Eur. Radiol. (2001) 11: 876–883

EXPERIMENTAL

Intracoronary delivery of Gd-DTPA and Gadophrin-2 for determination of myocardial viability with MR imaging

Y. Ni
C. Pislaru
H. Bosmans
S. Pislaru
Y. Miao
J. Bogaert
S. Dymarkowski
J. Yu
W. Semmler
F. Van de Werf
A. L. Baert
G. Marchal

Received: 8 September 2000
Revised: 16 November 2000
Accepted: 21 November 2000

Y. Ni (✉) · H. Bosmans · Y. Miao · J. Bogaert · S. Dymarkowski · J. Yu · A. L. Baert · G. Marchal
Department of Radiology,
University Hospitals,
Catholic University Leuven,
Herestraat 49, 3000 Leuven, Belgium
e-mail: e-mail:
Yicheng.Ni@med.kuleuven.ac.be
Tel.: + 32-16-343780
Fax: + 32-16-343765

C. Pislaru · S. Pislaru · F. Van de Werf
Department of Cardiology,
University Hospitals,
Catholic University Leuven,
Herestraat 49, 3000 Leuven, Belgium

W. Semmler
Institut für Diagnostikforschung GmbH,
Berlin, Germany

Abstract The aim of this study was to compare intracoronary (i.c.) administration of Gadophrin-2, a necrosis-avid contrast agent (NACA), and nonspecific agent Gd-DTPA for determination of myocardial viability (MV) in acute myocardial infarction (AMI) with MRI. Reperfused AMI was induced in 12 dogs by transcatheter balloon occlusion of coronary artery. In 6 dogs each, Gd-DTPA at 0.1 mmol/kg or Gadophrin-2 at 0.005 mmol/kg was administered into coronary artery by fast bolus ($n = 3$) or slow infusion ($n = 3$). Serial ECG-triggered cardiac MRI of T1-weighted segmented turbo fast low-angle shot (FLASH) sequence was conducted and compared with triphenyltetrazolium chloride (TTC) histochemical staining. The contrast ratio and infarct size were quantified and analysed statistically. No cardiovascular side effects were found with local delivery of both agents. After i.c. administration, Gadophrin-2 induced a strong (CR ≥ 1.78) and persistent (≥ 10 h) contrast enhancement of infarcted region. The infarct size defined with Gadophrin-2 was almost identical to that with TTC staining throughout the postcontrast period. With a dose 20 times higher, Gd-DTPA also strongly enhanced infarct-to-normal contrast; however, the enhancement diminished with time, i.e. from early strong to later faint enhancement and eventual loss of contrast. The delineated infarct size was also unstable, i.e. from early overestimation to later underestimation and eventual disappearance of the enhanced infarct. In combination with PTCA procedure, i.c. administration of MRI contrast agents may prove useful for post-procedure verification of diagnosis. The NACA-enhanced MRI may serve as an in vivo surrogate of postmortem histochemical staining for determination of MV. Although applicable in clinical setting, cardiac MRI with nonspecific Gd-DTPA is less reliable and should be performed within less than 1 h after contrast.

Key words Metalloporphyrins · Necrosis-avid contrast agents · Intracoronary injection · Acute myocardial infarction · MRI · Myocardial viability

Introduction

Myocardial viability (MV) remains a challenging topic in ischaemic heart disease, since timely and accurately verifying the exact status of MV is crucial for therapeutic options and, therefore, the eventual outcomes of the patients [1, 2, 3, 4, 5, 6]. If a stable irreversible myocardial infarction has already developed, the patient will unlikely benefit from reperfusion therapies including thrombolytic medication, coronary angioplasty and bypass surgery. These costly therapies may even evoke a secondary reperfusion damage to the jeopardized heart

[7, 8]. Instead, the patient should receive mainly symptomatic treatment or heart transplantation. On the contrary, if the ischaemic heart is still viable and potentially salvageable, active reperfusion measures are warranted in order to achieve as much as possible morphological and functional recovery [9, 10].

Despite tremendous efforts in this field, currently available imaging modalities, such as echocardiography, radiography and nuclear medicine, as well as newly emerging MRI, are still incapable of making explicit distinction between reversible and irreversible ischaemic myocardium. Alternatively, methods such as those to show regions of "perfusion-contraction" or "function-metabolism" mismatch have been recommended as indirect indicators of MV [11]. Being discontent with the current status, the editorial of a past issue of the journal "Circulation" stated that "the ideal imaging method for assessing viability should be able to delineate infarcted from noninfarcted tissue with the same resolution as shown in Fig. 2 (a hand-drawn diagram), in which infarction represents nonviable tissue and the rest of the heart represents viable myocardium" [12]. This standard implicates two essential elements: high spatial resolution and sufficient tissue contrast. Cardiac MRI is known to be advantageous over other modalities for its superb spatial resolution of 1–2 mm and intrinsic soft tissue contrast [13]. Unfortunately, plain MRI is not sufficient yet to explore the native contrast between nonviable and viable myocardium. Furthermore, commercially available gadolinium contrast agents nonspecifically enhance MRI signals of both reversibly injured and irreversibly infarcted myocardium [14, 15]; therefore, specific markers that can exclusively label either the viable or the dead are apparently needed [3, 12]. Similar to thallium used in nuclear cardiology, manganese-based MRI contrast agents preferentially retain in viable myocardium and might be useful in assessing myocardial viability if an effective but safe dose existed [16].

