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Title: Myocardial edema in Takotsubo syndrome mimicking apical hypertrophic cardiomyopathy: an insight into diagnosis by cardiovascular magnetic resonance

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Abstract: Myocardial edema is one of the characteristic features in the pathogenesis of Takotsubo syndrome. We report a middle aged man who presented with typical clinical and echocardiographic features of apical variant of Takotsubo syndrome. However, a cardiovascular magnetic resonance study performed 10 days after presentation did not show any apical 'ballooning' but revealed features of an apical hypertrophic cardiomyopathy on cine images. Tissue characterization with T2 weighted images proved severe edema as the cause of significantly increased apical wall thickness. A follow-up cardiovascular magnetic resonance study was performed 5 months later which showed that edema, wall thickening and the appearance of apical hypertrophic cardiomyopathy all resolved, confirming Takotsubo syndrome as the cause of the initial appearance. As the affected myocardium most commonly involves the apical segments, an edema induced increase in apical wall thickness may lead to appearances of an apical hypertrophic cardiomyopathy rather than apical ballooning in the acute to subacute phase of Takotsubo syndrome.

04 May, 2015

Dear Editor,

We would like to submit for your consideration the manuscript entitled **“Takotsubo syndrome with severe myocardial edema mimicking apical hypertrophic cardiomyopathy”** as a case report for *the Heart & Lung Journal*.

The case presentation and images are on a novel observation of significantly increased left ventricular (LV) apical wall thickness mimicking apical hypertrophic cardiomyopathy in the course of Takotsubo cardiomyopathy. The localised apical LV “hypertrophy” was demonstrated to be due to marked myocardial edema and resolved in the follow-up study. Such markedly increased apical wall thickness and the resulting LV morphology was not well defined in the course of Takotsubo cardiomyopathy before and may cause significant challenges in the diagnosis and acute management of these cases.

I declare that the manuscript containing original material is submitted solely to the *Heart & Lung Journal* and has not been published or being considered for publication elsewhere.

Thank you very much for consideration the manuscript for publication in *the Heart & Lung Journal*.

Kind Regards

Dr John Baksi

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London, UK

Response to reviewer`s comments:

Once again we would like to thank to the reviewer very much for his/her suggestions on improving the manuscript. We have revised the manuscript accordingly

- 1- We have added the suggested table
- 2- We have amended the references as suggested (we are grateful for the sympathy of the reviewer that it might be a mundane task to re-arrange the references and we are happy to say that thankfully in this case it did not require a change in the order of the references)

Myocardial edema in Takotsubo syndrome mimicking apical hypertrophic cardiomyopathy: an insight into diagnosis by cardiovascular magnetic resonance

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Abstract:

Myocardial edema is one of the characteristic features in the pathogenesis of Takotsubo syndrome. We report a middle aged man who presented with typical clinical and echocardiographic features of apical variant of Takotsubo syndrome. However, a cardiovascular magnetic resonance study performed 10 days after presentation did not show any apical 'ballooning' but revealed features of an apical hypertrophic cardiomyopathy on cine images. Tissue characterization with T2 weighted images proved severe edema as the cause of significantly increased apical wall thickness. A follow-up cardiovascular magnetic resonance study was performed 5 months later which showed that edema, wall thickening and the appearance of apical hypertrophic cardiomyopathy all resolved, confirming Takotsubo syndrome as the cause of the initial appearance. As the affected myocardium most commonly involves the apical segments, an edema induced increase in apical wall thickness may lead to appearances of an apical hypertrophic cardiomyopathy rather than apical ballooning in the acute to subacute phase of Takotsubo syndrome.

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Introduction

Myocardial edema is one of the characteristic features in the pathogenesis of Takotsubo syndrome (or stress-induced cardiomyopathy) ¹. It is not seen on routine echocardiography but can be demonstrated in the majority of patients on edema sensitive cardiac magnetic resonance (CMR) imaging sequences.¹ Edema usually does not cause any grossly visible increase in wall thickness but rarely may be severe enough to appear as significant 'hypertrophy' on echocardiography as well as CMR cine images. The most common anatomical variant of Takotsubo syndrome involves the apical segments, and the edema-dependent increase in apical wall thickness may raise the suspicion of apical hypertrophic cardiomyopathy. Recently there have been reports of cases in which significantly increased apical wall thickness during the course of Takotsubo syndrome were observed ^{2,3}, but no CMR studies were available in these cases to demonstrate the edema as the cause of the apparent hypertrophy.

