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ORIGINAL ARTICLE

Edema is a sign of early acute myocardial infarction on post-mortem magnetic resonance imaging

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Abstract The aim of this study was to investigate if acute myocardial infarction can be detected by post-mortem cardiac magnetic resonance (PMMR) at an earlier stage than by traditional autopsy, i.e., within less than 4 h after onset of ischemia; and if so, to determine the characteristics of PMMR findings in early acute infarcts. Twenty-one ex vivo porcine hearts with acute myocardial infarction underwent T2-weighted cardiac PMMR imaging within 3 h of onset of iatrogenic ischemia. PMMR imaging findings were compared to macroscopic findings. Myocardial edema induced by ischemia and reperfusion was visible on PMMR in all cases. Typical findings of early acute ischemic injury on PMMR consist of a central zone of intermediate signal intensity bordered by a rim of increased signal intensity. Myocardial edema can be detected on cardiac PMMR within the first 3 h after the onset of ischemia in porcine hearts. The size of myocardial edema reflects the area of ischemic injury in early acute (peracute) myocardial infarction. This study provides evidence that cardiac PMMR is able to detect acute myocardial infarcts at an earlier stage than traditional autopsy and routine histology.

Keywords Cardiac magnetic resonance · Post-mortem magnetic resonance · Acute myocardial infarction · Animal model · Radio-morphologic correlation

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Introduction

"Approximately every 25 s, an American will have a new coronary attack and approximately every minute, someone will die of one" [1].

Sudden cardiac death is an important public health issue [2] and a large portion of the cases referred to our institute for medico-legal autopsy have died from cardiac death with previously undiagnosed cardio-vascular disease. Recognition of acute myocardial infarction at autopsy can be difficult, particularly when death has occurred within a few hours after the onset of symptoms [3]. Myocardial infarcts are usually unapparent on macroscopic examination if survival time after an infarct is less than 12 h [3]. Even on routine histology examination, microscopic changes will be detectable no sooner than 4 h after the onset of symptoms [3]. Nevertheless, tissue changes like cell swelling are thought to occur within the first minutes of ischemia [3]. The increased water content in the myocardium is associated with increased density of hydrogen protons in the myocardium [4]. On magnetic resonance (MR) imaging, increased density of hydrogen proton is associated with

increased signal intensity on T2-weighted (T2W) images [5–7].

In the last decade, cardiac MR was introduced to post-mortem investigations [8–14]. Preliminary studies showed good correlation between autopsy findings and cardiac post-mortem MR (PMMR) in cases of acute, sub-acute, and chronic myocardial infarction [11–13]. However, investigators were occasionally confronted with cases where both case history and PMMR findings were consistent with sudden cardiac death from acute ischemic myocardial injury but neither macroscopic nor microscopic examination of the heart revealed any myocardial pathology [10, 13]. Such cases led to the hypothesis that MR might be able to diagnose early acute myocardial infarction at an earlier stage than traditional autopsy [8, 10, 13].

It was the aim of this study to investigate if early acute myocardial infarction can be detected by post-mortem cardiac MR within 4 h of the onset of ischemia in a prospective study using a porcine model; and if so, to determine the characteristics of MR findings in early acute infarcts.

Methods

The responsible local justice department approved this study. The animal experiments were approved by the veterinary service of the Canton of Bern, permission no. BE 109_09. The study was a joint research project between the Department of Clinical Research and the Institute of Legal Medicine at the University of Bern. The subjects for this prospective study consisted of 28 pigs selected during a period between January 6th, 2010 and September 23rd, 2011, depending on the logistical capacity of both institutes involved, including the availability of MR scan time.

The study protocol included the following procedure for each animal [15]: general anesthesia, fluoroscopy guided selective catheterization of the left coronary artery, complete occlusion of the left coronary artery distal to the first diagonal branch for 60 min with a semi-compliant over-the-wire catheter (Concerto, Occam, the Netherlands; balloon length 10 mm, diameter 2.5–3 mm), followed by reperfusion of 120 min. Afterward, the artery was re-occluded briefly and 60 mL of Evan's Blue were injected intravenously to stain the perfused segments of the myocardium. Finally, animals were sacrificed using intravenous potassium chloride. Each heart was excised immediately after death, rinsed, placed in a container with iced 0.9 % saline solution, and transported to the MR suite. Twenty-one animals completed the procedure. Seven animals died prematurely; either during catheterization ($n = 4$); during occlusion ($n = 2$); or during reperfusion ($n = 1$). These animals were excluded from the final study population.