Recently, one type of necrosis-avid contrast agent (NACA) has been discovered in a series of research that dramatically converted paramagnetic metalloporphyrins from "tumor-seeking" agents into "markers" of acute myocardial infarction (AMI) [17]. Porphyrin derivatives with so-called tumor-localizing properties have been studied for decades in cancer photodynamic therapy [18] and tumor imaging diagnosis [19]; however, the induced "specific" enhancement was found only attributable to a porphyrin retention in nonviable instead of viable tumoral components [20]. This finding was confirmed in animal models of "benign" necrosis with several porphyrin agents [21]. Eventually, a novel application of metalloporphyrins for visualization of AMI with MRI has been introduced [22, 23, 24, 25]. More recently, this new approach was accepted or further elaborated in multiple centres as a promising diagnostic strategy towards resolving MV [26, 27, 28].

Previous studies have demonstrated that MRI in conjunction with both intravenous (i.v.) and intracoronary (i.c.) injection of Gadophrin-2 (one porphyrin-derived NACA) may function as a virtue in vivo "histochemical staining" for determination of AMI [22, 23, 24, 25, 26, 27, 28, 29], although a noninvasive i.v. approach should be a predominant application. However, there still exists a belief among researchers that nonspecific agents, such as Gd-DTPA, would have the same ability as NACA to assess MV. In order to verify this issue, the present canine experiment was conducted by means of a direct comparison between Gadophrin-2 and Gd-DTPA for their MRI contrast behaviours in dogs with reperfused AMI.

Materials and methods

Models of reperfused myocardial ischaemia

Twelve mongrel dogs of 16–24 kg were sedated with intramuscular xylazin at 3.0 mg/kg (Rompun, Bayer, Leverkusen, Germany), anesthetized with intravenous sodium pentobarbital (15 mg/kg bolus plus 0.1 mg/kg min^{-1} infusion), intubated and artificially ventilated (Mark 7 respirator, Bird Corporation, Palm Springs, Calif.). The dogs underwent close-chest percutaneous transluminal cardiac intervention with conventional catheter laboratory facilities [25]. The left anterior descending (LAD) or circumflex (LCX) coronary artery was occluded by inflating a balloon occluder for 150 min, and was reperfused by deflating the balloon. The blood flow of the coronary artery was monitored with angiography before, during and after the procedure. This canine experiment complied with the current guidelines for use and care of laboratory animals of our institute.

Contrast administration

Gd-DTPA (Magnevist, Schering, Berlin, Germany) was commercially available and Gadophrin-2 (bis-Gd-mesoporphyrin) was produced and supplied by the Institut für Diagnostik Forschung (Berlin, Germany).

One hour after reperfusion, 20 ml of Gd-DTPA (0.1 mmol/kg; $n = 6$) or Gadophrin-2 (0.005 mmol/kg; $n = 6$) diluted with normal saline was administered through a coronary catheter as either a slow infusion ($n = 3$) over 10 min (Becton Dickinson Infusion Pump, Brezins, France) or a bolus at 1 ml/s ($n = 3$). Cardiophysiological parameters, such as ECG, heart rate and blood pressure, were monitored during the infusion sessions. For intraindividual comparison, 4 of the 6 dogs that had received Gd-DTPA were reinjected intracoronarily with Gadophrin-2 when local washout of Gd-DTPA was evident.

We chose i.c. administration in this study with the following rationales. Firstly, since percutaneous transluminal coronary angioplasty (PTCA) or stenting has become practical as a primary therapy for acute cardiac patients [30], local contrast delivery during PTCA in combination with a post-procedure MRI may represent a feasible diagnostic adjuvant. Secondly, with i.c. delivery, the localizing and enhancing properties of Gadophrin-2 and Gd-DTPA can be compared based mainly on a single pass of the agents through the reperfused myocardial vascular bed with a minimal influence of drug re-circulation. Thirdly, local delivery can increase intramural

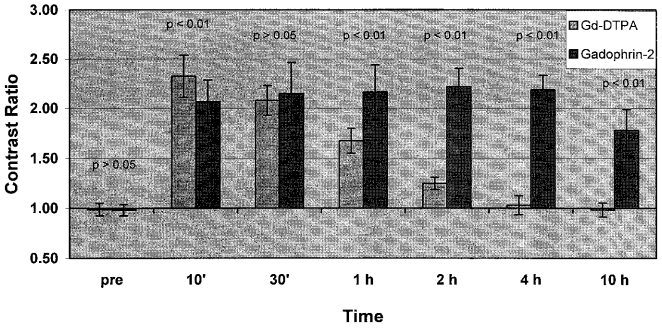

Fig. 1 Bar chart of time-dependent infarct-to-normal contrast ratio

but decrease systemic drug concentration so that the overall dose can be minimized for both economic and safety reasons. Lastly, this study was accomplished by means of local administration despite a limited supply of Gadophrin-2. The total i.c. dose used for 12 dogs equals only three-fifths of one i.v. dose for only one dog.

Cardiac MRI

Magnetic resonance imaging studies were conducted with a 1.5-T whole-body Vision scanner (Siemens, Erlangen, Germany) with a gradient slew rate of 25 mT/m in 0.3 ms. The dog was placed in a head coil with a supine position. Under ventilator-controlled breath-holding and ECG-pulse triggering, T1-weighted segmented turbo FLASH sequence was applied before and serially after contrast administration [25, 29]. The scheme started with an inversion recovery pulse, followed by a train of 33 rapid gradient echoes. The k space was filled from bottom to top. Magnitude image reconstruction was used. The gradient-echo acquisitions were characterized by TR/TE/flip angle of 7.5 ms/3.4 ms/25°, TI 450–550 ms, a field of view of 240 × 320 mm with a matrix of 165 × 256 and the bandwidth of 195 Hz/pixel. From the apex to the base in short-axis planes, the heart was scanned slice by slice at a thickness of 6 mm in successive breath-hold period of five to ten heartbeats. Following a precontrast baseline measurement, the acquisitions were repeated every 10 min during the first hour and every 30 min in up to 4 h after Gd-DTPA and 10 h after Gadophrin-2 injection.

