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DISSERTATION

Gewebecharakterisierung akuter myokardialer Schädigungen mittels kardialer Magnetresonanztomographie

Zur Erlangung des akademischen Grades
Doctor medicinae (Dr. med.)

vorgelegt der Medizinischen Fakultät Charité –
Universitätsmedizin Berlin

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Datum der Promotion: 27.03.2009

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1. Zusammenfassung

1.1. Zusammenfassung (deutsch)

Eine nichtinvasive myokardiale Gewebedifferenzierung ist insbesondere im Zusammenhang mit akuten Myokardschäden von großer klinischer Bedeutung. Die Kardiovaskuläre Magnetresonanztomographie (CMR) erscheint hier einzigartig geeignet, diese Aufgabe zu erfüllen. Besonders gut untersucht ist die Darstellung irreversibler myokardialer Schädigungen durch Late Gadolinium Enhancement (LGE). Weiterhin ermöglicht die exzellente Korrelation zwischen der sogenannten T2-Relaxationszeit und freiem myokardialem Wasser die Identifizierung myokardialer Ödeme, einem wesentlichen Kennzeichen sowohl von Myokardinfarkten als auch von einer akuten Myokarditiden. Darüberhinaus gestattet die Quantifizierung der myokardialen Signalintensität (SI) kurz nach Kontrastmittelgabe die Erfassung einer hyperämischen Reaktion, respektive des sogenannten capillary leackage, ebenfalls beides Merkmale einer akuten Inflammation.

Ziel dieser Arbeit ist es, anhand von Untersuchungen von Patienten mit akutem oder chronischem Myokardinfarkt (MI) als auch von Patienten mit akuter Myokarditis, das Potenzial der CMR in diesem Zusammenhang darzustellen.

Zunächst wird der Ansatz eines kombinierten T2-gewichteten und Late Enhancement Protokolls zur Differenzierung von akuten und chronischen Myokardinfarkten dargestellt. Dieser Ansatz beruht auf der Grundlage, das ein Ödem nur beim akuten Infarkt vorhanden ist.

Eine zweite Publikation diskutiert den Einsatz der MRT für den Nachweis einer rechtsventrikulären Beteiligung beim akuten Hinterwandinfarkt, dabei wurde die LGE-Technik angewendet, die es ermöglicht, die hohe räumliche Auflösung des CMR zu nutzen, um einen Infarkt im dünnwandigen rechten Ventrikel nachzuweisen.

In einer weiteren Arbeit wurde eine Kombination der T2-gewichteten und der kontrastverstärkten Techniken genutzt, um die Diagnostik inflammatorischer Reaktionen zu verbessern.

1.2. Abstract (English)

Myocardial tissue characterization particularly in the setting of acute myocardial injury is of paramount clinical importance. Cardiovascular magnetic resonance (CMR) imaging appears uniquely suited to accomplish this task. Due to its versatility, a wide range of myocardial injuries can be non-invasively identified. Particularly relevant is the ability to accurately quantify acute irreversible myocardial injury through late gadolinium enhancement (LGE) imaging. Furthermore the excellent correlation between the so-called T2 relaxation time and myocardial free water allows the technique to identify myocardial edema, a substantial feature of acute myocardial infarction as well as acute myocarditis. Finally the ability to monitor myocardial signal intensity changes early after contrast injection provides relevant information on the capillary integrity and hyperemia, which may be features of the acute myocardial inflammatory reaction.

This work presents data from patients with acute and chronic myocardial infarction as well as acute myocarditis, stressing the clinical utility of CMR to characterize the myocardial injuries in three clinical settings. First, it demonstrates the ability of a combined T2-weighted and LGE approach to differentiate acute from chronic myocardial infarction. The premise being that T2-weighted identified myocardial edema is a feature of acute but not of chronic myocardial infarction. Second, the ability of late gadolinium enhancement CMR to identify right ventricular involvement in acute myocardial infarction is illustrated. This comes secondary to the uniquely high spatial resolution of CMR allowing the technique to detect the infarcted, thin-walled right ventricle. Third, the ability of a comprehensive CMR imaging approach combining T2-weighted, early and late enhancement to detect acute myocarditis is shown. The approach utilizes the versatility of CMR allowing the detection of edema, capillary leakage and irreversible injury, which are all features of the acute myocardial inflammatory reaction.

