Percutaneous Treatment of Left Main Coronary Stenosis

To the Editor:

The multicenter report by Dr Ellis and colleagues of 107 patients with left main coronary obstruction who were not candidates for surgery and in whom an attempt was made to reopen the left main coronary vessel by percutaneous techniques with different devices has significant implications for the cardiac surgeon when the patient is a candidate for a surgical procedure. Ellis et al deserve to be congratulated for this important piece of information.

There have been numerous reports of patients who have undergone direct attempts to widen the left main trunk of the coronary artery to provide antegrade flow when the distal branches are not significantly involved with obstructions. One of the main complications of this approach is early restenosis of the vessel and, occasionally, total occlusion, with fatal consequences for the patient.

It appears that the main trunk of the coronary artery reacts unfavorably to endarterectomy procedures or any type of trauma damaging the intima. Occlusion of the left main artery has been reported after radiofrequency ablation for left-sided tachycardias and after PTCA done in the left coronary system. This has been seen after plain cardiac catheterization when the tip of the catheter injures the intima or when perfusion cannulas are positioned in coronary arteries directly to infuse cardioplegia during aortic valve surgery.

In our institution, we had a case in which the left anterior descending artery (LAD) and the circumflex vessel had separate origins from the aorta, both showing ostial obstructions. The LAD was given a saphenous patch at the ostia to widen its diameter, and the circumflex vessel was treated with an endarterectomy because its orifice was immediately below the LAD origin. Within a few days, the artery undergoing endarterectomy developed severe obstruction that required reoperation, but not so the LAD.

My question addresses this issue: In 53 patients, stents were implanted; in the other 54, only balloon angioplasty was performed. At the time of repeated angiography, 14.3% of the case patients who underwent stent implants were restenosed versus 50% of patients in whom only PTCA was performed (Table 6).

The authors mention under “Post–Hospital Discharge Outcome” that 9 survivors (10.6%) died of cardiac causes within 6 months. I wonder whether the important factor is not the presence of unstable angina or age but the fact that these patients did not have stents placed. In this same section, we read: “Of patients eligible for >4-month angiography, 70% had known studies, of whom 22.0% had restenosis (stenosis ≥50%).” The only variable related to risk of restenosis was ostial left main trunk, but I wonder whether the complication occurs due to lack of use of stents.


Response

Dr Molina addresses a key issue with regard to assessment of the clinical safety and utility of percutaneous interventions for patients with unprotected left main coronary stenoses. In experienced centers and in patients with relatively well-preserved left ventricular function, a percutaneous approach (either stenting or directional atherectomy) seems to be reasonably safe, at least in the short run. A better understanding of the risk of cardiac death within the first year after treatment is needed, however, and Dr Molina suggests that perhaps the 11% incidence of this untoward outcome in our initial series is due to the fact that only half the patients received coronary stents. This issue has certainly drawn our attention also, and in fact, we have extended our registry to include over 270 consecutively treated patients and specifically addressed this issue in a recent analysis (J Am Coll Cardiol. 1998;31:214A). In this analysis, 9% of patients died within 9 months after initially successful treatment, and in multivariate logistic regression analysis, left ventricular ejection fraction ≤30% and initial presentation with rest or progressive angina were both significant independent correlates of death (multivariate odds ratios 17.1 and 4.3, respectively). Stenting and directional atherectomy tended to be offered to lower-risk patients more often than was balloon angioplasty. After adjustment for the aforementioned risk factors, there was only a trend suggesting added risk with balloon angioplasty (P=0.13) compared with both stenting and directional coronary atherectomy. There was no discernible difference with regard to outcome between stenting and atherectomy. We recognize that this sort of analysis cannot always fully adjust for unmeasured variables, but short of a randomized trial, this is the best answer we have. Given that the
in-hospital cardiac mortality rate for patients with ejection fraction >30% who present with stable angina and who are treated with directional atherectomy or stenting is only 1.3% in this series and their 9-month mortality rate is 4.4%. It may be that now is an appropriate time for a randomized, controlled trial in such patients against the current gold standard: bypass surgery.

