Differential diagnosis of suspected apical ballooning syndrome using contrast-enhanced magnetic resonance imaging

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Aims
The apical ballooning syndrome (ABS) is a new diagnostic entity which is increasingly recognized. Precise magnetic resonance imaging (MRI) data are not yet available and there is little evidence for the differential diagnosis of ABS assessed by MRI.

Methods and results
Between January 2005 and January 2008, 6100 consecutive patients with diagnosis of acute coronary syndrome underwent left heart catheterization. In 59 patients (1.0%), coronary angiography revealed normal coronary arteries, but left ventriculography showed left ventricular dysfunction with apical ballooning. These 59 patients underwent cardiac MRI using a 1.5 T MRI scanner. In 13 patients (22.0%), MRI revealed diagnosis of myocardial infarction, in eight patients (13.6%) diagnosis of myocarditis. In all other 38 (64.4%) patients with suspected ABS, no delayed enhancement or signs of inflammation were detected. Follow-up MRI after 3 months showed a completely normalized left ventricular ejection in all patients with suspected ABS. Similarly, the end-diastolic volume and end-systolic volume improved at follow-up.

Conclusion
Cardiac MRI allows differentiating ABS from other rare causes with unobstructed coronary vessels such as myocarditis and coronary emboli with spontaneous lysis. Therefore, cardiac MRI can add valuable information in all patients with suspected ABS for further differential diagnosis.

Keywords
Apical ballooning syndrome • Takotsubo cardiomyopathy • Magnetic resonance imaging • Acute coronary syndrome

Introduction
The apical ballooning syndrome (ABS), also called takotsubo cardiomyopathy or ampulla cardiomyopathy, has first been described in Japan and has recently been recognized in western countries.1,2 Clinically, it is characterized by transient left ventricular apical wall motion abnormality, chest pain with electrocardiographic changes and minimal myocardial enzymatic release mimicking acute myocardial infarction, but without significant coronary artery disease.1-4 More recently, several case reports have described patients not presenting with typical apical but rather atypical mid-ventricular dysfunction.6-8 The true prevalence of the ABS is uncertain. Several studies showed a prevalence of up to 2.2% of patients presenting with acute coronary syndrome (ACS).3,4 The prognosis of patients experiencing this syndrome is generally favourable. Four-year survival was not different from that of an age- and gender-matched population.9 The pathophysiological mechanisms of this clinical entity have not yet been fully clarified. Coronary spasm, coronary emboli with spontaneous fibrinolysis, abnormalities in coronary microvascular function, regional myocarditis, and stunning as a result of excessive catecholamines due to a stressful event are some of the potential mechanisms.3-5
Cardiac magnetic resonance imaging (MRI) might be an imaging tool to further elucidate the underlying mechanisms. Another potential advantage of MRI is that it can be used to distinguish between different causative aetiologies including myocardial infarction and myocarditis. The purpose of this prospective trial was the assessment of cardiac MRI parameters for the identification and differential diagnosis of ABS.

**Methods**

**Study population**

Between January 2005 and January 2008, 6100 consecutive patients with diagnosis of an ACS, including ST- and non-ST-elevation myocardial infarction, underwent left heart catheterization at a tertiary care centre. In 59 patients, coronary angiography revealed normal coronary arteries, but left ventriculography showed left ventricular dysfunction with apical ballooning. These 59 patients with suspected ABS according to the diagnostic criteria proposed by the Mayo Clinic underwent cardiac MRI. Patients were excluded from MRI, if they were haemodynamically unstable or had contraindications for MRI at study entry such as implanted pacemakers, defibrillators, metallic intracranial implants, or severe claustrophobia. The study was approved by the local Ethics Committee and all patients gave written informed consent to participate in the cardiac MRI study.

**Magnetic resonance imaging**

On the basis of previous results, ABS was confirmed by MRI if patients had no signs of delayed enhancement typical for ischaemic heart disease or delayed enhancement patterns of myocarditis. MRI was performed on a 1.5 T scanner (Philips Intera CV, Best, The Netherlands). Left ventricular function was assessed by electrocardiogram (ECG)-gated cine steady-state free precession sequences in the two-chamber and four-chamber views as well as in the short cardiac axis from base to apex (30 phases per cardiac cycle; repetition time 3.7 ms, echo time 1.9 ms, flip angle 60°, typical voxel size 1.25 × 1.25 × 8.0 mm). In the last 14 patients, additional visualization of myocardial oedema was performed using a T2-weighted short-inversion-time, inversion-recovery (STIR) breath-hold pulse sequence (repetition time 2 × R–R interval, echo time: 80 ms, flip angle 180°, voxel size 0.71 × 0.71 × 8.0 mm) covering the entire left ventricle from true short axes from apex to base. Delayed enhancement images covering the whole ventricle in short axes and additionally in two-chamber and four-chamber views were followed-up by telephone contact. In case of a clinical event, these were confirmed by hospital records or contact to the general practitioner.

