avoid even when not visible, may have a significant effect on HBD activity since red blood cells are such a rich source of LDH. Plasma LDH activity after myocardial infarction reaches maximal levels in 48–72 hours, whereas plasma MB CK activity peaks at 12–24 hours. MB CK has for some time been shown by many investigators to be the most convenient, specific, sensitive, and cost-effective diagnostic marker for myocardial infarction.

Hermens et al claimed that HBD has indeed been used routinely since it has been used for five clinical trials. In contrast, CK has been used for numerous trials in North and South America, Europe, Australia, New Zealand, and South Africa. Hermens et al say that four studies have been done with the HBD and only one with CK MB after thrombolysis, but of course until now this clinical situation was considered inappropriate for the use of enzymatic markers. In this investigator’s view, until this method is validated in the setting of reperfusion, it should not be recommended to assess thrombolytic therapy. If indeed the conclusion by Hermens et al is correct, it represents a step forward and will provide a much-needed surrogate end point to assess thrombolytic therapy. Solid scientific progress begins with a reasonable hypothesis and suggestive scientific data (as provided by Hermens et al); however, the next step, namely, routine use of the CK method during thrombolytic therapy, requires appropriate scientific validation.

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Crea et al1 reported that although Sylven et al . . . found that both chest pain and coronary dilation occurred at the same intravenous bolus dose of adenosine, the presence of systemic effects and the lack of an appropriate dose-escalating approach are likely to account for the inability of their study to clearly separate the algogenic and the vasoactive effects of this substance.

This description is indeed wrong. An appropriate dose-response curve was used, and the vasoactive and algogenic effects of adenosine were clearly separated both with regard to their dose-response relations and to their time course. Even at the lowest dose of adenosine given, maximal coronary vasodilation was recorded while pain increased with the increasing dose of adenosine. Coronary sinus flow increase started before the appearance of pain, whereafter the pain had a more transient time course. We have further demonstrated the same relation in the forearm after adenosine injection into the brachial artery.2,4 Crea et al used infusions in their study, whereas we used bolus injections. Because of the short half-life of adenosine, different effects will be produced by bolus injection and infusion, which is important. Therefore, the systemic effects attributed to our study were avoided and were never observed by us, but were seen by Crea et al1 who have reported on infusion studies. Even if Crea et al1 did not observe any electrocardiographic signs of ischemia after intracoronary infusion, myocardial ischemia cannot be ruled out. With bolus injection, the time course for the pain is so short that ischemia due to a coronary steal could not have been the cause. With the bolus injection model, we have reported that intravenous administration of adenosine in healthy volunteers with serum concentrations in a relevant pathophysiologic range provokes an angina pectorislike pain at a time when peak adenosine concentration is present in the heart.2,4,5 Patients with ischemic heart disease reported that the pain is not different from their spontaneous angina pectoris whether adenosine was given by intravenous bolus or intracoronary route.6,7 The pain is provoked at extracellular adenosine receptors and follows an ordinary psychophysical power function.7 Ischemic pain in the forearm model is attenuated by theophylline, indicating the importance of endogenous adenosine for the pain response.8

We think our original hypothesis is well supported by our published results that adenosine is one messenger between ischemia and pain9 and that this hypothesis has obtained additional support by the study of Crea et al.1

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Reply

In 1986, Sylven et al1 observed that the intravenous administration of adenosine provokes anginalike chest pain and hypothesized that this substance might be a mediator of cardiac ischemic pain. This intriguing working hypothesis prompted us to compare the effects of intravenous adenosine administration in patients with silent and painful ischemia. We found in a preliminary report that patients with painful ischemia have more severe pain on lower doses of adenosine. However, we also noted that adenosine-induced chest pain was frequently rather different from the anginal pain experienced by the patients, suggesting an extracardiac origin.2 To establish whether adenosine was a mediator of the cardiac pain, we thought it necessary to study the effects of intracoronary adenosine administration at doses unable to cause symptoms during recirculation. Because Sylven et al3,4 had not carried out this crucial study, we decided to do so.5 Thus, in our article in Circulation, we proved that adenosine is, indeed, a mediator of cardiac ischemic pain, by demonstrating that its intracoronary administration, in the absence of electrocardiographic changes, reproduces the same anginal pain experienced by patients during daily life, at doses that did not provoke symptoms when infused into the right atrium.5 Furthermore, we identified doses of adenosine able to give maximal coronary vasodilation but no pain, proving that the former was not the cause of the latter. This observation also confirmed, as already indicated by the lack of electrocardiographic changes, that the pain provoked by adenosine was not due to myocardial ischemia; indeed, myocardial ischemia should already have been present at the time of maximal coronary vasodilation.

In this same article, we commented that Sylven6 could not define the relation between adenosine-induced cardiac pain and coronary vascular effects of adenosine for two reasons. First, the chest pain caused by intravenous administration of adenosine can be extra-cardiac in origin (i.e., caused by the systemic, rather than cardiac, effects of this substance). Second, even assuming a cardiac origin of chest pain, both maximal coronary vasodilation and chest pain were already observed, as pointed out by Dr. Sylven in his letter, at the lowest dose of adenosine they used, thus making it very difficult to rule out a cause-effect relation between these two events. We also commented that in their study a more appropriate dose range of adenosine (i.e., lower initial doses of adenosine) would have probably made it possible (as it was the case in our study) to identify a dose able to produce maximal coronary dilation but not chest pain, thus enabling them to rule out a cause-effect relation between vascular and algogenic effects of adenosine.

Finally, their observation that higher doses of adenosine produced more severe chest pain without changes of coronary blood flow is not convincing evidence, in our opinion, that the vascular and algogenic effects of adenosine are unrelated, because with systemic adenosine administration, the increase in severity of chest pain might also be extracardiac in origin.

We apologize to Dr. Sylven if in our paper our comments on his pioneering work were not sufficiently detailed.

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