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Acetylcholine and Endothelial Function

To the Editor:

Hasdai et al. reported that myocardial perfusion defects are produced in response to acetylcholine $10^{-4}$ mol/L IC. However, acetylcholine has dual effects on coronary artery tone depending on the intracoronary concentration of acetylcholine and the presence of coronary athereuma. In normal coronary arteries, vasodilation, mediated by the endothelial cells, occurs at low concentrations and vasoconstriction, mediated by a direct action on the smooth muscle cells, at higher concentrations. In atheromatous coronary arteries, constriction and dilation occur at low concentration and only constriction occurs at high concentrations of acetylcholine.2,3

We have studied the responses of epicardial coronary arteries to intracoronary infusion of acetylcholine in 15 patients with normal coronary arteriograms, chest pain, and risk factors for coronary artery disease. In 53% of patients, there was both constriction and dilation of proximal and distal segments coexisting not only in different coronary arteries but also in different segments of the same artery at $10^{-6}$ to $10^{-7}$ mol/L acetylcholine. At $10^{-4}$ and $10^{-3}$ mol/L, the dilatation response was blunted and constriction predominated.

We also studied the responses of stenotic and nonstenotic segments to intracoronary infusion of acetylcholine in 18 patients with coronary artery disease and stable angina. In all the patients and in 90% to 100% of the stenotic segments, vasoconstriction occurred at $10^{-5}$ to $10^{-4}$ mol/L acetylcholine (Figure). In particular, in response to $10^{-4}$ mol/L acetylcholine, both the stenotic segments and the adjacent reference segment constricted significantly ($26.7\pm4.3$ and $11.4\pm2.0\%$, respectively; Figure) with evidence of myocardial ischemia (ST segment change and/or chest pain in $\approx50\%$ of patients). These findings indicate that when acetylcholine is infused in high doses in the presence of atherosclerosis, its direct smooth muscle cell constrictor effects are dominant compared with the endothelial vasodilator effects. These smooth muscle cell responses to acetylcholine may be exaggerated and contribute to a reduction of the myocardial perfusion. Furthermore, our preliminary observations indicate that atherosclerotic segments that constrict in response to acetylcholine may vasodilate in response to substance P (an endothelium-dependent vasodilator).6 Substance P may therefore be a better test of endothelial function than a high dose of acetylcholine. It is difficult to conclude from either our studies or that of Hasdai et al that myocardial ischemia in these patients is due to microvascular endothelial dysfunction.

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Response

We have read with interest the letter to the editor by Dr Tousoulis and colleagues. They raised several very important issues regarding the coronary response to infusion of acetylcholine in humans. Tousoulis and colleagues demonstrated in 15 patients that acetylcholine infusion resulted in epicardial coronary vasoconstriction. Moreover, they emphasize an important point: that the response of the coronary vasculature to acetylcholine may be heterogeneous.
Their observation underscored the significance of measuring coronary blood flow and coronary vascular resistance in response to substances like acetylcholine and substance P, rather than measuring a single-segment change in diameter. The change in epicardial coronary artery diameter in response to acetylcholine does not necessarily correlate with the change in coronary blood flow (Hasdai et al, unpublished data, 1998). Because control of coronary blood flow to the myocardium is mainly at the level of the microcirculation, it is essential to follow the change in coronary blood flow in response to acetylcholine rather than the change in epicardial coronary artery diameter.

The next issue that Tousoulis et al raise is the differential response to acetylcholine versus substance P in patients with normal coronary arteries and chest pain. Previous investigations by Quyyumi et al compared coronary blood flow and coronary vascular rate in response to acetylcholine and substance P. They suggested that the dysfunction of the stimulatory capacity of the endothelial cell layer is not restricted to the muscarinic receptors and extends to others such as substance P. Thus, acetylcholine may serve as a clinically useful tool to assess the integrity of the endothelium. Moreover, previous studies established the relationship between the pharmacological response to acetylcholine and the physiological vasodilation response to metabolic stresses such as mental stress, exercise, and hyperemia.

