Measurement of myocardial infarct size from plasma fatty acid-binding protein or myoglobin, using individually estimated clearance rates


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Abstract

Objective: In patients with acute myocardial infarction (AMI), estimation of infarct size from the early markers, fatty acid-binding protein (FABP) and myoglobin (MYO), usually assumes average (fixed) rate constants (FCR) for protein clearance from plasma. However, individual variation in FCR is large. Renal dysfunction causes slower clearance of FABP and MYO from plasma and, hence, overestimation of infarct size in 20–25% of patients. We investigated whether or not more accurate values of infarct size could be obtained with individually estimated clearance rates.

Methods: Concentrations of FABP and MYO and, for comparison, activities of the established cardiac markers, creatine kinase (CK) and α-hydroxybutyrate dehydrogenase (HBDH), were assayed in serial plasma samples from 138 patients with AMI. Individual FCR values of FABP and MYO were estimated from plasma creatinine concentrations, sex and age.

Results: Individual FCR values varied from 0.4 to 2.4 h⁻¹. Use of these individual FCR values significantly improved the correlation between infarct size, as estimated from FABP or MYO on the one hand, and from CK and HBDH on the other. Approximately equal estimates of infarct size were obtained for all four marker proteins.

Conclusions: Using individually estimated clearance rates, renal insufficiency no longer hampers calculation of infarct size from FABP and MYO, and reliable estimates of total myocardial damage can be obtained within 24 h after first symptoms.

Keywords: Enzyme (kinetics); Infarction; Renal function

This article is referred to in the Editorial by A. van der Laarse (pages 247–248) in this issue.

1. Introduction

Non-enzymatic cardiac proteins, such as fatty acid-binding protein (FABP) and myoglobin (MYO), are increasingly being used as diagnostic markers of acute myocardial infarction (AMI) [1–4]. Each of these proteins is abundantly present in the soluble cytoplasm of cardiomyocytes. Due to their small size (15 and 17.8 kDa, respectively), they are released into plasma in significant amounts within 3 h of the onset of AMI, while plasma concentrations usually return to normal within 24 h [1–4]. These characteristics allow early confirmation of AMI, monitoring of coronary recanalisation or reinfarction, and early estimation of total myocardial injury (infarct size).

A drawback of both FABP and MYO, however, is that elimination from plasma takes place mainly by renal clearance [5–7]. The influence of renal function on estimation of infarct size was recently demonstrated in a study by Wodzig et al. [8]. It was found that, in the case of renal function...
dysfunction, reflected by increased plasma creatinine concentrations in 25% of patients, infarct size, as estimated from FABP and MYO, grossly overestimated the values obtained from established cardiac markers such as creatine kinase (CK) and α-hydroxybutyrate dehydrogenase (HBDH). Previously, Glatz et al. [9] had found higher values for infarct size estimated from plasma FABP than from HBDH or creatine kinase MB (CK-MB) activity. In their calculation of infarct size, Glatz et al. [9] as well as Wodzig et al. [8] used mean (fixed) clearance rates for FABP and MYO. However, large deviations from these fixed values may occur, because renal clearance of these small proteins is not only influenced by individual variation in renal function, but also by the age and sex of the patient [10,11].

The aim of the present study was to establish, in patients with confirmed AMI, if infarct size can be more accurately determined by using individually estimated clearance rates of FABP and MYO, assessed from plasma creatinine concentrations, sex and age.

2. Methods

2.1. Patients and blood sampling

Data were obtained from 149 patients with confirmed AMI, enrolled in the GUSTO (Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries) Enzyme Substudy [12]. After obtaining informed consent, patients received one of four intravenous thrombolytic regimens: (1) streptokinase with subcutaneous heparin; (2) streptokinase with intravenous heparin; (3) accelerated tissue plasminogen activator (t-PA) with intravenous heparin or (4) a combination of t-PA and streptokinase, along with intravenous heparin.

