Reviews in Cardiovascular Medicine

Rev. Cardiovasc. Med. **2022**; 23(3): 086
http://doi.org/10.31083/j.rcm2303086

Review

Rest contrast echocardiography unmasks hidden wall motion abnormalities in patients with chest pain. A case series and review of pertinent literature

Sergio Suma[1,*], Domenico Tuttolomondo[1], Nicola Gaibazzi[1]

[1]Cardiology Department, University Hospital of Parma, 43126 Parma, Italy
*Correspondence: sergiosuma.md@gmail.com (Sergio Suma)
Academic Editor: Ezra Abraham Amsterdam
Submitted: 20 November 2021 Revised: 13 January 2022 Accepted: 13 January 2022 Published: 4 March 2022

Abstract

We present a case series of three patients that underwent myocardial contrast echocardiography (MCE) in the setting of recent chest pain, as paradigmatic examples of the usefulness of contrast-echocardiography with very-low mechanical index imaging in the context of rest wall motion assessment. Moreover, we analysed the pertinent literature about the use of rest MCE in the context of chest pain of unknown origin, showing its diagnostic and prognostic impact. We think that MCE could play a key role in detecting chest pain subtended by previously unknown coronary artery disease (CAD). For example, in pts without significant electrocardiogram (ECG) modifications or in whom high sensitivity troponins show only borderline increase (still below the upper limit) or have no clearly significant delta. In such cases the more sensitive evaluation of wall motion (WM) powered by MCE could add diagnostic information, above all in pts with severe CAD but apparently normal WM at standard echocardiography.

Keywords: myocardial contrast echocardiography; ischemic heart disease; prognosis; chest pain

1. Case presentation

In this case series we present three patients (pts) that underwent myocardial contrast echocardiography (MCE) in the setting of recent chest pain, as paradigmatic examples of the usefulness of contrast-echocardiography with very-low mechanical index imaging in the context of rest wall motion assessment.

The first patient was a 57 years old man with no cardiovascular risk factors who presented to the emergency department (ED) due to chest pain on effort and also at rest. The ECG showed mild abnormalities on the anterior leads, and there was a mild increase of the troponin I levels. At transthoracic echocardiography (TTE) left ventricular wall motion (WM) was apparently normal with no regional abnormalities.

The second patient was a 40-year-old man with hypercholesterolemia who had chest pain on effort and again also at rest. In this case the ECG was unremarkable and the high sensitivity troponin I was between the limit of detection (LOD) and upper reference limit (URL) with no significant delta between two serial measurements. Again, at TTE there was an apparently normal segmental WM of the left ventricle.

Last patient was a 58-year-old woman with obesity and hypertension who was evaluated at the outpatients clinic for exertional chest pain with few episodes at rest. The ECG was unremarkable and the troponin was not measured at that time. TTE was apparently normal also in this case.

Since the symptoms were very typical in all the three cases and the suspect of coronary artery disease (CAD) was high, we integrated the TTE with contrast administration for better WM assessment. In all the cases, the more accurate evaluation of endocardial border could reveal WM abnormalities in the Left Anterior Descending (LAD) territory: in particular, in case 1 they involved the anterior mid-to-distal wall, the apex and the distal septum (see Fig. 1 for details, and **Supplementary Videos 1,2**), in case 2 the distal anterior wall, the apex and the distal septum (see Fig. 2 and **Supplementary Videos 3,4**), in case 3 the mid-to-distal septum, the apex and the latero-apical wall (see Fig. 3 and **Supplementary Videos 5,6**).

Moreover, even if the use of small boluses of contrast is not ideal for the study of myocardial perfusion (MP), the assessment of WM using real-time very low mechanical index (<0.2) provides collateral information regarding MP, which was reduced in these cases and further contributed to highlight the subtle WM abnormalities. Unfortunately, we did not evaluate the global longitudinal strain in these cases, which could had added useful information about the deformation of the left ventricle.

All the three-pts had severe left anterior descending coronary artery (LAD) stenosis which turned out to be subocclusive in all of the three pts. The first two pts underwent coronary angiography (Figs. 4,5), whereas the last patient underwent computed tomography (Fig. 6 and **Supplementary Video 7**) and will soon undergo coronary angiography as well.