Case report

A 44-year-old man presented with acute onset crushing central chest pain which radiated to the left arm and was associated with vomiting. There was no previous history of coronary artery disease, angina or a stressful trigger. Past medical history included hypertension (well-controlled with ramipril 7.5mg/day and indapamide 1.25mg/day) and ankylosing spondylitis with previous spine surgery. He did not have any history of diabetes. He was smoking 15-20 cigarettes a day and occasionally cannabis but he did not report use of cannabis or any other illicit drug prior to presentation. The patient's typical alcohol consumption was one bottle of wine every day, but he had consumed 2.5 bottles in the evening prior to presentation. On admission, he was hemodynamically stable with normal respiratory and cardiac auscultatory findings. His 12 lead electrocardiogram revealed ST elevation in leads II, III, aVF and V1-4

with widespread T wave inversion in leads aVL and V2-V6 (Figure 1). His Troponin-I was elevated at 12.2 ng/mL. The patient underwent emergency invasive coronary angiography with a presumptive diagnosis of an acute ST elevation myocardial infarction. Left and right coronary arteries showed only minor plaque disease. However, left ventriculography showed apical akinesia and ballooning with hypercontractility of the basal segments (Figure 2 A and B). This was confirmed on the subsequent echocardiography (Figure 2 C, Movie I). In the presence of apical dysfunction involving more than one coronary artery territory and the absence of culprit coronary artery disease, a diagnosis of Takotsubo syndrome was made. No obvious emotional or physical precipitator could be identified. The hospital course was uneventful and the patient was discharged on bisoprolol 5mg/day added to his current medication. CMR was not performed during the acute phase as it was not available in the admitting hospital. The patient was scheduled for an outpatient CMR study following discharge in the regional CMR referral center to exclude a myocardial infarction or myocarditis and to confirm the diagnosis of Takotsubo syndrome.

A CMR study was performed 10 days after initial presentation. Contrary to the typical CMR findings of Takotsubo syndrome, cine images revealed significantly thickened mid to apical left ventricular (LV) segments with preserved contraction and apical systolic cavity obliteration (Figure 3 A-F, Movies II and III). There was no apical ballooning. The cine images were in keeping with apical hypertrophic cardiomyopathy. However, edema sensitive T2 weighted (short tau inversion recovery, STIR) images revealed increased signal in the thickened myocardial segments (Figure 3G). This involved all mid-apical segments and was not localized to a coronary artery territory. There was also early gadolinium enhancement in keeping with hyperemia associated with edema and inflammation (Figure 3H). Subtle mid-wall late gadolinium enhancement was observed in the thickened segments (Figure 3I). When interpreted with the clinical presentation of the patient, the CMR findings suggested a sub-acute

phase of Takotsubo syndrome with increased wall thickness due to inflammation and edema. A follow-up CMR examination was performed 5 months after the initial scan. In this study, the previously increased wall thickness had completely normalized and all left ventricular segments demonstrated normal thickness and contractility (Figure 3J-L, Movie IV). The myocardial T2-STIR signal was normal and there was no late gadolinium enhancement. The normal myocardial findings support recovery following Takotsubo syndrome.

Discussion

Takotsubo syndrome (or stress-induced cardiomyopathy) typically results in presentation with acute chest pain (mimicking acute myocardial infarction) or heart failure, frequently with a history of stressful trigger or precipitating co-existent illness. Diagnosis is confirmed by left ventriculography or echocardiography when the typical apical hypo- or akinesia and basal hypercontractility are evident in the acute phase. Less common anatomical variants have been described¹ and may be difficult to assess by these techniques and detailed tissue characterization is not routinely possible with echocardiography. Superior delineation of myocardial borders by CMR provides detailed examination of different patterns of ventricular involvement in Takotsubo syndrome. Tissue characterization provides evidence for myocardial edema matching to areas of wall motion abnormalities and allows exclusion of other conditions such as myocardial infarction or myocarditis (Table-1). In a large prospective study of 256 patients presenting with Takotsubo syndrome, CMR study performed during the acute phase showed myocardial edema in more than 80% of patients with 4 different types of ventricular morphologies identified (apical, midventricular, basal and biventricular ballooning).¹ In the presented case, CMR was performed in the sub-acute phase when the apical ballooning had resolved. However there was marked edema leading to thickened appearance of the mid to apical LV walls. The increased

apical LV wall thickness mimicked apical hypertrophic cardiomyopathy in the context of the ECG appearance; without demonstration of edema differentiation from apical hypertrophic cardiomyopathy could be challenging.