MR imaging was performed using a 1.5 Tesla MR unit (Magnetom Avanto, Siemens, Erlangen, Germany). For imaging each heart was placed in a saline filled container (volume: 1.0 l; temperature: 21 °C) and positioned in the head coil. Due to time constraints, PMMR protocol was limited to a single short axis T2-weighted (T2W) turbo spin echo (TSE) sequence using the following parameters: repetition time (TR): 3860 ms, echo time (TE): 100 ms, slice thickness: 2.2 mm, field of view (FoV): 300 mm, matrix size: 512 × 512 mm, total scan duration: 16 min. Each heart was returned to the laboratory after imaging. Transportation time for each way was between 7 and 12 min.

Hearts were cut in slices of 15 mm from the apex to the mitral valve. We used a triphenyl tetrazolium chloride (TTC) (Sigma, St. Louis, MO, USA) solution for staining prior to fixation in formaldehyde. TTC staining is based on the activity of an enzyme called dehydrogenase [16]. Live cardiomyocytes contain dehydrogenases in the cytoplasm, whereas dead cells lose their dehydrogenases and are not stained by TTC [17]. This difference permits macroscopic differentiation between healthy and necrotic myocardium [16]. TTC stains viable tissue red, whereas the white or brown regions indicate infarcted myocardium [16]. Normal post-mortem tissue degradation annihilates the original difference between enzyme activity of healthy and ischemic myocardium over time. Therefore, staining should be initialized within 45 min after death. Heart specimens were photographed digitally before and after TTC staining.

All 21 cardiac PMMR datasets were analyzed on a digital picture archive and communication system workstation (IDS5, Sectra, Linköping, Sweden). For radio-morphologic correlation, PMMR images were reconstructed using multiplanar reformatting (MPR) to exactly match the slice orientation of the heart specimen. In a joint reading session PMMR findings and macroscopic findings on the porcine hearts were evaluated by a radiologist and a cardiovascular biologist. Conclusions were reached by consensus.

Results

Myocardial edema was present in all 21 cases. There was increased signal intensity in the entire ischemic tissue in all cases, typically characterized by a large central zone of intermediate hyperintensity and a zone of increased hyperintensity in the periphery of the ischemic tissue (Fig. 1a). This pattern was partially altered in seven cases featuring small spots of post-ischemic hemorrhage within the central zone. In these cases, the increased iron-content within the hemorrhagic spots induced a focal decrease of the intermediate hyperintense signal. The hyperintense zone in the periphery was not affected. In the fresh heart specimen, perfused regions were stained blue from the injection of Evan's blue. The occluded regions were not

stained blue (Fig. 1b). This allowed for macroscopic differentiation between perfused and non-perfused areas. However, the extent of non-perfused but viable tissue in the border zones could not be identified. After the enzyme-activity based staining with TTC the macroscopic differentiation between infarcted and viable tissue within the ischemic myocardium was more obvious. The viable tissue was stained red, the infarcted, necrotic tissue was a pinkish color (Fig. 1c). Correlation between the imaging and the gross specimen revealed good agreement between the myocardial edema on PMMR and the area of infarction on TTC stained slices. However, it is important to note that the extent of viable tissue in the border zone (i.e., TTC red positive, but Evan's blue negative) varied between cases. In several cases the margin of the edema on PMMR reached into the viable tissue. Overall, the myocardial edema was more prominent in the border zone of the anterior wall than the border zone in the interventricular septum (Fig. 1a).

Discussion

This study shows that early acute myocardial infarction can be detected by cardiac PMMR less than 4 h after the onset of ischemia in porcine hearts and that edema is a characteristic finding of early acute myocardial infarction on PMMR. These results provide evidence for the repeatedly postulated hypothesis that cardiac PMMR may be able to detect acute myocardial infarcts at an earlier stage than traditional autopsy and routine histology [8, 10, 13]. In this study, myocardial infarction appeared as myocardial edema with a central zone of intermediate hyperintensity and a rim of increased hyperintensity after 60 min of vascular occlusion and 120 min of reperfusion. In cases of post-ischemic hemorrhage, the signal of the central zone was focally decreased due to iron deposition.

Edema represents a very early tissue response to ischemic injury [5, 18, 19]. Abdel-Aty et al. [19] reported the appearance of myocardial edema in live dogs as soon as 28 ± 4 min after vascular occlusion. In our study, the size of the edema closely matched the size of the actual infarction. This result concurs with the findings from previous studies on early acute myocardial ischemia but is currently controversially discussed in clinical radiology [19–22]. Traditionally, T2W non-contrast MR images are used to quantify the area at risk within the heart (defined as the entire area of non-perfused or hypoperfused myocardium during vascular occlusion) [23]. The actual infarction is a subset of the area at risk; the difference between the two (as defined by contrast-enhanced MR) is considered to represent the salvageable myocardium in living patients [21]. Current data, including our findings, indicate that the duration and degree of ischemia, the duration of reperfusion, and the time interval between the onset of symptoms and MR imaging do all affect the imaging appearance of ischemic myocardial injury.