2. Introduction

Traditional cardiovascular imaging modalities like echocardiography or computed tomography rely on a single contrast mechanism, e.g. attenuation in computed tomography to differentiate healthy from diseased tissues. Cardiovascular magnetic resonance (CMR) imaging on the other hand is unique for the versatility of contrast mechanisms it targets[1]. By applying various pulse sequences, contrast can be created reflecting an array of tissue changes including edema[2], myocardial blood oxygenation[3] or tissue velocity. Applying external intravenous contrast medium widens the spectrum of tissue changes CMR detects to include perfusion[4], capillary leakage or irreversible injury[5]. In this work the value of CMR to characterize acute myocardial injury in the setting of myocardial infarction and myocardial inflammation will be addressed.

2.1. Estimating the age of irreversible injury

Differentiating acute from chronic irreversible myocardial injury is a frequent demand for clinical decision-making and yet represents a challenge for existing imaging modalities. Both patterns of injury present as a regional wall motion abnormality in echocardiography, and although wall thinning is a feature of chronic infarcts, this finding is not observed in non-transmural infarcts. In the absence of viable myocardial cells, both acute and chronic myocardial infarction (MI) fail to uptake radioactive tracers in radionuclide imaging and thus appear as fixed defects[6].

Late gadolinium enhancement (LGE) cardiovascular magnetic resonance (CMR) accurately detects irreversible myocardial injury. Yet, both acute and chronic infarcts exhibit LGE regardless of their age[5].

One aspect that has not been fully assessed in this setting is the utilization of myocardial edema to differentiate the two types of injuries. The mechanisms underlying the development of myocardial edema in acute MI are complex and appear to involve a disruption of the energy-regulated ionic transport mechanisms across the cell membrane following the ischemic insult[7]. With reperfusion, edema is further intensified and then gradually resolves as the infarct heals. A strong body of evidence supports the notion that T2-weighted CMR sensitively detects infarct-associated myocardial edema justifying its use in this setting.

2.2. Right ventricular involvement in acute MI

Another challenge in infarct patients is to identify right ventricular involvement in the setting of acute inferior MI. The thin-walled right ventricle falls behind the spatial resolution of radionuclide images. Right ventricular wall motion abnormalities are difficult to assess and

are not specific to irreversible injury. Finally ECG may be of limited utility particularly in patients with relatively late presentation. LGE imaging appears to be the suitable candidate in this clinical scenario[8]. The technique accurately detects irreversible injury as small as 1/1000 of the ventricular myocardium[9].

2.3. CMR in acute myocarditis

Identifying patients with acute myocarditis is another challenging task. Clinical presentations often mimic other disorders and may vary from flu-like symptoms or subclinical disease to acute heart failure and sudden cardiac death. Myocardial biopsy is invasive and lacks the sensitivity because of the focal nature of the disease. CMR sensitively identifies several processes inherent in the acute myocardial inflammatory reaction, namely edema (T2-weighted imaging)[10], hyperemia and capillary leakage (early global enhancement)[11] and focal irreversible injury (LGE)[12]. However, a comprehensive CMR protocol combining data obtained from each approach has not reached the clinical arena and yet appears promising for two reasons: First, the spectrum of myocardial injury caused by the disease is diverse ranging from mild inflammation with hyperemia or edema to frank necrosis. One would then expect that an imaging approach designed to detect only one of these injuries would lack sufficient sensitivity. Second, providing information on the various myocarditis-induced injuries could help identifying patients with a severe form of the disease or those with a potential unfavorable prognosis.

3. Aim

The aim of this work was to explore the clinical utility of CMR to differentiate acute from chronic myocardial infarction, detect right ventricular involvement in inferior myocardial infarction and finally to provide means for the non-invasive diagnosis of acute myocarditis.

