



## The control group revisited

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Quantitative analysis (relative or absolute) of the two most widely radionuclide procedures in our field, myocardial perfusion images (MPI) by SPECT or PET, is traditionally compared to normal subjects (control group). There are several commercially available software programs that make such comparison seamless and have served our field quite well. There are other measurements as well that are compared to a control group, such as ejection fraction, volumes, and synchrony.

Some have advocated, and rightfully so, that rest and stress MPI should be compared to each other rather than each to a normal database, but for some reason, such an approach is not often used in routine patient care. This approach is also not possible when stress imaging is only done (which is increasing).

The categorization of the results as normal or abnormal depends therefore, not only on the results in the patients but also on the control group. But, has the control group received adequate attention?

How are the subjects in the control group identified? Initially, patients with a low likelihood of having coronary artery disease (CAD) were used. These patients had no angina or angina equivalent symptoms, normal exercise performance, and no electrocardiographic or perfusion abnormalities at rest or during stress. It is important to keep in mind that decades ago almost 1/3 of patients undergoing stress MPI were in this group and so it was not difficult to identify a control group.

Few things have changed since then. First, the guidelines and appropriateness criteria correctly do not recommend that patients who fulfill the criteria for the control group be studied with MPI.

Second, more recent data suggest that abnormal coronary calcium score (CCS) and abnormal myocardial

blood flow (stress or relative) could be present despite normal MPI.

Third, the control group is often selected based on having a high-quality image and are often of ideal body weight. Neither these conditions are uniformly present in routine practice, where obesity is common, especially in the USA.

Fourth, the control group should be studied on comparable imaging systems, stress type, tracer and acquisition, and processing protocols to those used in the patients.

Lastly, the data in the control group are likely to have a range, the mean ( $\pm 2$  SD) is often used to define lower limits of normal, but that does not take into consideration the repeatability and reproducibility information and the variability between different software programs.

This means that some reclassification as to the presence and degree of abnormality could vary to a certain measure. It is likely that the reclassification will involve patients with mild and (maybe) moderate abnormality, (which, are most patients) but not those with severe abnormality, although the severity might be different. Also, it is uncertain whether these stipulations explain the differences between local vs core laboratory interpretation of images or the controversies on the role of ischemia detection in patient outcome.

There are obviously other important issues, such as differences between patients and control group in age, gender, race, weight, renal function, medications, and type of stress to mention only a few.

Then there is the issue of the warranty period; how long is the data in any control group valid and should a new control group be identified and how often? Artificial intelligence and deep learning models have shown improved accuracy compared with traditional quantitative approaches and their use might make the control group issues far less important, but the MPI measurements in these models also rely on a control group! Finally, even absolute myocardial blood flow during

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stress needs a control group to define what is normal or abnormal!

It is my lifelong devotion that keeps me re-examining what it seems like our umbilical cord and which initially seemed “fait accompli.”

Our imaging modality, in its current form, has served us and our patients well for 5 decades; that assurance is good enough for me, for now! Though the question remains, could we do better?

## Disclosures

*There is no COI.*

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