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Conductance, admittance, and hypertonic saline: should we take ventricular volume measurements with a grain of salt?

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UNDOUBTEDLY THE MOST COMPREHENSIVE way to assess contractile function of the heart relies on pressure-volume relationships, often called pressure-volume loops. Originally established in the canine model by Sagawa and coworkers, pressure-volume relationships allow us to determine indexes of ventricular performance that are independent of loading conditions and heart rate such as preload-recrutable stroke work (PRSW), end-systolic chamber stiffness (Ees or Emax), diastolic function (EDPVR), and load-independent contractility as derived from the dP/dt_{max} end-diastolic volume relation (2, 7). All these indexes require simultaneous recordings of left ventricular volumes and intraventricular pressures in vivo. Although more easily achievable in large animals and humans, real-time volume measurements in mouse hearts remain challenging.

With the advance of more powerful magnetic coils, the gold standard for assessing ventricular dimensions in the mouse has become magnetic resonance imaging (MRI). However, this technology is not widely available, does not allow high-throughput screening due to the associated costs, and requires steady-state conditions since data from multiple cardiac cycles are averaged. As an alternative, M-mode echocardiography is a powerful tool but yields less accurate data and is highly observer dependent. Therefore, high hopes have been placed on conductance volumetry, which allows real-time pressure and volume measurements with a single catheter placed in the left ventricle.

In 1981, Baan and coworkers developed a technique to quantify changes in ventricular volumes by exploiting the correlation between ventricular volume and electrical conductance of the blood within the ventricle (1). The conductance catheter has multiple ring electrodes mounted along its length, and an alternating current is applied to the outermost electrodes to create a local electric field (10). The field passes through the blood, muscle wall, and surrounding structures. The resistance of blood is substantially lower than that of the ventricular wall. Moreover, the resistance of the ventricular wall is assumed to be constant throughout the cardiac cycle, whereas blood resistance changes depending on the amount of blood in the ventricle. Therefore, the time-varying component of the conductance signal is thought to be predominantly due to the blood volume change within the ventricle. Unfortunately, although excellent at detecting volume changes, this approach by itself is not calibrated, making it difficult to measure absolute intraventricular volumes.

To overcome this problem, multiple approaches have been developed. For cuvette calibration, the multipolar catheter is first immersed in an artificial reservoir filled with blood. Not surprisingly, cuvette calibration is not a very reliable method to

determine ventricular volumes in vivo (6, 10). To date, aortic flow measurements to calibrate increases in signal together with hypertonic saline injections are a favored approach to correct left ventricular volumes. Injection of a small bolus of hypertonic saline causes an increase in ventricular conductance, whereas the conductance of surrounding structure remains constant. Consequently, a good estimate of the parallel conductance can be calculated. Unfortunately, due to the overall small volumes in the mouse, this method also introduces a substantial additional error (9, 14). In 2006, Jacobi and coworkers very carefully compared ventricular volumes measured with conductance catheters to MRI-derived data and found a very poor correlation between the two techniques (6). With improved calibration methods, Nielsen et al. were able to increase the reliability of catheter-derived volume estimates, but conductance-derived volumes continued to underestimate true ventricular volumes as assessed by MRI (9). Last year, Winter and coworkers compared conductance catheter measurements to MRI data in failing mouse hearts after coronary artery ligation (13). Consistent with the previous studies, they found that volumes and ejection fractions were lower when measured via conductance catheter, but group differences were evident for both groups.

Multi-frequency stimulation has been shown to improve the quality of parallel conductance estimates (4, 5), but unfortunately also not without limitations (9). Most recently, techniques based on complex admittance have been developed (8, 12). In contrast to the traditional disregard of changes in ventricular geometry and ventricular wall thickness, this new approach allows an estimate of the parallel admittance of cardiac muscle that can be used for real-time data correction. In this issue, Porterfield and coworkers (11) take dynamic changes both in the conductance of the ventricular wall and in the calibration factor α in Baan's equation over the course of the cardiac cycle into account. The basis of the admittance technique relies on a measurable phase difference due to the presence of myocardium between the input current and the output voltage, although there is no measurable phase angle in blood alone. The authors carefully compare volume measurements obtained with the complex admittance technique to cuvette-calibrated data and to measurements in the same animals calibrated using a flow probe and hypertonic saline injections. As expected, the traditional calibration methods produce data that correlate poorly with ventricular volumes obtained by echocardiography. Although still not perfectly accurate, Porterfield et al. (11) show that their approach, using admittance measurements and Wei's equation, clearly yields more realistic data than the traditional calibration techniques. The system has distinct advantages such as allowing closed chest measurements, eliminating the need for hypertonic saline injections, and yielding more reliable data even when the catheter is in an off-center position within the ventricle. This study is very much in accordance with a recent study by Clark and cowork-

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ers (3) who used a similar approach and measured larger ventricular volumes with a smaller associated standard deviation compared with traditional conductance measurements in the same animal. Importantly, Porterfield et al. demonstrate that their technique is well suited for hypertrophied hearts after aortic banding, and Clark et al. successfully use their admittance system in a myocardial infarction model, both demonstrating the validity of the approach under disease conditions.

The small size of the mouse heart together with the rapid heart rate remains a huge challenge for exact intraventricular volume measurements. The newly developed admittance-based techniques represent a very promising step forward in the field. However, even the current catheters still significantly reduce the cross-sectional area of the arteries through which they are introduced. For a 1.4-Fr catheter, this means that about one-third of the inner diameter of the aorta is taken up by the catheter, which is likely to have hemodynamic consequences (6). Unless conductance catheters can be even further miniaturized, this will remain a limitation. However, despite the inherent large error, conductance catheters offer a feasible alternative for volume measurements in the mouse heart when MRI studies are not possible and have been successfully used in numerous genetically altered mouse models. Therefore, further future advances and improvements of this technology will be eagerly awaited.

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