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GUEST EDITORIAL

Is Core Laboratory Essential for Using Echocardiography in Clinical Trials?

Controlled vs Random Error

Please see page 263 for the article by Hole *et al.* (doi:10.1053/euje.2002.0167) to which this editorial pertains.

Left ventricular remodelling is a natural, but harmful process after an acute myocardial infarction. The infarcted segments become thinner, conducive to being stretched, and even the viable myocardial segments dilate due to mechanical and neurohormonal changes taking place in this clinical setting[1]. The extent of left ventricular remodelling is determined by the size, location, and transmurality of myocardial infarction. The left ventricular dilatation and contractile dysfunction distort normal elliptical left ventricular geometry to a more spherical shape, resulting in worsening of diastolic function and haemodynamically significant mitral valve regurgitation, which perpetuate the cycle of left ventricular remodelling. It is not, therefore, surprising that left ventricular volume was found to be one of the most important prognostic factors in patients with acute myocardial infarction[2,3]. When dilatation of the left ventricle is minimized or reversed by a combination of treatments, a patient's prognosis does improve. Examples of these treatments are acute reperfusion therapy (thrombolysis, percutaneous coronary intervention, or surgical bypass procedure), ACE inhibitor started during acute phase of myocardial infarction[4–7], mechanical reduction of left ventricle size by surgery[8], a passive constraint device[9], and biventricular pacing[10].

Echocardiography is the most widely used imaging technique to assess left ventricular size and volume, due to the advantages of being portable, versatile and widely available, even though radionuclide and cardiac magnetic resonance imaging are considered better methods for measurement of left ventricular volume. Despite the practical advantages of echocardiography to assess left ventricular size and volume serially in clinical trials, it has the disadvantage of being more operator dependent in acquisition and interpretation. For echocardiography to be reliable in the measurement of left ventricular volume, both acquisition of the images and data analysis should be reliable and reproducible. During the acquisition, left ventricular long axis should not be foreshortened and the endocardial border should be clearly visible. Since both apical four and two (or five) chambers are used to calculate left ventricular volume by the biplane Simpson's disc method, both views should be obtained from the same transducer position during the same cardiac rhythm with a similar long axis dimension. When left ventricular volume is measured, left ventricular endocardial and blood pool interface should be traced manually incorporating the papillary muscles and trabeculations in the cavity. It has been well appreciated that echocardiography under-estimates the left ventricular size and volume because intra-cardiac structures (trabeculation) are frequently excluded from the left ventricular cavity. This problem can be minimized by utilizing a contrast agent, but its routine use will increase the cost of echocardiography study. It is also more forgiving in volume measurement to have a large as possible left ventricular size on screen. If left ventricular size is small with a longer field-depth, more error can occur with manual tracing of the endocardial border. The field-depth should be kept the same for both apical views, otherwise the measurement scale needs to be recalibrated each time when a different view is analysed unless images are digitally stored.

Since echocardiography is heavily operator dependent, acquisition and measurement of echocardiography introduce variability and human error. Therefore, it is essential to standardize the acquisition and analysis of echocardiography for clinical trials. That is exactly the function of the Core Laboratory (Core Lab). The standardization of acquisition is accomplished by providing manual for echocardiography technique, site visits, workshop, and continuous technical feedback to clinical sites. The Core Lab has experienced research sonographers and physician echocardiographers to measure echocardiographic variables after they undergo extensive quality control process as well as assessment of inter- and intra-observer variability. The Core Lab cannot eradicate all the variabilities but can make certain that errors in acquisition and measurements are controlled and do not occur randomly, which may be the case if multiple laboratories and investigators are involved in measurements.The article by Hole and his colleagues[12] in the current issue of the *European Journal*