Inclusion criteria for enrolment in the GUSTO study have been described in detail elsewhere [12,13]. In short, patients were eligible when they were admitted to hospital within 6 h after the onset of symptoms, had chest pain lasting for at least 20 min and showed electrocardiographic evidence of AMI ($\geq$0.1 mV of ST-segment elevation in two or more limb leads, or $\geq$0.2 mV in two or more contiguous precordial leads).

Blood samples were collected immediately before and 1, 3, 6, 12, 18, 24, 36, 48, 72 and 96 h after the start of thrombolytic therapy, resulting in 11 samples per patient. The exact sampling time was recorded in the GUSTO Enzyme Case Report Form and was expressed as time after onset of symptoms. Samples were collected in glass tubes containing dry heparin, to prevent clotting. After routine centrifugation, plasma was kept at $-20^\circ C$ in the local hospital and was transported in polystyrene boxes with dry ice to the central laboratory at Maastricht, The Netherlands, within eight weeks. Here, samples were stored at $-80^\circ C$ until assays were performed. In patients receiving thrombolytic therapy after AMI, plasma concentrations of FABP and MYO reach peak values within 6 h after the first symptoms and have largely returned to normal after 12 h (Fig. 2). Therefore, the adequacy of the sampling schedule of the present study for calculation of infarct size from plasma FABP and MYO concentrations could be checked as described [9], using patients who were sampled hourly up to 12 hours. Reduction of the schedule used in the present study caused no systematic effects, but introduced a 15% (SD) scatter in the calculated infarct size.

2.2. Analytical techniques

Fatty acid-binding protein was measured in duplicate in plasma samples by a non-competitive enzyme-linked immunoassorbent assay (ELISA), as described elsewhere [14], using an incubation time of 60 min. Samples were diluted with phosphate-buffered saline (pH 7.4) containing 0.1% bovine serum albumin and 0.05% Tween-20. The detection limit of the assay was 0.2 $\mu$g/l. Quality control was performed with human plasma, spiked with recombinant human FABP [14]. Intra- and inter-assay imprecision were 4.2 and 9.0%, respectively. Myoglobin was determined in duplicate in plasma by a turbidimetric immunoassay (Unimate 3 Myo, art 0751839, Roche, Mijdrecht, The Netherlands) on a Cobas Fara analyzer (Roche Diagnostic Systems, Basel, Switzerland). Plasma samples were diluted with saline (0.9% NaCl). For quality control, a commercial standard was used (Roche, art 07 5186). Intra- and inter-assay imprecision were 3.5 and 4%, respectively. Plasma concentrations of FABP and MYO were expressed in $\mu$g/l.

Activities of CK and HBDH were measured spectrophotometrically, in duplicate, at 25°C, using a centrifugal analyser (Cobas Bio System, Roche) and commercially available test kits (Diagnostica Merck, Darmstadt, Germany). The HBDH test is based on the preferential catalytic activity of the myocardial isoforms LDH$_1$ and LDH$_2$ of lactate dehydrogenase in the conversion of α-ketobutyrate, instead of pyruvate. Activities were expressed in micromoles of substrate converted per minute and per litre of plasma (U/l). Quality control was performed with a commercially available control serum (Precipath, Boehringer Mannheim, Germany). Intra- and inter-assay imprecision were 1.7 and 2.6% for CK, and 2.4 and 4.4% for HBDH.

Creatinine was analysed on a Beckman Synchron CX-7 system with a commercial test kit (CREA 442760, Beckman Instruments, Mijdrecht, The Netherlands). The assay is based on a modified Jaffé method, and measures the change in optical absorbance at 520 nm due to the formation of a creatinine–picrate complex in alkaline solution. Quality control was performed with a control serum from the manufacturer, and intra- and inter-assay imprecisions were 1.3 and 1.9%, respectively. Plasma creatinine concentrations, expressed in $\mu$mol/l, were mea-
sured in the first blood sample, taken at admission, and in blood samples taken 12 and 24 h thereafter. These three values, spanning the time interval during which clearance of FABP and MYO occurs (see below), were averaged.

