Utility of Cardiac Magnetic Resonance Imaging in Kounis Syndrome

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Aims and objectives

Kounis syndrome (KS) is the concurrence of acute coronary vasospasm with conditions associated with mast cell degranulation and the release of inflammatory mediators during an allergic reaction. Allergic or hypersensitivity mediators, such as various drugs, conditions, and environmental exposures, trigger coronary vasoconstriction and induce plaque rupture. During an event, acute coronary syndrome commences [1]. KS has been increasingly reported in clinical practice. Its true frequency is precisely unknown [2].

Kounis syndrome is divided into two subgroups: Type I occurs in patients with normal coronary arteries in whom the acute release of inflammatory mediators induces coronary artery spasm; In type II, coronary spasm occurs adjacent to dormant atheromatous plaques in which allergic stimulation results in plaque erosion or rupture leading to allergic myocardial infarction [3].

Generally, ST elevations on electrocardiogram (ECG), increased cardiac enzymes and coronary angiography findings were reported in previously published cases on Kounis syndrome diagnosis [2,4]. These techniques have been proven to be clinically useful, however, each has limitations that may reduce its diagnostic accuracy. For example, none of these procedures can assess the viability of the ventricular wall. In cardiac diseases, assessing the viability of affected myocardial tissue is very important for recovery following revascularization [5,6]. Moreover, previous studies have also shown normal ECG findings, cardiac enzymes, and coronary angiography in Kounis syndrome type 1 cases [2,7]. Novel complementary techniques are needed to support clinical and laboratory findings in patients with suspected Kounis syndrome in the assessment of myocardial viability.

According to our review of literature, there has been no study using magnetic resonance imaging (MRI) on Kounis syndrome except for one case report [8]. Recently, MRI has become an important diagnostic tool in cardiac imaging. MRI not only evaluates myocardial perfusion but also demonstrates the morphology and function of myocardial tissue [9,10]. MRI with a gadolinium enhanced contrast agent offers high spatial resolution and can differentiate between non-ischemic and ischemic heart disease [11].

Inspired by this information, we evaluated patients who attended to the Emergency or Cardiology department with complaints of Kounis syndrome by cardiac MRI and aimed to identify cardiac MRI findings in patients with known or suspected Kounis syndrome type 1 with an emphasis on the additive clinical information.
Methods and materials

This prospective study was approved by the institutional ethics committee, and written informed consent was obtained from all patients before enrollment.

Between March 2012 and August 2013, 33 consecutive patients (18 men, 15 women) whose age ranged from 18 to 57 years (mean 36±11.3 years) underwent CMRI for chest pain complaints, which presented simultaneous with the symptoms of allergies. All patients underwent CMRI (with and without contrast enhancement) within 24 hours after clinical evaluation.

The patients who have at least one of the disorders of the ECG or cardiac enzymes, in addition to chest pain and allergic clinical symptoms, were included in this study. Five patients who have abnormal cardiac enzymes and troponins underwent conventional coronary angiography or computed tomography coronary angiography. Seven patients were excluded due to a history of myocardial infarction/coronary artery disease (n=2), claustrophobia (n=2), age under 18 or over 60 years (n=2), and poor image quality (n=1). The final study cohort consisted of 26 patients (14 men, 12 women; mean age 35±11.5 years).

MR Imaging

All other patients were examined with a 1.5-T MRI with an 8-channel cardiac coil placed around the patient's chest. All of the patients underwent precontrast, first-pass, and delayed MR images. In the cardiac MRI protocol, ECG-gated, dark blood, half-Fourier, single-shot, fast spin echo sequence (HASTE) was performed in axial and coronal planes for localization.

After two rapid surveys to determine the exact heart axis, three short-axis planes (apical, equatorial, and basal) as well as four- and two-chamber views were acquired. Short-axis cine SSFP images were obtained to cover the entire left ventricle. The imaging parameters are as follows: TR/TE, 770/35; slice thickness, 3-5 mm; matrix, 192x256; contiguous sections, 10-14; slice gap, 0 mm; temporal resolution 40 ms; and number of phases, 20.