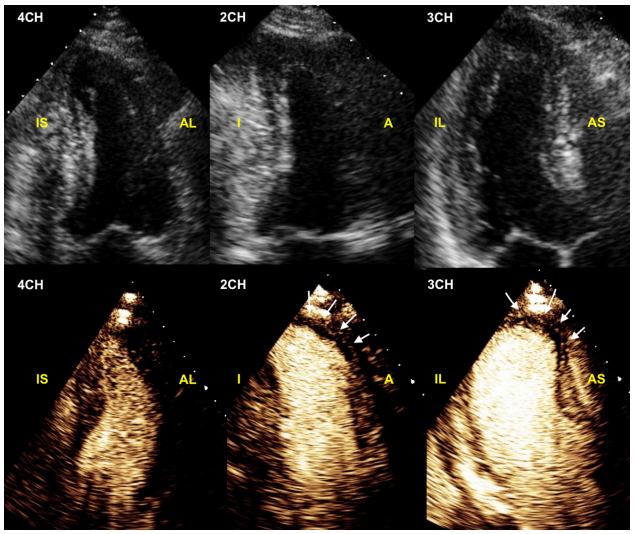

Fig. 1. TTE of patient 1 comparing standard views (at the top) with MCE (below). MCE shows WM and MP abnormalities in the anterior mid-to-distal wall, the apex and the distal septum (see arrows). 4CH, 4-chambers view; 2CH, 2-chambers view; 3CH, 3-chambers view; IS, Infero-septal wall; AL, antero-lateral wall; I, Inferior wall; A, Anterior wall; IL, infero-lateral wall; AS, antero-septal wall.

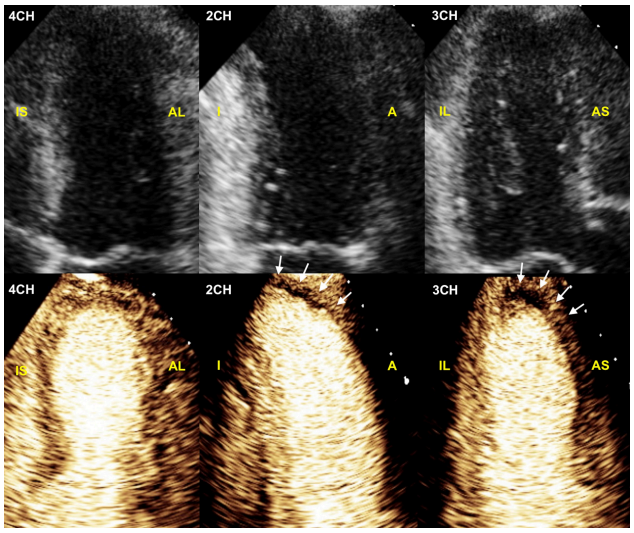

Fig. 2. TTE of patient 2 comparing standard views (at the top) with MCE (below). MCE shows WM and MP abnormalities in distal anterior wall, the apex and the distal septum (see arrows). 4CH, 4-chambers view; 2CH, 2-chambers view; 3CH, 3-chambers view; IS, Infero-septal wall; AL, antero-lateral wall; I, Inferior wall; A, Anterior wall; IL, infero-lateral wall; AS, antero-septal wall.

2. Review of the published literature with MCE used for wall motion evaluation

The use of rest MCE in the context of chest pain was evaluated in different studies either or both for WM and