2.3. Possible effects of sample storage on concentrations of FABP and MYO

In the Enzyme Substudy of the GUSTO trial, patients were recruited up to February 1993, and CK and HBDH activities were determined within six weeks after arrival of plasma samples in Maastricht. However, FABP and MYO concentrations were determined in 1996, and possible effects of this three-year period of storage at −80°C were investigated. In 1993, 0.5 ml aliquots of plasma were stored in sealed plastic tubes (Hoffmann-La Roche, Cobas Bio System). Upon reopening of the sample tubes in 1996, it was globally verified that sample volumes had not changed. In addition, HBDH activities were redetermined in 60 plasma samples, with activities between 20 and 500 U/l, and a linear regression of $y=1.09x-5.6$ ($r=0.99$) was obtained. It was concluded that no significant sample evaporation had occurred.

The effects of storage on the determination of FABP and MYO were studied in 38 plasma samples from patients with AMI, with FABP concentrations of between 5 and 350 µg/l, and MYO concentrations of between 36 and 1210 µg/l, as measured in January 1995. These samples were not from GUSTO patients, but they were obtained, anticoagulated and stored in exactly the same way. Redetermination of these samples in March 1998 resulted in the following linear regression equations: $y=1.08x-4.5$ ($r=0.99$) for FABP, and $y=0.95x-21$ ($r=1.0$) for MYO. It is concluded that storage had no significant effects on FABP and MYO concentrations.

2.4. Determination of infarct size

Cumulative release of protein per litre of plasma, from the onset of AMI ($t=0$) up to time $t$, is indicated by $Q(t)$ and was calculated from the expression [15]:

$$Q(t) = C(t) + \int_0^t C(\tau) \exp[ERR (\tau - t)] d\tau$$

$$+ FCR \int_0^t C(\tau) \, d\tau$$

The three terms are the quantity of released protein still present in plasma at time $t$, the extravasated quantity of protein at time $t$, and the quantity of protein eliminated from plasma up to time $t$, all expressed per litre of plasma. The integration parameter, $\tau$, is not a true variable because the integrals are always evaluated from $\tau=0$ up to $\tau=t$. Therefore, the true variable is only time $t$.

$C(t)$ is the plasma protein concentration or enzyme activity at time $t$, corrected by subtraction of normal steady-state values, $C_0$. The latter were obtained from the lowest plasma values if they did not exceed maximal values of 80 U/l for CK, 120 U/l for HBDH, 12 µg/l for FABP and 90 µg/l for MYO. Otherwise, fixed mean values of 40 U/l, 82 U/l, 2 µg/l and 33 µg/l were used for CK, HBDH, FABP and MYO, respectively.

The parameters TER and ERR represent the fractional rate constants for transcapillary escape and extravascular return of protein. Parameter values for HBDH and CK in man are TER=0.014 h⁻¹ and ERR=0.018 h⁻¹ [15] and those estimated for FABP and MYO are TER=1.9 h⁻¹ and ERR=0.94 h⁻¹ [16]. FCR is the fractional catabolic rate constant for the elimination of protein from plasma. For HBDH and CK, fixed mean FCR values of 0.015 h⁻¹ and 0.20 h⁻¹ were used, respectively [15], while the FCR values for FABP and MYO were estimated individually (see below).