Another issue raised by Tousoulis et al is the correlation between the degree of atherosclerosis and the response to acetylcholine. We have previously demonstrated that there is no relationship between the degree of coronary atherosclerosis by intravascular ultrasound and the response to acetylcholine. Thus, it is difficult to predict the response of the endothelium to pharmacological stimuli on the basis of the degree of coronary atherosclerosis.

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Heart Rate Variability Standards

To the Editor:

The special report on heart rate variability by the European Society of Cardiology and North American Society of Pacing and Electrophysiology presented important standards of measurement for heart rate variability analysis. In the report, the frequency range of the total power was defined as 0.04 to 0.4 Hz, the low-frequency (LF) component as 0.04 to 0.15 Hz, and the high-frequency (HF) component as 0.15 to 0.4 Hz. There are several problems in the calculation of specific spectral powers using these standards of measurement in heart rate variability analysis.

As stated in the report, the HF component is respiration related, and the distribution of the power and the central frequency of LF and HF components are not fixed but vary in relation to changes in autonomic modulations of heart period in the short-term recordings. Therefore, integrating the HF power within the all-frequency range of 0.15 to 0.4 Hz might have inherent error, especially when the respiration rate does not fall within this range for patients who have tachypnea or are under controlled respiration. Because the maximum frequency in the spectrum is the Nyquist frequency (half the sampling frequency), it might be better to use the Nyquist frequency as the upper limit of both HF power and total power.

When the direct current is excluded by baseline or trend removal in the calculation of spectral powers, the nonharmonic components in the very-low-frequency (VLF) region (<0.04 Hz) can be removed. In this case, it is not necessary to set a cutoff limit (0.04 Hz in most instances) for LF power or total power. In addition, the purpose of normalization of the LF and HF powers by the total power is to minimize the effect of the changes in total power on the values of LF and HF components. The placement of a cutoff at 0.04 Hz to the lower limit of total power will result in incomplete normalization of the LF and HF components. Finally, if a lower limit (0.04 Hz in most instances) was set to the LF power, the VLF power (≤0.04 Hz in most instances) must be dealt with for the sake of completeness. However, the physiological explanation of the VLF component is much less defined than other components in the spectrum. The existence of a specific physiological process attributable to these heart period changes might even be questioned. The VLF is then a dubious measure and should be avoided.

In spectral analysis used in sciences such as physics or chemistry, integration of the area under the peak rather than fixed-range integration is usually suggested to evaluate the relative contribution of a specific frequency to total power. Thus, a peak-related integration according to the respiration rate might be a better method of representing HF power. Fixed-range integration is justified only if no apparent peak can be identified in the HF range.

Because of the above considerations, it seems that the area of spectral peaks within the entire range of 0 Hz to the upper limit of HF peak or to the Nyquist frequency can be used as the total power, the area of spectral peaks within the range of 0 to the lower limit of HF peak as the LF power, and the area under the HF peak as the HF power. If no apparent peak related to respiration can be identified, the total power can be defined as the area of spectral peaks within the entire range of 0 Hz to the Nyquist frequency, the LF power as the area of spectral peaks within the range of 0 to 0.15 Hz, and the HF power as the area of spectral peaks within the range of 0.15 Hz to the Nyquist frequency.

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Heart Rate Variability Standards

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Role of Lymphocytes in Heart Disease

To the Editor:

Recently, Ommen et al. published in Circulation a very important observation: that relative lymphocyte concentration could be a prognostic marker in patients with symptomatic heart failure. I would like to add something about the importance of the cellular immune system in cardiovascular disease. I have shown that in acute myocardial infarction (AMI), a low CD4/CD8 ratio and low CD4 cell count on the first day of AMI strongly correlated with low ejection fraction and high myocardial mass destruction, as reflected by high creatine kinase levels. Patients with the lowest CD4 counts on admission and those whose CD4 counts did not rise had a reinfarction or death. Another study demonstrated that patients with AMI had significantly diminished delayed-type hypersensitivity and reduced numbers of T lymphocytes.