Histochemical staining

At the end of imaging study, the dog was killed with intravenous overdose of pentobarbital and the heart was excised. To facilitate a precise slice-to-slice match between MRI and histochemical preparations, the excised heart was embedded with 3% agar, cooled at –20°C for 15 min, sectioned at 6-mm thickness by using a calibrated slicer in a short-axis slice similar to that of MRI, and stained with 1% triphenyltetrazolium chloride (TTC) solution for 10 min. By this staining, normal myocardium appeared brick red and the infarcted area was unstained [23, 24, 25]. The TTC-stained specimens were photographed and digitally stored on the Kodak Photo CD for later computer-assisted planimetry.

Imaging quantitative analysis

The signal intensities (SI) of infarcted and normal myocardium were measured with an operator-defined circular region of interest (ROI) with 60–320 pixels. The size and location of the ROI were kept constant for measurements at different time points. The infarct-to-normal contrast was expressed as contrast ratio (CR) and calculated with the formula $CR = SI_{infarct}/SI_{normal}$. The averaged CR before and after Gd-DTPA or Gadophrin-2 administration was plotted as a function of time.

The coloured images of TTC staining on photo-CD and the black-and-white MR images were transferred to a PC for planimetric analysis using a commercial program Adobe Photoshop 5.0. The reddish LV wall and the discoloured infarct regions were contoured manually on the computer screen and the number of pixels was determined automatically. The black-and-white MR images were processed similarly, but the contouring was based on SI of the normal myocardium and contrast-enhanced area on MRI. The infarct size (IS) was expressed as a percentage of the infarcted area over the entire area of left ventricle (LV), i.e. $IS_{infarct}$ (%) = $Pixels_{infarct}/Pixels_{LV} \times 100\%$. The IS obtained with TTC staining was regarded as a gold standard (IS_{true}) for each slice. The IS obtained from each corresponding slice on Gd-DTPA and/or Gadophrin-2-enhanced MRI ($IS_{contrast}$) at a certain time point was converted into a relative IS using the formula $IS_{relative}$ (%) = ($IS_{contrast}$)/(IS_{true}) × 100%. The mean $IS_{contrast}$ with Gd-DTPA and Gadophrin-2 were plotted as a function of time in comparison with the IS_{true} defined with TTC. The differences in degree and extent of contrast enhancement with the two agents were analysed using the unpaired Student's *t*-test (Microsoft Excel 7.0). A value of $p < 0.01$ was considered significant.

Results

General conditions

All dogs survived the experimental procedures including anaesthesia, AMI induction, i.c. injection of Gd-DTPA and/or Gadophrin-2 and cardiac MRI. Both slow infusion and fast bolus of both agents at applied doses caused no detectable adverse effects, a finding similar to a previous observations with only slow infusion of Gadophrin-2 in comparison with normal saline [29].

Outcome of TTC staining

Altogether 125 axial slices (10 per heart in 7 dogs and 11 per heart in 5 dogs each) of 6 mm thick were obtained and stained with TTC. The infarct was found in two to six consecutive slices of the heart from all dogs and the infarct size varied from 4 to 95% of LV surface area on different slices. In total, 53 infarct-containing slices were obtained for planimetry and statistical analysis.

MRI findings

The time course of contrast enhancement with Gd-DTPA and Gadophrin-2 is shown in Fig. 1. Before contrast, the infarct was undetectable on T1-weighted MRI (CR≈1.0). Immediately after i.c. injection of Gd-DTPA