2.5. Estimation of individual FCR values for FABP and MYO

Using data on creatinine excretion over 24 h in 249 individuals, aged between 18 and 92 years, Cockcroft and Gault [10] and Gault et al. [11] derived the following expression for glomerular filtration rate, expressed in ml/h/kg: in males: $GFR=72.0 \times (140-\text{age (in years)})/\text{[mean plasma creatinine (in } \mu\text{mol/l}]$. In females, 15% lower values were found. From nomograms in ref. [17], plasma volume $V_{pl}$, expressed in ml/kg, was estimated as $V_{pl}=44.9 \times 0.127 \times (\text{age} - 50)$ in males, and as $V_{pl}=42.4 \times 0.114 \times (\text{age} - 50)$ in females. Using mean plasma creatinine concentrations, the sex and age of each individual, FCR values, expressed as h⁻¹, were calculated from these expressions as $\text{FCR}=\text{GFR}/V_{pl}$.

2.6. Expression of infarct size in gram equivalents of heart muscle per litre of plasma

For quantitative comparison of results from different markers, infarct size was expressed in gram equivalents of myocardium per litre of plasma (g eq/l). To this end, cumulative release of protein per litre of plasma, that is, $Q(24)$ for FABP and MYO, and $Q(72)$ for CK and HBDH, was divided by the myocardial content of the specific protein per gram wet weight of tissue. Values of 865 U/g, 123 U/g, 0.57 mg/g and 2.30 mg/g were used for myocardial content of CK, HBDH, FABP and MYO, respectively [18,19].

2.7. Statistical analysis

Statistical analysis was performed using standard software (SPSS). Mean values±SEM were calculated. The non-parametric paired Wilcoxon test was used to test
differences between two parameters. Friedman’s two-way analyses of variance by ranks (paired) was performed to test differences between multiple parameters. If the Friedman test indicated a significant ($P < 0.05$) difference, multiple comparisons were made [20].

3. Results

3.1. Patients

Patients who had cardioversion ($n = 9$) or reinfarction ($n = 2$) were excluded from the present study because of possible skeletal muscle damage or insufficient sampling, respectively. Baseline characteristics of the remaining 138 patients, 108 men and 30 women, are shown in Table 1. Except for the percentage of women, there were no significant differences in baseline characteristics and, for further analysis, data from the four treatment groups were taken together. Due to death, haemolysis, missing samples and administrative errors, infarct size could not be calculated in one, two, seven and ten patients, for FABP, MYO, CK and HBDH, respectively.

3.2. Plasma creatinine, glomerular filtration rate, plasma volume and FCR

Average plasma creatinine concentrations at admission, and 12 and 24 h later were 94±2, 97±2 and 104±4 μmol/l, respectively. The overall range was 49–337 μmol/l. In a subgroup of 31 patients (26 men and five women), mean plasma creatinine concentrations were above the upper reference limit, i.e. 110 μmol/l for men and 97 μmol/l for women, and this group of patients was classified as having renal dysfunction. Mean plasma creatinine concentrations in this group were 118±5, 134±7 and 156±10 μmol/l, in the three successive samples, respectively. In the total group of 138 patients, the mean calculated glomerular filtration rate was 61±1 (range, 17–104) ml h$^{-1}$ kg$^{-1}$, the mean plasma volume was 43±0.2 (range, 39–47) ml kg$^{-1}$ and the mean FCR was 1.4±0.03 (range, 0.4–2.4) h$^{-1}$. As shown in Fig. 1, an approximately normal distribution of FCR values, with a peak of 48 patients with FCR values between 1.3 and 1.5 h$^{-1}$, was found. As indicated in Fig. 1, FCR values below 1.0 h$^{-1}$ were only found in patients with renal dysfunction.

The gradual rise in creatinine levels, measured at admission and after 12 and 24 h, indicated that a single measurement at 12 h could probably have been used. Indeed, the ratio of FCR, as calculated from such a single creatinine value, divided by FCR, as calculated from the averaged value of creatinine, was 1.02±0.007, $n = 136$.

