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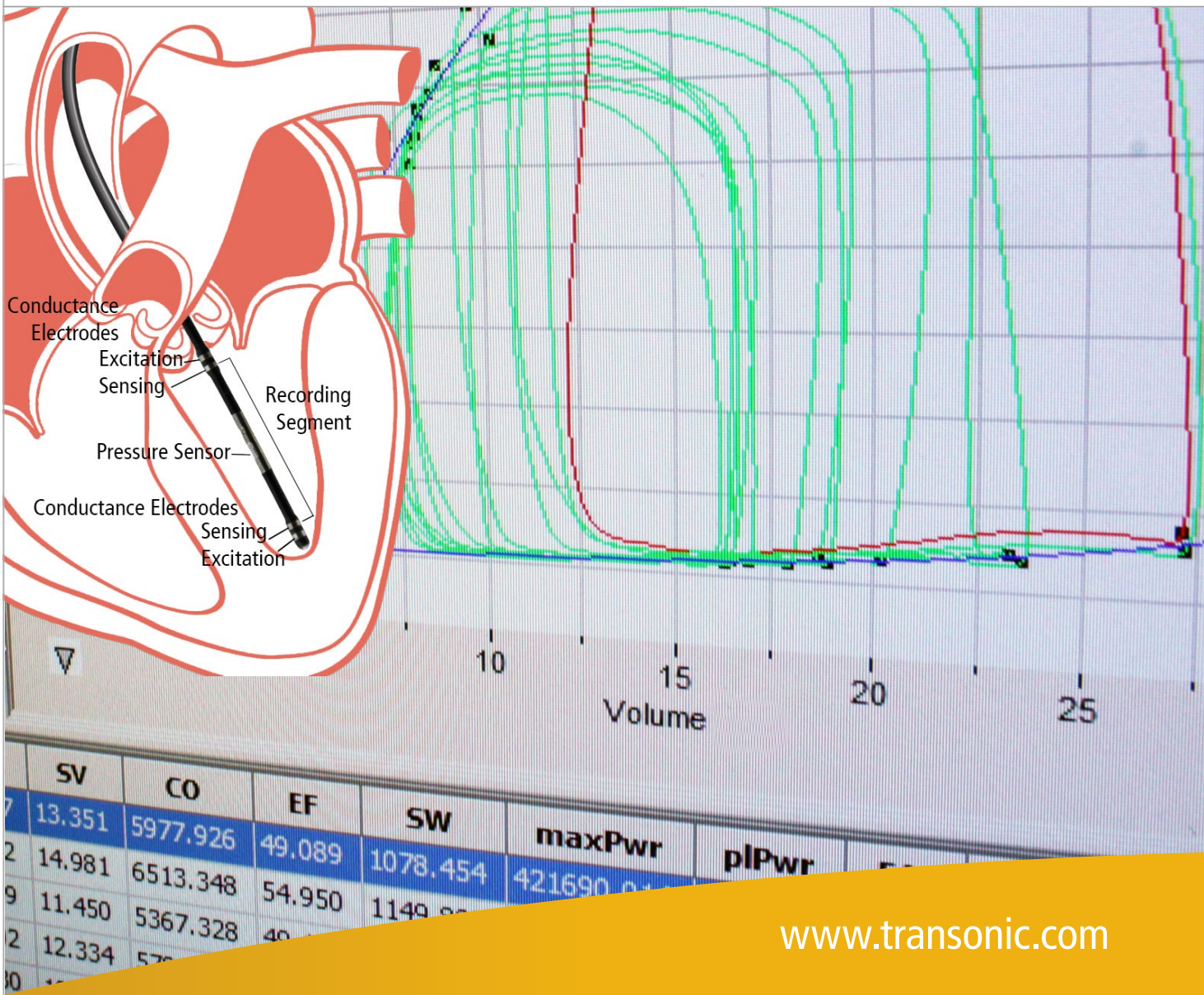
THE MEASURE OF BETTER RESULTS.

Understanding PV Loops: Technology & Theory



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Introduction: Why Study PV Loops?

"Physiologists, and in particular physician physiologists, have often fallen into the trap of measuring certain cardiovascular parameters to explain cardiac performance because they could be measured, rather than because they should be measured."

William J. Mazzei, M.D. 1998

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 form part of the picture of heart performance. Pressure-Volume (PV) loops provide a range of hemodynamic parameters which are not readily measurable by other methods; including 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. When it is the best method to measure the contractile parameter of interest including ESPVR and EDPVR.
2. When a comprehensive analysis of cardiac function is needed, such as for phenotyping.
3. When the parameter of greatest interest is unknown during drug or genetic studies.

