Do we need a new definition for post-stress reduction in LVEF beyond the numerical values?

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In this issue of the Journal, Obiedate et al. highlighted the prognostic value of post-adenosine reduction in LVEF among Jordanian population with negative myocardial perfusion imaging (MPI) studies.

The principal conclusion emerging from this excellent work is that post-adenosine reduction in LVEF in the setting of normal MPI was not associated with higher cardiac event rate at 2 years of follow-up: a finding that correlates with similar reports which concluded the same finding in relation to treadmill exercise, Dipyridamole, and recently regadenoson stress as well.[1–4]

The current study has evoked a series of thoughtful ideas and highlighted some important concepts. Some of these thoughts and concepts are revisited below:

PATHOPHYSIOLOGIC MECHANISMS OF POST-STRESS REDUCTION IN LVEF

The finding of post-stress reduction in LVEF was initially suggested as a high-risk finding related to significant CAD. However, the true pathophysiologic mechanism is still a matter of debate. Below are discussed the relevant pathophysiologic mechanisms and their impacts:

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- *First*, it could be due to persistent changes in LV loading pressure with subsequent higher LV volumes and reduced LVEF (*Volumetric theory*).[5]
  This could be the main explanation of such a phenomenon in case of dilated cardiomyopathy or even subclinical heart muscle disease. It is unlikely to occur in a heart with normal volume and LVEF. This situation should be considered as a different phenomenon from the transient ''ischemic'' LV cavity dilation with a different spectrum of MACEs from the true ischemic category.[5]
- *Second*, inducible myocardial ischemia leads to transient (post-stress) LV dilatation. As a matter of fact, we do not see the actual endocardium on SPECT imaging. We usually rely upon the edge of the tracer distribution, so that if there is reduction in tracer uptake in the subendocardial rim, this will be reflected as higher cavity size and lower LVEF (indeed, without true change in LV volumes). Here, stress-induced LV dilatation is simply a reflection of ischemia (*Subendocardial ischemia theory*).[5]
  Its utility in clinical imaging may bring attention to larger, primarily subendocardial regions of inducible ischemia, rather than an unremarkably normal MPI study in these discreet cases of subendocardial ischemia.[5–7]
- *Third*, the last possibility is that severe inducible ischemia led to unstable LV pressure and volume (*a mixture of reversible ischemia and actual volume changes*). In such a situation, it should be also thought of as a marker of severe myocardial ischemia.[5]

Based on the above pathophysiologic outlines, the reduction in LVEF detected among the current study cohort could not be classified according to the second or third suggested pathophysiologic mechanisms—simply because both mechanisms depend on sizable myocardial ischemia, which is not the case with normal MPI studies.

Even though the possibility of significant subendocardial ischemia was suggested, the extremely low hard and soft cardiac event rates among the study population stand against this possibility.

Then, the first pathophysiologic mechanism seems to be the most suitable explanation for reduction in LVEF among the studied population. However, the results of the current study showed that in patients with $\geq 5\%$ reduction in LVEF, the mean post-stress and resting LVEDV showed no statistically significant differences (94 ± 31 and 90 ± 31 mL, respectively; P value = .19). This very insignificant volumetric change could not explain a reduction in LVEF $> 5\%$. In contrast, the mean post-stress LVESV was significantly higher than the mean resting LVESV (39 ± 24 vs 32 ± 23ml, respectively; $P < .001$). Thus, the $\geq 5\%$ reduction in LVEF was most probably related to an increase in LVESV rather than an increase in LVEDV. This is an important finding that might point to an initial step in the cascade of LV systolic dysfunction and correlates with the lower hard and soft cardiac event rates among this cohort.

MATHEMATICAL ERRORS IN QUANTIFICATION OF VOLUMES

As a matter of fact, the expected incidence of post-stress stunning is quite low as long as the MPI study is normal. Variations in MPI analysis (proper contouring) and/or quality of the perfusion scan (quality of ECG gating, subdiaphragmatic activity, type of tracer, target-to-background ratio, motion artifacts…etc.)—all of these—may participate in the occurrence of false-positive post-stress reduction in LVEF. Partly, this could explain the poor correlation with adverse outcomes in the studied cohort.[8]

The predictive accuracy of this phenomenon is generally good in the presence of elevated volume, reduced LVEF, and/or perfusion abnormalities. However, in patients with otherwise normal MPI, post-stress reduction in LVEF is likely to be a measurement variance rather than a real pathophysiologic change especially when LV volumes and LVEF are still within the normal limits.[5]

OTHER VARIABLES THAT MAY INFLUENCE POST-STRESS REDUCTION IN LVEF

Post-stress reduction in LVEF may be effected by multiple variables including: type of stress, one versus two day protocol, single versus dual isotope, body mass index (BMI), gender, heart rate, blood pressure, clinical/subclinical valvular and/or heart muscle disease, left ventricular hypertrophy as well as different RV loading conditions that might affect LV performance.[8]

Subclinical heart muscle disease is not uncommon especially in association with hypertension and some chronic systemic diseases. For example, the relation between subclinical cardiomyopathy and chronic hepatitis C was highlighted by Wiese et al. They showed that in these patients, there is latent impairment of the contractile reserve that could be unmasked as post-stress drop in LVEF.[9]

With exercise, the LV size gets slightly smaller compared to the resting size, and the normal limits in both situations might need to be adjusted accordingly.