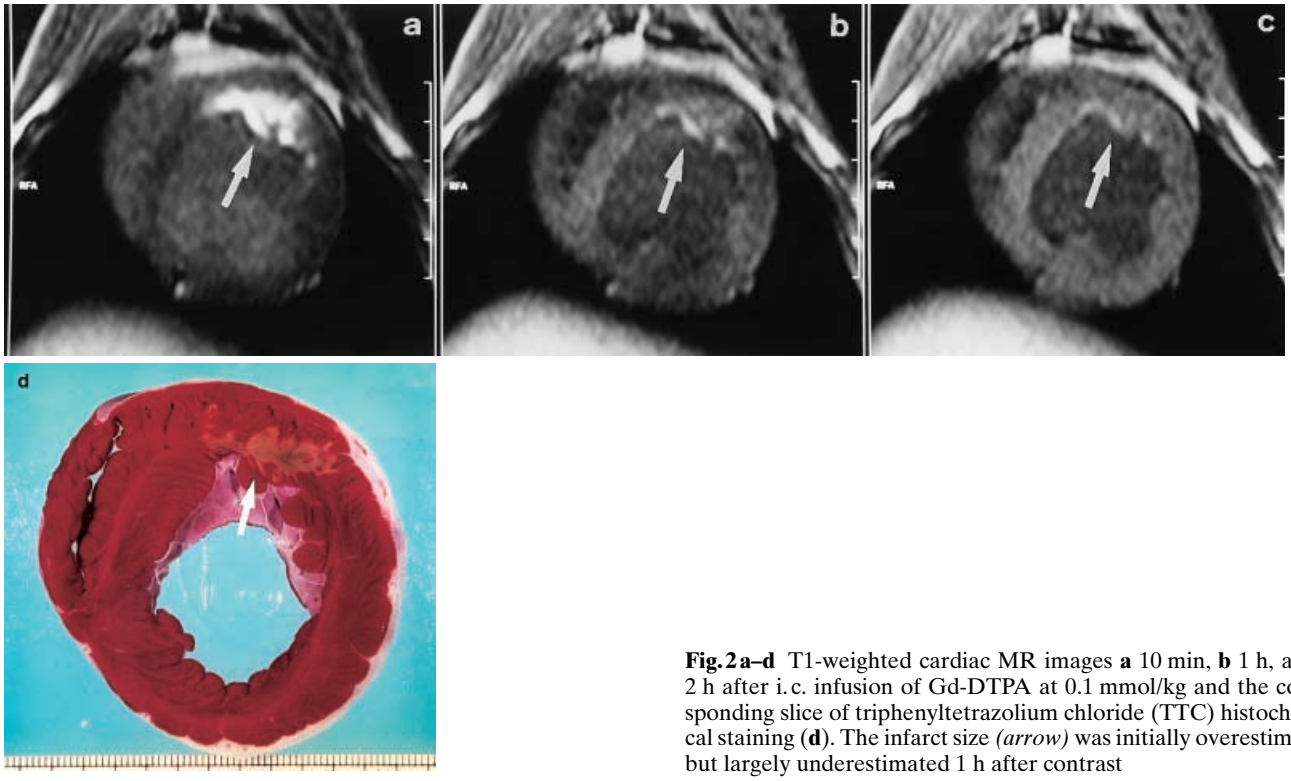

Fig. 2 a–d T1-weighted cardiac MR images **a** 10 min, **b** 1 h, and **c** 2 h after i.c. infusion of Gd-DTPA at 0.1 mmol/kg and the corresponding slice of triphenyltetrazolium chloride (TTC) histochemical staining (**d**). The infarct size *(arrow)* was initially overestimated but largely underestimated 1 h after contrast

at 0.1 mmol/kg, a strong infarct-to-normal contrast was created (CR = 2.32 ± 0.2); however, this contrast enhancement steadily diminished with time and disappeared virtually after 2 h (Figs. 1, 2). By contrast, Gadophrin-2 at 0.005 mmol/kg induced a comparably strong (CR ≥ 1.78 ± 0.21) but persistent contrast enhancement up to 10 h (Figs. 1, 3).

As demonstrated by the graph of time-dependent relative infarct size (Fig. 4), in comparison with the true infarct size defined with TTC staining, Gd-DTPA enhanced MRI overestimated the infarct size by more than 20% at the beginning (Figs. 2, 4). A correct but only transient match in size occurred around 30 min after contrast, followed by an underestimation and eventual disappearance of the infarct because of a gradual contrast fading (Fig. 2, 4). On the contrary, the infarct size defined with Gadophrin-2 enhanced MRI kept almost identical to that with TTC staining throughout 10 h of postcontrast period (Figs. 3, 4).

The distinctive contrast behaviours of Gd-DTPA and Gadophrin-2 can be better demonstrated by intraindividual comparisons (Fig. 5). The major imaging features of the two agents are summarized in Table 1. Visually, Gadophrin-2-enhanced MRI mirrored TTC histochemical staining in every topographic details such as transmural, subendocardial, subepicardial, patchy, scattered and small infarcts as well as involved papillary muscles (Figs. 2, 3, 5).

Discussion

Until recently, an in vivo technique for making an absolute distinction between viable and dead tissues has not been available. This is the major obstacle hampering the progress in clinical and experimental research for resolving MV [12, 31]. Alternatively nonspecific methods have been applied for cardiac imaging. However, T2-weighted plain MRI largely overestimates irreversibly damaged myocardium [25, 28, 29], whereas Gd-DTPA nonspecifically enhances both infarct and periinfarct border zone on T1-weighted MRI [14, 15, 27]. In the present comparative study, a normal dose of Gd-DTPA and a minimal dose of Gadophrin-2 were intracoronarily delivered either in different dogs for interindividual comparison or consecutively in the same dogs for intraindividual comparison. Serial T1-weighted MRI sessions were conducted to show the evolutions of the intensity and extent of contrast enhancement in the time course with both agents and to correlate with corresponding postmortem histochemical findings. The results indicated that it is Gadophrin-2, but not Gd-DTPA, that specifically enhanced the necrotic myocardium and served as an intravital surrogate of postmortem TTC histochemical staining. To our knowledge, so far NACA and the nonspecific agent have not been compared intracoronarily for determination of MV with MRI. In a proposed comprehensive "one-stop-shop"