The imaging appearance of early acute myocardial infarction in our study corresponds closely to what Jackowski et al. describe as acute myocardial infarction (i.e., one day to one week old) in their work on PMMR in human hearts [11–13]. According to their experience, early acute myocardial infarction (i.e., less than 24 h old) is represented by small hypointense focal spots on PMMR [11–13]. This finding was not observed in our study and has not been described in previous studies of living subjects [5, 18–24]. However, it is difficult to identify the cause for this discrepancy given the methodological differences between the controlled conditions of our prospective animal study (with defined times of occlusion and reperfusion) and the uncontrolled conditions of studies with human cadavers (where the duration of occlusion, the occurrence of reperfusion, the time of survival after onset of symptoms, and the post-mortem interval are often unknown). In addition,

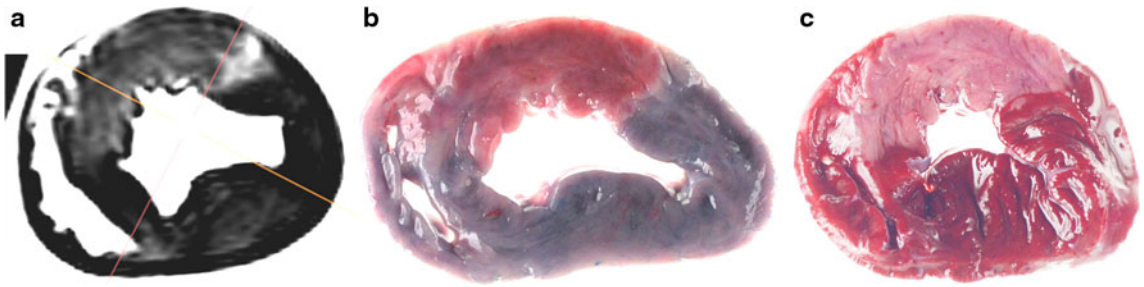

Fig. 1 Comparison between **a** post-mortem cardiac MR, **b** fresh porcine heart after staining with Evan's blue, and **c** fixed heart specimen, stained with TTC. Ischemia-induced myocardial edema is visible on **a** as a large region of increased signal intensity. Characteristically, a large, central zone of intermediate signal intensity is bordered by a rim of high signal intensity, which is most prominent on the anterior wall of the left ventricle. On **b**, this border zone between the infarcted and healthy tissue the myocardium is of a pinkish color. However, necrotic and viable myocardium can only be reliably distinguished after staining with TTC (**c**). The size of the myocardial edema on MR **a** corresponds to the size of ischemia on the stained heart specimen (**c**)

the influence of temperature on image contrast should also be taken into account when discussing diverging findings on PMMR [25]. Nevertheless, it is important to note that in our animal model edema appeared after 3 h of occlusion/reperfusion.

A few limitations of this study deserve discussion. First, it would have been desirable to modify the protocol of the study, i.e., to individually alter occlusion and reperfusion time in order to investigate the influence of ischemia with and without reperfusion on the appearance of early acute infarction on PMMR separately. The authors hope to investigate this in a future study. Second, assessing microscopic changes would have added value to this study and might have allowed improving our understanding of the PMMR appearances of early acute myocardial infarction. However, all subjects enrolled in this study were a small subset of a clinical (non-forensic) study investigating the effects of reperfusion injury in early acute myocardial infarcts. The clinical study protocol could not be adapted according to our needs and it precluded the collection of samples for histology. Finally, it may be criticized that a model study cannot reflect the variety of findings in real cases of sudden cardiac death. While this may be true, it is not necessarily a limitation: because of the complexity of real cases it is elementary to first investigate the capability of cardiac PMMR to detect early acute myocardial infarction under controlled conditions.

Conclusions

Edema is a very early reaction to ischemic myocardial injury and can be detected by post-mortem MR within the first 3 h after the onset of ischemia in porcine hearts. The size of myocardial edema reflects the area of ischemic injury in early acute myocardial infarction. Based on the results of this study it is our suggestion to use cardiac PMMR in cases of suspected cardiac death prior to autopsy in order to enhance the quality of post-mortem investigations, whether they are performed in the course of forensic investigation or during hospitality-based morbidity/mortality review.

Key Points

1. Detection of acute myocardial infarction at autopsy can be difficult if death has occurred within the first few hours after the onset of symptoms.
2. Myocardial edema represents an early response to ischemia and reperfusion injury and can be detected by PMMR 3 h after vascular occlusion in porcine hearts.
3. The size of myocardial edema reflects the area of ischemic injury in early acute myocardial infarction.
4. PMMR is able to detect acute myocardial infarcts at an earlier stage than traditional autopsy and routine histology.

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