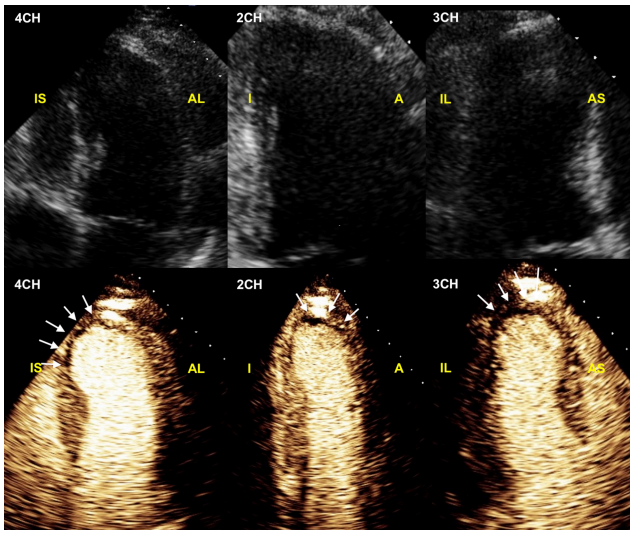

Fig. 3. TTE of patient 3 comparing standard views (at the top) with MCE (below). MCE shows WM and MP abnormalities in the mid-to-distal septum, the apex and the latero-apical wall (see arrows). 4CH, 4-chambers view; 2CH, 2-chambers view; 3CH, 3-chambers view; IS, Infero-septal wall; AL, antero-lateral wall; I, Inferior wall; A, Anterior wall; IL, infero-lateral wall; AS, antero-septal wall.

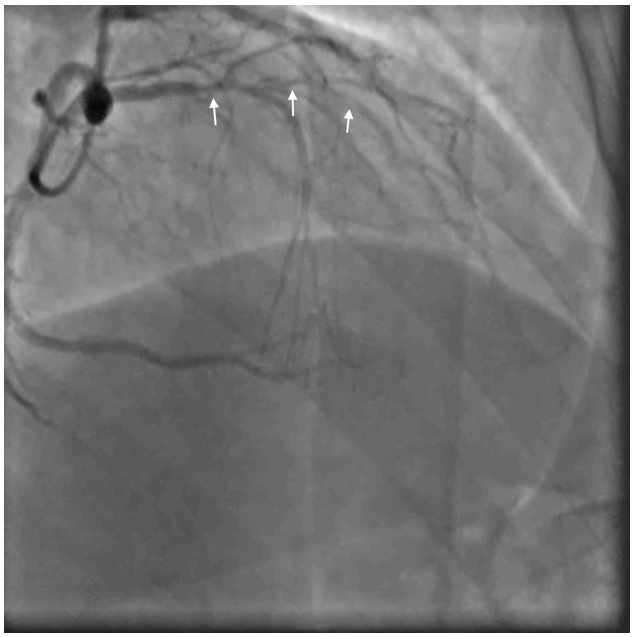

Fig. 4. Coronary Angiogram in patient 1. The angiogram shows severe sub-occlusive multiple stenosis (arrows) in the LAD course.

MP assessments (Table 1, Ref. [1–6]). The studies that evaluated only MP were not included in our review.

Rinkevich *et al.* [1] studied the MCE in predicting events in pts with chest pain (CP) who presented to the emergency department (ED) with non ST-elevation at the ECG; in particular they analysed 1017 pts, assessing both

Table 1. List of studies using MCE in the context of chest pain.

Study/Year	N° patients	Setting	Contrast agent	Contrast Infusion modality	Contrast echo modality for wall motion	WM and/or MP evaluation	Comparator/ Endpoint
Rinkevich *et al*. 2005 [1]	1017	CP	Optison	Continuous infusion	Real-time MI <0.3	WM and MP	MACE
Tong *et al*. 2005 [2]	957	CP	Optison	Continuous infusion	Real-time harmonic unknown MI	WM and MP	mTIMI score
Wei *et al*. 2010 [3]	1166	CP	Optison	Continuous infusion	Real-time MI <0.3	WM and MP	MACE
Kalvaitis *et al*. 2006 [4]	957	CP	Optison	Continuous infusion	Real-time MI <0.3	WM and MP	Time/MACE
Porter *et al*. 2013 [5]	2014	CP	Definity	Continuous infusion	Both real-time MI <0.2 and real-time harmonic higher MI	WM and MP	MACE

ACS, Acute Coronary Syndrome; CP, Chest pain of unknow origin with no ST-segment elevation at the ECG; MI, mechanical index; WM, wall motion; MP, myocardial perfusion; MACE, Major adverse cardiovascular events. Meta-analysis [6] was not included in the tab.