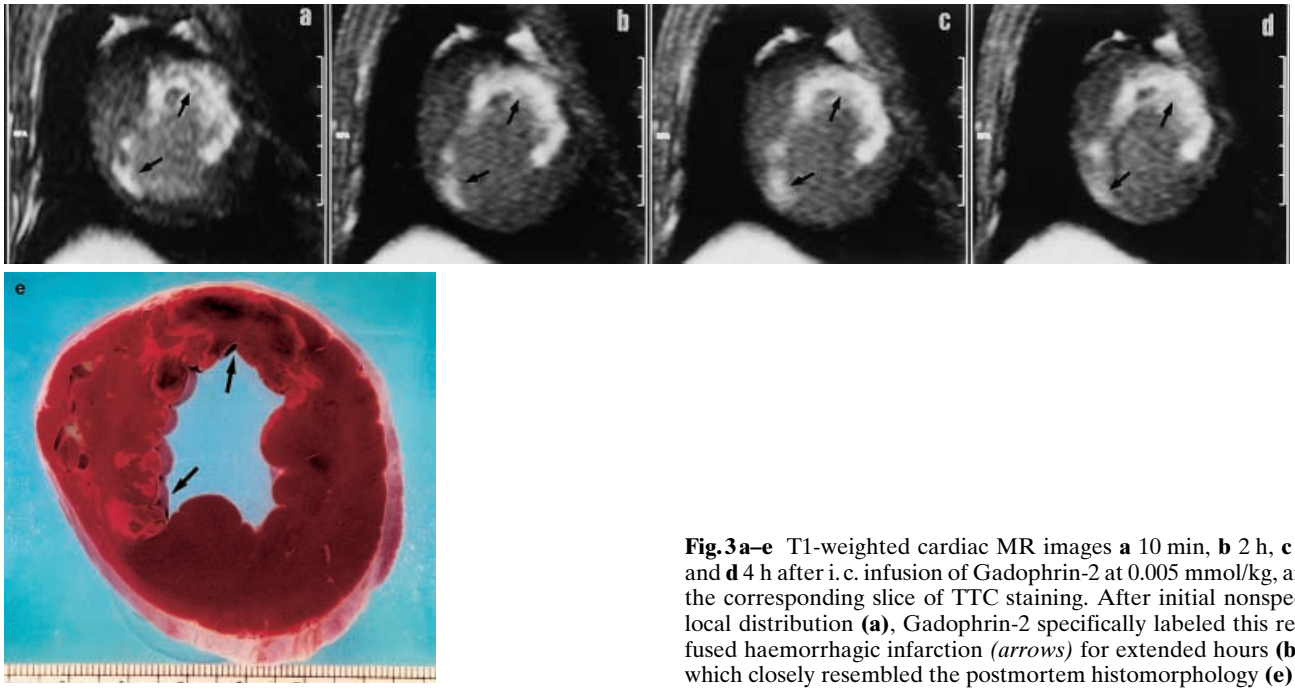

Fig. 3 a–e T1-weighted cardiac MR images **a** 10 min, **b** 2 h, **c** 3 h, and **d** 4 h after i.c. infusion of Gadophrin-2 at 0.005 mmol/kg, and **e** the corresponding slice of TTC staining. After initial nonspecific local distribution **(a)**, Gadophrin-2 specifically labeled this reperfused haemorrhagic infarction *(arrows)* for extended hours **(b–d)**, which closely resembled the postmortem histomorphology **(e)**

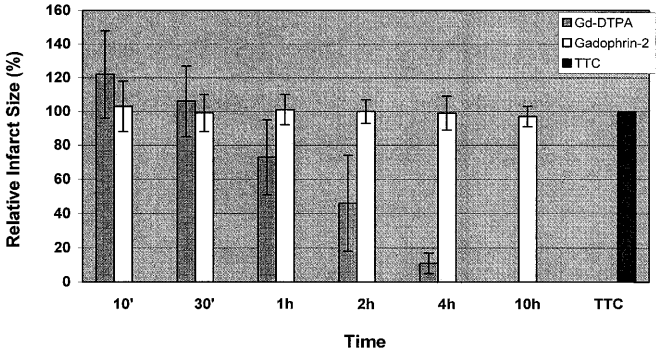

Fig. 4 Bar chart of time- and TTC-dependent relative infarct size

cardiac MR package for MV assessment, NACA represents the only key factor that can provide a clear-cut distinction between viable and necrotic myocardium [31].

As an interventional therapy complementary to noninvasive thrombolytic medication, PTCA or stenting has become one of the standard therapeutic options for patients in danger of myocardial infarction [30]. Intracoronary drug delivery in conjunction with the PTCA procedure has already been applied in clinical cardiology for additional diagnostic and therapeutic benefits [32, 33]. Since no obvious side effects have been noticed with i.c. administration of MRI contrasts, this technique can be feasible to incorporate with the anyhow invasive procedures of primary, rescue, immediate and delayed PTCA or stenting. The reason why so far i.c. administration of MRI contrast media for the assessment of MV after PTCA has not been proposed is most likely due to a lack of appropriate contrast agent.

With a simple kinetics of wash-in and washout, in the present study, intracoronarily infused Gd-DTPA at a 20-times higher dose strongly enhanced the infarct due to an enlarged distribution space and a temporal plasma-to-tissue gadolinium concentration gradient. Following an over 20% exaggeration of infarct size shortly after contrast, the enhanced area matched most closely to the true infarct size only at about 30 min after injection and rapidly diminished in size thereafter. Therefore, such nonspecific enhancement was unstable in terms of both the extent and degree. In theory, the area enhanced with a nonspecific agent can accurately match the necrotic myocardium only at a certain "optimal" postcontrast phase, e.g. at 30 min after contrast in this particular experiment. Outside this phase, the infarct size is either overestimated or underestimated. However, as it is influenced by multiple factors such as the extent of ischaemia or infarction, the degree and duration of myocardial injury, residue coronary flow and collateral circulation, as well as the dose, timing and method of contrast administration, this "optimal" phase is individually variable (as reflected by the broad standard deviations in Fig. 4) and, therefore, practically uncatchable. However, since Gd-DTPA is clinically available, it can be used with PTCA for an approximate diagnosis as long as cardiac MRI is performed within one hour to avoid false negative findings due to contrast washout. This means the MRI unit should be located almost next door to the

