Added value of contrast echocardiography in characterization of nonischemic cardiomyopathy

Shufang Pi1,3,4,5, Yingwu Liu1,3,4,5, Tong Li1,3,4,5, Wenjin Peng1,3,4,5, Dong Wang2,3,4,5, Lei Huang1,3,4,5 and Ningdong Kang6

Abstract
Nonischemic cardiomyopathy (NICM) is a group of noncoronary heterogenous myocardial diseases. The heterogenous nature of NICM has impeded its diagnosis. In the present case series, we demonstrate the added value of using contrast echocardiography in the characterization of NICM. Two patients of advanced age were admitted for possible acute coronary syndrome, which was subsequently excluded by coronary angiography. Conventional and contrast echocardiography revealed characteristic structural and dynamic features of the left ventricle that were compatible with two distinct NICM diseases: stress-induced cardiomyopathy and noncompaction of the ventricular myocardium. Contrast echocardiography characterizes the cardiac structure and allows for real-time assessment of myocardial motion and perfusion. It may help to distinguish diseases with different etiologies.

Keywords
Nonischemic cardiomyopathy, contrast echocardiography, Takotsubo cardiomyopathy, noncompaction of the ventricular myocardium, myocardial disease, case series

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1Heart Center, Third Central Hospital of Tianjin, Tianjin, China
2Department of Ultrasonography, Third Central Hospital of Tianjin, Tianjin, China
3Tianjin Institute of Hepatobiliary Disease, Tianjin, China
4Tianjin Key Laboratory of Artificial Cell, Tianjin, China
5Artificial Cell Engineering Technology Research Center of Public Health Ministry, Tianjin, China
6The Russell H. Morgan Department of Radiology and Radiological Sciences, The Johns Hopkins Hospital, Baltimore, MD, USA

Corresponding author:
Dr. Yingwu Liu, Heart Center, Third Central Hospital of Tianjin, No. 83 Jintang Road, Hedong District, Tianjin 300170, China.
Email: liuyingwu1966@126.com
Introduction
Nonischemic cardiomyopathy (NICM) is composed of a heterogeneous group of non-coronary cardiac disorders characterized by ventricular hypertrophy or dilatation and exhibiting mechanical or electrical myocardial dysfunction. Recent advances in contrast echocardiography allow for reliable visualization of the cardiac structure (e.g., apical abnormalities) and real-time assessment of myocardial function (e.g., motion and perfusion). We herein present two cases to demonstrate the unique role of contrast echocardiography in the evaluation of NICM.

Case Description
Case 1
A 60-year-old woman presented to the emergency department with a 6-hour history of precordial tightness. The symptom started soon after an intense argument with family members. An electrocardiogram (ECG) demonstrated T-wave inversion in leads I, II, III, AVF, and V1–6 (Figure 1), and the plasma myocardial bound isoenzymes were elevated [creatine kinase–myocardial band (CK-MB), 9.2 ng/mL; myoglobin, 52.0 ng/mL; and cardiac troponin I, 2.24 ng/mL]. The patient was diagnosed with acute non-ST-elevation myocardial infarction. The initial management was directed at the treatment of myocardial ischemia and included aspirin, clopidogrel, low-molecular-weight heparin, and a statin.

Subsequent coronary angiography revealed <50% luminal stenosis in the anterior descending branch of the left coronary artery with estimated Thrombolysis in Myocardial Infarction (TIMI) flow grade 3. Left ventricular angiography showed hyperdynamic basal contraction but hypokinesis of the apical and mid-segments in the systolic frames, resulting in a round bottom and narrow neck of the left ventricle. Contradictory movement was detected between the apical and basal myocardium (Figure 2). The patient was further evaluated by contrast echocardiography (SonoVue, 59 mg; Shanghai Bracco Sine Pharmaceutical Corp., Shanghai, China) to exclude microvascular dysfunction, which can also lead to abnormal wall

Figure 1. Inverted T waves (arrows) in leads I, II, III, AVF, and V1–6 in Case 1.
movement. Contrast echocardiography with left ventricular opacification (LVO) showed smooth endocardial boundaries with no defects (Figure 3(a)). Contradictory movement was detected in the apical myocardium, but the myocardial perfusion was normal as shown by myocardial contrast echocardiography (MCE) (Figure 3(b)).

The patient was considered to have stress-induced cardiomyopathy based on the coronary angiography findings, contrast echocardiography findings, and clinical history. The prior medications were discontinued, and coenzyme Q10, trimetazidine, angiotensin-converting enzyme inhibitors, and beta-blockers were administered to improve myocardial function. The myocardial enzymes returned to normal levels 8 hours after symptom onset (CK-MB, 1.1 ng/mL; myoglobin, 41.9 ng/mL; and cardiac troponin I, 0.09 ng/mL). At the 1-week follow-up, echocardiography revealed reduced apical movement, and the contradictory movement had disappeared. No abnormalities were noted at the 1-month follow-up, and the prior medications were discontinued.