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**Figure 1** Trial profile.
four-chamber views were acquired in all patients ~15 min after the administration of a ‘double-dose’ (0.2 mmol/kg body weight) of gadobutrol (Gadovist, Schering, Germany) using a 3D inversion recovery gradient echo sequence (repetition time 4.4 ms, echo time 1.3 ms, flip angle 15°, voxel size 1.37 x 1.37 x 5.0 mm). Inversion times were adjusted to null normal myocardium.

Offline image analysis was performed on a dedicated workstation (ViewForum release 5.2, Philips Medical Systems, Best, The Netherlands). The endocardial borders were drawn manually on each dynamic image. Left ventricular ejection fraction (LVEF), end-diastolic and end-systolic volume (ESV) were calculated from the short-axis views. The T2-weighted images and the delayed enhancement images were assessed for oedema and any scar or fibrosis. All measurements and assessments were performed by operators blinded to the clinical patient data at the MR laboratory, which has excellent intra- and interobserver variability as well as excellent repeatability for infarct size measurement.

Statistical analysis
Each categorical variable is expressed as number and percentage of patients. Continuous parameters were estimated as mean ± standard deviation or as median with the corresponding inter-quartile range (IQR) for parameters not normally distributed. Differences between groups, i.e. those with ABS and those with other differential diagnosis, were assessed by Fisher’s exact or the χ² test for categorical variables and by the Student t-test for continuous data with normal distribution. Otherwise the non-parametric Wilcoxon rank-sum test was used. Differences between paired samples, i.e. comparisons of MRI results for patients with ABS at baseline and follow-up, were assessed using the paired t-test for continuous data with normal distribution and otherwise by the non-parametric Wilcoxon rank-sum test. Since there were multiple comparisons, the Bonferroni correction was used for the stated P-values. All statistical tests were performed with SPSS software, version 14.0. A two-tailed P-value <0.05 was considered statistically significant.

Results
Patient population
Of the 6100 patients enrolled with an ACS, 59 (1.0%) patients (53 female, age 70 ± 11 years) were identified with suspected ABS without significant coronary artery disease in left heart catheterization. The percentage of female patients with suspected ABS of the 2035 female patients with ACS was 2.6%.

Magnetic resonance imaging
The median time delay between left heart catheterization and MRI was 2 days (IQR 1–4). In 13 patients (22.0%), cardiac MRI revealed subendocardial or transmural enhancement in the distribution of a coronary artery compatible with myocardial infarction (Figure 2) and in eight patients (13.6%) a mid-wall and/or subepicardial enhancement which was compatible with acute myocarditis (Figure 3).

In all other 38 (64.4%) patients (36 female, age 73 ± 10 years), no delayed enhancement was detected (Figure 4) (Table 1). In these patients, diagnosis of ABS was made according to the earlier-mentioned criteria. Among those patients with STIR imaging for the determination of oedema, in 10 of the 14 patients MRI revealed

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**Figure 2** Patient with myocardial infarction without significant coronary artery stenosis. (A) Transmural delayed enhancement in the four-chamber view. (B) End-systolic functional image mimicking apical ballooning in the two-chamber view. (C) Laevocardiography in the right anterior oblique view showing the typical apical ballooning shape.
oedematous myocardium depicted as high signal intensity areas (Figure 4). In two patients, MRI confirmed the presence of apical left ventricular thrombus and in 16 patients (42%) initial involvement of the right ventricle (Table 2).

**Prognosis and follow-up**

Each of the 38 patients survived the acute event. Clinical follow-up was completed for all patients with ABS and revealed no major adverse cardiac events at a median follow-up of 3.3 months (IQR 3–5). Two patients died due to a primarily non-cardiac cause (patient 1: chronic obstructive pulmonary disease, patient 2: pulmonary embolism). The clinical functional status assessed by New York Heart Association classification improved from 2.9 ± 0.8 to 1.2 ± 0.4 (P < 0.001). Follow-up MRI after 3 months was available in 32 patients (84%). Reasons for not performing follow-up MRI were death (n = 2) and refusal (n = 4). Follow-up MRI showed a completely normalized LVEF in all patients. Similarly, the end-diastolic volume (EDV) and ESV improved at follow-up (Table 2). Thus, in these patients, the diagnosis ABS could be confirmed corresponding with the diagnostic criteria for the ABS proposed by the Mayo Clinic and the MRI parameters defined earlier (Figure 1). None of the patients with ABS had a recurrence of ABS.

