Diagnostic value of contrast echocardiography in Tako-Tsubo cardiomyopathy

Valeur diagnostique de l’échocardiographie de contraste dans la cardiomyopathie de Tako-Tsubo

Nicolas Mansencal, Denis Pellerin, Aurélie Lamar, Alain Beauchet, Rami El Mahmoud, Rémy Pillière, William J. McKenna, Olivier Dubourg

Service de cardiologie, hôpital universitaire Ambroise-Paré, Assistance publique—Hôpitaux de Paris (AP—HP), université de Versailles—Saint-Quentin (UVSQ), 92100 Boulogne, France
Centre de référence pour les maladies cardiaques héréditaires, hôpital universitaire Ambroise-Paré, AP—HP, 9, avenue Charles-de-Gaulle, 92100 Boulogne, France
Department of Cardiology, The Heart Hospital, University College London Hospitals, NHS Foundation Trust, London, United Kingdom
Department of Public Health, UVSQ, hôpital universitaire Ambroise-Paré, AP—HP, 92100 Boulogne, France

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Summary
Background. — Tako-Tsubo cardiomyopathy is a clinical entity mimicking acute coronary syndrome. Assessment of left ventricular function may be difficult using conventional echocardiography.
Aims. — To characterize left ventricular systolic function using contrast echocardiography in Tako-Tsubo cardiomyopathy.
Methods. — We prospectively studied 63 consecutive women admitted for suspected acute coronary syndrome who underwent coronary arteriography, biplane left ventricular angiography and conventional and contrast echocardiography; 25 women had Tako-Tsubo cardiomyopathy (group 1), 25 women had proven coronary artery disease (group 2) and 13 women had no significant coronary lesion (group 3). Echocardiographic interpretation was performed by two observers: a physician trainee (observer 1) and an experienced investigator (observer 2).

Abbreviations: ACS, acute coronary syndrome; CAD, coronary artery disease; LV, left ventricular; TTC, Tako-Tsubo cardiomyopathy.

* Corresponding author. Fax: +33 1 49 09 53 44.
E-mail address: nicolas.mansencal@apr.aphp.fr (N. Mansencal).

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Background

Tako-Tsubo cardiomyopathy (TTC) is characterized by transient stress-induced left ventricular (LV) dysfunction in the absence of significant coronary lesions [1–7]. The pathogenesis of this disease is still uncertain and several hypotheses have been proposed [2,3,7,8]. The LV dysfunction does not correspond to a single coronary artery distribution, suggesting that it cannot be explained by coronary artery occlusion. However, the clinical presentation usually mimics an acute coronary syndrome (ACS) [4,5] and an occlusion of the left anterior descending coronary artery, and may lead to misdiagnosis. Postmenopausal women are most likely to be affected by TTC, resulting in a TTC prevalence of 3% among women with a suspicion of ACS [9]. This elderly population may thus be fragile and may present renal failure. Biplane LV angiography and cardiac magnetic resonance are two imaging tools used for the analysis of global and regional LV dysfunction in TTC, allowing confirmation of LV regional wall motion abnormalities extending beyond a single epicardial coronary distribution. However, these two examinations have several limitations: LV angiography is invasive, renal failure is a contraindication and complications may occur, whereas cardiac magnetic resonance is of limited availability and cannot be performed in case of claustrophobia.

Echocardiography is used in TTC for the assessment of LV systolic function and to detect cardiac complications [3,9]. However, routine echocardiography may provide suboptimal images of the LV endocardial borders. New contrast agents may improve echocardiographic imaging quality, leading to its use for left heart opacification and myocardial characterization [10–15]. LV contrast cavity opacification has been shown to assess regional wall motion abnormalities accurately in patients with coronary artery disease (CAD) [15]. Patients with TTC have regional wall motion abnormalities without significant coronary artery stenosis [5,16].

Results. — Left ventricular segments were assessed for wall motion abnormalities, which were present in 70 and 88% (observer 1) and in 91 and 99% (observer 2), using conventional and contrast echocardiography, respectively (P < 0.0001). Accuracy for the diagnosis of Tako-Tsubo cardiomyopathy was improved significantly for both observers using contrast echocardiography: for observer 1, sensitivity was 56 and 88%, respectively, using conventional and contrast echocardiography (P = 0.01), whereas for observer 2, sensitivity was 72 and 96%, respectively (P = 0.04). Interobserver agreement was excellent using contrast agent (kappa = 0.85 vs 0.34 using conventional echocardiography). The blinded review of left ventriculograms distinguished Tako-Tsubo cardiomyopathy from coronary artery disease correctly in 96% of cases.

Conclusions. — Contrast echocardiography could be used in routine practice to replace left ventricular angiography in Tako-Tsubo cardiomyopathy.