One possible explanation for the “lymphopenia” phenomenon is the increase in cortisol during a stress response, which causes a decrease in the relative concentration of lymphocytes. Another possible explanation is that T lymphocytes modulate smooth muscle proliferation during vascular repair. Rats that lacked T lymphocytes had larger myocardial lesions than normal rats. It is assumed that T lymphocytes produce interferon-γ, which inhibits smooth muscle cell proliferation. Thus, it might be that the relative depletion in T lymphocytes is not just a marker but also a causative factor in the deterioration of myocardial function in AMI and heart failure.

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is not new. Similar proposals as the one by Drs Kuo and Chen were made and dismissed in the past.

There is very little experience with physiological interpretation of heart rate variability components if the respiration is forced, by a pathological process or by instruction, to an extreme frequency that falls outside the limits of 0.15 to 0.4 Hz. Extending the upper limit of the high-frequency component beyond 0.4 Hz would only be applicable to extreme tachypnea of >24 respiratory cycles per minute. This is linked to extreme sympathetic overdrive under which it is rather difficult to interpret the high-frequency component. Moreover, because the cardiac period signal is discrete rather than continuous, it is difficult to properly estimate respiratory arrhythmia under such conditions of very fast tachypnea.

Regular periodic bradypnea of <8 respiratory cycles per minute may appear with forced metronome breathing. In such a case, the recommendations made by the Task Force cannot be applied blindly. More importantly, however, forcing a subject into an extremely slow respiration rate is again sympathetically stimulating, which makes it difficult to compare the heart rate variability components with those obtained under different circumstances.

The very-low-frequency component seems indeed to be a dubious measure because its physiological background is not known. It is likely that even with short-term recordings, these components reflect nonstationarity of heart rate modulations. Consequently, extending the limits of low-frequency components below 0.04 Hz would pollute the measurement and make the physiological interpretation even more difficult, especially when the dominant spectral peak belongs to the very-low-frequency component.

It is important to understand that the proposals of frequency components made in our report are based on experience with existing physiological models that allow interpretation of individual components. This is quite different from making a proposal based merely on hypothetical speculations.

Our report clearly suggested that if parametric methods are used for the spectral analysis, the integration of the area under individual components should be used, whereas fixed-range integration was proposed for a nonparametric spectral analysis, which is, in practice, much more frequently used. Drs Kuo and Chen seem to forget that even when parametric methods are used, total power is not a simple sum of high-, low-, and very-low-frequency components. Frequently, other components are present that cause the sum of normalized high-frequency and normalized low-frequency components not to be constant.

Finally, Drs Kuo and Chen forget that for practical reasons, the definitions of high- and low-frequency components must not depend on the duration of the analyzed RR-interval series. For instance, if their proposal were applied to 24-hour recording, the results would be completely meaningless.

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Response

We appreciate Dr Blum’s interest in our article. He raises the intriguing hypothesis that the relative lymphocytopenia observed in acute myocardial infarction (AMI) and in chronic congestive heart failure (CHF) may be a cause rather than an effect.

We have documented decreases in the total and relative number of circulating lymphocytes during AMI and advanced CHF. However, the kinetics of these changes may be different. In AMI, most patients have a rise in endogenous cortisol with associated lymphocytopenia and granulocytosis. In our experience, these changes in the peripheral blood rapidly returned to normal if the patient had an uncomplicated AMI (unpublished observations). In contrast, only a minority of patients with CHF have lymphocytopenia. We do not have any information about its duration.

Additional studies are necessary to determine if the relative lymphocytopenia is an effect of the stress response, as we have suggested, or a cause of myocardial dysfunction, as Dr Blum suggests.

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Circulation. 1998;98:1587b-1590
doi: 10.1161/01.CIR.98.15.1587.b

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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