Revascularization After Myocardial Infarction

To the Editor:
Madsen et al 1 compared an invasive strategy of coronary arteriography and revascularization with a conservative strategy in patients with inducible myocardial ischemia after thrombolysis for a first myocardial infarction. Just over 500 patients aged ≤69 years and able to perform an exercise test were randomized to each strategy. The invasive-strategy patients underwent 266 angioplasty procedures and 147 bypass operations. There was no significant difference in mortality between the 2 groups at a median of 2.4 years. Rates of reinfarction and of readmission for unstable angina were 5.6% and 17.9%, respectively, for the invasive strategy and 10.5% and 29.5%, respectively, for the conservative strategy. From this, Madsen et al conclude that all subjects with inducible ischemia after a thrombolysed first myocardial infarction should be revascularized and then extend this sweeping recommendation, without any analysis of costs, days hospitalized, and quality of life, to all postinfarction patients with inducible ischemia.

It is unclear why in this study the invasive strategy’s absolute reduction of only 4.9% in the occurrence of myocardial infarction and of 11.6% in the number of admissions for unstable angina over 2.4 years, statistical significance notwithstanding, with no demonstrated reduction in mortality, constitutes sufficient clinical justification for sending all patients with inducible ischemia for coronary revascularization. Should patients with inducible ischemia who are symptomatic and limited to ≤5 metabolic equivalents (METs) be managed in the same way as asymptomatic patients with inducible ischemia performing ≥7 METs or >10 METs? Should all patients be similarly treated regardless of the degree of ST-segment depression or regardless of the threshold at which ischemia appears? Why should their risk be assumed to be the same? The study by Madsen et al provides no information on the occurrence of events in these clinically pertinent subsets of patients with inducible ischemia. Furthermore, it is questionable to randomize patients with inducible ischemia and a poor exercise performance (<5 METS), because several studies in both stable angina and after myocardial infarction have shown that such patients have a poor prognosis and therefore should undergo an “invasive strategy.” 2–7 The randomization of such patients loads the question prognosis and therefore should undergo an “invasive strategy” but rather in terms of an invasive strategy versus conservative strategy examining this interesting question. Such a trial would have posed the question not in terms of an invasive versus a conservative strategy but rather in terms of an invasive strategy versus the most optimal medical therapy, including β-blockers and lipid-lowering agents. Such a study would also have focused on subjects with inducible ischemia whose clinical management is presently uncertain (<5 METs exercise) and who ideally would have had a single identifiable culprit lesion on coronary arteriography. In the meantime, the findings of Madsen et al do not justify a blanket recommendation to revascularize all patients with inducible ischemia after myocardial infarction.

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Letters to the Editor must not exceed 400 words in length and may be subject to editing or abridgment. Letters must be limited to three authors and five references. They should not have tables or figures and should relate solely to an article published in Circulation within the preceding 12 weeks. Only some letters will be published. Authors of those selected for publication will receive prepublication proofs, and authors of the article cited in the letter will be invited to reply. Replies must be signed by all authors listed in the original publication.
Response

In reply to the comments made by Drs Bogaty and Dagenais, we would like to make the following remarks.

In our article, we suggest that all patients with inducible postinfarction ischemia should be "referred to coronary arteriography and revascularization accordingly" because this strategy resulted in the above-mentioned reduction in the incidence of acute myocardial infarction (AMI) and unstable angina.

We are preparing an analysis of cost benefit, but our primary aim was to evaluate the clinical effect; hence, the above conclusion.

Whether the results and conclusions are valid for all subgroups of patients is a general question for all intervention studies. We are preparing subanalysis of various subgroups, and so far, these results have not changed our overall conclusion.

There are, to the best of our knowledge, no controlled studies of high-risk post-AMI patients (other than the present study) that show a prognostic benefit of revascularization; hence, we do not see any ethical problem in randomizing such patients.

Drs Bogaty and Dagenais are surprised that we could show a difference, even though the patients were not a high-risk group. What the study shows is that postinfarction patients with ischemia constitute a proper group to select for procedures such as angiography, whether high risk or not.

In our article, we have already commented on the use of β-blockers. With regard to cholesterol-lowering treatment, the study was initiated before publication of the 4S study, but the effect on mortality will probably be found in both groups.

We still believe that our study gives scientific support for the widespread practice of catheterization of all postinfarction patients with ischemia, with subsequent revascularization.