While myocardial edema is a well-recognized feature of Takotsubo syndrome, this is the first report of significant but reversible LV wall thickening secondary to oedema observed in the absence of typical ventricular morphology of Takotsubo syndrome on CMR. There are two reports of cases where significantly increased LV apical wall thickness was observed in the course of Takotsubo syndrome.^{2,3} In both reports the initial presentation was apical dysfunction and the patients developed increased apical wall thickness in the sub-acute phase. The authors' explanations for the apparent "hypertrophy" were beta-adrenergic stimulation leading to hypertrophic cellular signaling in one² and previously undiagnosed apical hypertrophic cardiomyopathy which was masked by apical ballooning on presentation but became overt again as the Takotsubo syndrome resolved in the other³ report. Unfortunately, CMR studies were not performed in either of the studies and it is tempting to hypothesize that the observed increased wall thickness could have been due to marked myocardial edema in these cases.⁴ A third case has been reported more recently where the authors clearly delineated the course of apical wall thickening and then its resolution on echocardiographic follow-up of a patient with Takotsubo syndrome.⁵ Moreover, the authors observed that the appearance of apical "hypertrophy" was coinciding with transient deep T-wave inversions in precordial leads very much resembling to that of a typical apical hypertrophic cardiomyopathy. Unfortunately direct evidence of myocardial edema as demonstrated by a CMR study was again not available for the case.⁵ All these reports and ours suggest that this phenotypical appearance may be common in the sub-acute phase of Takotsubo syndrome and may cause important diagnostic confusion.

In the large studies of Takotsubo syndrome patients, the imaging features of Takotsubo syndrome either by echocardiography or by CMR (or both) are mostly derived from studies performed in the very acute phase and then later in the follow-up.¹ As such, imaging features in the sub-acute phase of Takotsubo syndrome are less well-known.^{6,7} In keeping with this, while the presence of myocardial edema in the acute phase of Takotsubo syndrome is now a well-established finding on CMR studies, data on the course of myocardial edema during the subacute to recovery phase of Takotsubo syndrome is limited. Although there is a general clinical impression that almost full recovery of Takotsubo syndrome occurs within 1-2 weeks with the observation of normalized LV ejection fraction, studies suggest that myocardial edema lasts substantially longer than this. In one such study, Neil et al assessed the course of myocardial edema with CMR in a group of patients with Takotsubo syndrome during the acute presentation and at 3 months follow-up⁸. They showed that myocardial edema as estimated by myocardial signal intensity in T2 weighted images was prominent in the acute phase and decreased substantially at 3 months follow-up which was also reflected in a decrease in calculated LV mass. However, they found that even at 3 months the signal intensity was still higher than the controls suggesting a protracted course before full recovery of myocardial edema in Takotsubo syndrome. Supporting the findings of this study, Ahtarovski et al demonstrated that in contrast to rapid improvement of systolic function in Takotsubo syndrome patients, the recovery of diastolic function is significantly delayed which is probably associated with late recovery of edema causing stiffening of the myocardium⁹.

The paucity of data regarding the imaging characteristics of patients in the subacute phase of Takotsubo syndrome and the imaging features of ours and similar previous cases suggest that the phenotype described in this report may be more common than reported in the literature. We hypothesize that the transition from the acute apical ballooning to the recovery phase with resolution of

wall motion abnormalities and tissue edema in Takotsubo syndrome may involve a sub-acute stage which is probably associated with more severe myocardial edema than the acute phase. This may also be the stage where some late gadolinium enhancement may be observed more commonly since late gadolinium enhancement most probably reflects enlarged extracellular matrix volume in Takotsubo syndrome.¹⁰ Moreover, besides the diagnostic implications; it is interesting to understand the pathophysiology and why the myocardial edema is more severe in the subacute phase than the acute phase in Takotsubo syndrome. On the other hand, while we have clearly proved in our case that the increased wall thickness and the appearance of an apical hypertrophic cardiomyopathy was reversible and was due to severe edema, Takotsubo syndrome has been reported in patients with hypertrophic cardiomyopathy¹¹ and caution is needed to differentiate these cases. The ability of CMR to characterize the myocardium is of great value in interrogating the substrate for the appearance of the myocardium during the course of the pathological process, but a follow-up study has an important role in determining whether Takotsubo syndrome has occurred in the presence or absence of a co-existing HCM phenotype.