**Patient characteristics: apical ballooning syndrome vs. other causes mimicking apical ballooning syndrome**

Except of age and hyperlipoproteinaemia (HLP), there were no differences in patient characteristics (gender, coronary risk factors) between patients with presumed coronary emboli with spontaneous lysis and myocarditis in comparison with those with classical ABS. In patients with ABS, emotional stress as a trigger could be identified in 23 patients (60.5%) vs. 1 (4.8%) (P < 0.001) with no ABS. Triggering conditions that preceded the onset of ABS were endogenous (emotional) stress in eight patients (21.0%) [death of a relative (n = 1), invalid relative (n = 1), confrontational arguments (n = 2), cat run away (n = 1), working stress (n = 3)], and in 15 patients (39.5%) exogenous (physical) stress [trauma (n = 2), surgical procedure (n = 8), exacerbation of chronic obstructive pulmonary artery disease (n = 1), vomiting and diarrhoea (n = 1), duodenal ulcer (n = 1), acupuncture (n = 1), endoscopic retrograde cholangio-pancreatography (n = 1)].

**Discussion**

To our best knowledge, this is the largest prospective report of suspected ABS patients undergoing MRI systematically, which serves as a powerful clinical tool for characterizing myocardial abnormalities, such as necrosis, fibrosis, oedema, and metabolite deposition. For the detection and quantification of myocardial infarction, delayed enhancement MRI has emerged as the new gold standard. Typically delayed enhancement due to myocardial infarction shows subendocardial or transmural enhancement. However, delayed enhancement is not specific for myocardial infarction and can occur in a variety of other disorders, such as myocarditis and cardiomyopathies. In non-ischaemic myocardial disease, the delayed enhancement usually does not occur in a coronary artery distribution and is often mid-wall rather than subendocardial or transmural. Contrast enhancement occurs frequently in the setting of myocarditis and is associated with active myocarditis as defined by histopathology. In contrast, in patients with ABS, most commonly, no pathological signal activity can be documented in late enhancement imaging excluding myocardial infarction or myocarditis. Delayed enhancement MRI has therefore a potential role in the evaluation of parameters for the identification of ABS and also for differential diagnosis as shown in our trial where approximately one-third of the patients showed other causes mimicking ABS. In the setting of ABS, determining the exact aetiology is directly related to treatment, secondary prevention, and potentially patient outcome.

The prevalence of the ABS ranges from 0.1–2.2% of patients presenting with ACS. In our prospective study, the frequency of suspected ABS was 1.0%. The percentage of female patients with suspected transient left ventricular ABS of all female patients

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**Figure 3** Patient with typical delayed enhancement pattern of myocarditis. Arrows denote mid-wall, subepicardial-delayed enhancement with a patchy distribution with severe foci within the myocardium. (A) Two-chamber view. (B) Four-chamber view.
presenting with an ACS was significantly higher (at 2.6%), which is in line with previous reports. 2–4

**Magnetic resonance imaging**

In this study, the typical features of ABS on cardiac MRI are myocardial oedema in the apical region, left ventricular dysfunction with recovery at 3 month follow-up with the absence of necrotic, fibrotic tissue, or scar formation. MRI provides morphological and precise functional information of left ventricular function in patients with ABS. Cine MRI demonstrated the characteristic apical contractile dysfunction and identified diffusely distributed wall motion abnormalities. The extended wall motion abnormalities in most cases did not correspond to the perfusion territory of a single epicardial coronary artery and also extended to the right ventricle. The lack

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**Figure 4** Late gadolinium enhancement cardiovascular magnetic resonance in a patient with apical ballooning syndrome. (A and B) Functional images acquired at acute phase demonstrate apical ballooning (A: end-diastolic, B: end-systolic) in the absence of late gadolinium enhancement (C). A repeat scan 3 months later showed complete normalization of ventricular function (D and E), with no late enhancement (F). T2-weighted images showing oedema in the apical region in a patient with apical ballooning syndrome (G–I).
of delayed enhancement demonstrates that the area of apical ballooning does not undergo irreversible damage and might explain the complete normalization of left ventricular function in patients with ABS. Nevertheless, as most of the patients experienced minimal enzyme release, there might be some myocardial damage. Although delayed enhancement MRI has the unique advantage of allowing visualization of even microinfarctions at very high spatial resolution, the current resolution might be unable to detect this discrete and diffuse myocardial necrosis.