4. Methods

4.1. Cardiovascular magnetic resonance

4.1.1. Image acquisition

CMR studies were performed in a 1.5 Tesla system (Signa CV/*i*, GE medical systems, Milwaukee). Localization was performed using breath-hold real time and steady-state free precession images of true anatomical axes of the heart. A breath-hold; black-blood, T2-weighted triple inversion recovery sequence[13] in 3 (basal, midventricular and apical) short axis slices (TR 2xRR,TE 65ms, TI 140ms, slice thickness 15mm, gap 5 mm, FOV 34 to 38 cm, matrix: 256x256, number of excitations =1) was applied. Breath-hold SSFP images (TR

3.8ms, TE 1.6ms, number of phases =30) were acquired in 2- and 4-chamber views to assess global ventricular function. In myocarditis patients, a free breathing spin echo sequence in four axial slices was applied both before and immediately after (acquisition time: 3 to 4 minutes) the intravenous injection of 0.1 mmol Gadolinium-DTPA (Magnevist®, Schering, Germany) using an automated injector (Medrad, PA). Following the acquisition of these spin echo images, an additional dose (0.1 mmol) of gadolinium-DTPA was injected and a breath-hold contrast-enhanced inversion-recovery gradient-echo sequence (TR 5.5ms, TE 1.4ms, TI 225-275 ms as individually optimized to null myocardial signal, matrix 256x192, slice thickness/gap 15/5 mm) was applied after a delay of 10 minutes in 3 short and 3 long (2-, 3- and 4-chamber views respectively) axis slices.

4.1.2. Image analysis:

In infarction patients, LGE and T2 images were analyzed using a validated software (MASS, Medis, Leiden, Netherlands). Endocardial and epicardial borders were manually traced in each slice and the myocardium was divided into 16 equi-angular segments (6 basal, 6 mid-ventricular and 4 apical) starting from the anterior insertion of the right ventricle. The mean signal intensity (SI) of each segment and of the background noise was measured. Contrast to noise and signal to noise ratios were calculated. Qualitative analysis was performed by the consensus agreement of two observers who were blinded to the patients' clinical data. Images were evaluated for the presence or absence of focal or areas of high T2 SI or LGE.

Spin-echo images: ROIs covering the left ventricular myocardium as well as within a skeletal muscle in the same slice were manually drawn in the non-contrast images and copied to the post-contrast images to calculate myocardial global relative enhancement (GRE)[11].

T2-weighted images: ROIs were drawn covering the left ventricular myocardium and within a skeletal muscle in the same slice. The myocardial SI was related to that of the skeletal muscle.

4.2. Patients

In general, patients were not enrolled if they were clinically unstable, had severe arrhythmia or known contraindications to CMR (claustrophobia, cardiac pacemaker and aneurysmal clips)

4.2.1. Differentiating acute from chronic MI:

Seventy-three MI patients (57±10 years, 40 males) were studied in two groups. Group A consisted of 15 acute MI patients who were studied twice, on day one and 3 months after MI. In group B, 58 patients with acute or chronic MI underwent one CMR scan.

4.2.2. Detecting right ventricular infarction:

Thirty-seven (54±11 years, 28 males) patients with acute inferior MI were enrolled.

MI diagnosis was established based on infarct-typical ECG changes combined with > two-fold elevation of creatine kinase and/or positive troponin T. The reference for infarct localization was the site of ECG-changes in conventional 12-lead ECG and/or the territory of the culprit vessel as defined by coronary angiography in the acute phase.

MI was considered acute if the clinical event occurred <2 weeks ago and chronic if it occurred > 4 weeks ago.

4.2.3. Detecting acute myocarditis:

Twenty-five patients (44±17 years, 18 males) were enrolled fulfilling the following inclusion criteria:1) Symptoms and signs suggestive of cardiac disease (angina pectoris, dyspnea, palpitations), 2) Evidence for myocardial injury as defined by ECG changes (ST-segment changes, conduction defects) and elevated serum markers (creatine kinase 'CK', troponin T or I) and 3) Exclusion of coronary artery disease by angiographic and/or clinical criteria.

4.3. Statistics

Values are presented as mean ± SD. A p-value < 0.05 was considered significant. Statistical analysis was performed using commercially available software (SPSS 11.0® for Macintosh®). All statistical tests were 2-tailed. Agreement between methods and inter-observer agreement was measured using Kappa statistics. Continuous variables were compared using the paired t-test when normally distributed, and the Mann-Whitney-U-test when not normally distributed. Non-continuous data were compared using the Chi-Square test.