3.3. Time–concentration curves of marker proteins in plasma and infarct size

| Table 1 | Baseline characteristics of different treatment groups |

<table>
<thead>
<tr>
<th>Baseline variables</th>
<th>All patients</th>
<th>SK with s.c. hep.</th>
<th>SK with i.v. hep.</th>
<th>tPA with i.v. hep.</th>
<th>SK+tPA i.v. hep.</th>
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</thead>
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<tr>
<td>Number of patients</td>
<td>138</td>
<td>37</td>
<td>24</td>
<td>45</td>
<td>32</td>
</tr>
<tr>
<td>Age (years)</td>
<td>59±1*</td>
<td>60±2</td>
<td>62±2</td>
<td>59±2</td>
<td>58±2</td>
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<tr>
<td>Female sex (%)</td>
<td>22</td>
<td>27</td>
<td>38</td>
<td>20</td>
<td>9</td>
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<td>Anterior infarct location (%)</td>
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<td>43</td>
<td>38</td>
<td>48</td>
<td>53</td>
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<td>Inferior infarct location (%)</td>
<td>49</td>
<td>49</td>
<td>58</td>
<td>48</td>
<td>41</td>
</tr>
<tr>
<td>Posterior infarct location (%)</td>
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<td>3</td>
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<td>0</td>
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<tr>
<td>Lateral infarct location (%)</td>
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<td>5</td>
<td>4</td>
<td>0</td>
<td>6</td>
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<tr>
<td>Previous AMI (%)</td>
<td>16</td>
<td>22</td>
<td>13</td>
<td>13</td>
<td>16</td>
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<td>Previous CABG (%)</td>
<td>3</td>
<td>3</td>
<td>4</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Time to treatment (h)</td>
<td>3.1±0.1</td>
<td>3.0±0.2</td>
<td>3.2±0.3</td>
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<tr>
<td>Clinical events</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke, all types (%)</td>
<td>1</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>3</td>
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<tr>
<td>Shock (%)</td>
<td>2</td>
<td>0</td>
<td>4</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Angioplasty (%)</td>
<td>9</td>
<td>16</td>
<td>17</td>
<td>4</td>
<td>0</td>
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<tr>
<td>30-day mortality (%)</td>
<td>3</td>
<td>3</td>
<td>4</td>
<td>2</td>
<td>3</td>
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<tr>
<td>Infarct size</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>calculated from HBDH (g eq/l)</td>
<td>4.8±0.3</td>
<td>5.4±0.6</td>
<td>4.9±0.9</td>
<td>4.5±0.4</td>
<td>4.6±0.7</td>
</tr>
<tr>
<td>number of patients</td>
<td>128</td>
<td>34</td>
<td>21</td>
<td>44</td>
<td>29</td>
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</tbody>
</table>

*Mean±SEM; SK = streptokinase; tPA = tissue type plasminogen activator hep. = heparin; s.c. = subcutaneous; i.v. = intravenous; CABG = coronary artery bypass grafting.
Fig. 1. Distribution of individual FCR values for FABP and MYO. Columns present total number of patients with FCR values within the interval of the indicated value ±0.1 h⁻¹. Shaded area presents patients with renal dysfunction.

3.3. Cumulative release during 72 h

Cumulative release during 72 h is shown in the lower part of Fig. 2. After 72 h, the mean cumulative release was 4.8±0.3 g eq/l for HBDH and 5.0±0.3 g eq/l for CK. In 91 patients whose HBDH values were available up to 96 h, cumulative release increased by only 5% from 72 to 96 h. Similarly, cumulative release of CK increased by only 2% from 72 to 96 hours (n=94). Therefore, infarct size was estimated from Q(72) for both markers.

Fig. 3 presents scatter plots of individually calculated infarct sizes for different markers. For FABP and MYO, infarct sizes were calculated with individual FCR values. High correlations were obtained, and linear regression equations approximated the lines of identity. As explained in the Discussion, HBDH was used as the reference protein in Figs. 3 and 5, because of its smaller error in calculated infarct size.