However, in those undergoing additional STIR imaging, a majority of patients revealed myocardial oedema indicating acute ischaemia or inflammation without loss of myocardial integrity. This is consistent with previous results showing similar apical oedema in patients with ABS. Although myocardial oedema occurs in irreversibly injured myocardium, it frequently also extends to reversibly injured myocardium and was shown to closely match the myocardial ‘area at risk’ or inflammation. Thus, the myocardial oedema in patients with ABS might represent an initial catecholamine-induced myocardial stunning due to

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<th>Table 1</th>
<th>Patient characteristics</th>
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<tr>
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<td>ABS (n = 38)</td>
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<tr>
<td>Age, years</td>
<td>73 (10.1)</td>
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<tr>
<td>Female sex, n (%)</td>
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<td>23 (60.5)</td>
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<td>Elevated troponin, n (%)</td>
<td>30 (78.9)</td>
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<td>ECG changes, n (%)</td>
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<td>34 (89.5)</td>
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<td>5 (13.2)</td>
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<td>HLP, n (%)</td>
<td>4 (10.5)</td>
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Continuous data are presented as mean ± SD.
*The exact P-value of the variable stressful event is P = 0.000 and therefore highly significant. The exact P-value of the variable age as well as HLP is P = 0.010 and therefore (very) significant.
microvascular dysfunction. Another fact supporting a microcirculatory disturbance is the previously reported diminished coronary flow reserve using a Doppler guide wire.\textsuperscript{23} In addition, a reduced coronary flow velocity in the absence of relevant coronary artery stenosis was also observed as measured by TIMI frame count method immediately after onset of ABS.\textsuperscript{24,25}

Inflammation might also play a role as this has been shown in endomyocardial biopsy specimens demonstrating focal, mononuclear, inflammatory areas of fibrotic response and characteristic contraction bands.\textsuperscript{26,27} Contraction bands have been reported in several clinical settings of extensive catecholamine production, such as phaeochromocytoma or subarachnoid haemorrhage, showing that catecholamines may be an important link between emotional stress and cardiac injury.\textsuperscript{26–28} In ABS, plasma catecholamines were elevated at the time of presentation and significantly higher when compared with patients presenting with Killip III myocardial infarction.\textsuperscript{29} Thus, although the exact mechanism of ABS is still unclear, an underlying role of catecholamines is suggested.\textsuperscript{3,5,26–28} The myocardial oedema might reflect the interstitial mononuclear inflammatory response as a result of sympathetic overdrive. Thus, even if oedema is not specific for ABS, it could be a substantial clue for the diagnosis and pathophysiology supporting the hypothesis of impaired microcirculation and subsequent non-specific inflammation as a causative mechanism.

In addition, a lack of delayed enhancement in the dysfunctional apical regions allows distinguishing between different causative aetiologies including myocardial infarction (presumed coronary embol with spontaneous lysis and coronary spasm) and classical myocarditis.\textsuperscript{10,29} Differentiating ABS from acute myocardial infarction is important, because of different treatment strategies and different prognoses. Treatment of myocardial infarction includes reperfusion strategies and may pose patients with ABS at unnecessary risks.\textsuperscript{29} Furthermore, patients with ischaemic heart disease benefit from secondary preventive pharmacotherapy, whereas in patients with ABS, the left ventricular dysfunction usually resolves without any specific treatment.\textsuperscript{3,4,10} Myocardial infarction with typical extensive delayed enhancement in the distribution of a coronary artery was detected in approximately a quarter of patients despite the presence of unobstructed coronary arteries. The mechanism of infarction in these patients may be explained by spontaneous arterial recanalization, embolism, or coronary spasm. All patients received antithrombotic and antiplatelet therapy prior to catheterization, which might have resulted in recanalization of the occluded vessel.

Clinically, myocarditis is also suspected in patients with clinical and electrographic evidence of ACS and having normal coronary angiograms. In one study, myocarditis was the most likely non-coronary artery disease-related cause of abnormal troponin elevations.\textsuperscript{29} Furthermore, there are several case reports with left ventricular apical ballooning that appeared to be caused by biopsy-proven acute myocarditis.\textsuperscript{31,32} In contrast to ABS, myocarditis frequently causes enough myocardial injury and scarring to result in late enhancement on MRI.\textsuperscript{18} In line with these results, a portion of patients in the current trial showed subepicardial or mid-wall-delayed enhancement characteristically for myocarditis. Thus, although clinically indistinguishable with similar wall motion abnormalities, patients with ABS differ substantially from the typical profile of myocarditis with regard to MRI gadolinium uptake. These data are very well in line with a recent report of Sharkey et al.,\textsuperscript{33} who also found that MRI in patients with ABS did not reveal any evidence of subepicardial enhancement.