5. Results

Four studies were discarded (all in the acute MI patients): three due to poor image quality resulting from severe motion artefacts and one patient could not complete the examination. All patients underwent successful reperfusion therapy (PTCA and stenting) as evidenced by the establishment of TIMI grade 3 flow in the infarct related artery. Four patients underwent thrombolytic therapy as well. The mean time to reperfusion was 10.2±7 hours. In myocarditis

patients the average duration between the onset of cardiac symptoms and CMR was 5.6 ± 4.2 days.

5.1. Acute and chronic MI:

Acute MI (LGE plus high T2 signal) was identified with a sensitivity of 92% and 96% and specificity of 92% and 100% for both observers, respectively, (figure 1). The interobserver agreement to designate MI as acute or chronic (LGE without high T2 signal) was high (Kappa =0.89; $p<0.0001$). LGE was visible in all cases in the acute and follow-up studies with no significant contrast to noise differences between the two studies in the segment-based (1.9±1.5 vs. 1.3±1.0;p=ns) or in the ROI-based analysis (5.4±3.5 vs. 5.8± 3.5; p=ns). In T2-weighted, the contrast to noise dropped significantly in the follow-up study from 2.7±1.1 to 0.1±1.2 ($p<0.0001$). The presence of a transmural high T2 SI was characteristic of acute infarcts regardless of their reperfusion status, time to reperfusion, presence or absence of collaterals, STEMI or non-STEMI infarct types.

5.2. Right ventricular infarction:

Late gadolinium enhancement was positive for RV infarction (enhancement extending from the inferior left ventricular myocardium or the inferior interventricular septum into the right ventricular free wall in any one or more of the CMR images, figure 2) in 21/37 patients (59%).

The two blinded CMR observers reached independent agreement on presence or absence of RV involvement in 34 patients (kappa = 0.83). LGE detected RV involvement more frequently than ECG, echocardiography or physical examination separately. The results of the LGE-CMR study however showed good agreement with the results of the combined non-CMR tests (kappa=0.623).

5.3. Acute myocarditis:

The best diagnostic performance was obtained when any two of the criteria obtained by the three techniques were positive (T2: signal-intensity ratio 1.9; GRE: signal-intensity ratio 4.0; LGE: Presence of visually detectable bright areas) in the same patient (figure 3). This approach had 76% sensitivity, 95.5% specificity and 78% diagnostic accuracy. Specifically, GRE and T2 were positive in 64%, LGE and T2 in 40 %, LGE and GRE in 36%. The three sequences were all positive in 32% of the patients and in none of the controls.

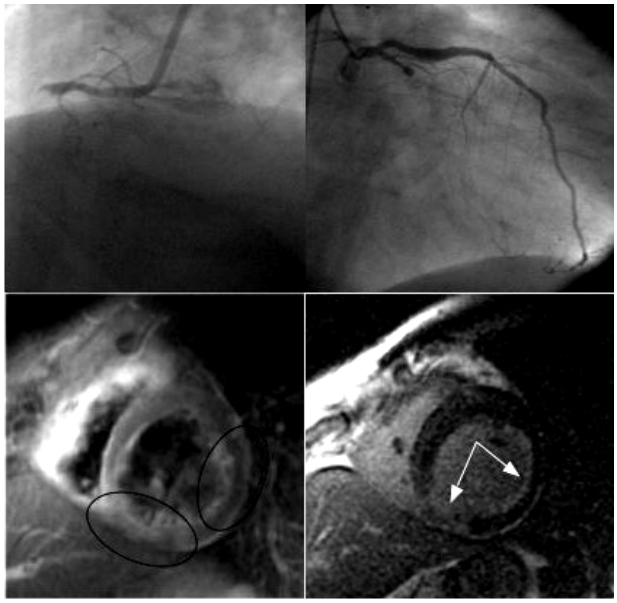

Figure 1: Acute on top of chronic myocardial infarction: Top coronary angiography showing occluded both RCA and LCX. Bottom: LGE (bottom, right) indicating irreversible injury in both RCA and LCX territories (arrows). T2 weighted image (bottom, left) reveals a high signal intensity in the inferior myocardium and a normal or even darker signal intensity in the lateral wall (circles) establishing that the acute event was in the RCA territory.