3.4. Cumulative release of cardiac proteins in patients with renal insufficiency

Fig. 4 presents cumulative release of HBDH, CK, FABP and MYO in the subgroup of 31 patients with renal dysfunction. Relatively low values (range, 0.4–1.4 h⁻¹) were obtained for individual FCR values in these patients. The effect of FCR on calculated infarct size was demonstrated by performing these calculations also with the mean, fixed FCR value of 1.4 h⁻¹, as found in the present study. For FABP, mean infarct sizes of 5.8±0.8 and 8.5±1.2 g eq/l were obtained for individual versus mean FCR values (P<0.0005). For MYO, these values were 5.5±0.7 and 7.8±1.1 g eq/l, respectively (P<0.0005).

Using infarct size calculated for HBDH as a reference, Fig. 5 illustrates its relationship with infarct sizes of FABP and MYO in patients with renal dysfunction. Left panels show results for a fixed mean value of FCR=1.4 h⁻¹ for FABP and MYO. Right panels show results for individually estimated FCR values. Use of these latter values improved correlations and shifted regression equations towards the line of identity. In contrast, in patients without renal insufficiency, these correlations did not markedly improve by using individual instead of mean FCR values for FABP and MYO (data not shown).
4. Discussion

4.1. FCR as a determinant of error in calculated infarct size

When plasma concentrations of marker proteins in patients with AMI have returned to their normal values, extravasated protein has returned to plasma and has also been eliminated. The first term (protein still present in plasma) and the second term (extravasated protein) in the expression for $Q(t)$ will then both vanish, and infarct size is simply calculated from the third term by multiplication of the integral (area under the plasma curve) with FCR.

Using fixed mean values for FCR, scatter due to biological variation in FCR will then be fully present in calculated infarct size. This explains why error is relatively small for HBDH. Due to its slow elimination (1.5% h$^{-1}$), a large part of the released HBDH will still be present in

Fig. 2. Mean plasma levels (upper figure) and infarct size (lower figure) of CK (□), HBDH (■), FABP (●) and MYO (○), as a function of time after onset of AMI. Concentrations of FABP and MYO are expressed in μg/l and activities of CK and HBDH in U/l. Infarct size, expressed in gram equivalents per litre of plasma, was calculated with individual FCR values for FABP and MYO, and with fixed mean FCR values for CK and HBDH. The SEM is indicated and sometimes was smaller than the symbol size.
plasma after 72 h (Fig. 2) and can be measured directly. The error in FCR will then have only limited influence, and the total error in $Q_{\text{HBDH}}(72)$ was estimated at 10–15% [21]. Therefore, HBDH was used as the reference protein in the present study.

Large proteins, like CK and HBDH (LDH), are eliminated from plasma by the liver [22], and protein turnover studies have generally shown limited individual variation, of 10–20%, in FCR, even in patients with AMI [23]. Much larger variability (40–60%) is found in renal clearance rates, especially after AMI [16]. This is confirmed in the present study by the wide range (0.4–2.4 h$^{-1}$) of FCR values for FABP and MYO (see Fig. 1). If fixed mean values for FCR were used, this large variability would be fully present as error in calculated infarct size. The use of individual FCR values eliminates part of this error.

4.2. Use of similar clearance rates for creatinine, FABP and myoglobin

Renal clearance rates, as calculated in the present study, were shown to correlate well with total glomerular filtration rates estimated from creatinine or inulin (5.2 kDa) [10,11]. Because of their larger molecular sizes, however, clearance of FABP and MYO could be slower. For electrically neutral dextrans, size-restriction in glomerular
Fig. 4. Infarct size, expressed in g eq/l, in patients with renal insufficiency. Symbols are as indicated in Fig. 2. The infarct size of FABP and MYO, as calculated with a mean fixed FCR value of 1.4 h^{-1} (see text), is indicated by (×) for FABP and by (∆) for MYO.

