Author's response to reviews

Title: Contrast stress echocardiography in hypertensive heart disease

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Cardiovascular Ultrasound

Thank you for giving us the opportunity to resubmit a revised version of our case report entitled “Contrast stress echocardiography in hypertensive heart disease”. We have responded to the individual comments and suggestions raised by the reviewers in the revised version of the manuscript as detailed below. We hope that you will find the manuscript improved and suitable for publication in Cardiovascular Ultrasound.

Sincerely yours,
Mai Tone Lønnebakken
On behalf of the authors

Reviewer's report:
This is a well written case report highlighting a very common clinical scenario. The prevalence of microvascular dysfunction in hypertensive patients. The alternative ischemic cascade is a clear clinical finding disclosed by cardiac imaging techniques and it still requires a good laboratory model. It was initially described in cardiac syndrome X by Kemp et al. in 1973 with pacing left ventriculography, and later observed with stress echocardiography. The left ventricle is hyperdynamic during stress, in spite of the frequent occurrence of chest pain and ST-segment depression: it is “too good to be ischemic,” at least when the usual pattern of classic ischemia due to coronary artery stenosis is considered. The alternative cascade refers to a sequence of clinical events, during which the occurrence of ischemia usually cannot be proven, although in a subset of patients a reduction in coronary flow reserve, and/or a metabolic evidence of inducible ischemia, and/or a strictly subendocardial stress-induced hypoperfusion have been described. Thus, while few would argue that induced myocardial dysfunction is an accurate marker of regional ischemia, the occurrence of ECG changes and demonstration of regional abnormal vasodilator reserve may or may not be associated with ischemia. In this debate, one should consider that the absence of stress-induced dysfunction does not rule out the ischemic nature of the electrocardiographic abnormalities. There are a few issues that authors should address:

1. Please expand the pathophysiologic mechanisms. There is a large body of evidence on this issue that authors should address.

We thank the reviewer for careful evaluation of our manuscript. As suggested, we have expanded the pathophysiological mechanisms. We have also included 2 new references on diagnosis of microvascular dysfunction by Doppler derived coronary flow reserve using vasodilator stress echocardiography (new number 7) and by contrast echocardiography (new number 8). The following changes have been made in the manuscript:
1) Abstract, page 2: “Hypertension is associated with atherosclerosis and cardiac and vascular structural and functional changes. Myocardial ischemia may arise in hypertension independent of coronary artery disease through an interaction between several pathophysiological mechanisms, including left ventricular hypertrophy, increased arterial stiffness and reduced coronary flow reserve associated with microvascular disease and endothelial dysfunction.”

2) Introduction page 3, from line 1: “Hypertension is associated with atherosclerosis and cardiovascular structural and functional changes predisposing hypertensive patients to myocardial ischemia also in the absence of significant epicardial coronary artery disease through a number of pathophysiological mechanisms.”

3) Introduction page 3 from line 12: “In addition, coronary microvascular dysfunction is common in hypertension and contributes to left ventricular ischemia [6]. Recently the diagnostic and prognostic value of Doppler derived coronary flow reserve measurement by vasodilator stress echocardiography was demonstrated [7]. However, myocardial hypoperfusion may also be directly visualized by contrast stress echocardiography [8].”

4) Conclusion page 8: “Chronic uncontrolled hypertension is associated with development of cardiovascular complications including atherosclerosis, left ventricular hypertrophy, arterial stiffening and microvascular dysfunction. This can cause symptomatic myocardial ischemia even in the absence of significant epicardial coronary artery stenoses.”

2. Please expand the clinical implications of the present findings.

As suggested by the reviewer, clinical implications have been expanded, see also response to point 4 and 5 below.

We have added the following to discussion page 7, last paragraph:
“Also in hypertensive patients, development of wall motion abnormalities during stress echocardiography is associated with increased cardiovascular event rate [22]. Hypertension is associated with both increased prevalence of severe coronary artery disease as well as increased prevalence of non-obstructive ischemic heart disease. Echocardiographic diagnosis of microvascular disease should not be made unless obstructive coronary artery disease has been ruled out by coronary angiography or coronary computer tomographic angiography [22,23]. Diagnosis of non-obstructive ischemic heart disease is challenging and requires use of multimodality imaging as demonstrated by the present case. In particular vasodilation stress echocardiography assessing coronary flow reserve and myocardial perfusion assessment by contrast stress echocardiography or magnetic resonance imaging have proven useful in diagnosis of non-obstructive ischemic heart disease, while this diagnosis may often be missed on conventional stress echocardiography assessing only wall motion abnormality [7,22,23]. Coronary flow reserve < 1.91 during adenosine stress has been associated with increased cardiovascular risk in hypertensive patients independent of the presence of wall motion abnormalities [7]. Furthermore, a coronary computer tomographic angiography study recently documented reduced prognosis in women with non-obstructive ischemic heart disease [24]. Therefore, diagnosing symptomatic myocardial ischemia in hypertensive patients without significant coronary artery disease has important clinical implications and should initiate aggressive anti-hypertensive and anti-ischemic treatment as well as risk factor modification to improve symptoms and prognosis.”

3. Please address that there are several studies showing the reduction of
coronary flow reserve during vasodilator stress testing in hypertensives and this is not only a diagnostic conundrum but it has clear-cut prognostic implications.

We thank the reviewer for this comment which is now included in the Discussion page 6, second paragraph: “Non-obstructive coronary artery disease is not uncommon in hypertensive patients undergoing coronary angiography due to chest pain, and detection of reduced Doppler derived coronary flow reserve during vasodilator stress echocardiography, reflecting microvascular disease and endothelial dysfunction in such patients, has been shown to predict worse prognosis in spite of normal wall motion score during conventional stress echocardiography [7,17].”