In our first-pass MR imaging protocol, four slices of a single-shot turbo FLASH sequence with saturation recovery preparation (TR/TE, 298/1.66 ms; inversion time, 200 ms; flip angle, 12°; temporal resolution, 1.5 s; matrix, 96x128; slice thickness, 6-8 mm) displaying the optimal view of the related pathology were chosen from the cine and black blood studies. For each slice, 20-40 consecutive images were acquired.

Delayed enhancement magnetic resonance imaging was performed 10 min after 0.2 mmol/kg injection of gadopentetate dimeglumine (Gd-DTPA, Magnevist, Bayer
Healthcare, Germany). The DE-MRI protocols include the following: TR/TE, 298/1.66 ms; inversion time, 200 ms; flip angle, 12°; temporal resolution, 1.5 s; matrix, 96x128; slice thickness, 6-8 mm. In the first-pass MRI protocol, four slices of single-shot turbo FLASH sequence with saturation recovery preparation displaying the optimal view of the related pathology were chosen from cine and black blood sections. Reduction of breathing artifacts was performed by breath-holding in end-expiration during scanning. ECG rhythm, blood pressure, and symptoms were continuously monitored.

**Image evaluation**

All images were transferred to a workstation (Syngo Via Console, software version 2.0; Siemens AG Medical Solutions, Germany) for evaluation, and two experienced radiologists [MK, (10 years); AO, (3 years) of cardiovascular imaging experience] reviewed all images independently. Interpretation discrepancies were resolved by means of a consensus. Quantification of LV volumes and EF was performed as previously described [12].

The MR images were evaluated as follows: (1) Myocardial defect in the early phase (first-pass) of contrast agent; (2) Characteristics of myocardial contrast enhancement in delayed MR images; (3) Edema in T2-weighted images; (4) Hypokinesia in cine MR images; (5) Localization of defect; and (6) Calculation of ejection fraction (EF).

**Statistical Analysis**

The definitive statistical analysis of this study was made using the SPSS version 20.0 for Windows (Chicago, Illinois) statistical software. The normalities of the variables were analyzed using the Kolmogorov-Smirnov test. There were no normally distributed numerical variables. Non-normally distributed numerical variables (EF values) are shown as medians (minimum-maximum), and categorical variables are shown in percentages.
Results

Kounis syndrome type 1 was the diagnosis for all patients. Fourteen (53.8%) of 26 patients were men. The most common cause of the allergy was drugs (Fig. 1) and this has been reported in 16 patients (analgesics in 7, antibiotics in 6, lansoprazol in 2, antidepressant in 1). Other agents were shown in Fig. 2 (food allergy in 5 patients, bee sting in 3 patients, and hair dye in 2 patients).

ST elevation in ECG in 9 patients, nonspecific ECG in 10 patients, tachycardia in 9 patients, bradycardia in 2 patients, atrial fibrillation in 1 patient, and normal ECG in 6 patients were found. All patients were kept under surveillance at the hospital for approximately 24 hours. Five patients who have abnormal cardiac enzymes and with suspicious signs for Kounis syndrome underwent conventional coronary angiography (n=2) and computed tomography coronary angiography (n=3), which were in the reference range without vasoconstriction. All patients were discharged from hospital with full recovery.

Demographics characteristics and MRI findings are shown in Table 1.

| Table 1. Demographics and Cardiac MRI characteristics of patients with Kounis syndrome |
|---------------------------------|-------------------|
| **Characteristics** | **Patients (n=26)** |
| **Demographics** | |
| Age, years | 35±11.5 |
| Male sex, n (%) | 18 (53.8) |
| **MRI finding** | |
| First-pass contrast defect (%) | 26 (100) |
| Late phase non- enhancement (%) | 26 (100) |
| T2 edema, n (%) | 26(100) |
| Hypokinesia, n (%) | 12 (46) |
| Interventricular septum, n (%) | 14 (53.8) |
| Left ventricle free wall, n (%) | 8 (30.7) |
| Apex, n (%) | 4 (15.4) |

CE-MRI demonstrated early-phase (first-pass) subendocardial contrast defect and T2-weighted images showed high signal intensity consistent with edema for all lesion
areas. There was no transmural myocardial involvement detected in any of the patients. Early-phase subendocardial contrast defect was reported as follows: the interventricular septum in 14 (53.8%) patients, the left ventricular free wall in 8 (30.7%) patients (Fig. 3A, B), and the left ventricle apex in 4 (15.4%) patients (Fig. 4A, B). None of the lesion areas were found upon contrast enhancement on DE-MRI. Moreover, hypokinesia was demonstrated in 12 (46%) patients in the contrast defect area.