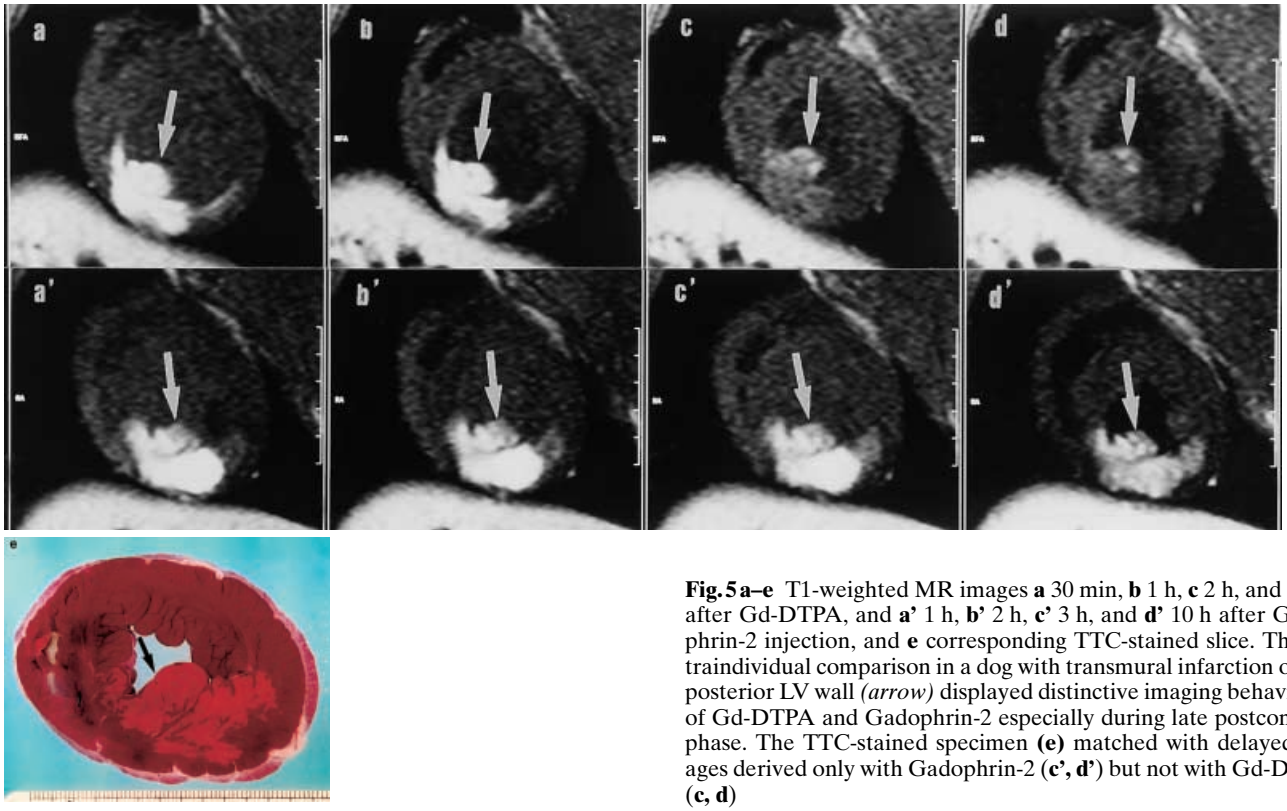

Fig. 5 a–e T1-weighted MR images **a** 30 min, **b** 1 h, **c** 2 h, and **d** 3 h after Gd-DTPA, and **a'** 1 h, **b'** 2 h, **c'** 3 h, and **d'** 10 h after Gadophrin-2 injection, and **e** corresponding TTC-stained slice. The intraindividual comparison in a dog with transmural infarction of the posterior LV wall *(arrow)* displayed distinctive imaging behaviours of Gd-DTPA and Gadophrin-2 especially during late postcontrast phase. The TTC-stained specimen **(e)** matched with delayed images derived only with Gadophrin-2 (**c', d'**) but not with Gd-DTPA (**c, d**)

Table 1 Comparison between Gd-DTPA and Gadophrin-2 after intracoronary injection in acute reperfused myocardial infarction

Contrast agents	Dose (mmol/kg)	Infarct/normal contrast ratio	Infarct size	Imaging window (h)	Optimal phase (h)
Gd-DTPA	0.10	2.3–1.0 (unstable)	Inaccurate	< 2	~ 0.5
Gadophrin-2	0.005	2.2–1.8 (stable)	Accurate	≥ 10	≤ 10

cath-lab for a quick transportation and a shortened injection-imaging interval. This problem can be solved in the future when dedicated equipment for MRI guided coronary intervention becomes available [34].

On the other hand, only a minimal dose of Gadophrin-2 already enabled a persistent, precise and stable enhancement in irreversibly damaged myocardium for an extended period. This feature creates an ample imaging window that may allow a post-PTCA MRI examination conducted in an unhurried fashion. The accurate information derived with this technique can be invaluable for confirmation of the diagnosis, justification of the PTCA intervention, estimation of MV, modification of the therapy and prediction of the prognosis. In view of the striking and prolonged enhancement of the infarcts caused by only one pass of the locally delivered agent, this study provides further insight into the strong affinity of metalloporphyrins for necrosis.