**Case 2**

A 78-year-old man presented to the emergency department with a 1-week history of exertional dyspnea and orthopnea with an intermittent productive cough after a cold. The patient had no history of hypertension or family hereditary diseases. His blood pressure was 127/90 mmHg and heart rate was 94 beats/minute. His heart sounds were irregularly irregular with a variable S1. Lung auscultation revealed coarse breath sounds. Bilateral lower extremity edema was present. An ECG showed atrial fibrillation and left anterior fascicular block: rS

![Figure 2](image2.png)

**Figure 2.** Left ventricular angiography shows hyperdynamic (white arrows) basal contraction but hypokinesis (black arrows) of the apical and mid-segments in the systolic frames. AO, aorta; LV, left ventricle.

![Figure 3](image3.png)

**Figure 3.** (a) Left ventricular opacification demonstrates smooth endocardial boundaries with good left ventricular filling and no filling defects. (b) Myocardial contrast echocardiography shows no abnormalities. LV, left ventricle.
type in leads V1–3; a low and bidirectional T wave in leads I, AVL, II, III, AVF, and V4–6; and ST-segment depression in leads V5–6. The patient was admitted with diagnoses of atrial fibrillation and heart failure, and an old anterior myocardial infarction was suspected.

Subsequent Holter examination revealed an additional arrhythmia involving multiple premature ventricular contractions (couplet or triplet complexes). The elevated B-type natriuretic peptide concentration (1,830 pg/mL) further supported a diagnosis of heart failure. Echocardiography showed that all four cardiac chambers were enlarged (diameter of left atrium, left ventricle, right atrium, and right ventricle: 41, 56, 40, and 18 mm, respectively). The thickness of the interventricular septum and left ventricular wall was normal, but the myocardial mobility was diffusively reduced, and the contractility of the left ventricle was impaired (ejection fraction of 31%). Diagnoses of cardiomyopathy and cardiac dysfunction were evident based on the aforementioned echocardiographic findings. Coronary disease was excluded because of the angiography findings (mild lumen stenosis in the mid-segment of the anterior descending and right coronary arteries with TIMI flow grade 3). Left ventricular angiography confirmed the decreased myocardial mobility, and an enlarged intertrabecular space at the apical and anterior wall was suspected (Figure 4).

Contrast echocardiography by LVO revealed prominent trabeculations in the lateral-apical wall of the left ventricle. The trabeculations were associated with deep intertrabecular recesses filled with slow blood flow and were in continuity with the left ventricular cavity. LVO depicted a two-layered myocardial structure consisting of a thin outer compacted layer and a thicker inner noncompacted layer (Figure 5). The measured thickness of the compacted and noncompacted layers of the lateral wall was 4.3 and 8.8 mm, respectively, and that of the apical wall was 6.8 and 15.5 mm, respectively. The patient was diagnosed with noncompaction of the ventricular myocardium (NVM). The patient was treated with benazepril, metoprolol, furosemide, spironolactone, and warfarin and was discharged without remarkable adverse events.

This study protocol was approved by the Ethics Committee of Tianjin Third Central Hospital, and both patients provided informed consent.

Discussion

Contrast echocardiography is a rapidly evolving technique that enhances discrimination between the myocardium and blood and allows for evaluation of the myocardial microcirculation. LVO and MCE are two common applications of contrast echocardiography.

LVO is achieved by intravenous administration of contrast agents (i.e., microbubbles), which can generate echo contrast that enable clear visualization of endometrial...
boundaries and subtle anatomical features. The microbubbles further permeate the coronary microcirculation, enabling myocardial enhancement (known as MCE). This technique allows for evaluation of the perfusion of the myocardial microcirculation, and the contrast filling reflects the survival and mobility of the myocardial tissue. It has been widely used to assess myocardial ischemia and necrosis.\(^4,5\)

The patient in Case 1 was diagnosed with stress-induced cardiomyopathy, also known as Takotsubo syndrome (TS).\(^6,7\) The classic left ventricular appearance of a round bottom and narrow neck (resembling a Japanese octopus trapping pot) is perhaps one of the most helpful diagnostic features. TS has high prevalence in women of advanced age and is commonly associated with emotional or physical stress. The main symptom is chest pain, which is often accompanied by elevated serum kinase levels. The ECG manifestations are similar to those of myocardial infarction. TS is a reversible process with a good prognosis, and patients can recover within a few days or months. In Case 1, the ECG findings, enzyme levels, and symptoms suggested myocardial infarction. The immediate coronary angiography allowed us to exclude this possible cause from coronary artery disease (i.e., atherosclerosis).

