A Flow Measurement Guide
for Industry Bioengineers

PRESSURE VOLUME LOOP TECHNOLOGY

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Pressure Volume Cardiac Function Measurements for Pre-clinical R & D Studies and Validations

Pressure Volume (PV) Loops

Scientists have historically relied on systemic blood pressure, blood flow, and ventricular pressure to report changes in heart performance. These are all important parameters, but only inform about part of the picture of heart performance. PV Loops provide a range of hemodynamic parameters which are not readily measurable by other methods. These include changes in contractility, elastance, power, energetics and efficiency.

What is even more powerful about PV loops is that they provide quantitative measurements of parameters, not just qualitative results. This makes PV loops the single most comprehensive measurement of hemodynamics and cardiac function available.

There are three main areas of cardiovascular assessment where PV loops provide the ideal measurement approach:

1. To measure the heart's contractile parameter of interest including ESPVR and EDPVR.
2. For a comprehensive analysis of cardiac function, such as for phenotyping.
3. When the parameter of greatest interest is unknown during drug or genetic studies.

How Pressure Volume Loops Look

The mechanical events occurring during the cardiac cycle consist of changes in pressure in the ventricular chamber which cause blood to move in and out of the ventricle. It is therefore advantageous to display left ventricular pressure (LVP) as a function of left ventricular volume (LVV) to show the relationship between intraventricular pressure and volume throughout the cardiac cycle. This is achieved by plotting the volume on the x-axis and pressure on the y-axis simultaneously (see figure on next page). The resulting plot of pressure versus volume for one cardiac cycle forms a pressure-volume loop (PV loop).

As a heart beats, the PV points move around the loop in a counter clockwise direction. The point of maximal volume and minimal pressure (i.e., the bottom right corner of the loop) corresponds to the onset of systole. During the first part of the cycle, pressure rises but volume stays the same (isovolumic contraction). Ultimately, LVP rises above aortic pressure (AoP), the aortic valve opens (B), ejection begins and volume starts to drop.

Although AoP is not explicitly plotted, several features of AoP are readily obtained from the PV loop. After the ventricle reaches its maximum activated state (C, upper left corner of PV loop), LVP falls below AoP, the aortic valve closes and isovolumic relaxation commences. Finally, filling begins with mitral valve opening (D, bottom left corner).

PV loops provide values of several parameters and variables of physiologic importance: the maximum or end-diastolic volume (EDV) volume of the cardiac cycle; the minimum end-systolic volume (ESV) ventricular volume at the end of the ejection phase. The difference between EDV and ESV is the stroke volume (SV) or the amount of blood ejected during the cardiac cycle.

On the pressure axis, near the top of the loop is the point at which the ventricle begins to eject (ventricular pressure just exceeds aortic pressure and volume starts to decrease). This diastolic blood pressure (DBP) reflects the pressure existing in the aorta at the onset of ejection.

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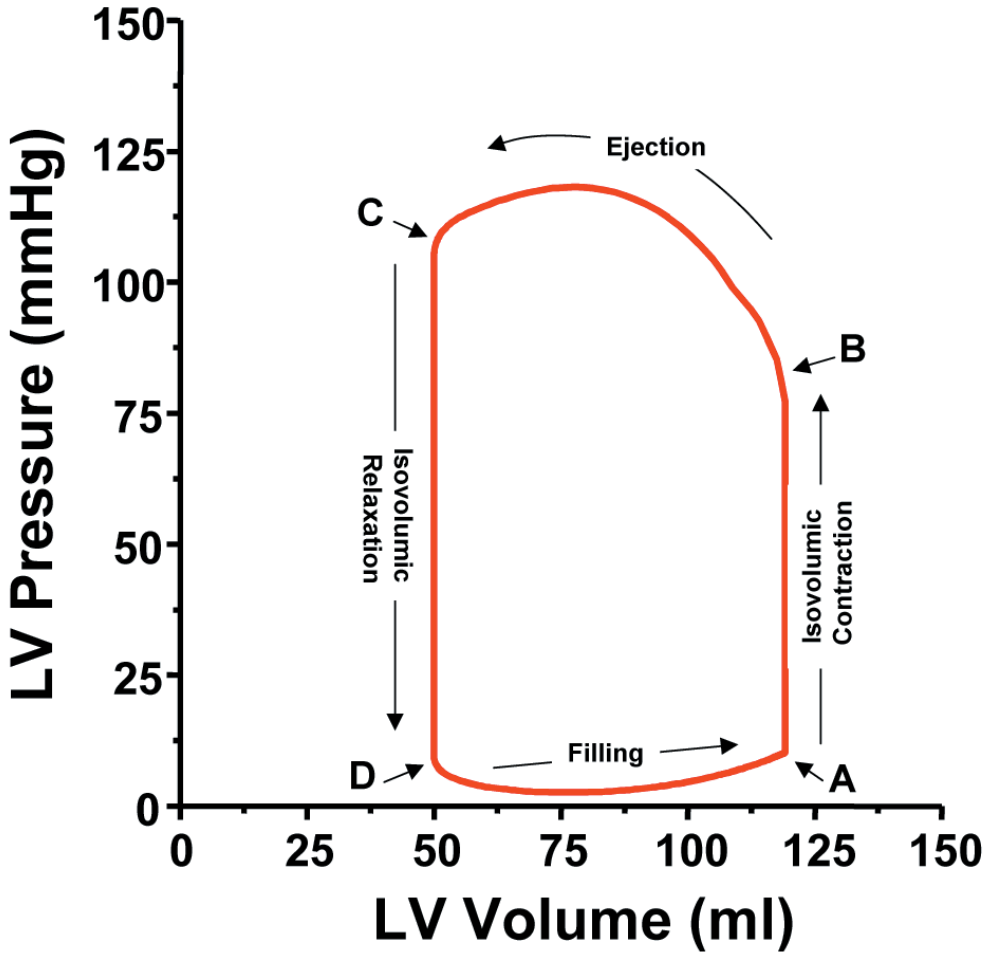
During the ejection phase, aortic and ventricular pressures are essentially equal; therefore, the point of greatest pressure on the loop also represents the greatest pressure in the aorta, and this is called the systolic blood pressure (SBP). One additional pressure, the endsystolic pressure (Pes) is identified as the pressure of the left upper corner of the loop; At the bottom of the loop, the pressure of the left lower corner (the point at which the mitral valve opens and ejection begins) is roughly equal to the pressure existing in the left atrium (LAP) at that point in time. The pressure of the point at the bottom right corner of the loop is the pressure in the ventricle at the end of the cardiac cycle (end-diastolic pressure or EDP).



