Revascularization After Myocardial Infarction

To the Editor:

Madsen et al 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, was not acknowledged and then extended this sweeping recommendation, without any analysis of costs, days hospitalized, and quality of life, to all postinfarction patients with inducible ischemia.

There were no significant differences in reinfarction rates or the number of admissions for unstable angina 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, was not acknowledged and then extended this sweeping recommendation, without any analysis of costs, days hospitalized, and quality of life, to all postinfarction patients with inducible ischemia.

An opportunity was missed to perform a more satisfactory trial 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.

Gilles R. Dagenais, MD
Department of Medicine
University of Montreal
Montreal, Quebec, Canada

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 revascularized 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.

Jan Kyst Madsen, MD, PhD
Associate Professor
Peer Grande, MD, PhD
Associate Professor
Rigshospitalet
Copenhagen, Denmark

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.7,8

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.

Antonio Ceriello, MD
Chair of Internal Medicine
University of Udine
Udine, Italy


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±11 μmol/L. Although ascorbic acid has the capacity to scavange superoxide anion, the rate constant for that reaction (3.3×1010 mol⁻¹·s⁻¹) is ≈10⁻⁹-fold less than the rate constant for the reaction between superoxide anion and NO (1·10¹⁰ mol⁻¹·s⁻¹). Therefore, the basis of an estimated local NO concentration of 0.1 to 1 μmol/L,1 we 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. We also disagree with Dr Ceriello’s implication that his prior studies using ascorbic acid, glutathione, and an analogue of N-acetylcysteine (thiopronine) provide additional support that scavenging of superoxide accounts for the effect of ascorbic acid. Although glutathione is known to interact with superoxide, the rate of this reaction (10^2 to 10^3 mol L^-1 s^-1) 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 thiopronine would involve some effect on intracellular redox state, as suggested by our recent publication.

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. 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. In the Diabetes and Metabolism paper, Dr Ceriello reported that the same dose of ascorbic acid increased the extent of postischemic reactive hyperemia in diabetic subjects. Subsequent studies have demonstrated that peak reactive hyperemia is largely an endothelium-independent response. Furthermore, the latter study was flawed because ascorbic acid and the other compounds used in the study induced large changes in baseline forearm blood flow (and presumably blood pressure), making it hard to interpret the findings. On the basis of those publications, Dr Ceriello claims “paternity” for the idea that “oxidative stress” plays a role in vascular dysfunction in atherosclerosis and related disease states. In response, we can only refer Dr Ceriello to earlier and concurrent work on this subject.

John F. Keaney, Jr, MD
Joseph A. Vita, MD
Boston University School of Medicine
Boston, Mass

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.

Jun-ichiro Nishi, MD
Masao Yoshinaga, MD
Yuichi Nomura, MD
Department of Pediatrics
Faculty of Medicine
Kagoshima University
Kagoshima, Japan


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.

Adnan S. Dajani, MD
Kathryn A. Taubert, PhD
Patricia L. Ferrieri, MD
For the Writing Group
American Heart Association
Dallas, Tex


Variability of the Lumped Constant for [18F]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\text{glu}) in the ischemic and reperfused isolated rat heart1 concludes that the lumped constant (LC) for [18F]-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,2 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.,3 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.4 A reploting 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\text{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 glucose and insulin was associated with this model.5 This is never the case with in vivo investigation with the glucose clamp. In the recent publication in Circulation,1 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.3

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\text{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 ischemia at low FFA levels. The LC for FDG is clearly preserved by maintaining glucose at normal levels in the presence of increased insulin concentrations and almost negligible concentrations of circulating FFAs.

Kathryn A. Taubert, PhD
American Heart Association
Dallas, Tex


vention to obviate this problem and allow FDG PET to be used for the assessment of tissue viability.

Christopher G. Rhodes
Paolo G. Camici
MRC Cyclotron Unit
Imperial College School of Medicine
Hammersmith Hospital Campus
London, UK


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.

Heinrich Taegtmeyer, MD, DPhil
UT-Houston Medical School
Houston, Tex

Torsten Doenst, MD
Department of Cardiovascular Surgery
University of Freiburg
Freiburg, Germany


Prevalence of Penicillin-Resistant Viridans Streptococci in the Oral Flora of Japanese Children at Risk for Infective Endocarditis
Jun-ichiro Nishi, Masao Yoshinaga and Yuichi Nomura

Circulation. 1999;99:1272b-1276
doi: 10.1161/01.CIR.99.9.1272.b

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/99/9/1272b

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/