Comments on “Quantification of Myocardial Infarct Size After Coronary Reperfusion by Serum Cardiac Myosin Light Chain II in Conscious Dogs” (Circ Res 1989;65:684–694)

The September 1989 issue of Circulation Research contained an interesting study by Dr. M. Isobe et al. In this study the release in plasma of creatine kinase (CK) after coronary occlusion in the dog is compared with histologically assessed infarct size. It is suggested that, in the setting of reperfusion, myosin light chain II is a better indicator of infarct size than CK because reperfusion causes more release of CK per gram of infarcted tissue than observed after permanent coronary occlusion. From Table 1 it follows that the ratio of total CK release/infarct size is 579, 574, and 381 IU·l⁻¹·g⁻¹ for reperfusion after 3 hours, reperfusion after 6 hours, and permanent occlusion, respectively. These figures indeed suggest enhanced CK release after reperfusion.

However, these values are subject to error because of the use of individual values for the disappearance rate constant Kd of CK from plasma. Such apparent disappearance rates are much lower than the actual elimination rates. In the present study, for instance, values of Kd of the order of 0.0010 to 0.0015 min⁻¹ were found (Table 1), whereas bolus injections and infusions of CK have produced elimination rates of the order of 0.005 minute⁻¹. These low apparent disappearance rates are caused by tailing release of CK during part of the elimination phase and, as shown in Figure 5 of the study by Isobe et al., reperfusion causes a significant shortening of the release phase and thus will produce higher values of Kd. Indeed, Table 1 quotes mean values of 0.00129 minute⁻¹, 0.00154 minute⁻¹; and 0.00109 minute⁻¹ for the 3-hour reperfusion, the 6-hour reperfusion, and the permanent occlusion groups, respectively. If instead of these values a fixed value of Kd = 0.0048 minute⁻¹ was used, as in the original Shell method,² the ratios of CK release/infarct size would have been (0.0048/0.00129)×579 = 2.154, (0.0048/0.00154)×574 = 1.789, and (0.0048/0.00109)×381 = 1.678 IU·g⁻¹·l⁻¹, respectively, and these differences are clearly not significant in view of the standard errors of about 30%.

In this respect, Figure 7 is also somewhat misleading because, owing to a single outlying value, linear regression of CK release versus infarct size produced a slope of 175 in the permanent occlusion group, instead of the mean value of 381 from Table 1.

In conclusion, the data presented in this study do not support the conclusion that CK is subject to reperfusion-induced enhancement of the ratio of CK release/infarct size. To decide whether light chain II could still be a superior marker of infarct size, it would be very interesting if the authors could give the figures for normal CK activity (international units per gram) and light chain II content (nanograms per gram) of myocardium as determined for their assay conditions. This would allow an estimate of the completeness of recovery in plasma for both markers.

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References

Reply to the Preceding Letter

We thank Dr. W.Th. Hermens for his interest in our article, “Quantification of Myocardial Infarct Size After Coronary Reperfusion by Serum Cardiac Myosin Light Chain II in Conscious Dogs,” in which we evaluated the relation between infarct size measured histologically and infarct size calculated on the basis of plasma levels of creatine kinase (CK) or serum cardiac myosin light chain. The problems and potential sources of error in infarct sizing by plasma CK level have been described in our article and in Dr. Hermens’ letter. The experimental and mathematical basis for the enzymatic model as a measure of infarct size are indeed a matter of controversy. Among the problems, estimation of the CK disappearance rate (Kd) from the circulation is one of the most significant factors that affects the estimation of infarct size, because the magnitude of the integrated CK value is directly proportional to the Kd value used to calculate it.

It may be true, as Dr. Hermens points out, that the use of individual Kd values calculated from the terminal portion of the plasma CK curve can induce errors. However, the possibility of errors arising from the use of a constant Kd should be considered as well. In patients, Sobel et al. found a Kd of 0.001±0.0001/min (mean±SEM). This value implies a standard deviation of approximately 0.0005, or a value half as great as the Kd itself. Thus, an underestimation or overestimation of total CK by 50% would have occurred in cases with a Kd of 1 SD above or below the mean. Results from Dr. Hermens’ laboratory on plasma clearance of injected CK in eight dogs showed that the clearance constant ranged from 0.27 to 0.47/hr (0.36±0.030, mean±SEM), as did results from another laboratory (from 0.0039 to 0.0091/min). Thus, errors in estimating the total release of CK from a constant Kd value are by no means insignificant. Furthermore, the methods for estimating the constant Kd value also call for some consideration. Kd values have been reported for normal animals³,⁴ and for animals with coronary occlusion without reperfusion³ by intravenous injection of partially purified exogenous CK. As is obvious from our Figure 7 and from another report,⁶ reperfusion significantly increases the entry ratio of CK from infarcted myocardium into the circulation. Changes in the entry ratio might alter the clearance of the enzyme from the circulation. Therefore, another experiment would be necessary to establish whether a Kd value estimated for normal animals or animals with nonreperfused infarction is valid for animals with early reperfusion.

It is also uncertain whether early coronary reperfusion influences a Kd calculated from the terminal portion of individual CK activity curves. However, we assumed that CK is removed expo-
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