However, atypical myocarditis without delayed enhancement but with oedema cannot entirely be ruled out as a cause of ABS in some of these patients.\textsuperscript{34} This needs further investigation by a comprehensive MRI protocol and histopathological confirmation.

In two patients, MRI confirmed the presence of apical left ventricular thrombus, a potential early complication of ABS. These two patients had characteristically moderate-to-severe impairment of LVEF (patient 1: LVEF 36%, patient 2: LVEF 40%). The left ventricular thrombus formation is presumably caused by low blood flow in the apex during apical ballooning dyskinesia. As previously described, the thrombi fully resolved at 3 month follow-up, without specific therapy and without causing thrombo-embolic complications.\textsuperscript{30} Thus, this transient complication may not require aggressive anticoagulation in patients with ABS.\textsuperscript{30}

Recently, two reports systematically evaluated right ventricular (RV) involvement in patients with ABS,\textsuperscript{35,36} which was also
observed in 42% of the current study. Significant bilateral pleural effusion was evident only in RV involvement, indicating pleural effusion as a reliable indicator of RV involvement, as previously described. Furthermore, patients with RV involvement had significantly lower LVEF than those without RV involvement. Thus, clinicians should be aware of RV involvement, because it might have a significant impact on patient morbidity, management, and outcome.

Prognosis and follow-up

The prognosis of our patients experiencing ABS was generally favourable, as reported in previous studies. In a recent review, in-hospital mortality was reported in three of 286 patients. However, some complications have also been observed in patients with ABS, like apical thrombi, ventricular rupture, ventricular tachycardia, pulmonary oedema, or cardiogenic shock. These also showed a favourable clinical course in most cases. However, as these patients did not undergo systematic MRI, it cannot be completely ruled out that these patients had fulminant myocarditis or acute myocardial infarction with spontaneous fibrinolysis as observed in one-third of the current patient cohort. Recently, a 4 year survival of patients with ABS has been reported, which was not different from that of an age- and gender-matched population.

Patient characteristics: apical ballooning syndrome vs. other causes mimicking apical ballooning syndrome

Clinical profiles of our patients with ABS were similar to those reported in other recently published series. Initial clinical presentation mimicked ACS in most patients, with the combination of chest pain, dyspnoea, ECG abnormalities, and a mild elevation in cardiac biomarkers. Affected patients were typically post-menopausal women who had experienced a stressful event, either physical or emotional. In this study, the most common triggering stressors were disease-related circumstances, in particular, surgical operations. This trigger was the major difference in patient characteristics between patients with ABS vs. those with other causes mimicking ABS. In addition, HLP and older age were significantly different between the patient groups. The reason for the much more common occurrence in post-menopausal women is still unclear. Sex hormones may exert important influences on the sympathetic neurohormonal axis and on coronary vasoreactivity. Furthermore, women appear to be more vulnerable to sympathetically mediated myocardial stunning, as evidenced by increased catecholamine production and transient left ventricular dysfunction after subarachnoidal haemorrhage. As a possible alternative explanation, post-menopausal alteration of endothelial function in response to reduced oestrogen levels has been advocated.

A limitation of this analysis is the relatively small number of patients, although it is one of the largest trials reported yet. As ABS has a relatively rare incidence, only a few patients are treated annually even in large centres, thus rendering large studies impossible, unless prospective multicentre registries are launched. Another limitation is the time delay between presentation and the cardiac MRI study. It cannot be excluded that in some patients, early wall motion abnormalities, such as RV involvement or oedema, have been missed.

In conclusion, ABS is an acute and reversible left ventricular dysfunction, mimicking ACS which has a prevalence of ~1% in our patient series. Thus, clinicians should consider this syndrome in the differential diagnosis of ACS, especially in post-menopausal women with a recent history of stress. MRI is a useful technique to identify patients with suspected ABS and allows differentiating ABS from other rare causes with unobstructed coronary vessels, such as myocarditis and coronary emboli with spontaneous lysis or coronary spasm. Therefore, cardiac MRI can add valuable information in all patients with suspected ABS for further differential diagnosis and guidance of medical therapy.

Conflict of interest: none declared.

References

11. Teraoka K, Kiuchi S, Takada N, Hirano M, Yamashina A. No delayed enhancement in patients with ABS has been reported, which was not different from that of an age- and gender-matched population.


