

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

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13 Running head: Admittance versus conductance

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36 Undoubtedly the most comprehensive way to assess contractile function of the heart relies on
37 pressure-volume relationships, often called pressure-volume loops. Originally established in the
38 canine model by Sagawa and co-workers, pressure-volume relationships allow us to determine
39 indices of ventricular performance that are independent of loading conditions and heart rate such
40 as preload-recrutable stroke work (PRSW), end-systolic chamber stiffness (Ees or Emax),
41 diastolic function (EDPVR), and load-independent contractility as derived from the dP/dtmax-
42 end-diastolic volume relation [2, 7]. All these indices require simultaneous recordings of left
43 ventricular volumes and intra-ventricular pressures *in vivo*. While more easily achievable in large
44 animals and humans, real-time volume measurements in mouse hearts remain challenging.
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46 With the advance of more powerful magnetic coils, the gold standard for assessing ventricular
47 dimensions in the mouse has become magnetic resonance imaging (MRI). However, this
48 technology is not widely available, does not allow high-throughput screening due to the
49 associated costs, and requires steady-state conditions since data from multiple cardiac cycles are
50 averaged. As an alternative, M-mode echocardiography is a powerful tool, but yields less
51 accurate data and is highly observer-dependent. Therefore, high hopes have been placed on
52 conductance volumetry, which allows real-time pressure and volume measurements with a single
53 catheter placed in the left ventricle.
54

55 In 1981, Baan and co-workers developed a technique to quantify changes in ventricular
56 volumes by exploiting the correlation between ventricular volume and electrical conductance of
57 the blood within the ventricle [1]. The conductance catheter has multiple ring electrodes mounted
58 along its length and an alternating current is applied to the outermost electrodes to create a local
59 electric field [10]. The field passes through the blood, muscle wall, and surrounding structures.
60 The resistance of blood is substantially lower than that of the ventricular wall. Moreover, the
61 resistance of the ventricular wall is assumed to be constant throughout the cardiac cycle, whereas
62 blood resistance changes depending on the amount of blood in the ventricle. Therefore, the time-
63 varying component of the conductance signal is thought to be predominantly due to the blood
64 volume change within the ventricle. Unfortunately, while excellent at detecting volume changes,
65 this approach by itself is not calibrated, making it difficult to measure absolute intra-ventricular
66 volumes.
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68 To overcome this problem, multiple approaches have been developed. For cuvette calibration,
69 the multipolar catheter is first immersed in an artificial reservoir filled with blood. Not
70 surprisingly, cuvette calibration is not a very reliable method to determine ventricular volumes *in*
71 *vivo* [6, 10]. To date, aortic flow measurements to calibrate increases in signal together with
72 hypertonic saline injections are a favored approach to correct left ventricular volumes. Injection
73 of a small bolus of hypertonic saline causes an increase in ventricular conductance while the
74 conductance of surrounding structure remains constant. Consequently, a good estimate of the
75 parallel conductance can be calculated. Unfortunately, due to the overall small volumes in the
76 mouse, this method also introduces a substantial additional error [9, 14]. In 2006, Jacobi and co-
77 workers very carefully compared ventricular volumes measured with conductance catheters to
78 MRI-derived data and found a very poor correlation between the two techniques [6]. With
79 improved calibration methods, Nielsen *et al.* were able to increase the reliability of catheter-
80 derived volume estimates, but conductance-derived volumes continued to underestimate true
81 ventricular volumes as assessed by MRI [9]. Last year, Winter and co-workers compared

82 conductance catheter measurements to MRI data in failing mouse hearts after coronary artery
83 ligation [13]. Consistent with the previous studies, they found that volumes and ejection fractions
84 were lower when measured via conductance catheter, but group differences were evident for both
85 groups.

86
87 Multi-frequency stimulation has been shown to improve the quality of parallel conductance
88 estimates [4, 5], but unfortunately also not without limitations [9]. Most recently, techniques
89 based on complex admittance have been developed [8, 12]. In contrast to the traditional disregard
90 of changes in ventricular geometry and ventricular wall thickness, this new approach allows an
91 estimate of the parallel admittance of cardiac muscle that can be used for real-time data
92 correction. In this issue, Porterfield and co-workers [11] take dynamic changes both in the
93 conductance of the ventricular wall and in the calibration factor alpha in Baan's equation over
94 the course of the cardiac cycle into account. The basis of the admittance technique relies on a
95 measurable phase difference due to the presence of myocardium between the input current and
96 the output voltage, while there is no measurable phase angle in blood alone. The authors
97 carefully compare volume measurements obtained with the complex admittance technique to
98 cuvette calibrated data and to measurements in the same animals calibrated using a flow probe
99 and hypertonic saline injections. As expected, the traditional calibration methods produce data
100 that correlate poorly with ventricular volumes obtained by echocardiography. While still not
101 perfectly accurate, Porterfield *et al.* [11] show that with their approach using admittance
102 measurements and Wei's equation clearly yields more realistic data than the traditional
103 calibration techniques. The system has distinct advantages such as allowing closed chest
104 measurements, eliminating the need for hypertonic saline injections, and yielding more reliable
105 data even when the catheter is in an off-center position within the ventricle. This study is very
106 much in accordance with a recent study by Clark and co-workers [3] who used a similar
107 approach and measured larger ventricular volumes with a smaller associated standard deviation
108 compared to traditional conductance measurements in the same animal. Importantly, Porterfield
109 *et al.* demonstrate that their technique is well suited for hypertrophied hearts after aortic banding,
110 and Clark *et al.* successfully use their admittance system in a myocardial infarction model, both
111 demonstrating the validity of the approach under disease conditions.

112
113 The small size of the mouse heart together with the rapid heart rate remains a huge challenge
114 for exact intra-ventricular volume measurements. The newly developed admittance-based
115 techniques represent a very promising step forward in the field. However, even the current
116 catheters still significantly reduce the cross-sectional area of the arteries through which they are
117 introduced. For a 1.4 F catheter, this means that about one third of the inner diameter of the aorta
118 is taken up by the catheter, which is likely to have hemodynamic consequences [6]. Unless
119 conductance catheters can be even further miniaturized, this will remain a limitation. However,
120 despite the inherent large error, conductance catheters offer a feasible alternative for volume
121 measurements in the mouse heart when MRI studies are not possible and have been successfully
122 used in numerous genetically altered mouse models. Therefore, further future advances and
123 improvements of this technology will be eagerly awaited.

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