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Vitamin C and Endothelial Dysfunction: What Is New?

To the Editor:

Several papers recently published in Circulation,1–3 and 1 in the Journal of Clinical Investigation,4 report that vitamin C is able to improve endothelial dysfunction. In each of these studies, the hypothesis is formulated that vitamin C may cause such an effect through its antioxidant activity, protecting NO from inactivation by superoxide anion.

Regarding all these studies, 3 questions should be taken into consideration:

1. The reported experiments do not constitute a strong support for the attribution of the effects of vitamin C to its antioxidant action. A demonstration that different antioxidants reproduce the same effect would have been useful.

2. Clinical trials based on the administration of vitamin C should be suggested with caution. Apart from the possibly increased risk of the formation of urinary oxalate stones during therapy with megadoses of ascorbic acid,5 vitamin C has been shown to increase the production of advanced glycation end products in diabetic patients.6 Moreover, several studies have demonstrated that vitamin C contributes only about 10% to the total antioxidant capacity of plasma.2,8

3. The bibliographies of all the above-mentioned studies do not adequately correspond with the existing literature. Indeed, my studies on the protective effects of several antioxidants, among with vitamin C, against endothelial dysfunction in diabetic patients9 and the antihypertensive effects of the same substances10 were published in 1990 and 1991, respectively. If my publications had been cited, the authors would have reported much of their works as refined and more-detailed confirmations of previously known data. Moreover, they would have found extensive evidence to support the hypothesis that vitamin C exerts certain effects because it is an antioxidant, as illustrated in my review on the possible role of oxidative stress in hypertension, published in 1993.11 In fact, my studies showed that the same effect observed with vitamin C can be reproduced with 2 other antioxidants, thiopronine and glutathione, respectively.9,10

The question of missing citations is surely an important one, and particularly so when the paternity of a finding or concept of some value is to be attributed.

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Response

We are grateful for the opportunity to respond to Dr Ceriello’s comments concerning our recent publication in Circulation.1 In response to his comments, we offer the following points.

We agree that our study, as well as others, did not directly examine the mechanism responsible for improved endothelial vasomotor function with ascorbic acid in patients with or at risk for vascular disease. However, we disagree with Dr Ceriello’s characterization that our study concluded “vitamin C may cause such an effect through its antioxidant activity, protecting NO from inactivation by superoxide anion.” In our study, ascorbic acid treatment produced a plasma concentration of $114\pm1\mu mol/L$. Although ascorbic acid has the capacity to scavenger superoxide anion, the rate constant for that reaction $(3.3\times10^{-10}\text{ mol }L^{-1}\text{ s}^{-1})$ is $\approx 10^{-5}$-fold less than the rate constant for the reaction between superoxide anion and NO $(1.9\times10^{-9}\text{ mol }L^{-1}\text{ s}^{-1})$.3,4 Moreover, the concentration of vitamin C in plasma is in the order of 50–100 mMol/L.3 Therefore, one would predict that an ascorbic acid concentration of 10 to 100 mMol/L would be
required to effectively compete for the reaction between NO and superoxide anion. This prediction was recently confirmed in our laboratory using an in vitro model of superoxide-mediated endothelial dysfunction. As mentioned in our initial article and in a more recent study, an effect of ascorbic acid on cellular redox state or glutathione metabolism should be considered. It remains possible that an effect of ascorbic acid to scavenge superoxide anion may contribute to the findings of other recent studies that used intra-arterial infusions that produced ascorbic acid concentrations in the 1 to 10 mmol/L range.6

We also disagree with Dr Ceriello’s implication that his prior studies using ascorbic acid, glutathione, and an analogue of N-acetylcysteine (thioprine) provide additional support that scavenging of superoxide accounts for the effect of ascorbic acid.5,6 Although glutathione is known to interact with superoxide, the rate of this reaction (101 to 102 mol L-1 s-1)59 dictates that glutathione competition with NO for superoxide would require extremely high glutathione concentrations (>100 mmol/L). A more plausible explanation for a concerted action of ascorbic acid, glutathione, and thioprine would involve some effect on intracellular redox state, as suggested by our recent publication.5

Finally, Dr Ceriello was very concerned that we had not cited his papers published in the journals Diabetes and Metabolism (Paris) and Clinical Science in 1990 and 1991, respectively.7,8 Although we thank Dr Ceriello for bringing his work to our attention, we could not have cited those papers as previous demonstrations that ascorbic acid improves endothelial function because neither paper specifically examined endothelial function. The Clinical Science paper demonstrated that a rapid intravenous infusion of ascorbic acid (1 g) acutely lowers systemic blood pressure in patients with diabetes and/or hypertension.9 In the Diabetes and Metabolism paper, Dr Ceriello reported that the same dose of ascorbic acid increased the extent of postischemic arteriolar dilation after acute hypertension. Circ. Res. 1994;90:2285–2290.