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of contrast echocardiography in TTC has not been evaluated previously. The objective of this prospective single-centre study was to assess the accuracy of contrast echocardiography in the detection of TTC in patients who presented with suspected ACS.

**Methods**

**Study population**

From January 2005 to December 2008, among 3466 patients referred for coronary angiography, 1298 patients presented with suspected ACS (Fig. 1). A diagnosis of TTC was made in 25 consecutive women. From this population with suspected ACS, 63 women were enrolled prospectively. These women were divided into three groups: 25 women with acute TTC (group 1), 25 women with proven CAD (group 2) and 13 women without significant coronary lesion or LV dysfunction (group 3). Groups 2 and 3 were age- and sex-matched with group 1.

All included patients \((n = 63)\) underwent coronary arteriography, biplane LV angiography, conventional transthoracic echocardiography and contrast echocardiography; for patients presenting with TTC \((n = 25)\), all these examinations were performed less than 24 hours after the onset of symptoms [16]. Contrast echocardiography was used for LV opacification and perfusion analysis. The diagnosis of TTC was defined as: an acute chest pain during a stressful incident associated with ST-segment abnormalities and/or increased serum troponin level; transient regional LV systolic dysfunction with regional wall motion abnormalities extending beyond a single epicardial coronary distribution assessed by LV angiography; and no coronary artery lesions [9]. All patients from group 2 presented with single-vessel disease with chronic occlusion of the left anterior descending coronary artery associated with LV systolic dysfunction, documented by coronary arteriography and LV angiography. Patients from group 3 had no significant CAD and no LV wall motion abnormalities. The study was approved by our institutional review board.

**Left ventricular angiography**

At the end of coronary arteriography, biplane LV angiography (i.e. right anterior oblique and left anterior oblique) was performed and provided the diagnostic gold standard for the assessment of LV systolic function in this study. LV ejection fraction was calculated using biplane LV volumes, according to Simpson’s rules. LV regional wall motion (presence or not of abnormalities) was assessed systemically for each LV segment. To compare the reliability of echocardiography, the left ventriculograms from groups 1 and 2 were also evaluated by an independent experienced reviewer (R.E.M.), who was unaware of the clinical and coronary angiographic findings. This blinded reading classified each patient as having TTC or CAD.

**Echocardiographic protocol**

The same echocardiographic protocol was performed in all patients using a Siemens/Sequoia Acuson C512 system (Acuson, Mountain View, CA, USA) equipped with multifrequency transducers and capable of low energy \((0.2 \text{ to } 0.3 \text{ mechanical index})\). All echocardiographic studies were performed by two experienced physicians (N.M. and O.D.). The apical four-chamber and two-chamber views were assessed systematically by conventional and contrast transthoracic echocardiography in all patients. Echocardiography was performed according to the recommendations of the American Society of Echocardiography [17]. LV ejection fraction was calculated using Simpson’s biplane method. All conventional
Figure 2. Echocardiographic apical four-chamber view. Takotsubo cardiomyopathy assessed by conventional (A and C) and contrast (B and D) echocardiography. A and C were performed in diastole and B and D in systole. The white arrows indicate difficulties in assessing apical and lateral wall motion using conventional echocardiography, whereas the left ventricle was well-visualized by contrast agent. LA: left atrium; LV: left ventricle.

Echocardiographic examinations were performed using second harmonic imaging with a 1.9-mechanical index. At the end of conventional transthoracic echocardiography, LV contrast cavity opacification was performed by peripheral venous injection of Sonovue (Bracco Altana, Inc., Milan, Italy), using a low mechanical index (0.2 to 0.3), to avoid the destruction of microbubbles. An initial bolus of 1.0 ml was followed if necessary by a second intravenous bolus (0.5 ml); CPS software (Siemens/Acuson, Mountain View, CA, USA) was used for LV analysis.

All echocardiographic studies were recorded digitally and stocked on a TomTec workstation (TomTec Imaging Systems GmbH, Unterschleissheim, Germany). Interpretation was performed by two observers: a physician trainee (observer 1) and an experienced investigator (observer 2). The two observers were blinded to clinical data and diagnosis. Three cardiac cycles of the parasternal long- and short-axis views, and apical four-chamber and two-chamber views were stored in cineloop format for offline analysis. The quality of endocardial delineation in 17 LV segments was assessed by observer 2 and used to determine the number of well-visualized LV segments by conventional and contrast echocardiography. Both observers assessed systematically LV regional wall motion (presence or not of abnormalities) in each segment using conventional and contrast echocardiography and then classified each patient as having TTC or CAD. TTC was defined as a circular LV dysfunction [16], whereas LV wall motion abnormalities corresponding to a single epicardial coronary artery suggested the presence of CAD.