All patients revealed EF values within the normal range (60-75%±11%). Scanning times of the examinations were between 25 and 30 min. All patients underwent the complete examination without complications. None of the patients developed MI or death.
Fig. 1: Figure 1. Distribution of allergic agents in Kounis syndrome type 1.

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Fig. 2: Prevalence of drugs among allergic agents.

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**Fig. 3:** In interventricular septum and left ventricle free wall, A. First-pass image shows hypointens subendocardial contrast defect (arrows) B. Myocardial contrast enhancement disappear on DE-MR image.

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**Fig. 4:** In left ventricle apex, A. First-pass image shows hypointens subendocardial contrast defect (white arrows). B. Myocardial contrast enhancement disappear on DE-MR image (black arrows).

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Conclusion

To the best of our knowledge, our study is the first original study describing CMR findings in KS type 1 patients. The present study has demonstrated that subendocardial involvement, contrast defect on first-pass MR images, noncontrast enhancement on delayed images, and sensitivity to the left ventricle are specific findings for patients with Kounis syndrome type 1.

Kounis syndrome is a acute coronary event with allergic or hypersensitivity reactions. The explanation for this hypersensitivity reaction was thought to be mast cells located between cardiomyocytes in the internal layer of arteries and around coronary vessels. Acute release of inflammatory mediators in these patients can induce either coronary artery spasm without an increase of cardiac enzymes and troponins or coronary artery spasm which may progress to acute myocardial infarction (MI) with elevated cardiac enzymes and troponins in KS type 1. This type represents a manifestation of endothelial dysfunction or microvascular angina. While coronary arteries are normal in type 1, type 2 patients have preexisting plaques [4]. The present study consisted of KS type 1 patients.

In myocardial diseases, the assessment of the viability of affected myocardial tissue is very important for recovery following revascularization. It is possible to distinguish between viable and non-viable myocardial tissue using dynamic contrast-enhanced MRI [6].

Current diagnostic measurements used to assess myocardial involvement in Kounis syndrome, such as electrocardiography (ECG), cardiac enzymes, and troponin levels, are relatively insensitive to small but potentially significant functional change. Various cases reported that cardiac biomarkers and electrocardiographic changes do not lead as they guide in KS [8]. Therefore, biopsy may also be necessary to characterize the underlying cause of myocardial disease, such as myocarditis and Kounis syndrome.

In these circumstances, cardiac imaging can help provide supportive diagnostic information. Echocardiography or single-photon emission computed tomography (SPECT) may miss myocardial involvement particularly when it is small or subendocardial due to low spatial resolution [10]. Coronary CT angiography is highly valuable, but its value is limited for characterization of myocardial lesions. It needs a contrast agent and has radiation exposure [13]. The newer imaging modalities, such as MRI, offer an overall assessment of the myocardial tissue. Advantages of MRI are its non-invasiveness, multiplanar capability, and excellent soft tissue contrast. Cardiac MRI also maintains high spatial and temporal resolution, and can therefore depict myocardial structure and function in great detail. Previous studies reported that CE-MRI added diagnostic information over clinical examination for the patients with symptoms of acute coronary syndrome [14].
Hypersensitivity myocarditis and KS are two cardiac entities of allergic etiology affecting the myocardium and coronary arteries, respectively [2]. The myocardium and the coronary arteries can be particularly affected by hypersensitivity condition. Moreover, the allergic reactions may also progress to myocardial infarction [15]. Therefore, differential diagnosis is very important [2]. Kounis syndrome is asynchronization of acute coronary entity with mast cell degranulation via inflammatory mediators released during an allergic and anaphylactic reaction [16]. These two entities can mimic each other and be clinically indistinguishable. The presence of eosinophils, atypical lymphocytes, and giant cells on myocardial biopsy suggests hypersensitivity myocarditis, whereas the biopsy is typically normal in KS [2]. However, this procedure is invasive and has not been widely available in daily clinical practice.