Prevalence of Penicillin-Resistant Viridans Streptococci in the Oral Flora of Japanese Children at Risk for Infective Endocarditis

To the Editor:

Viridans streptococci in oral flora are most frequently involved in infective endocarditis. The American Heart Association published new recommendations1 for the prevention of bacterial endocarditis in which the initial amoxicillin dose was reduced to 2 g and the second dose was no longer recommended. These alterations were based on a recent study that indicated a 2-g dose resulted in adequate serum levels for several hours and caused fewer gastrointestinal adverse effects.2 In the study, most oral streptococci that cause endocarditis were considered to be penicillin susceptible (minimal inhibitory concentrations [MIC] <0.1 mg/L), and some isolates were slightly less susceptible (MIC 0.1 to 0.5 mg/L).3 However, the recent susceptibilities of viridans streptococci in the oral flora of patients at risk for endocarditis are unknown.

We investigated the susceptibilities to penicillin G and amoxicillin of 60 viridans streptococcal isolates from 31 Japanese children (mean age, 6.7 years) at risk for infective endocarditis due to cardiac disease. The subjects had not been treated with antibiotics for ≥3 months before the study. Twenty-four (40%) isolates were penicillin resistant (MIC ≥0.25 mg/L for penicillin G), and 17 (28.3%) isolates were high-level resistant (MIC 4 to 8 mg/L for penicillin G). Nineteen (31.7%) isolates showed MICs of 4 to 16 mg/L for amoxicillin (13 isolates with MIC 4 mg/L, 5 with MIC 8 mg/L, and 1 with MIC 16 mg/L). The penicillin-resistant isolates were cultured from 19 (61.3%) of 31 children, suggesting a high prevalence of penicillin-resistant viridans streptococci in the oral flora of Japanese children at risk for endocarditis.

The tested strains in this study were not isolates that caused endocarditis but potent pathogens of this disease. The mean serum amoxicillin level 2 hours after the 2-g dose was reported to be 12.8 mg/L,2 which was adequate for all isolates tested except 1 with MIC 16 mg/L for amoxicillin. The mean serum level after 6 hours was 2.9 mg/L, which was reported to be well above the MIC for viridans streptococci.2 However, in our study, 31.7% of isolates showed MICs above the mean serum level at 6 hours. Fluckiger et al3 recently reported that the most important parameter for successful prophylaxis was the duration of an inhibitory concentration of amoxicillin in the serum. According to the new recommendations, the serum amoxicillin level 6 hours after the initial dose may be below the MICs of high-level


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penicillin-resistant isolates. Penicillin-resistant viridans streptococci were prevalent in the oral flora of Japanese children. In the United States, high rates of penicillin resistance were reported among viridans streptococci isolated from blood. In areas where penicillin-resistant viridans streptococci are prevalent, the second dose may be necessary for prophylaxis of endocarditis. It is important to monitor the susceptibilities of viridans streptococci in the oral flora of patients at risk for infective endocarditis.

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Response

The observations of Dr Nishi and associates of recovery of penicillin-resistant α-hemolytic streptococci from the oral cavities of 61% of Japanese children at risk for endocarditis is of considerable interest. We do share the concern of these investigators about antimicrobial prophylaxis; however, some specific points need to be emphasized.

α-Hemolytic streptococci in the oral cavity represent numerous species, not all of which are equally capable of causing endocarditis. The recovery of antimicrobial-resistant α-hemolytic streptococci from 325 blood cultures reported by Doern et al included 4 different species, and no information was provided about the clinical status of individuals from whom these cultures were obtained. To adequately address the significance of resistant α-hemolytic streptococci, it is imperative that the rate and degree of antimicrobial resistance of α-hemolytic streptococci recovered from blood cultures of individuals with endocarditis be carefully monitored.