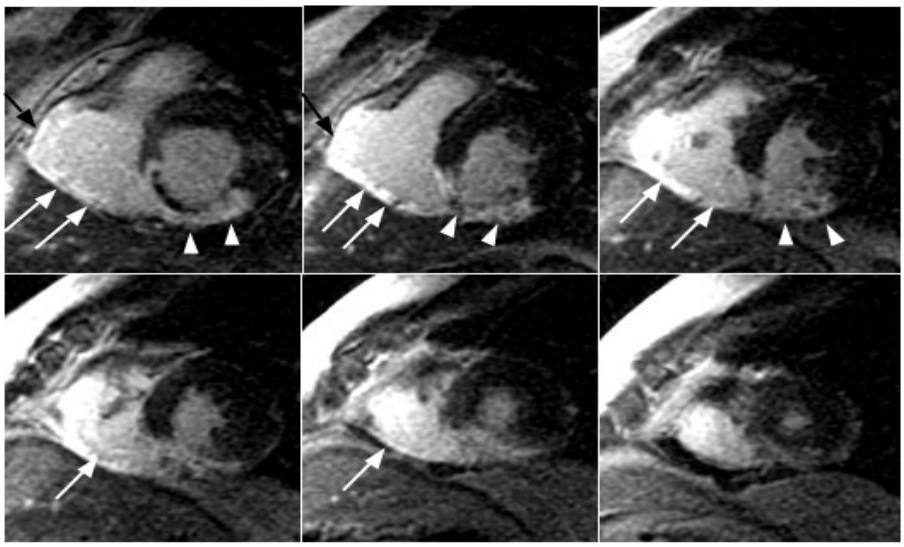

Figure 2: Short axis coverage of the heart from base to apex using late gadolinium enhancement imaging. This male 43-year-old patient presented with acute inferior myocardial infarction. CMR one day after infarction showing extensive late enhancement extending from the inferior and inferolateral left ventricular segments (arrowheads) to the inferior and free walls of the right ventricle (arrows) indicating extension of the infarction to involve the right ventricle[14].

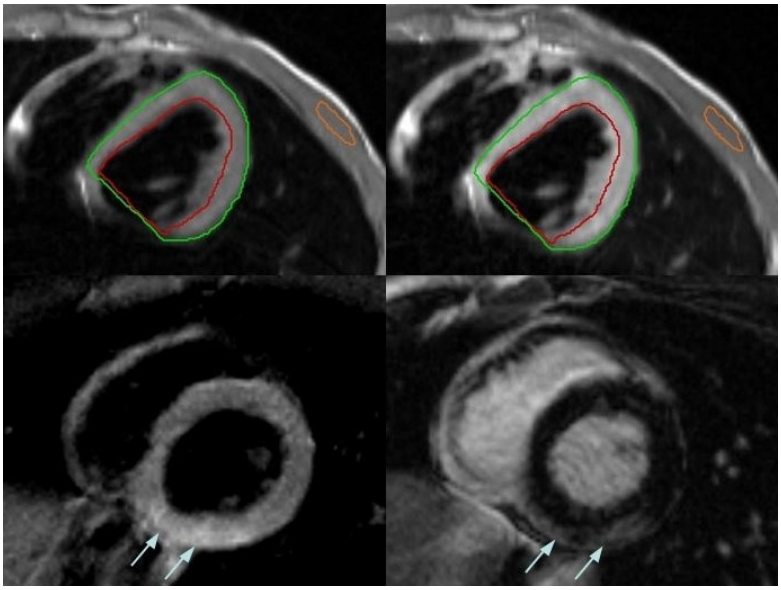

Figure 3: Comprehensive cardiovascular magnetic resonance in a 15 year old male presenting with acute chest pain, elevated troponin, ST-segment elevation and negative coronary angiography. Top: Pre (left) and early post (right) gadolinium-DTPA axial T1-weighted spin echo images of the same slice. The intense myocardial enhancement relative to that of the skeletal muscle is even visually appreciable (exact value = 6.8). The T2-weighted image (bottom, left) shows a posterolateral, predominantly subepicardial focal high T2 signal intensity, which corresponds to a similar subepicardial area of late gadolinium enhancement (arrows, bottom, right) with possible pericardial enhancement as well[15].