In the group which showed $> 10\%$ reduction in post-stress LVEF in the current study, the mean resting and post-stress LVEF values were 72.8 ± 8.8 and 61.1 ± 8.6%, respectively. This indicates that all LVEF measurements were normal even at post stress. Also, the mean resting and post-stress LVEDV values among the same group were, respectively, 82 ± 20 and 86 ± 22 mL compared to 94 ± 34 and 96 ± 35 mL in the group with $< 10\%$ reduction in LVEF. The normal LVEF as well as the small LV volumes at rest and post stress are indicative of lower-risk index related to post-stress reduction in LVEF as long as the EF and volume measurements are still above normal values.

Again, correction of these volumetric parameters to BMI-, gender-, and stress-specific normal limits may improve its predictive accuracy.[5,10]

One more thing related to this point, the current study included 234 (42%) males. The higher female / male ratio participated led to the slightly lower LV volumes and high LVEF among the study cohort, so that, minimal change in LVESV will replicate a significant reduction in LVEF despite normal LV volumes, LVEF, and a low MACEs. Relying upon the absolute numbers in such situation may be fallacious.[11,12]

Obiedate et al. showed that in the group with $> 5\%$ reduction in post-adenosine LVEF, history of CAD was a predictor of this phenomenon. This could (in the setting of normal MPI) point to impaired vasoactive response due to functional abnormalities of the coronary microcirculation, which may occur secondary to endothelial dysfunction, autonomic neuropathy, and/or impaired coronary flow reserve.[13]

STRESS-ONLY AND RADIATION EXPOSURE

The current guidelines of ASNC is encouraging the use of stress-only protocol, which is indicated as one of the effective tools to reduce radiation exposure.[14]

Many nuclear cardiac laboratories in Egypt and the Middle East are using 2-day stress-rest as the routine SPECT imaging protocol. If the stress set of images showed normal perfusion and functional parameters, the stress-only pathway is considered.[15] Many reports

showed that stress-only protocol is as predictive as stress-rest protocol in this low-risk category.[12]

However, resting dimensions and functional data (including TID) are lost with stress-only protocol. In the current issue, Obiedate and his colleagues showed that even with post-stress reduction in LVEF > 10%, still there is a very low cardiac event rate as long as the MPI study is normal. It comes with a comfortable message that, even with stress-only protocols, we do not miss important functional information and that post-stress LVEF could be used safely.

REDUCTION IN LVEF POST STRESS: IS IT AN ABSOLUTE NUMBER?

As mentioned before, we and others have recommended previously the importance of reporting different functional variables on gated SPECT (LV volumes, LVEF, LV mass index …etc.) as normalized values to age, sex, BMI …etc.[5,10]

Rozenski et al. reported that women had a relatively higher mean resting LVEF than men and relatively lower volumes.[3]

In the current article, 58% of the study cohort were females with small-sized LV dimensions and relatively high LVEF. So measurement variances are relatively common and pose a technical challenge to accurately detect changes between post-stress and rest values.

In their article in the current issue, Obiedate et al. evaluated a consecutive cohort, whereas no exclusion criteria were adopted in the current study. So patients with clinical/subclinical myocardial and/or valvular heart disease were not excluded in our study. This relative heterogeneity of the study cohort is a critical remark that should be considered in upcoming studies in this field.

DO WE NEED A NEW DEFINITION FOR REDUCTION IN POST-STRESS LVEF?

Is a reduction in LVEF post stress simply a percentage drop in EF that exceeds inter- and intraobserver variability of the technique used? Regardless of whether the resting EF is normal or abnormal, and more importantl point is if the post-stress EF remains within normal limits or becomes significantly abnormal?

Indeed, gated SPECT variables are necessarily subject to error due to poor edge detection especially when we consider the different loading conditions in the post-stress and rest states. In such cases, outlying measurements lead to false values especially with otherwise normal MPI. Because post-stress reductions in LVEF and TID are inherently ''high-risk'' findings, it is essential to understand the probability of being falsely positive. However, before reaching to this conclusion, we need to make sure that we chose the true index of severity: TID versus mere post-stress reduction in LVEF.

Mandour Ali et al. reported that simple post-stress LV cavity dilatation in otherwise normal MPI studies should be only cautiously reported as a high-risk finding of significant CAD, instead it is better considered as a measurement variance.[5]

This is particularly true for vasodilator stressors based on the reports that showed that vasodilator-stress by itself was associated with post-stress reduction in LVEF. So that in such situation TID should be only cautiously interpreted as a marker of high-risk CAD.[16]

Valdiviezo et al. reported that there was neither significant difference between survival nor in severity of CAD among those with normal SPECT scans in the presence of TID after 9 years of follow-up.[17]

Abidov et al. reported approximately 1% per year increase in event rate among patients with normal MPI in presence of TID, but only in the highest quartile of elevated TID values.[18]

Gomez et al. demonstrated that, a decrease in post-regadenoson LVEF showed low specificity for severe/extensive CAD and conferred no prognostic value even among those with > 10% reduction in post-stress LVEF.[4]

So, on basis of these multiple reports do we need to set a new definition of this phenomenon that could improve its predictive accuracy and eliminate the confounder factors?

Authors of this editorial suggest that establishing a new definition of post-stress reduction in LVEF is probably the key word to rearrange the mixed data in this area and improve specificity of this finding in predicting high-risk CAD.

Disclosure

Mohamed Mandour Ali, Ahmed Aaty, Alia Abdelfattah, and Adel Allam have no conflicts of interest related to this work.

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