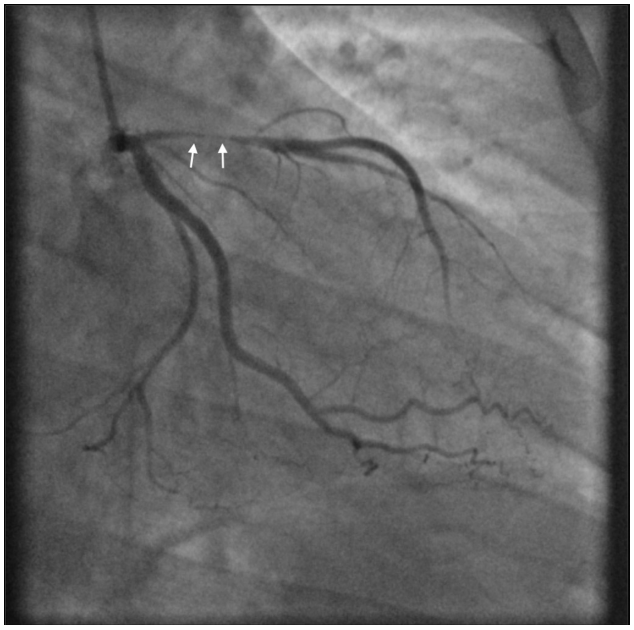

Fig. 5. Coronary Angiogram of patient 2. The angiogram shows a sub-occlusive focal proximal stenosis of the LAD (arrows).

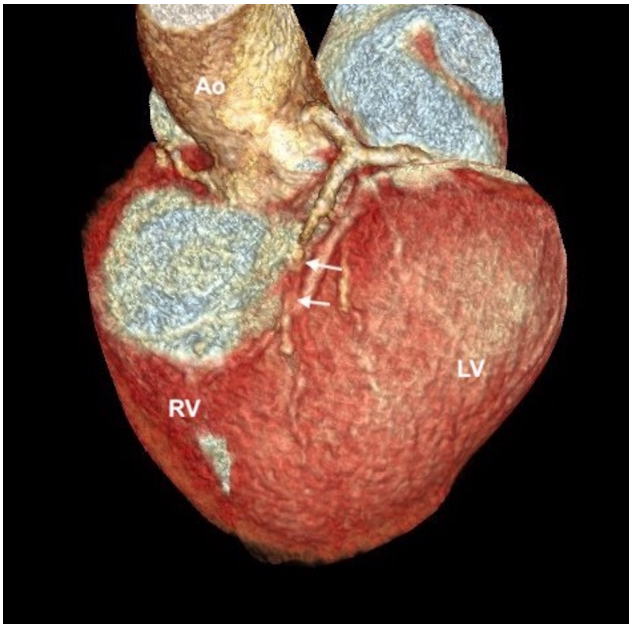

Fig. 6. Computed Tomography of patient 3 showing a sub-occlusive stenosis in the mid-LAD (arrows). Ao, Aorta; LV, Left Ventricle; RV, Right Ventricle.

regional WM and MP with MCE in addition to the standard ECG evaluation, with a mean follow-up of 7.7 months. Considering only rest WM data, which is the main purpose of the current review, 43 pts with normal WM had events and 249 events (85% of all events) took place in patients with rest WM abnormalities assessed with contrast.

On the multivariable Cox regression analysis, history of hypertension (p = 0.028), ECG (p = 0.0001), WM (p < 0.0001), and MP (p < 0.0001) were significant predictors of cardiac events. Abnormal WM increased the risk of events by five-fold when compared with normal WM (95% CI, 3.4–7.2), whereas abnormal MP increased the risk by only twofold when compared with normal MP (95% CI, 1.5–2.7).

They concluded that early assessment of WM (and MP) on MCE added significant diagnostic and prognostic value to routine evaluation in pts presenting to the ED with suspected cardiac CP and no ST-segment elevation. There was no standard (without contrast) echocardiography included in the standard clinical comparison control, so that MCE for rest WM assessment was compared to clinical assessment and ECG only. Furthermore, Troponin assessment was not included in the study.