6. Discussion

In this work the versatility of CMR contrast mechanisms was exploited to provide new insights into the acute myocardial injuries associating myocardial infarction and myocarditis. Of particular importance is the emerging role of myocardial edema imaging using T2-weighted sequences. Acute myocardial inflammation of which edema is a substantial feature is now recognized as a common pathological pathway of reperfusion injury as well as the acute response of the myocardium to pathogens such as the case in viral myocarditis. Accordingly CMR edema imaging may be viewed as a non-specific marker of acuteness complementing additional more specific markers of injury like late gadolinium enhancement as a marker of irreversible injury. The distribution (focal or global) as well as morphological features (transmurality) however may offer additional clues to increase the specificity of edema imaging.

6.1. Irreversible injury and edema

This work has shown that an approach combining LGE and T2-weighted CMR is a clinically reliable tool to differentiate acute from chronic MI. While LGE is a powerful marker of non-viability and therefore detects infarction at any disease stage, transmural high T2 signal accurately identifies the area of the acute event[16].

Despite a substantial difference in tissue structure between acute and chronic MI, both injuries exhibited LGE, which reflects the increased volume of distribution of gadolinium-DTPA secondary to extracellular space expansion in acute MI and chronic myocardial scars[5]. In acute MI however, there is loss of membrane integrity of the already edematous cardiomyocytes allowing communication between the extra- and intracellular spaces. Moreover, the induction of reperfusion marks the rapid evolution of an inflammatory-like response of which interstitial edema is a substantial feature[17]. In chronic MI on the other hand, enlargement of the extracellular space is mostly the result of the relatively large collagen matrix[6] in the absence of myocardial edema and hence high T2 signal intensity.

6.2. Right ventricular involvement in acute MI

ECG, echocardiography and clinical presentation are clinically used to indirectly detect RV infarction. LGE however uniquely 'directly' identifies irreversible injury and this should in theory increase the specificity of the test to differentiate RV infarction from ischemia, stunning or hibernation[14]. Establishing the diagnosis of RV infarction is crucial because the acute MI management strategy differs substantially if the RV is involved in which case volume loading instead of the classical deloading should be implemented[18].

6.3. Acute myocardial inflammation

The 'Any-Two' approach has the potential to increase the diagnostic performance of CMR in the clinical setting as well as in multicentre trials[15]. A significant fraction of acute myocarditis patients present with a clinical picture mimicking that of acute MI representing a diagnostic challenge. Acute MI is characterized by focal transmural high T2 signal and subendocardial or transmural LGE[16]. This is different from the subepicardial LGE of myocarditis with no focal high T2 signal in the majority of cases[15].

6.4. Limitations and technical considerations

To suppress ventricular blood signal, the T2 sequence requires that the blood be expelled out of the slice during systole, which may not be the case especially in patients with reduced wall motion in whom the non-suppressed blood signal may hinder accurate identification of the endocardial border[13]. This however did not affect image interpretation since all our acute infarcts showed a transmural signal abnormality.

The parameter that should be used as the 'gold standard' to identify myocarditis remains a controversial issue. Some investigators used endomyocardial biopsy to identify the disease[12] and many others[11, 19] relied instead on a combination of clinical, laboratory, ECG and angiographic findings. We have also relied on this later approach for two reasons: First, the sensitivity of endomyocardial biopsy to identify myocarditis is limited possibly secondary to the focal nature of the disease[20]. Second, the majority of our myocarditis patients were young with an acute, often fairly unstable presentation; thus we did not want to subject this group of patients to unnecessary invasive procedures.

6.5. Conclusion

This work illustrated the versatility of cardiovascular magnetic resonance for characterizing acute myocardial injuries in three frequent clinical scenarios. Combining late gadolinium enhancement with T2-weighted sequences enabled differentiating acute from chronic myocardial infarcts. Late gadolinium enhancement accurately identified right ventricular involvement in the setting of acute inferior left ventricular infarction. Finally, using a comprehensive approach combining early and late enhancement techniques together with T2-weighted sequences, a higher diagnostic accuracy to identify acute myocarditis could be achieved.