filtration starts at a molecular Stokes radius of 2 nm [24], whereas the Stokes radius of MYO is 1.9 nm [25]. For anionic dextrans, however, size-restriction was observed for a radius of 1.8 nm [26]. As both FABP (pI 5.1) and MYO (pI 7.0) are negatively charged at physiological pH, clearance rates for these proteins could thus be slightly lower than those calculated in the present study. This could explain a slight overestimation of infarct size for FABP and MYO, as suggested by Fig. 2. An average FCR value of 1.2 h^{-1}, instead of 1.4 h^{-1}, would have resulted in equal estimates of infarct size for all four proteins. A recent study showed that thrombolytic therapy had no influence on FABP/HBDH or MYO/HBDH release ratios [27], and the observed overestimation for FABP and MYO is thus not related to such therapy.

4.3. Possible causes of variable renal clearance in AMI patients

Of the AMI patients studied, 22% had mean plasma creatinine levels above the upper reference limit and, hence, were labelled as having renal dysfunction. High plasma creatinine concentrations in these patients could not be explained by previous AMI (in only five of 31 patients), the size of the present infarction (r=0.04, P=0.60), or infarct location (48% anterior and 45% inferior). Moreover, high plasma creatinine levels could not be caused by additional injury of skeletal muscles because the mean MYO/FABP concentration ratio in plasma, a measure to discriminate between skeletal and cardiac muscle injury [3], was rather constant in these patients (5.1±0.5). Other factors, like hypertension (in 13 out of 31 patients), previously existing kidney dysfunction (creatinine was elevated at admission in 19 patients) or diabetes (no information available) could have been responsible for renal insufficiency.

4.4. Expression of infarct size in gram equivalents of myocardium

In the present study, cumulative protein release was expressed in gram equivalents of myocardium by using tissue protein contents, as measured with the same analytical techniques in biopsies and autopsies of relatively healthy hearts. However, pathological changes of these values will generally occur. In hearts from patients who died after AMI, for example, hypertrophy, and variably reduced protein content, are common [19,28–30]. Such variability, however, is not observed in the release ratios of different marker proteins. The upper part of Fig. 3, for instance, shows highly correlated release of CK and HBDH, with approximately the same ratio as expected from healthy myocardium.

This seeming discrepancy has been explained by the phenomenon of ‘muscle dilution’. In pathological hearts, the ratios of cytosolic marker proteins had remained
unchanged, in spite of considerable variability in overall protein content [28]. Apparently, the pathological changes could be described by invasion of essentially unaltered muscle tissue by non-muscle components, like collagen, fat or oedema. This implied that estimates of infarct size from different muscle proteins could still be compared, as also demonstrated in the present study. The term gram equivalent (of healthy myocardium) was adopted [28] to indicate that one gram equivalent of infarct size could correspond to as much as 1.5–2.0 grams of tissue in severely pathological hearts.

4.5. Concluding remarks and clinical application

Traditional myocardial marker proteins, like CK, CK-MB, LDH (HBDH) and AST, have been shown to be powerful risk markers in patients with AMI, and this was recently also demonstrated for the cardiospecific troponins [31,32]. Compared to these latter proteins, FABP and MYO lack the diagnostic advantage of cardiospecificity, but have the quantitative advantage of being small cytosolic proteins, rapidly released into circulation and allowing early estimation of the total extent of myocardial injury. In this era of acute reperfusion therapy of AMI, where the emphasis is also on shorter length of stay in hospital, early estimation of infarct size is useful to evaluate the patient’s prognosis at an earlier stage, and also to evaluate the effect of therapeutic interventions on infarct size in clinical studies. The present study shows that, using individually estimated clearance rates for FABP and MYO, reliable estimates of myocardial infarct size can be obtained within 24 h, while for the established markers CK or HBDH, a time span of 72 h is required. Moreover, 20–25% of patients with elevated creatinine values need no longer be excluded from such measurements, even though they may have renal insufficiency. In clinical practice, measurement of creatinine at admission and after 12 and 24 h could be reduced to a single measurement after 12 h, with only minor consequences for the precision of infarct size estimation.

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References