We could not identify a clear precipitant for the Takotsubo syndrome in our patient. This is not totally unexpected as in the study by Eitel et al, up to one third of patients with Takotsubo syndrome did not have an identifiable precipitant despite detailed analysis of clinical history¹. However, the history of alcohol excess in our patient might have been relevant to his presentation. Takotsubo syndrome has been defined in patients with delirium tremens; possibly related to the hyperadrenergic state associated with it.^{11,12} A recent large case-control study showed significantly increased risk of Takotsubo syndrome in patients with delirium tremens but also a modest increase in the risk with alcohol withdrawal compared to alcoholism alone.¹² Our patient did not have any features of delirium tremens on presentation although it might be speculated that he could be in a state of subclinical alcohol

withdrawal after the binge consumption which may have contributed to his presentation with Takotsubo syndrome.

In conclusion, myocardial edema in the acute to subacute phase of Takotsubo syndrome may be severe enough to cause significant thickening of the involved segments mimicking apical hypertrophic cardiomyopathy. This LV morphologic pattern has not been well defined in the course of Takotsubo syndrome before and caution is necessary to avoid misdiagnosis in such cases.

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Figure Legends

Figure 1

ECG from admission showing ST elevation in leads V2-V4 and inferior leads and T wave inversion in leads V2-V6.

Figure 2

Left ventriculography and echocardiography images. End diastolic (A) and end-systolic (B) frames of left ventriculography showing apical ballooning and basal hypercontractility in systole. End-systolic frame from the apical four chamber view by echocardiography confirming apical ballooning; there is no increased apical wall thickness in this study which was in the acute phase (C and Movie I).

Figure 3

End diastolic (A, B, C) and end systolic (D, E, F) frames from the cine movies of two chamber (A and D), four chamber (B and E) and apical short axis (C and F) views. There was significantly increased mid to apical LV wall thickness (maximum apical wall thickness at end diastole, 15mm). LV indexed volumes were at the lower end of normal range with an ejection fraction of 71% and raised mass index ($98\text{g}/\text{m}^2$). These cine images and calculated indexed volumes and mass in isolation are most suggestive of an apical hypertrophic cardiomyopathy phenotype. T2 weighted short tau inversion recovery (STIR-T2) images revealed increased transmural myocardial signal in mid to apical segments; the myocardial to skeletal muscle signal intensity ratio was 2.9 proving myocardial edema (G). Enhancement of the affected myocardium early after gadolinium injection was consistent with hyperemia associated with

edema (H). Subtle patchy mid-wall late gadolinium enhancement is seen in the areas of increased wall thickness (I). Images J-K are end-diastolic cine frames from the follow-up CMR performed 5 months after the initial study (only end-diastolic frames shown for comparison with the images of the initial study; A-C, see Movie IV for full cardiac cycle). The wall thickness was completely normal with a maximum apical wall thickness of 8mm. LV mass index regressed to 82 g/m². LV volumes and ejection fraction were within normal range and there was no regional wall motion abnormality. There was no myocardial edema on T2 weighted images or late gadolinium enhancement (not shown) all in keeping with recovery from Takotsubo cardiomyopathy.

Abstract:

Myocardial edema is one of the characteristic features in the pathogenesis of Takotsubo syndrome. We report a middle aged man who presented with typical clinical and echocardiographic features of apical variant of Takotsubo syndrome. However, a cardiovascular magnetic resonance study performed 10 days after presentation did not show any apical 'ballooning' but revealed features of an apical hypertrophic cardiomyopathy on cine images. Tissue characterization with T2 weighted images proved severe edema as the cause of significantly increased apical wall thickness. A follow-up cardiovascular magnetic resonance study was performed 5 months later which showed that edema, wall thickening and the appearance of apical hypertrophic cardiomyopathy all resolved, confirming Takotsubo syndrome as the cause of the initial appearance. As the affected myocardium most commonly involves the apical segments, an edema induced increase in apical wall thickness may lead to appearances of an apical hypertrophic cardiomyopathy rather than apical ballooning in the acute to subacute phase of Takotsubo syndrome.

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In conclusion, myocardial edema in the acute to subacute phase of Takotsubo syndrome may be severe enough to cause significant thickening of the involved segments mimicking apical hypertrophic cardiomyopathy. This LV morphologic pattern has not been well defined in the course of Takotsubo syndrome before and caution is necessary to avoid misdiagnosis in such cases.

References

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Figure Legends

Figure 1

ECG from admission showing ST elevation in leads V2-V4 and inferior leads and T wave inversion in leads V2-V6.