Tong *et al.* [2] compared WM and MP analysis with modified Thrombolysis In Myocardial Infarction (TIMI) risk score (mTIMI, which is TIMI score not including troponin levels) in 957 pts presenting to the ED with CP and a nondiagnostic ECG. Cumulative pts outcomes were determined at three time points: early (within 24 hours), intermediate (up to 30 days), and late (>30 days). Pts were subdivided in low (score <2), intermediate (score 3 or 4) or high (score >5) risk depending on their TIMI or mTIMI scores. The mTIMI score was unable to discriminate between intermediate and high risk pts at any point of the follow-up, while only 2 of 523 pts with normal WM had an early primary event. There was an incremental prognostic value of WM evaluation over mTIMI score to predict intermediate and late events. But it should be emphasized that rest MCE WM was not assessed with very low mechanical index imaging but rather with harmonic low mechanical index, which has lower yield to detect WM abnormalities compared with very low mechanical index imaging. The full TIMI score could not improve upon these results at any follow-up time point.

Wei *et al.* [3] enrolled 1166 pts (cohort 1) with a validation cohort (cohort 2) of 720 pts; all pts presented to ED with CP lasting 30 minutes or more and there wasn't any ST-segment elevation on the ECG. Wall motion (WM) and myocardial perfusion (MP) were separately assessed by MCE. Any abnormality or ST changes on ECG (odds ratio [OR] 2.5; 95% confidence interval [CI], 1.4–4.5, $p = 0.002$, and OR 2.9, 95% CI, 1.7–4.8, $p < 0.001$, respectively), abnormal WM with normal MP (OR 3.5, 95% CI, 1.8–6.5, $p < 0.001$), and abnormal WM with abnormal MP (OR 9.6, 95% CI, 5.8–16.0, $p < 0.001$), so that either or both WM and MP were significant predictors at the multivariate analysis for nonfatal myocardial infarction and cardiac death. Apparently, there was no comparison between WM assessed with MCE and without contrast, so that in this well-conducted study, there remains the clinical question whether contrast WM assessment is superior or not to standard WM assessment without contrast.

Kalvaitis *et al.* [4] explored the effect of time delay of the use of MCE in the ED. In particular 957 pts were enrolled, they presented to ED with CP and no ST-elevation at the ECG and were divided into 4 quartiles depending on the time between their last episode of CP and the MCE evaluation. Pts in quartile I had MCE during ongoing CP (time delay of 0 minutes). The time delays in quartiles II, III, and IV were 54 $\pm$ 44, 213 $\pm$ 54, and 556 $\pm$ 184 minutes, respectively ($p < 0.001$). In each quartile, pts with normal WM had the lowest incidence of events, whereas those with both abnormal WM and MP had the highest incidence of events. Pts with abnormal WM but normal MP had an intermediate event rate. They concluded that timing of MCE did not affect the ability to predict event rate at 24 hours in pts with CP. Again, it should be emphasized that rest MCE WM was not assessed with very low mechanical index imaging but rather with harmonic low mechanical index, which has lower capability to detect WM abnormalities compared with very low mechanical index imaging.

Wyrick *et al.* [7] analysed the cost-efficiency of MCE in 957 pts presenting to ED with CP and no ST-elevation at the ECG, but this analysis is most probably conducted on the same patient cohort studied by Kalvaitis *et al.* [4], so we did not include it in our review.

Porter *et al.* [5] compared patient outcome after stress real-time MCE (RTMCE), using very-low mechanical index, versus conventional stress echo with low mechanical index and harmonic imaging (CSE). Outpatient and inpatient subjects admitted for chest pain with normal or equivocal troponin underwent exercise or dobutamine stress echocardiography and were randomized prospectivey to either RTMCE or CSE. For CSE they used definity contrast when the delineation of the endocardial border was not adequate (63% of the studies). 2014 pts were evaluated with a mean follow-up of 2.6 years. At peak stress it was observed more frequently an abnormal RTMCE then an abnormal CSE ($p < 0.001$) hence resulting in a more frequent revascularization ($p = 0.004$). In RTMCE there was a higher rate of WM abnormalities ($p < 0.01$) which were an indipendent predictor of death/nonfatal myocardial infarction for RTMCE but not for CSE ($p = 0.005$). This is a signal that RTMCE, as now supported by European and American guidelines, [8,9] is superior to standard contrast-echocardiography-using higher mechanical index (0.2–0.4) and harmonic imaging to detect mild WM abnormalities.