To measure myocardial signal intensity, frames were analysed using the offline software Syngo AutoTracking Contrast Quantification (Axius, Siemens Medical Solutions USA, Inc., Malvern, PA, USA). Peak myocardial signal intensity was measured in the different parts of the left ventricle in all patients. Regions of interest were placed in segments with and without wall motion abnormalities. At least three measurements were performed in each segment. Myocardial signal intensity was analysed according to the presence (or not) of wall motion abnormalities; the contrast intensity of the LV cavity was also measured.

Statistical analysis

Continuous variables are presented as mean ± standard deviation and ranges, unless otherwise specified. Categorical data are presented as absolute values and percentages. Continuous and categorical variables were compared with use of the Chi² test, paired t tests, unpaired t tests or Fisher’s exact test, as appropriate. Confidence intervals were calculated using the confidence interval analysis software version 2.1.2 (BMJ, London, UK). Interobserver agreement in the interpretation of contrast echocardiography was assessed by the kappa statistic. A P-value <0.05 was considered significant. Statistical analysis was performed.
Results

Population characteristics

The mean ages of patients in groups 1, 2 and 3 were 73 ± 11 years, 71 ± 10 years and 72 ± 13 years, respectively. Mean angiographic LV ejection fraction was 37.7 ± 9% in group 1, 36 ± 6% in group 2 and 68 ± 3% in group 3. In group 1, 19 patients (76%) presented with a typical pattern of TTC with akinesia of the LV mid and distal segments of all walls, with compensatory hyperkinesia of the base, and six patients (24%) had a pattern of midventricular ballooning syndrome (limited akinesia of the mid segments of all LV walls). Among patients with TTC, the mean peaks of plasma creatinine kinase and troponin I were 325 ± 258 IU/l and 7.9 ± 7.6 μg/l, respectively. Plasma B-type natriuretic peptide levels in patients from group 1 and group 2 were not significantly different (P = 0.45). All patients with TTC presented with a complete recovery of LV systolic function at 1-month follow-up.

Left ventricular function

In TTC patients, 425 LV segments were studied by echocardiography: 379 (89%) and 420 (99%) LV segments were well-visualized using conventional and contrast echocardiography (Figs. 2 and 3), respectively (P < 0.0001). Both observer 1 and observer 2 confirmed the majority of wall motion abnormalities with conventional and contrast echocardiography (70 and 88%, P < 0.0001 and 91 and 99%, P < 0.0001, respectively). LV ejection fraction was greater (42 ± 11%) when assessed by conventional echocardiography (vs 37.7 ± 9% by LV angiography, P < 0.0001) and 38.2 ± 8.5% using contrast agent (P = 0.42 compared with LV angiography).

Accuracy of echocardiography for distinguishing TTC from CAD was improved using contrast for both observers (Table 1). For observer 1, sensitivity was 56% and 88%, respectively, using conventional and contrast echocardiography (P = 0.01), whereas for observer 2, sensitivity was 72 and 96%, respectively (P = 0.04). Agreement between the two observers was excellent using contrast agent (kappa = 0.85 vs 0.34 using conventional echocardiography). The blinded review of left ventriculograms distinguished TTC from CAD correctly in 96% of cases.

Perfusion analysis

Contrast intensity of the LV cavity was 30.1 ± 1.6 dB among patients with TTC vs 29.9 ± 1.4 dB in group 2 and 29.7 ± 1.4 dB in group 3 (P = 0.38). In segments without wall motion abnormalities, myocardial signal intensity was similar in the three groups (18.7 ± 5 dB in group 1, 18.4 ± 3 dB in...
mann et al. [19] have demonstrated that LV opacification was well-visualized by conventional echocardiography. Hoffmyocardium. In this study, only 89% of LV segments were characterized by complete recovery of LV systolic function in patients presenting with ACS. This use of contrast agent is clinically relevant, allowing the substitution of LV angiography for contrast echocardiography in TTC.