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Conductance: Theory of Operation

Deriving ventricular volume from a Conductance Catheter is based on Ohm's Law:

Voltage (V) = Current (I) X Resistance (R) V = IR

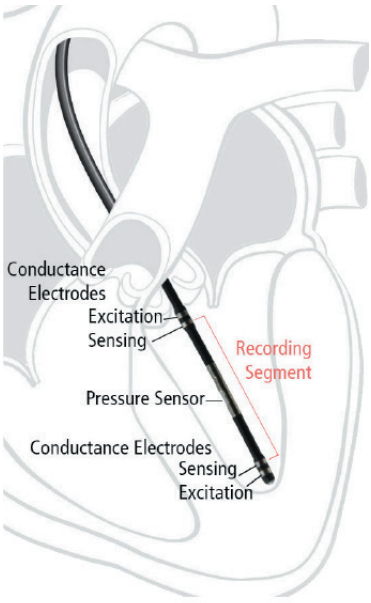
Conductance (G) rather than resistance is the parameter of interest. Since conductance is the inverse of resistance, Ohm's Law can be rewritten as:

Voltage = Current/Conductance V = I/G

Conductance Catheters are comprised of both excitation electrodes and recording electrodes. The excitation electrodes (most distal and proximal electrodes on the Catheter) generate an electrical field inside the heart from the aortic valve to the apex. This field is generated as a result of an alternating current being applied (at a constant magnitude) between these 2 outermost electrodes. The inner recording electrodes measure voltage change which is proportional to a change in resistance.

The electrical field cannot be restricted to just the blood volume and must pass through some of the cardiac muscle. This means that the measured conductance value (Gx) is actually a combination of blood conductance (Gb) and muscle or parallel conductance (Gp).

In 1981, Dr. Baan et. al. proposed a relationship between time-varying measurements of total conductance (Gx) to time-varying changes in ventricular volume (Vol) (1). This volume formula takes into account the distance between the recording electrodes (L), blood resistivity, and the parallel conductance (Gp). It also takes into account the non-uniform nature of the electrical field with the field correction factor, alpha. Alpha is considered an estimate of the slope between conductance derived volume and true volume. Dr. Baan assumed alpha to be 1, as he used stacked cylinder model for LV. Later he reassessed the LV model changing from a stacked cylinder into a spheroid and used 0.69 for alpha. Recently published alpha values have ranged from 0.5 to 1.01, where the alpha of 0.5 is reported in larger mammals and alpha 1.01 comes from rodent PV research studies. Moreover, if the PV Catheter is positioned off-center in the LV, report-



WEI'S EQUATIONS

$$Vol = \frac{1}{(1-\frac{G_b}{\gamma})}\rho L^2(G_b)$$

ρ = Blood resistivity

L = Measuring electrode distance

G_b = Measured blood conductance

SV = Stroke volume

Field Correction Factor:

$$\gamma = \frac{-b \pm \sqrt{b^2-4ac}}{2a}$$

$$a = SV - \rho L^2(G_{b-ED} - G_{b-ES})$$

$$b = -SV \cdot (G_{b-ED} + G_{b-ES})$$

$$c = SV \cdot G_{b-ED} \cdot G_{b-ES}$$

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ed alpha ranges from 0.07 to 0.37 in mice.