The following was added to Discussion, page 7, last paragraph: “In particular vasodilation stress echocardiography assessing coronary flow reserve and myocardial perfusion assessment by contrast stress echocardiography or magnetic resonance imaging have proven useful in diagnosis of non-obstructive ischemic heart disease, while this diagnosis may often be missed on conventional stress echocardiography assessing only wall motion abnormality [7,22,23]. Coronary flow reserve <1.91 during adenosine stress has been associated with increased cardiovascular risk in hypertensive patients independent of the presence of wall motion abnormalities [7].”

4. Please address on the basis of the significant clinical experience of the your group how to evaluate these subset of highly symptomatic patients and how to treat them.

As suggested by the reviewer, we have expanded how to evaluate and treat this subset of highly symptomatic patients in the Discussion, page 7 last paragraph:

“Also in hypertensive patients, development of wall motion abnormalities during stress echocardiography is associated with increased cardiovascular event rate [22]. Hypertension is associated with both increased prevalence of severe coronary artery disease as well as increased prevalence of non-obstructive ischemic heart disease. Echocardiographic diagnosis of microvascular disease should not be made unless obstructive coronary artery disease has been ruled out by coronary angiography or coronary computer tomographic angiography [22,23]. Diagnosis of non-obstructive ischemic heart disease is challenging and requires use of multimodality imaging as demonstrated by the present case. In particular vasodilation stress echocardiography assessing coronary flow reserve and myocardial perfusion assessment by contrast stress echocardiography or magnetic resonance imaging have proven useful in diagnosis of non-obstructive ischemic heart disease, while this diagnosis may often be missed on conventional stress echocardiography assessing only wall motion abnormality [7,22,23]. Coronary flow reserve <1.91 during adenosine stress has been associated with increased cardiovascular risk in hypertensive patients independent of the presence of wall motion abnormalities [7]. Furthermore, a coronary computer tomographic angiography study recently documented reduced prognosis in women with non-obstructive ischemic heart disease [24]. Therefore, diagnosing symptomatic myocardial ischemia in hypertensive patients without significant coronary artery disease has important clinical implications and should initiate aggressive anti-hypertensive and anti-ischemic treatment as well as risk factor modification to improve symptoms and prognosis. In particular, performing 24 hour ambulatory blood pressure recording for optimal assessment of blood pressure is important in resistant hypertension. Improved blood pressure control in resistant hypertension may be obtained by adding a small dosage of an aldosterone blocker or amiloride, the latter particularly effective in hypertension in Africans [9]. Furthermore, treatment with
angiotensin converting enzyme inhibitors or statins improves microvascular function and symptoms in non-obstructive ischemic heart disease [25].”

5. Please address the comparative value of other imaging techniques in the same clinical scenario.

Following the suggestion from the reviewer, the following has been added to Discussion, page 7, last paragraph: “Diagnosis of non-obstructive ischemic heart disease is challenging and requires use of multimodality imaging as demonstrated by the present case. In particular vasodilation stress echocardiography assessing coronary flow reserve and myocardial perfusion assessment by contrast stress echocardiography or magnetic resonance imaging have proven useful in diagnosis of non-obstructive ischemic heart disease, while this diagnosis may often be missed on conventional stress echocardiography assessing only wall motion abnormality [7,22,23]. Coronary flow reserve <1.91 during adenosine stress has been associated with increased cardiovascular risk in hypertensive patients independent of the presence of wall motion abnormalities [7]. Furthermore, a coronary computer tomographic angiography study recently documented reduced prognosis in women with non-obstructive ischemic heart disease [24].”

6. Please address the lack of quantification for contrast echocardiography and the still open safety concerns. Moreover, the high cost of a single exam when compared to vasodilator stress testing with Doppler quantification of coronary flow reserve.

Vasodilator stress echocardiography was not performed in the reported case. The point of the case report is to demonstrate the usefulness of another method, contrast stress echocardiography, in detecting microvascular dysfunction. We are not aware of any randomized study comparing head-to-head diagnostic performance of coronary flow reserve by vasodilator stress testing and myocardial perfusion assessment by contrast stress echocardiography. Based on this, it seems premature to compare cost-benefit of the tests. We agree with the reviewer that quantitative contrast echocardiography still has to prove itself, and this was not used in the present case. The safety of contrast echocardiography and potential side effects are well documented in prior publications and should hamper use of contrast echocardiography as indicated by current guidelines.

We have added the following to Discussion, page 7 second paragraph: “Contrast stress echocardiography is particularly suited to detect myocardial ischemia. In accordance with current guidelines a contrast agent should be added during stress echocardiography when 2 or more left ventricular segments cannot be sufficiently evaluated [19,20]. This does not only improve wall motion assessment [20] but allows simultaneous evaluation of myocardial ischemia as contrast microbubbles are isolated intravascular tracers directly reflecting myocardial perfusion and capillary density [20]. Even if direct quantification of myocardial perfusion has proven difficult so far, qualitative detection of delayed contrast enhancement has been shown to be more sensitive to detect coronary artery disease than wall motion alone [21]. As ultrasound contrast often is indicated due to image quality, simultaneous assessment of myocardial perfusion adds important information on regional myocardial ischemia with high spatial resolution without extra cost. Furthermore, the safety of contrast echocardiography and potential side effects are well documented [20].”

Minor: please proofread the manuscript there are a few typos throughout the Manuscript
The manuscript has been carefully proofread and detected typos corrected.

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

**Declaration of competing interests:**
'I declare that I have no competing interests'