TTC is defined by transient LV dysfunction and is characterized by complete recovery of LV systolic function [1–7,18]. The clinical presentation of TTC usually mimics ACS, but LV systolic dysfunction during the acute phase is circumscribed, with LV regional wall motion abnormalities extending beyond a single epicardial coronary distribution, and is therefore different from the dysfunction found in patients with CAD [16]. Echocardiography is used for the assessment of LV systolic function and TTC complications [4,5,9,16], but the accuracy of conventional two-dimensional echocardiography may be limited by inadequate characterization of the myocardium. In this study, only 89% of LV segments were well-visualized by conventional echocardiography. Hoffmann et al. [19] have demonstrated that LV opacification by Sonovue increased the accuracy of echocardiography significantly. Furthermore, they found strong correlations between contrast echocardiography and cineventriculography and cardiac magnetic resonance ($r = 0.83$ and $r = 0.77$, respectively). Observer variability is related to image quality and LV opacification with a contrast agent is particularly valuable when image quality is suboptimal [13]. We hypothesized that contrast echocardiography could increase the diagnostic accuracy for TTC during the acute presentation. In fact, contrast agent increased the visualization of LV segments significantly (by 10%), thus improving the calculation of LV ejection fraction: no significant difference was observed between LV angiography and contrast echocardiography ($P = 0.42$), whereas a significant difference was found between LV angiography and conventional echocardiography ($P < 0.0001$). This improvement of visualization of LV wall motion by contrast agent increases the accuracy of TTC diagnosis, regardless of the experience of the observer. Indeed, in the experienced investigator’s hands, sensitivity was 72 and 96%, respectively, in conventional and contrast echocardiography, whereas for the physician trainee, sensitivity increased from 56 to 88%. This increased accuracy of echocardiography using contrast agent was also associated with better interobserver reproducibility. Interestingly, in this study, when a blinded analysis of contrast echocardiography and LV angiography by two experienced investigators was performed, the accuracy of these two examinations was similar (96% correct diagnosis). According to these results, contrast echocardiography could be used in routine practice to assess LV systolic function non-invasively, replacing LV angiography in TTC. Furthermore, LV angiography is not performed systematically in many centres. Women presenting with TTC are mainly postmenopausal and this elderly population may present renal failure, which is a contraindication for LV angiography. Cardiac magnetic imaging is an alternative to LV angiography, but has several limitations: its availability is low and women presenting with claustrophobia cannot undergo this non-invasive imaging examination. Some women presenting with suspected ACS may have no assessment of LV function, leading to misdiagnosis of TTC. Thus, this strategy of using contrast echocardiography in women presenting with suspected ACS is clinically relevant because it allows the systematic assessment of LV systolic function in this high-risk population.

Meimoun et al. [20] and Abdelmoneim et al. [21] have reported recently that abnormal microvascular perfusion was observed during the acute phase of TTC, suggesting that microvascular dysfunction could be a plausible pathophysiological mechanism for cardiac dysfunction in TTC. In our study, we assessed myocardial perfusion partially by measuring myocardial signal intensity using contrast agent. This variable was significantly lower in segments with wall motion abnormalities in TTC, compared with in patients from group 3 ($P < 0.0001$). In patients presenting with occlusion of the left anterior descending coronary artery, myocardial signal intensity was even lower than in patients with TTC ($P < 0.0001$). Thus, microvascular impairment is observed during the acute phase of TTC where catecholamine toxification may be limited by inadequate characterization of the myocardium.

### Table 1 Accuracy of conventional and contrast echocardiography in distinguishing Tako-Tsubo cardiomyopathy from coronary artery disease.

<table>
<thead>
<tr>
<th>Observer 1</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Positive predictive value</th>
<th>Negative predictive value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conventional echocardiography</td>
<td>56 (37–73)</td>
<td>64 (45–80)</td>
<td>61 (41–78)</td>
<td>59 (41–76)</td>
</tr>
<tr>
<td>Contrast echocardiography</td>
<td>88 (70–96)</td>
<td>84 (65–94)</td>
<td>85 (67–94)</td>
<td>88 (69–96)</td>
</tr>
<tr>
<td>Observer 2</td>
<td>Sensitivity</td>
<td>Specificity</td>
<td>Positive predictive value</td>
<td>Negative predictive value</td>
</tr>
<tr>
<td>Conventional echocardiography</td>
<td>72 (52–86)</td>
<td>88 (70–96)</td>
<td>86 (65–95)</td>
<td>76 (58–88)</td>
</tr>
<tr>
<td>Contrast echocardiography</td>
<td>96 (81–99)</td>
<td>96 (81–99)</td>
<td>96 (81–99)</td>
<td>96 (81–99)</td>
</tr>
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Values are % (95% confidence interval).
city is observed [7] but is less pronounced than in the case of coronary occlusion.

The main limitation of our study is that continuous infusion of contrast agent was not performed because of limitations of its use. Thus we could not quantify myocardial perfusion fully by contrast agent. However, in routine practice, contrast echocardiography is performed mainly for LV cavity opacification, which is possible using a bolus of contrast agent, and the quantification of myocardial perfusion was only used in our study for the assessment of TTC pathogenesis. Finally, the use of Sonovue has several restrictions and, at present, physicians have to wait 7 days before using this contrast agent when a patient presents with an ACS. Other contrast agents do not have these restrictions of use, but are not available in France [22].

Conclusion

This study found that LV global and segmental systolic function may be difficult to assess using conventional echocardiography in TTC. Physicians should be aware of the current Sonovue use restrictions. However, the use of contrast agent with left heart opacification is an accurate non-invasive imaging method for assessment of LV systolic function among women with suspected ACS and could be used in routine practice to replace LV angiography in TTC.

Conflict of interest statement

None.

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