Since the concentration gradient caused by recirculatory Gadophrin-2 delivered intracoronarily at 0.005 mmol/kg is negligible, this specific enhancement can mainly be attributed to an affinity of NACA to necrosis through only a one-pass contact. The NACA-necrosis affinity has been proposed mainly on observational basis and proven indirectly by a local retention of gadolinium with multifold higher concentration relative to that of normal myocardium [17, 29]. It is presumably attributed to some kind of physicochemical interactions between the agent and the denatured debris of the necrotic tissues [17, 29, 35]. The newly proposed albumin-binding mechanism, i.e. stagnation of the agent in necrosis after being bound to intra- and/or extravascular albumin [36], failed to be proven in a recent comparative study [35]. Therefore, the exact mechanisms governing such a unique targetability have yet to be further elucidated. Instead of an immediate enhancement after i.c. injection, one recent paper showed a maximum enhancement of reperfused MI in cats 1–3 h after i.v. injection of Gadophrin-2 [28], suggesting a crucial role of administration manner in the contrast behaviours of the

NACA. Although a favourable safety margin in i.v. dosage of Gadophrin-2 has been shown in preclinical studies, the dark colour and unwanted side effects may render clinical use of this agent unfeasible [20, 23]. However, recent efforts in developing nonporphyrin species of NACA may likely bring about light-coloured or colourless, more effective and less toxic compounds which can be more clinically applicable than Gadophrin-2 [37].

In conclusion, after i.c. administration, nonspecific Gd-DTPA and necrosis-avid Gadophrin-2 displayed distinctive imaging behaviours towards reperfused AMI. In comparison with a transient unstable enhancement caused by a normal dose of Gd-DTPA, a minimal dose of Gadophrin-2 induced a strong and persistent contrast enhancement only in necrotic myocardium. Contrast-enhanced cardiac MRI in conjunction with PTCA intervention may prove feasible for post-procedural MV assessment. The NACA technique is particularly suitable for this application, but it is still under preclinical development. Nonspecific agents are clinically applicable, but cardiac MRI should be performed within 1 h after contrast. More extensive research on validation of this application is needed before it can advance to clinical stage.

Acknowledgement This project was supported in part by the ECR Research and Educational Fund 1997, research grant G.0304.97 N of the national Fund for Scientific Research, Belgium, and a research subsidy from Institut für Diagnostikforschung GmbH, Berlin, Germany. Part of the study was presented at ECR 1999.

References

1. Dilsizian V, Bonow RO (1993) Current diagnostic techniques of assessing myocardial viability in patients with hibernating and stunned myocardium. Circulation 87: 1–20
2. Udelson JE (1994) Can technetium 99m-labeled sestamibi track myocardial viability? J Nucl Cardiol 1: 571–575
3. Iskandrian AS (1996) Myocardial viability: unresolved issues. J Nucl Med 37: 794–797
4. Wackers FJT (1996) Radionuclide detection of myocardial ischemia and myocardial viability: Is the glass half empty of half full? J Am Coll Cardiol 27: 1598–1600
5. Beller GA (1996) Comparison of 201Tl scintigraphy and low-dose dobutamine echocardiography for the noninvasive assessment of myocardial viability. Circulation 94: 2681–2684
6. Dilsizian V (1996) Myocardial viability: contractile reserve or cell membrane integrity? J Am Coll Cardiol 28: 443–446
7. Darius H, Buerke M, Lindemann S, Horstick G, Meyer J (1997) Mechanism of reperfusion damage after thrombolysis and 'direct PTCA'. Fibrinol Proteol 11 (Suppl 2):117–121
8. Maxwell SRJ, Lip GYH (1997) Reperfusion injury: a review of the pathophysiology, clinical manifestations and therapeutic options. Int J Cardiol 58: 95–117
9. Heusch G, Schulz R (1997) Characterization of hibernating and stunned myocardium. Eur Heart J 18 (Suppl D):D102–110
10. Braunwald E (1989) Myocardial reperfusion, limitation of infarct size, reduction of left ventricular dysfunction, and improved survival: Should the paradigm be expanded? Circulation 79: 441–444
11. Sambuceti G, Giorgetti A, Corsiglia L, Marini C, Schneider Eicke J, Brunelli C, Marzullo P, L'Abbate A, Capponnetto S, Parodi O (1998) Perfusion-contraction mismatch during inotropic stimulation in hibernating myocardium. J Nucl Med 39: 396–402
12. Kaul S (1995) There may be more to myocardial viability than meets the eye. Circulation 92: 2790–2793
13. Van der Wall EE, Vliegen HW, de Roos A, Bruschke AVG (1996) Magnetic resonance techniques for assessment of myocardial viability. J Cardiovasc Pharmacol 28 (Suppl 1):37–43
14. Saeed M, Wendland M, Takehara Y, Masui T, Higgins C (1992) Reperfusion and irreversible myocardial injury: identification with a nonionic MR imaging contrast medium. Radiology 182: 675–683
15. Judd RM, Lugo-Olivieri CH, Arai M, Kondo T, Croisille P, Lima JA, Mohan V, Becker LC, Zerhouni EA (1995) Physiological basis of myocardial contrast enhancement in fast magnetic resonance images of 2-day-old reperfused canine infarcts. Circulation 92: 1902–1910
16. Bremerich J, Saeed M, Arheden H, Higgins CB, Wendland MF (2000) Normal and infarcted myocardium: differentiation with cellular uptake of manganese at MR imaging in a rat model. Radiology 216: 524–530
17. Ni Y, Marchal G, Herijgers P, Flameng W, Petré C, Hilger CS, Ebert W, Maier FK, Semmler W, Baert AL (1996) Paramagnetic metalloporphyrins: from enhancers for malignant tumors to markers of myocardial infarcts. Acad Radiol 3: 395–397
18. Pass H (1993) Photodynamic therapy in oncology: mechanisms and clinical use. J Natl Cancer Inst 85: 443–456
19. Saini SK, Jena A, Dey J, Sharma AK, Singh R (1995) MnPcS4: a new MRI contrast enhancing agent for tumor localization in mice. Magn Reson Imaging 13: 985–990
20. Ni Y, Marchal G, Yu J, Lukito G, Petré C, Wevers M, Baert AL, and Ebert W, Hilger CS, Maier FK, Semmler W (1995) Localization of metalloporphyrin induced "specific" enhancement in experimental liver tumors: comparison of magnetic resonance imaging, microangiographic and histologic findings. Acad Radiol 2: 687–699
21. Ni Y, Petré C, Miao Y, Yu J, Cresens E, Adriaens P, Bosmans H, Semmler W, Baert AL, Marchal G (1997) Magnetic resonance imaging-histomorphologic correlation studies on paramagnetic metalloporphyrins in rat models of necrosis. Invest Radiol 32: 770–779
22. Ni Y, Marchal G, Petré C, Lukito G, Herijgers P, Flameng W, Yu J, Hilger CS, Ebert W, Maier FK, Semmler W (1994) Metalloporphyrin enhanced magnetic resonance imaging of acute myocardial infarction. Circulation 90 (Suppl):I-468