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of Echocardiography confirms the essential role of the Core Lab in a large clinical trial, Left Ventricular Remodelling Study (LEVEREM), conducted in 32 Norwegian hospitals[12]. Echocardiography was performed in 756 patients with acute myocardial infarction at baseline and after 3 months, from which left ventricular volume was measured using the biplane Simpson's method by local investigators and the Core Lab. The prognostic value for subsequent clinical end point was significant both for the 3-month values and the changes from baseline to 3 months measured by the Core Lab but not by local investigators. Although this study was confined to the measurement of the left ventricular volume and ejection fraction, a similar conclusion can be anticipated in measuring other two-dimensional and Doppler echocardiographic parameters for other clinical trials using the assessment of valvular regurgitation, regional wall motion analysis and diastolic function. The larger the variability of measurements, the more patient numbers are required for a clinical trial. Less variability will make the sample size for a clinical trial smaller, which is efficacious in terms of the cost and length of a trial. The patients in the study by Hole and his colleagues[12] had relatively small left ventricular size (ejection fraction $\geq$40% and the mean left ventricular end-diastolic volume was 150–160 cc), compared with other clinical trials using echocardiography and heart failure. Therefore, the small volume change from baseline to 3 months must have been very difficult to detect, which made Core Lab's measurements with less variability critical for the success of the trial. The investigators noticed that there was a worse correlation between measurements for the echocardiographic parameters made by the local investigators and the Core Lab in patients with larger ventricles. Less controlled random measurement errors by multiple local investigators, such as in tracing of the endocardial, probably amplified differences in measurements in larger ventricles. Since a smaller, less remodelled left ventricular is expected in patients who were treated with a thrombolytic therapy, it would have been interesting to analyse whether the benefit of the Core Lab was present in both groups of patients with or without thrombolysis. Is Core Lab essential in all clinical trials using echocardiography? If patient population is large, it may be feasible to use local investigators' measurements or to decentralize the readings to several Core Labs as suggested by the investigators of Val-Heft (Valsartan in Heart Failure) multicentre international randomized trial[13]. If Doppler velocity measurements are endpoints of clinical trial (as in natural history study of bicuspid aortic stenosis with or without a statin lipid-lowering agent or clinical study of evaluating a new prosthetic valve), it may be possible to utilize local investigators' readings with quality control by a Core Lab, since the variability in Doppler reading should be less than that of two-dimensional echocardiographic measurements. However, more human errors will be introduced when more individuals are involved in data measurements no matter how good they are. I fully agree with the conclusion of current study by Hole and his colleagues[12] that the use of a Core Lab is critical in multicentre studies employing echocardiographic measurements.

A Core Lab is essential in multicentre trials to minimize random errors and inter-observer variability. Understandably, however, Core Lab does make measurement errors. Even in the most experienced hands, left ventricular volume measured by echocardiography is usually smaller than actual volume. Left ventricular volume measurement is more accurate and less variable if a contrast agent is used to enhance the left ventricular endocardial border[14] when compared with volume measured by magnetic resonance imaging. Therefore, it would have been instructive to have a reference value against which left ventricular volume by the Core Lab could be compared in the current study. If better endocardial border definition by an intravenous contrast agent reduces measurement errors and variabilities, will it be possible to conduct multicentre trial without a Core Lab? A new clinical trial will provide an opportunity to address those interesting questions. STICH (Surgical Treatment in Ischaemic Heart Failure) trial is an international multicentre randomized study designed to identify the most optimal therapeutic strategy in patients with ischaemic heart failure[15]. The patients with EF $\leq$35%, coronary artery disease and heart failure will be randomized to intensive medical therapy and coronary bypass surgery with or without ventricular reduction surgery. In this trial, multiple imaging techniques will be obtained; echocardiography, nuclear imaging, and cardiac magnetic resonance imaging. A subset of patients will have a contrast enhancement of left ventricular endocardial border definition. These imaging techniques will be performed serially at the baseline, 4 months and 2 years later. The STICH trial will be able to compare the echocardiographic data with data from another reference technique.

The study by Hole and his colleagues[12] clearly demonstrated the importance of an Echocardiography Core Lab for the multicentre clinical investigation. By employing the Core Lab, we will be able to reduce the number of the patient population and the duration of the clinical trial, which will benefit patient care by being able to introduce the concept and treatment tested in the clinical trials to the patients earlier rather than later.

American Society of Echocardiography (ASE) has acknowledged this important role of echocardiography in clinical trials and the 'clinical trial writing group' in ASE is preparing a comprehensive recommendation for appropriate use of echocardiography and Echo Core Lab for clinical trials which will be published soon.

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