The current American Heart Association recommendations may have to be reconsidered if and when the rate of resistance of α-hemolytic streptococci to penicillin (or amoxicillin) reaches levels of concern. Depending on the degree of resistance, a second dose of amoxicillin 6 hours after the initial dose may not necessarily be the best solution. A totally different prophylactic regimen may have to be recommended in this situation.

We believe that monitoring susceptibilities of α-hemolytic streptococci from blood cultures of patients with endocarditis may be our best guide.

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Variability of the Lumped Constant for $[^{18}F]2$-Deoxy-2-fluoroglucose and the Experimental Isolated Rat Heart Model: Clinical Perspectives for the Measurement of Myocardial Tissue Viability in Humans

To the Editor:

The recent publication of findings on the utilization rate for glucose (MR$_{glu}$) in the ischemic and reperfused isolated rat heart concludes that the lumped constant (LC) for $[^{18}F]2$-deoxy-2-fluoroglucose (FDG) is variable under conditions in which free fatty acids (FFAs) are the main metabolic substrate. The article thus signals a cautionary message to those workers using FDG in the fasted state. However, what is not stated in the take-home message is the important finding that the LC is unaffected by ischemia and reperfusion when circulating FFAs are low.

The authors assert that the coadministration of glucose and FFAs results in a far more physiological condition than glucose alone, and thus they pay scant attention to the equally physiological condition in which insulin levels are increased and FFA concentrations greatly diminished. This is unfortunate, because many cardiac studies are now performed using the euglycemic clamp, whereby a true physiological steady state is preserved by maintaining glucose at normal levels in the presence of increased insulin concentrations and almost negligible concentrations of circulating FFAs.

Clearly, the in vivo assessment of glucose utilization with FDG will always require recognition of the prevailing metabolic state of the myocardium. This is illustrated by the work of Bøtker et al, who showed variations in the in vivo value of the LC in humans. However, this variation of the LC appears to have minimal clinical relevance to the body of scientific knowledge resulting from studies using FDG protocols with the euglycemic clamp. A replotting of the data presented by Bøtker et al for a value of LC = 1.0 (the value used by our group and others) indicates minimal systematic error in MR$_{glu}$ for a wide range of plasma insulin values.

Worrisome aspects of the data produced with use of the isolated heart preparation exist. A complete lack of an increase in FDG uptake with the coadministration of insulin is associated with this model. This is never the case with in vivo investigation with the glucose clamp. In the recent publication in Circulation, there is a troubling variability in the uptake of FDG during the acute period of ischemia, and a significant and unexplained loss of tracer during the first half of the reperfusion period; is this an experimental issue? Moreover, the clinical significance of a value for LC with such large variability (0.86 ± 0.50) is not clear.

These uncertainties overshadow the other important issues, such as the assertion that hibernating myocardium is ischemic. Blood flow to hibernating myocardium has been shown to be within normal limits in most patients.

The findings of the work in the isolated heart have begun to answer the question as to whether FDG can be used noninvasively to identify meaningful differences in MR$_{glu}$ in various pathological conditions in humans. The LC for FDG has been shown to be invariant during the administration of epinephrine, increased workload, and acute ischemia and reperfusion after acute myocardial infarction at low FFA levels. The LC for FDG is clearly affected by nutritional changes, but the euglycemic clamp represents a physiologically appropriate methodological inter-
vention to obviate this problem and allow FDG PET to be used for the assessment of tissue viability.

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Response

Drs Rhodes and Camici are correct when they question the clinical significance of our in vitro observations on the tracer/tracee relation of FDG and glucose. We were careful to point out in the discussion of our article that protocols more closely reflecting clinical circumstances will have to be investigated. The issue is not a comparison between in vivo and in vitro models for the noninvasive assessment of glucose uptake. The issue is to recognize that the LC is not a static but rather a dynamic value, as our experiments have shown. The change of the LC precludes the quantitative measurement of myocardial glucose uptake with FDG. Without quantitation, it is in turn not possible to address mechanisms regulating glucose uptake by the normal, ischemic, and reperfused myocardium. At present, quantitation remains an elusive goal. Moreover, lack of quantitation is a major obstacle for the use of FDG as a research tool in cardiac metabolism.

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Prevalence of Penicillin-Resistant Viridans Streptococci in the Oral Flora of Japanese Children at Risk for Infective Endocarditis
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