Although angiography is a standard method to detect luminal narrowing in the coronary arteries, it is not reliable for detection of the blood signal within capillaries. Compared with coronary angiography, contrast echocardiography can reliably depict blood vessels with much smaller diameters (40 vs. 100 \(\mu\)m).\(^8\) One-third of the blood volume in the coronary circulation is distributed to the myocardium, constituting the myocardial blood volume, and 90% of this volume resides in the capillaries. In contrast echocardiography MCE, the steady state of the signal in the myocardium is achieved with continuous intravascular administration of microbubbles, and the signal reflects the capillary blood volume.\(^9\) The high-resolution images allow for identification of the location and extent of malperfused (i.e., necrotic) myocardium.\(^10\)

The diagnosis of TS is usually based on the absence of coronary artery disease and the pattern shown on left ventricular angiography. However, contrast
echocardiography MCE can be used to evaluate the myocardial microcirculation and has added value in the diagnosis of TS; its three main benefits in this regard are as follows. First, other diseases, such as cardiomyopathy caused by sepsis\textsuperscript{11} or diabetic myocardial microvascular disease,\textsuperscript{12} can have a similar clinical presentation when multiple coronary arteries are affected. Although the impaired microcirculation associated with these diseases is irreversible, TS is reversible. MCE is important for the differential diagnosis of these diseases. Second, despite the unclear mechanism, it is generally accepted that a high concentration of catecholamines triggers TS and leads to changes in the myocardial microcirculation and metabolism.\textsuperscript{13} Therefore, MCE may provide temporal information on the progression of TS.\textsuperscript{14} Third, a recent study focused on “reverse TS,” in which wall motion abnormalities are present at the base and mid-segments with preserved motion or hyperkinesis of the apex.\textsuperscript{13} The diagnosis is merely based on the suboptimal appearance of the left ventricular pattern, and MCE has added value in such cases. Although both left ventricular angiography and MCE are subjective assessments by visual inspection, the combined approaches (i.e., adding MCE) could improve the diagnostic accuracy for TS.

In general, MCE shows perfusion defects in the myocardial apex, but such defects were not detected in our cases. This could be due to the timing of the contrast echocardiography examination. Previous studies have shown that the wall movement in patients with TS returns to normal within weeks (within 48 hours at the earliest), and the microcirculation recovers faster than the wall motion.\textsuperscript{13} In the present cases, we performed contrast echocardiography approximately 18 hours after the disease onset, at which time the microcirculation might have returned to normal. Contrast echocardiography assessment immediately after admission might help to capture the acute apical perfusion defects.

In our cases, MCE was performed to exclude possible microvascular disease, which can induce abnormal wall movement. We believe that accurate assessment requires cautious integration of the clinical presentation, coronary anatomy, and ventricular and myocardial imaging (Left ventricular angiography with LVO and MCE).

The patient in Case 2 was diagnosed with NVM, a rare congenital cardiomyopathy resulting from the failure of myocardial development during embryogenesis.\textsuperscript{15} It is characterized by multiple prominent ventricular trabeculations with intertrabecular spaces communicating with the ventricular cavity. Myocardial biopsy is the gold standard for diagnosis of NVM. Both cardiac magnetic resonance imaging and echocardiography can be used for diagnosis, but echocardiography is more widely used in general clinical settings because of its convenience and cost-effectiveness. The three diagnostic criteria are as follows. First, a two-layered myocardial structure with a thin compacted outer (epicardial) band and a thicker, noncompacted inner (endocardial) layer must be present, and the measured thickness of the noncompacted (NC) layer is more than twice of that of the underlying compacted (C) layer in systole (i.e., NC/C > 2).\textsuperscript{16} Second, multiple prominent ventricular trabeculations and deep intertrabecular recesses are present. Third, blood flow is seen through deep recesses in continuity with the ventricular cavity. However, the diagnosis is limited by the poor acoustic condition produced by the surrounding fat, emphysema, and coarctation of the intercostal space.

In Case 2, the use of conventional echocardiography was limited because of obesity. We chose contrast echocardiography
(i.e., LVO), which can enhance the myocardial contrast, improve the delineation of trabeculations and recesses, and generate accurate measurement of the wall thickness and sizes of trabeculations and recesses.\textsuperscript{17,18} Our findings, including the NC/C ratio, multiple trabeculations/deep intertrabecular recesses, and slow blood flow within the recesses (which communicated with the ventricular cavity) confirmed the diagnosis of NVM.

We have herein demonstrated the added value of contrast echocardiography in NICM, using two representative cases (Takotsubo cardiomyopathy and noncompaction cardiomyopathy) as examples. In fact, contrast echocardiography has been used in the diagnosis of other types of NICM, including hypertrophic cardiomyopathy\textsuperscript{19} and dilated cardiomyopathy.\textsuperscript{20} Future studies that include larger samples are needed to evaluate this diagnostic test and its cost-effectiveness.

Although cardiac magnetic resonance imaging is a standard method for the diagnosis of NVM, it is not widely available. Contrast echocardiography is less expensive, easy to use, and preferred for identifying suspected NVM, especially when cardiac magnetic resonance imaging is unavailable. However, the use of contrast echocardiography is limited by its sound window, particularly for patients with apical hypertrophy, endocardial fibroelastosis, metastatic disease, and apical thrombus formation. In these circumstances, cardiac magnetic resonance imaging is required for the diagnosis of NVM.\textsuperscript{21}

In conclusion, contrast echocardiography improves the assessment of the global and local myocardial structure and allows for real-time assessment of myocardial motion and perfusion. It is easy to implement for the characterization of NICM. Its applications show merit for future large clinical studies.

**Declaration of conflicting interest**

The authors declare that there is no conflict of interest.

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