Reviewer's report

Title: Contrast stress echocardiography in hypertensive heart disease

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Reviewer: Rosa Sicari

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.

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

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.

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.

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

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.
Minor: please proofread the manuscript there are a few typos throughout the manuscript

**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'