Finally, Qian *et al.* [6] made a meta-analysis about prognostic value of resting MCE evaluating both WM and MP. Seven studies met criteria, including 3668 patients. When patients had abnormal MP and WM, the relative risk (RR) to predict MACE was 6.1 (95% CI, 5.1–7.2) and 14.3 (95% CI, 10.3–19.8) for death/non-fatal myocardial infarction compared to patients with normal MP and WM. This was true also for patients with abnormal MP and WM in comparison with abnormal WM and normal resting MP to predict MACE (RR, 1.7; 95% CI, 1.5–1.9) and death/non-fatal myocardial infarction (RR, 2.2; 95% CI, 1.8–2.7) when compared to abnormal WM with normal resting MP.

3. Discussion

Contrast agents in conjunction with very low MI contrast real-time imaging increase the accuracy of WM assessment, both through endocardial border enhancement [10–15] and by simultaneously providing collateral information on MP (MP defects always precede WM abnormalities) [16–23], which in turns enhances the visual capability to detect a WM abnormality, if present. This can be particularly helpful in cases of poor acoustic windows, as well as in cases of difficult evaluation of the anterior wall and of the apex. In this not-unusual context, MCE could be of great interest in the routine evaluation of wall motion

in pts with chest pain of uncertain origin. Indeed, our cases were paradigmatic examples of how very-low-MI MCE setting could reveal WM abnormalities not obvious at the first evaluation at the TTE without contrast. MCE in these cases changed the clinical management of these pts moving up the way for revascularisation.

In fact, the importance and usefulness of MCE for better rest WM assessment in the evaluation of CP has been only partially demonstrated in the studies reported above, in terms of risk stratification, diagnostic and prognostic impact as well as cost-efficiency. Most such studies were actually performed several years ago, most were single-centre, most used echocardiography machines not anymore commercially available (as it is also the case for the contrast media used) and they used impractical long continuous infusion of contrast. Furthermore, no study compared the usefulness of an enhanced evaluation of WM by MCE with the standard evaluation of WM by standard echocardiography (with no contrast), which is probably the most compelling practical clinical issue.

This could be of great interest in the context of the ED for the evaluation of CP of unknown origin, even in the current era of high-sensitivity troponins, beyond the already defined applications of MCE in stress-echocardiography [24–27].

Indeed, we think that there remain many grey-cases in the daily routine practice, in which MCE could play a key role in detecting chest pain subtended by previously unknown CAD. For example, in pts without significant ECG modifications or in whom high sensitivity troponins show only borderline increase (still below the upper limit) or have no clearly significant delta. In such cases the more sensitive evaluation of WM powered by MCE could add diagnostic information, above all in pts with severe CAD but apparently normal WM at standard echocardiography.

4. Conclusions

In conclusion, more and contemporary studies are warranted to confirm the usefulness of MCE in pts with CP despite the availability of high sensitivity troponins; as shown in the reported cases, we believe that MCE, through the detection of otherwise apparently and falsely normal WM could play an important role in the detection of underlying CAD as a cause of acute/subacute CP admitted to the ED.

5. Limitations

The small number of cases (3) obviously does not allow the authors to provide any information on the overall accuracy of their method, including sensitivity, specificity, and predictive accuracy.

Author contributions

SS and NG performed the echocardiograms of the clinical cases presented; SS, NG and DT selected the images and the video for the paper; SS, NG and DT performed the review of the pertinent literature. All authors contributed to editorial changes in the manuscript and read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Acknowledgment

We would like to express our gratitude to all the peer reviewers for their opinions and suggestions.

Funding

This research received no external funding.

Conflict of interest

The authors declare no conflict of interest. Nicola Gaibazzi is serving as one of the Guest editors of this journal. We declare that Nicola Gaibazzi had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to Ezra Abraham Amsterdam.

Supplementary material

Supplementary material associated with this article can be found, in the online version, at https://www.imrpress.com/journal/RCM/23/3/10.31083/j.rcm2303086.

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