Figure 2

Left ventriculography and echocardiography images. End diastolic (A) and end-systolic (B) frames of left ventriculography showing apical ballooning and basal hypercontractility in systole. End-systolic frame from the apical four chamber view by echocardiography confirming apical ballooning; there is no increased apical wall thickness in this study which was in the acute phase (C and Movie I).

Figure 3

End diastolic (A, B, C) and end systolic (D, E, F) frames from the cine movies of two chamber (A and D), four chamber (B and E) and apical short axis (C and F) views. There was significantly increased mid to apical LV wall thickness (maximum apical wall thickness at end diastole, 15mm). LV indexed volumes were at the lower end of normal range with an ejection fraction of 71% and raised mass index (98g/m^2). These cine images and calculated indexed volumes and mass in isolation are most suggestive of an apical hypertrophic cardiomyopathy phenotype. T2 weighted short tau inversion recovery (STIR-T2) images revealed increased transmural myocardial signal in mid to apical segments; the myocardial to skeletal muscle signal intensity ratio was 2.9 proving myocardial edema (G). Enhancement of the affected myocardium early after gadolinium injection was consistent with hyperemia associated with

edema (H). Subtle patchy mid-wall late gadolinium enhancement is seen in the areas of increased wall thickness (I). Images J-K are end-diastolic cine frames from the follow-up CMR performed 5 months after the initial study (only end-diastolic frames shown for comparison with the images of the initial study; A-C, see Movie IV for full cardiac cycle). The wall thickness was completely normal with a maximum apical wall thickness of 8mm. LV mass index regressed to 82 g/m². LV volumes and ejection fraction were within normal range and there was no regional wall motion abnormality. There was no myocardial edema on T2 weighted images or late gadolinium enhancement (not shown) all in keeping with recovery from Takotsubo cardiomyopathy.

Figure 1

Figure 2

Figure 3

CMR findings in clinical conditions associated with acute chest pain and troponin rise

	Cine images (Ventricular morphology)	LGE	Myocardial edema * (T2w-STIR images)	Follow-up study †
Takotsubo syndrome	Apical ballooning/akinesia Rarely mid-ventricular or basal “inverted” ballooning variants	None ‡	+ Matching to regions of ballooning/akinesia and not restricted to a single coronary artery territory	Resolution of apical ballooning with normalisation of LV systolic function Resolution of myocardial edema
Myocarditis	Mostly normal Rarely regional wall motion abnormality or in case of extensive involvement global LV hypokinesia may be present	Mostly + Mid-wall and/or subepicardial	+ matching to regions of LGE and in non-coronary distribution	Resolution of myocardial edema LV dysfunction may resolve or persist Regional LGE may resolve or persist
Acute myocardial infarction	Regional wall motion abnormality mostly present but may not be discerned when infarct is very small and focal	+ Subendocardial to transmural Evidence for MVO may be seen on LGE images	+ matching to regions of LGE and in coronary distribution	Resolution of myocardial edema but the regional LGE and wall motion abnormalities persist
Hypertrophic cardiomyopathy §	Asymmetrical LV hypertrophy Apical thickening and systolic cavity obliteration in the apical variant	Mostly + Patchy mid-wall	None	No relevant dynamic changes in imaging features
Idiopathic dilated cardiomyopathy §	Dilated LV with impaired systolic function	+/- Mid-wall	None	No relevant dynamic changes in imaging features

LGE: Late gadolinium enhancement, T2w-STIR: T2 weighted short tau inversion recovery, LV: left ventricle, MVO: microvascular obstruction

* As demonstrated in the case presented here, when myocardial edema is severe it may be lead to appearances of significantly increased wall thickness of the affected segments on cine images. Wall thickness later normalises with resolution of the edema which can be proved by a follow-up study.

† There are no established guidelines on the need or the timing of a follow-up CMR study. A follow-up study may help to confirm the initial diagnosis and to show the resolution of the

findings seen in the acute phase. Depending on local resources a reasonable approach might be to repeat the CMR study in 3 to 6 months after the acute presentation.

‡ LGE has rarely been reported in cases of Takotsubo syndrome but the general consensus is that LGE is not a common or an expected CMR imaging feature of Takotsubo syndrome.

§Patients with hypertrophic and idiopathic dilated cardiomyopathies may present with chest pain or breathlessness and the troponin levels may be raised. This may be related to the cardiomyopathic process itself and can be clinically proved if the CMR findings do not show any imaging features of a possible coexistent acute pathology such as a concomitant acute myocardial infarction or a Takotsubo syndrome.

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