local and systemic factors and is unlikely to be explained by a single mechanism, whether spasm or other.

We have also stressed that our results should not be extrapolated to all forms of coronary spasm. Our patients were representative of chronic Prinzmetal's variant angina only.[1] All patients, as mentioned in the article, had focal coronary spasm. Duration of episodes of ST segment elevation ranged from 2 to 23 minutes, as assessed by continuous ECG monitoring. Dr Boyd's question of what intimal damage was caused by spasm in our patients is impossible to answer in the clinical setting, and equally difficult is the quantification of the magnitude of shear stress during episodes of spasm, or its impact on the vascular endothelium. This is unfortunate in view of recent suggestions[2] that both mode of onset and duration of coronary artery spasm may be important in the development of intimal damage. The limitations extend even further as factors that play a major role in rapid stenosis progression, such as lipid composition and strength of the plaque fibrous cap, cannot be measured in patients.

Contrary to Boyd's assumption, only three patients in the study had "spastic" stenoses >50% diameter reduction, and none of the patients had long stenoses or extensive disease. Reflection of the latter is that 9 of the 10 patients had negative exercise tests. The role of calcium antagonists in preventing plaque progression should be considered. However, three stenoses progressed in our patients, two were located in nonspastic segments, and one in a spastic site.

The two studies[3,4] cited by Dr Boyd that appear to suggest that "recurrent prolonged focal coronary vasospasm does have a real potential to lead to atherosclerosis" have been discussed in our article.[1] Marzilli et al[3] describe one patient with vasospastic angina in whom coronary atheroma subsequently developed at the spastic site. Based on this case, the authors hypothesized that spasm may lead to atheroma. The hypothetical nature is clearly stated in the title.[3] The other is a study by Gertz et al[4] who in order to mimic prolonged vasoconstriction subjected the left anterior descending coronary artery of 4 dogs and the right common carotid artery of 15 rabbits to 1-hour partial ligation with a suture thread. This method of inducing "transient," prolonged, arterial diameter reduction is unlikely to closely reproduce the circumstances surrounding coronary artery spasm in patients with Prinzmetal's angina pectoris. Thus, the results of the study,[4] although of importance, should be analyzed cautiously. A recent study by Kuga et al[2] in Gottingen miniature pigs, however, is of relevance. Using an experimental model that more closely resembles human coronary spasm (still not the ideal model, as atherosclerosis is created rapidly by cholesterol feeding, coronary denudation and x-ray irradiation), Kuga et al[2] observed that serotonin-induced coronary artery spasm could cause intramural hemorrhage, which in turn could result in acute progression of coronary stenosis. Their study also showed that prolonged spasm resulted in myocardial infarction without progression of organic stenosis, a finding consistent with our results in patients.

We believe that despite the limitations inherent to its clinical nature, our study helps to put the complex issue of coronary stenosis progression in perspective.

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Coronary Atherosclerosis on Angiography—Progress or Regress, and Why?

Waters et al[1] studied the prognostic significance of angiographic progression of coronary atherosclerosis. Not unexpected, they found that an increase in diameter stenosis of 15% or more predicted a greater risk of future coronary morbidity and mortality than did a lesser increase, and they claimed angiographic end points as worthy surrogates for hard, clinical events in trials.

In the angiographic cholesterol-lowering trials, the mean decrease of stenosis or increase of lumen diameter seen after a similar period of time was only less than 2%, however.[2-4] Such small changes are impossible to see with the naked eye, and their meaning is not obvious. Most important, a slight increase of vessel diameters may be due to both progress and regress of atherosclerosis because coronary vessels overcompensate an early, subendothelial deposition of atheroma by a widening of the lumen diameter.[5]

Even if vascular changes did reflect changes of atherosclerosis, the data from the study of Waters et al and from the angiographic trials do not support that such changes are related to the blood cholesterol levels. In the study of Waters et al, for instance, the total cholesterol and LDL-cholesterol concentrations of 141 patients whose stenosis progressed by more than 15% did not differ significantly from the concentrations of 194 nonprogressors. In the trials, however, the mentioned trivial reduction of stenosis was seen after a decrease of LDL-cholesterol by 36% to 46%.

No relationship was found either in a number of angiographic follow-up studies; progress and regress of atherosclerosis occurred whether the cholesterol concentration was high or low, or whether it increased or decreased during the observation period.[6]

The findings in a recent angiographic trial using diet and physical exercise as intervention were also unsupportive, as the mean serum cholesterol concentration of the progressors in the intervention group decreased just as much as that of the regressors.[7]

Finally, the results from the trials using the hard end points are disappointing. In a recent overview of all controlled, randomized studies, total mortality, the only definitely unbiased end point, had increased after intervention,[8] and noncoronary mortality had increased significantly.[9]

Altogether, the evidence is weak that a high cholesterol level is causal in atherosclerosis and coronary heart disease. The recent recommendation to change direction for cholesterol policy[10] seems adequate.