This approach assumes alpha to be a constant with a single value for a uniform current field distribution (in reality electrical field strength decreases non-linearly with distance). Alpha can be calculated from the SV conductance ratio or by cuvette calibration. Both of these methods give a single constant value for alpha. Parallel or muscle conductance (Gp) is often determined by hypertonic saline injection which temporarily changes blood conductance but not myocardial conductance, allowing for the parallel conductance value to be determined from the graph of changing conductance. This produces a single constant value for parallel conductance.

Impact of Physiology on Conductance Measurements

At systole there is relatively little blood in the ventricle which means that a larger portion of the electrical field passes through the myocardium. Thus, myocardial resistance contributes more to the total measured conductance than blood at this time. However, because the hypertonic saline bolus method provides an average measurement of muscle contribution, it is typical for the derived volume to be overestimated at systole.

At diastole there is a large quantity of blood in the ventricle and the heart walls have expanded. This means that most of the electrical field is passing though blood with a very small contribution from the myocardium. Thus, the measured conductance value is almost entirely blood conductance. However, the same value of parallel conductance is still subtracted from the total conductance which leads to an under estimation of blood volume.

The electrical field strength decreases in a non-linear manner with increasing field size. This means measurements of blood conductance further from the Catheter do not have the same strength as those nearer to the Catheter. Without correction this leads to an under estimation of total volume. The larger the volume which is being measured, the greater the under estimation. Volume measurements at diastole are thus more prone to under estimation than those at systole. Alpha attempts to correct some of this error but fails to address the non-linearity of the electric field or the varying strength the under estimation has at different phases of the heart cycle.

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Admittance Theory of Operation

Admittance technique is an extension of the Conductance method which measures both resistive and capacitive properties of blood and muscle. In the electric field blood is purely resistive, but muscle has both capacitive and resistive properties. This allows separation of the muscle component of conductance from that of blood, using electric field theory.

The capacitive property of muscle causes a time (phase) delay in measured signal (see graph at bottom right). By tracking this delay known as the phase angle in real time and mathematically relating it to the resistance of the myocardial tissue, the ADV500 System allows continuous, non-invasive tracking of muscle/parallel conductance (Gm) throughout the heartbeat. The phase angle reports heart tissue intrusion into the field as the heart contracts and expands, and as expected, this measurement is greatest at systole and lowest at diastole. This provides a great advantage over classical conductance volumetry which treats parallel conductance as a constant, rather than a dynamic variable which changes throughout the cardiac cycle.

The ADV500 system employs an equation developed by Dr. Chia-Ling Wei to convert conductance to volume instead of the traditional Baan's equation. In Baan's equation the Field Correction Factor, alpha ( ), is assumed to be constant despite the non-linear nature of the electrical field . However, Wei's equation corrects for the nonhomogeneous nature of the Catheter's electrical field distribution by assuming a non-linear relationship between conductance and volume, thus improving accuracy over a wider volume range.

To measure blood volume in real time, values are needed for myocardial conductivity and permittivity, blood resistivity, and reference stroke volume. Default values for 'Heart Type' (S/E ratio) are provided and most commonly used. However, researchers can study this value using a tetrapolar surface probe provided with the ADV500. Stroke volume can be measured via other technologies.

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Admittance Volume: The New Gold Standard

While cardiac pressure volume (PV) loops are now considered to be the gold standard in cardiac function assessment and are used to determine myocardial contractility, compliance, muscle energetic and other important quantitative measures of function, Transonic Scisense PV Catheter technology has emerged as the most reliable research method to generate real-time ventricular PV loops in the intact heart.

Now, as a result of recent advancements in the field through the use of "admittance" instead of the older "conductance" technology, Transonic Scisense PV Catheters incorporate the latest admittance technology and high fidelity pressure sensors to meet the stringent demands of cardiovascular research.

PV loops provide the ideal measurements:
1. When contractile parameters including ESPVR and EDPVR need to be measured.
2. When a comprehensive analysis of cardiac function is needed.
3. When the parameter of greatest interest is elusive during drug or genetic studies.

Transonic Scisense Catheters provide the unique ability to measure almost every imaginable hemodynamic and contractile index of ventricular function with a single instrument. Rodent Pressure Volume Catheters are specifically designed for use with mice and rat sized ventricles. These minimally invasive Catheters are available with a range of volume electrode spacings to fit any rodent ventricle size. Variable Segment Length Catheters are also available for even more flexibility in matching ventricle sizes. Transonic Scisense Pressure Volume Catheters for large animals range in size from 3.5F to 7.0F to span the entire range of heart sizes from rabbits to cows. Variable Segment Length Catheters provide excellent flexibility in matching ventricle sizes. All 7.0F Catheters are available with an optional lumen to allow drug administration, blood sampling or guide wire insertion.

Catheters are used with the ADVantage Pressure-Volume System, a significant technical advancement in the field of animal cardiac function research. It is the only catheter-based system to accurately quantify true ventricular volume in real time using admittance technology. The ADVantage system Phase signal provides real time feedback about Catheter position to ensure quality measurements from every procedure.