurgitation due to flail leaflets and
no signs of left ventricular dysfunction is to perform a randomized, controlled trial.

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Response

We appreciate the interest of R.B.A. van den Brink et al in our recent publication on early surgery in patients with mitral regurgitation due to flail leaflets.1 They raise an important question regarding the adequacy of our age adjustment and point to expected survival data relative to a 5-year age difference, suggesting that our “linear” age term in the Cox model does not adequately account for the increasing mortality at older ages. Several points need to be made in response to this concern:

First, it is not at all clear how relevant expected survival data for entire living populations are to the question of how to adjust survival data for a specific disease. Although comparison with expected survival data is useful for large populations, in particular of young patients, it is more difficult to interpret in older patients for several reasons.

The symptoms in the general “elderly” population of comparison are unknown, but it is a common observation that a notable percentage of this population expresses limitation in exercise capacity. Physical activity and exercise capacity are associated with long-term mortality,2 so that the exact expected survival of patients may vary according to their symptoms. Therefore, it is possible that the expected survival of mostly asymptomatic and elderly patients, such as those in the conservative treatment group, may well be far better than the “standard” expected survival.

Comorbidity is an important determinant of survival3 but is indeterminable in the general population. Comorbidity increases with age but cannot be adjusted for in the comparison to expected survival. Indeed, a population with comorbidity lower than the general population may have an expected survival that is better than “standard.” Conversely, the results of our study held true after adjustment in multivariate analysis for comorbidity.

The subset of 50-year-olds who have a disease may be a very different subset from the subset of 70-year olds who have the same disease. Indeed, if we had large enough populations of patients with a disease and without surgical intervention, we would almost certainly want to use these populations as the reference populations for calculating the appropriate age adjustments. Thus, internal age adjustment is not to be lightly dismissed in favor of the use of general external populations.

Second, the point may have been missed that, although age was biased in favor of the early-surgery group, the very important prognostic factor of symptoms was weighted against the early-surgery group. Because we appropriately controlled for age but also for the baseline predictors of outcome,4 a very sizable narrowing due to age adjustment was strongly counteracted by the adjustment for these predictors of outcome.

Third, it is incorrect to say that the proportional hazards model with a linear age term makes a linear adjustment for age. Despite the term “linear,” age enters into the Cox model in an exponential way. In our fitted model, every year of age was associated with a multiplicative factor of 1.1 in the hazard function. This factor is compounded, so that at a 5.4-year age difference, the factor is 1.67, or 67% higher, and at 10 years, it is 2.8, ie, a 3-fold higher risk. If we apply the 2 modes of correction (Cox model and expected survival based on the 1980 US white population) to the early-surgery group, a 5.4-year age difference decreases the expected 10-year survival from 79% to 67% using our Cox model and to 65% using the expected survival, demonstrating the magnitude of the age adjustment used in our model and the fact that these 2 modes of correction produce very similar results. Therefore, the association of outcome with treatment strategy cannot be attributed to our approach to age adjustment.

van den Brink et al correctly echo our statement that only a randomized trial can give a completely reliable answer to the question of the impact of early surgery on the outcome of severe mitral regurgitation. However, we believe that the results of our observational study suggest strongly that early surgery provides an improved outcome, and these results represent a first step in the consideration of this option for patients with severe mitral regurgitation. The considerable recent improvements in surgical results5–7 make this option clinically viable until a randomized trial is completed.

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Metabolism of Fatty Acids and Glucose
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