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Reply

In response to the letter of Dr Henry Buchwald, with the introduction of computer-assisted quantification of coronary angiography (cQCA), a controversy evolved whether this would be superior to the former visual interpretation of coronary angiograms. Dr Buchwald defends human panel readings and doubts that "cQCA yields a higher accuracy when comparing the two angiograms years apart. . . ." However, several studies comparing visual estimates (including human panel readings) with cQCA[1,2] demonstrated that visual assessments of plaque size, especially when based on percent diameter stenosis (PDST), considerably overestimate lesion size in the high range (>50%) and underestimate it in the lower range (<50%) and by this describe significantly more three-vessel disease than cCQA ($P<.05$).[1]

We agree that visual assessment of PDST—when done by experienced angiographers—might be close to the value assessed by cQCA; however, in general, visual estimates are fraught by large interobserver variabilities,[3] as shown also in the "evaluation of the human panelists" in CLAS,[4] especially when assessing changes in PDST over time. Hence, visual estimates ask for a higher number of patients to reach significance than cQCA, because they are not able to recognize already small changes in PDST (few percent). This can also be concluded from a comparison between studies on lipid lowering measures based on human panel readings (POSCH, CLAS) and those based on cQCA (FATS, Life style, STARS); in the latter, changes in PDST of 0.3% to 5%, too small to be recognized by visual approach, were included and allowed a significant separation between regressing and progressing stenoses ($P<.001$). Hence, cQCA has several advantages: among others it eliminates the considerable interobserver variability of visual interpretation especially when analyzing diameter changes; it also allows to recognize accurately even small diameter changes (few percentages), provided there is adequate quality of cinefilms. A disadvantage is the loss of accuracy in small vessels (diameter <1.0 mm) due to insufficient pixel density, where we still have to depend on visual estimation. However, in discussing accuracy, one should always remember that even by overcoming the technical limitations and improving accuracy beyond visual capacity through cQCA, insurmountable biological limitations remain as the angiogram is a luminogram and therefore cannot inform on the many pathological processes confined entirely to the vessel wall.

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Reply

We are grateful to Dr Lasley for his interest in our recent work! This manuscript revealed that ischemic preconditioning increases 5′-nucleotidase activity and adenosine release during the ischemic preconditioning procedure and reperfusion and forwarded the hypothesis that increases in adenosine release contribute to the infarct size-limiting effect of ischemic preconditioning. Dr Lasley raised several important and essential concerns.

The first issue is as to whether our observation is consistent with other previously reported metabolic effects of ischemic preconditioning. Murray et al[2] reported that ischemic preconditioning slows the rate of ATP depletion during the early episode of sustained ischemia, which may be partially attributable to the prolonged metabolic effects of transient adenosine receptor activation.[3,4] Stimulation of adenosine receptors attenuates β-adrenoceptor–mediated hyperfunction of myocardium and inhibits Ca^{2+} channel and Na^{+}/Ca^{2+} exchange, all of which may exert metabolic effects of the myocardium and preserve ATP content.[5,6] In our study,[1] adenosine release during the ischemic preconditioning procedure was gradually increased with repeated cycles of reperfusion after coronary occlusion (Table 1 in Reference 1), which may efficiently make the myocardium resistant to sustained ischemia due to a significant exposure to endogenous adenosine. Indeed, in our preliminary study,[7,8] when ectosolic 5′-nucleotidase is inhibited by AOPCP (α, β, methyleneadenosine 5′-diphosphate) during the ischemic preconditioning procedure, potency of the infarct size-limiting effect of ischemic preconditioning was reduced to half. Therefore, an increase in 5′-nucleotidase activity and adenosine release during the ischemic preconditioning procedure observed in our study[1] may sufficiently reconcile with the current hypothesis of the infarct size-limiting effect of ischemic preconditioning. We further postulate the hypothesis that enhanced release of adenosine in the ischemic preconditioning group also contributes to the infarct size-limiting effect because potency of the infarct size-limiting effect of ischemic preconditioning is reduced to half when ectosolic 5′-nucleotidase activity is blunted by AOPCP only during the reperfusion period following sustained ischemia.[7,8]

The second issue is as to whether changes in 5′-nucleotidase activity, which can be assessed by adenine nucleotides and nucleosides, are consistent with our observation. In Murray's literature,[2] the adenosine content of subendocardium in the ischemic preconditioning group is reduced during an early period of sustained ischemia (up to 20 minutes) compared with the control group. However, at 40 minutes of sustained ischemia, the adenosine content in the ischemic preconditioning group becomes comparable with the control group. Because myocardial 5′-AMP level, a substrate for 5′-nucleotidase, is markedly smaller in the ischemic preconditioning group than in the control group, 5′-nucleotidase activity may be increased in the ischemic preconditioning group compared with the control group during sustained ischemia. Of course, we should be careful when we speculate 5′-nucleotidase activity from the data of adenosine and 5′-AMP concentrations, because the adenosine content is not determined only by the concentrations of 5′-AMP and 5′-nucleotidase activity

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