7. Appendix

7.1. References

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7.2. Abbreviations

CMR: Cardiovascular magnetic resonance

ECG: Electrocardiogram

GRE: Global relative enhancement

LGE: Late gadolinium enhancement

LCX: Left circumflex artery

MI: Myocardial infarction

RCA: Right coronary artery

RV: Right ventricular

SI: Signal intensity

STEMI: ST segment elevation myocardial infarction

8. Erklärung über den Eigenanteil der Publikationen

Der Promovend hatte folgenden Anteil an den eingereichten Publikationen:

Abdel-Aty H, Boye P, Zagrosek A, Wassmuth R, Kumar A, Messroghli D, Bock P, Dietz R, Friedrich MG, Schulz-Menger J.Diagnostic performance of cardiovascular magnetic resonance in patients with suspected acute myocarditis: comparison of different approaches. J Am Coll Cardiol. 2005 Jun 7;45(11):1815-22.

Beitrag im Einzelnen:

- Das Studiendesign wurde zu 80 % von mir konzipiert, an der vorausgegangenen Literaturrecherche betrug mein Anteil 100 %.
- Das Manuskript wurde zu 100% von mir verfasst.
- Die gesamte statistische Auswertung erfolgte zu 100 % durch mich.

Abdel-Aty H, Zagrosek A, Schulz-Menger J, Taylor AJ, Messroghli D, Kumar A, Gross M, Dietz R, Friedrich MG. Delayed enhancement and T2-weighted cardiovascular magnetic resonance imaging differentiate acute from chronic myocardial infarction. Circulation. 2004 May 25;109(20):2411-6.

Beitrag im Einzelnen:

- Das Studiendesign wurde zu 100 % von mir konzipiert, an der vorausgegangenen Literaturrecherche betrug mein Anteil 95 %.
- Das Manuskript wurde zu 95% von mir verfasst.
- Die gesamte statistische Auswertung erfolgte zu 100 % durch mich.

Kumar A, **Abdel-Aty H**, Kriedemann I, Schulz-Menger J, Gross CM, Dietz R, Friedrich MG. Contrast-enhanced cardiovascular magnetic resonance imaging of right ventricular infarction. J Am Coll Cardiol. 2006 Nov 21;48(10):1969-76.

Beitrag im Einzelnen:

- Das Studiendesign wurde zu 50 % von mir konzipiert, an der vorausgegangenen Literaturrecherche betrug mein Anteil 60 %.
- Die Datenauswertung erfolgte zu 60% durch mich.
- Das Manuskript wurde zu 20% von mir verfasst.
- Die gesamte statistische Auswertung erfolgte zu 100 % durch mich.

Prof. Rainer Dietz Hassan Abdel-Aty

9. Publikationen

Abdel-Aty H, Zagrosek A, Schulz-Menger J et al. Delayed enhancement and T2-weighted cardiovascular magnetic resonance imaging differentiate acute from chronic myocardial infarction. *Circulation*. 2004; 109 (20):2411-6

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2. **Abdel-Aty H**, Zagrosek A, Schulz-Menger J et al. Delayed enhancement and T2-weighted cardiovascular magnetic resonance imaging differentiate acute from chronic myocardial infarction. *Circulation*. 2004; 109 (20):2411-6

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11. Lebenslauf

Mein Lebenslauf wird aus Datenschutzgründen in der elektronischen Version meiner Arbeit nicht mit veröffentlicht.

12. Eidesstattliche Versicherung

Hiermit erkläre ich an Eides statt, dass die vorliegende Dissertation mit dem Titel '**Gewebecharakterisierung akuter myokardialer Schädigungen mittels kardialer Magnetresonanztomographie'** von mir selbst und ohne die unzulässige Hilfe Dritter verfasst wurde, auch in Teilen keine Kopie anderer Arbeiten darstellt und die benutzten Hilfsmittel sowie die Literatur vollständig angegeben sind.

Berlin, den 18.04.2008 Hassan Abdel-Aty

Widmung:

Diese Arbeit ist meiner Frau Maria Heinrich gewidmet, die mich während meines Studiums stets unterstützt hat. Ohne sie wäre diese Arbeit nicht möglich gewesen.

Danksagung:

Mein besonderer Dank gilt meiner Betreuerin Frau Prof. Dr. Jeanette Schulz-Menger für die Einführung in das wissenschaftliche Arbeiten auf dem Feld der MRT Herzdiagnostik. Sie stand mir mit vielen konstruktiven Vorschlägen und Ideen während dieser Arbeit zur Seite. Weiterhin gilt mein Dank meinem Doktorvater Herrn Prof. Dr. Rainer Dietz für die Übertragung dieser Arbeit und die Unterstützung durch die von ihm geleitete Klinik.