23. Marchal G, Ni Y, Herijgers P, Flameng W, Petré C, Bosmans H, Yu J, Ebert W, Hilger CS, Pfefferer D, Semmler W, Baert AL (1996) Paramagnetic metalloporphyrins: infarct avid contrast agents for diagnosis of acute myocardial infarction by magnetic resonance imaging. Eur Radiol 6: 1–8
24. Herijgers P, Laycock SK, Ni Y, Marchal G, Bogaert J, Bosmans H, Petre C, Flameng W (1997) Localization and determination of infarct size by Gd-mesoporphyrin enhanced MRI in dogs. Int J Cardiac Imaging 13: 499–507
25. Pislaru S, Ni Y, Pislaru C, Bosmans H, Miao Y, Bogaert J, Semmler W, Marchal G, Van de Werf F (1999) Noninvasive measurements of infarct size after thrombolysis with a necrosis-avid MRI contrast agent. Circulation 99: 690–696
26. Stillman AE, Wilke N, Jerosch-Herold M (1999) Myocardial viability. Radiol Clin North Am 37: 361–377
27. Saeed M, Bremerich J, Wendland MF et al. (1999) Reperfused myocardial infarction as seen with use of necrosis-specific versus standard extracellular MR contrast media in rats. Radiology 213: 247–257
28. Choi SII, Choi SH, Kim ST et al. (2000) Irreversibly damaged myocardium at MR imaging with a necrotic tissue-specific contrast agent in a cat model. Radiology 215: 863–868
29. Ni Y, Pislaru C, Bosmans H, Pislaru S, Miao Y, Van de Werf F, Semmler W, Baert AL, Marchal G (1998) Validation of intracoronary delivery of metalloporphyrin as an in vivo "histochemical staining" for myocardial infarction with MR imaging. Acad Radiol 5 (Suppl 1):37–41
30. Ryan TJ, Ryan TJ Jr, Jacobs AK (1999) Primary PTCA versus thrombolytic therapy: an evidence-based summary. Am Heart J 138: 96–104
31. Ni Y (1998) Myocardial viability. In: Brady LW, Donner MW, Heilmann HP, Heuck FHW, Baert AL, Youker JE (eds) Medical radiology: diagnostic imaging and radiation oncology; Bogaert J, Duerinckx AJ, Rademakers FE (volume eds) Magnetic resonance of the heart and great vessels: clinical applications. Springer, Berlin Heidelberg New York, pp 113–132
32. Giordano A, Trani C, Lombardo A, Maseri A (1997) Detection of hibernated myocardium using intracoronary technetium-99m-sestamibi. Q J Nucl Med 41: 46–50
33. Marzilli M, Orsini E, Marraccini P, Testa R (2000) Beneficial effects of intracoronary adenosine as an adjunct to primary angioplasty in acute myocardial infarction. Circulation 101: 2154–2159
34. Jacob AL, Regazzoni P, Steinbrich W, Messmer P (2000) The multifunctional therapy room of the future: image guidance, interdisciplinarity, integration and impact on patient pathways. Eur Radiol 10: 1763–1769
35. Ni Y, Adzamli K, Miao Y, Cresens E, Yu J, Periasamy MP, Adams MD, Marchal G (2001) MRI contrast enhancement of necrosis by MP-2269 and Gadophrin-2 in a rat model of liver infarction. Invest Radiol 36
36. Hofmann B, Bogdanov A, Marecos E, Ebert W, Semmler W, Weissleder R (1999) Mechanism of Gadophrin-2 accumulation in tumor necrosis. J Magn Reson Imaging 9: 336–341
37. Ni Y, Cresens E, Adriaens P, Miao Y, Verbeke K, Dymarkoski S, Verbruggen A, Marchal G (in press) Necrosis avid contrast agents: introducing nonporphyrin species. Acad Radiol