Recently, cardiac MRI is being used in a growing number of clinical applications for cardiac diseases. Previous studies have reported that CMRI can differentiate acute myocarditis from acute myocardial infarction [11]. To the best of our knowledge, no studies on cardiac MRI in Kounis syndrome have previously been published. Cardiac MRI may depict ventricular volume, ejection fraction, ventricular mass, infarct size, and myocardial viability. Dynamic CE-MR images are useful in the identification of myocardial enhancement and involvement areas. Following the administration of contrast, the myocardium typically shows homogeneous enhancement, and appears washed out on delayed images. First-pass perfusion images demonstrate myocardial blood flow and ischemic tissue [17]. Delayed myocardial enhancement MRI was developed primarily for description of myocardial scarring due to myocardial infarction. The myocardial scarring or fibrosis appears as hyperenhanced that is characteristically subendocardial or transmural area in a coronary artery distribution on late-phase CE-MR images [18]. For this reason, a case having delayed contrast enhancement in myocardial scar was excluded from the present study.

In acute myocarditis, the presence of delayed enhancement is patchy and does not conform to any particular coronary artery distribution. It usually appears in the subepicardial or mid-wall myocardial layers and never in the subendocardial area [19].

The term hibernation refers to the myocardium that has decreased myocardial contractile function (hypokinesia or dyskinesia) and reduced coronary blood flow owing to coronary arterial spasm. The reduced coronary blood flow causes the myocytes to enter into a low-energy state. This study demonstrated hypokinesia in 46% of the affected areas. Hibernating myocardial tissue is viable and can be restored toward normal by revascularization. Delayed enhancement MRI may be used to identify viable versus nonviable myocardium. Hibernating myocardial tissue is always in the subendocardial area and conforms to a particular coronary territory, and contrast enhancement is unexpected in late-phase MR images [11].

In our study, the myocardial lesions were localized in the subendocardial area and definitely conformed to one of the particular coronary territories in all patients unlike myocarditis. We also did not detect any subendocardial contrast enhancement or contrast
defect on delayed-phase images in myocardial tissue. In light of these findings, we evaluated lesion areas as hibernating myocardium tissue and identified the myocardial involvement of Kounis syndrome type 1. In first-pass MR images, the myocardial contrast defect may be due to coronary spasm and any contrast enhancement of a lesion means the viability of the tissue.

Myocardial edema is used to differentiate acute from chronic MI. T2-weighted imaging is the standard imaging technique used to detect acute myocardial edema. Myocardial edema can be detected by T2-weighted images as early as 30 minutes after the onset of ischemia, and is thought to represent reversible myocardial injury in the absence of late gadolinium enhancement [6]. The edema is a generic tissue response to acute insults and a nonspecific finding for myocardial disease [11]. In our study, T2-weighted images of edema were evident in the lesion area in all patients.

Previous studies performed on the basis of ECG reported that the right coronary artery spasm was more frequently determined than the left coronary artery spasm in Kounis syndrome [20]. In the present study, we found that the septum and the left ventricle free wall were susceptible for all patients with Kounis syndrome. We speculated that the explanation for this septal involvement would be the diameter of the perforating branches. Because the perforating branches which supply the septum have lesser calibration, they may be particularly sensitive to vasospasm. However, we did not explain the left ventricle free wall involvement by the same mechanism.

Our study has several limitations. Firstly, the study was not blinded. It would be difficult to disregard available information in patients presenting to the emergency department with a suspicion of acute coronary syndrome. Secondly, this study was a cross-sectional study with a small sample size. Thirdly, we did not provide histopathological confirmation of our findings. Finally, we evaluated response to treatment as clinical because follow-up MRI was not performed.

In conclusion, CE-MRI allows the assessment of the heart of patients with known or suspected Kounis syndrome type 1. CMRI may be performed in patients presenting with chest pain and allergy in the emergency department and could be a complementary procedure to clinical and laboratory findings for clarification in cases of diagnostic uncertainty, such as myocarditis or Kounis syndrome. We think, our study may guide further research on KS and contribute to the diagnosis of Kounis syndrome type 1.
References


