Letter to the Editor

Enzymatic Infarct Size and Its Significance for Evaluation of Thrombolytic Therapy After Acute Myocardial Infarction

The February 1990 issue of Circulation contained an editorial comment by Dr. R. Roberts concerning our study on enzyme recovery from dog heart.² We appreciate Roberts' interest in our study, and we agree with him that there is urgent need for methods allowing quantitative estimation of myocardial injury. We feel, however, that some of Roberts' remarks could cause confusion regarding the implications of our study. First, we will briefly pay attention to these remarks, and then we will discuss the application of these methods in thrombolytic therapy of acute myocardial infarction (AMI).

Roberts states that "the elimination rate for CK [creatine kinase] determined by the present investigators is 0.51 hr⁻¹, which is almost twice that used by previous investigators." In fact, we used a value for the fractional catabolic rate constant FCR₉K=0.36/hr⁻¹ correctly quoted elsewhere in Roberts' editorial comment, that is close to the values found by other investigators,² including the value of 0.29/hr⁻¹ published by Roberts. Obviously a 24% higher value of FCRK has only a marginal influence on the change in the recovery from 15% to 100%.

Roberts confirms our estimate of 6–7% variability in myocardial enzyme activity but, surprisingly, still questions our approach to measurement of enzyme depletion only in the ischemic area. Because less than 15% of the total left ventricular CK content is released after permanent ligation of the left anterior descending coronary artery, the 6–7% uncertainty in the CK activity of a whole ventricular homogenate implies about 50% uncertainty in estimated depletion. Such a large error should be avoided.

Roberts also suggests that elimination rates and extravascular volumes are only theoretical concepts and states, "I think the comment by Dr. R. Roberts concerning our study on enzyme validity of the estimated depletion. Such a large error should be avoided. Roberts confirms our estimate of 6–7% variability in myocardial enzyme activity but, surprisingly, still questions our approach to measurement of enzyme depletion only in the ischemic area. Because less than 15% of the total left ventricular CK content is released after permanent ligation of the left anterior descending coronary artery, the 6–7% uncertainty in the CK activity of a whole ventricular homogenate implies about 50% uncertainty in estimated depletion. Such a large error should be avoided.

Roberts also suggests that elimination rates and extravascular volumes are only theoretical concepts and states, "I think the theoretical value is arbitrary and some independent proof is required." It is true that any compartmental model simplifies the true physiological situation, but it still provides an accurate description of plasma enzyme kinetics. Independent proof of the validity of the two-compartment model, as asked for by Roberts, has been obtained from turnover studies with radiolabeled plasma proteins (reviewed in Reference 30 of article) and from intravascular and intramuscular injections and infusions of enzyme preparations in the dog (see References 15–17 in our article).

It is considered a major shortcoming that we studied permanent ischemia instead of reperfusion. The finding of 100% recovery after permanent ischemia, with ample time for local enzyme activation, makes it highly improbable, however, that less complete release will be found after reperfusion. This is recognized by Roberts when he mentioned, "If all of the CK is released, despite sustained coronary occlusion, it would simply be released faster with earlier reperfusion."

The aspect emphasized by Roberts is the estimation of infarct size with thrombolytic therapy after AMI. Our study considered CK and HBD (α-hydroxybutyrate dehydrogenase), enzymes included in our first clinical study on enzymatic infarct size.³ HBD, however, is considered less important by Roberts because "in man HBD remains elevated in the plasma for 10 to 14 days, is less specific than CK-MB for myocardium, and has not been used routinely in man." These three objectives to the use of HBD require further consideration.

In humans, HBD is indeed eliminated from plasma much slower than CK, but in contrast to Roberts' suggestion, this is a major advantage in its quantitative use. Slow elimination implies that most of the HBD activity released from the infarction is still present in plasma when release has stopped and that this plasma activity can be accurately determined. In contrast, CK-MB has almost completely been eliminated from plasma by that time and estimation of total released activity is more prone to error because of uncertainty in the individual values of the elimination constant.

As a result, the overall error in estimated total enzyme release is only 10% for HBD versus 20% for CK.⁴ Moreover, because of its slow elimination, the time-activity curve of HBD changes only gradually and can be accurately integrated from only seven plasma samples taken at 12-hour intervals.⁴ Routine use is, therefore, much simpler for HBD than for CK-MB, which requires 4–6-hour samples and isoenzyme separation.

Although HBD activity is present in many tissues other than myocardium, the relevant point is whether extramyocardial release of HBD is a practical problem in patients with AMI. Early autopsy-controlled studies have demonstrated a sensitivity of "heat-stable" lactate dehydrogenase (LDH) (approximately equivalent to HBD) of 86–90% in the detection of AMI.⁵ A direct comparison of LDH- and CK-isoenzymes showed a specificity of 97% for LDH versus 85% for CK.⁶ If only nonhemolytic plasma or serum samples are used, HBD allows specific detection of myocardial injury because the main additional extramyocardial sources of enzyme release in patients with AMI, the liver, and skeletal muscle contain predominantly the isoform LDH₂, to which the HBD assay is insensitive.⁷ It should also be noted that quantitative use of CK-MB is hampered by large variability and inherent uncertainty of its normal activity in myocardium.

Roberts' statement that HBD has not been applied routinely in humans is incorrect. To date, five clinical studies⁸–¹³ have confirmed the favorable therapeutic effects of thrombolysis by a reduction of enzymatic infarct size. Four studies were based on HBD or LDH; only one¹¹ was on CK-MB. In a somewhat broader perspective, heat-based stable LDH was used in the earliest clinical studies⁶ and in the first comparison of enzymatic infarct size with histological estimates in autopsies.¹⁵

HBD has important quantitative and practical advantages over CK-MB, has comparable specificity for the detection of myocardial injury in patients with AMI, and has been used in extensive clinical trials. We consider HBD (or LDH) the enzyme of choice in the evaluation of thrombolytic therapy in patients with AMI.

W.Th. Hermens
F.H. van der Veen
G.M. Willems
R.S. Reneman
Research Institute for Cardiovascular Diseases
Maastricht, The Netherlands

References


Enzymatic infarct size and its significance for evaluation of thrombolytic therapy after acute myocardial infarction.

W T Hermens, F H van der Veen, G M Willems and R S Reneman

_Circulation_. 1990;81:1719-1720
doi: 10.1161/01.CIR.81.5.1719

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1990 American Heart Association, Inc. All rights reserved.
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:
http://circ.ahajournals.org/content/81/5/1719.citation