EXAMPLES OF CARDIOVASCULAR PATHOLOGY THAT CAN BE EXAMINED BY PV LOOPS

- Myocardial Infarction
- Dilated (Diabetic) Cardiomyopathy
- Left Ventricular Hypertrophy
- Right Ventricular Hypertrophy
- Restrictive Cardiomyopathy
- Aortic Valve Stenosis
- Mitral Valve Stenosis
- Aortic Regurgitation (Aortic Insufficiency)
- Mitral Regurgitation
- Right Ventricular Function and Pulmonary Hypertension

All About Contractility

The single greatest advantage of PV loops is the ability to determine the contractility of the heart independent of preload and afterload. By an occlusion procedure (typically the inferior vena cava) a series of pressure-volume loops are created which can be analyzed for a multitude of load independent parameters which are unavailable from other hemodynamic measurement techniques such as echocardiography, MRI and cardiac CT.

PV LOOP MEASUREMENTS

VARIABLE	DESCRIPTION
ESP	End-Systolic Pressure
EDP	End-Diastolic Pressure
ESV	End-Systolic Volume
EDV	End-Diastolic Volume
HR	Heart Rate
Max dP/dt	Maximum Derivative of Pressure
Min dP/dt	Minimum Derivative of Pressure
Max dV/dt	Maximum Derivative of Volume
Min dV/dt	Minimum Derivative of Volume
CO	Cardiac Output
EF%	Ejection Fraction
SV	Stroke Volume
SW	Stroke Work
Ea	Arterial Elastance
maxPwr	Maximum Power
plPwr	Preload Adjusted Power
Eff	Efficiency
PE	Potential Energy
PVA	Pressure-Volume Area
ESPVR	End-Systolic PV Relationship
EDPVR	End-Diastolic PV Relationship
PRSW	Preload Recruitable Stroke Work
E(t)	Time-Varying Elastance
Tau	Isovolumic Relaxation Constant

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Glossary of Pressure-Volume Terms

AFTERLOAD

Afterload is the mean tension produced by a chamber of the heart in order to contract. It can also be considered as the 'load' that the heart must eject blood against. Afterload is therefore a consequence of aortic large vessel compliance, wave reflection and small vessel resistance (LV afterload) or similar pulmonary artery parameters (RV afterload).

ARTERIAL ELASTANCE (Ea)

This is a measure of arterial load and its impact on the ventricle. Calculated as the simple ratio of ventricular end-systolic pressure to stroke volume.

CARDIAC CONTRACTILITY

The intrinsic ability of the heart to contract independent of preload and afterload. On a cellular level it can be characterized as the change of developed tension at given resting fiber length. Used interchangeably with Cardiac Inotropy.

CARDIAC INOTROPY

The ability of the heart muscle to generate force through contraction. Used interchangeably with Cardiac Contractility.

CARDIAC OUTPUT (CO)

Cardiac output is defined as the amount of blood pumped by the ventricle in unit time.

COUPLING RATIO

Indication of transfer of power from the ventricle to the peripheral vasculature.

DERIVATIVE OF PRESSURE (dP/dt)

Reported as max and min rate of pressure change in the ventricle. dP/dt are dependent on load and heart rate. LV dP/dt max occurs before aortic valve closure.

DERIVATIVE OF VOLUME (dV/dt)

Rate of volume change in the ventricle. Maximum and minimum values of dV/dt are normally reported.

EJECTION FRACTION (EF%)

Ejection fraction is the ratio of the volume of blood ejected from the ventricle per beat (stroke volume) to the volume of blood in that ventricle at the end of diastole. It is widely clinically misunderstood as an index of contractility, but it is a load dependent parameter. Healthy ventricles typically have ejection fractions greater than 55%.

E-MAX

Maximum point in the pressure-volume relationship occurring at the end of systole. E-max is directly related to the contractile state of the ventricle chamber. This number is different for each individual heart beat, representing the maximal systolic elastance (E-max) at that moment in time.

END-DIASTOLIC PRESSURE (EDP)

Pressure in the ventricle at the end of diastole.

END-DIASTOLIC PRESSURE VOLUME RELATIONSHIP (EDPVR)

The EDPVR describes the passive filling curve for the ventricle and thus the passive properties of the myocardium. The slope of the EDPVR at any point along this curve is the reciprocal of ventricular compliance (or ventricular stiffness).

END-DIASTOLIC VOLUME (EDV)

Volume in the ventricle at the end of diastole.

END SYSTOLIC ELASTANCE (Ees)

Slope of the end systolic pressure volume relationship.

END-SYSTOLIC PRESSURE (ESP)

Pressure in the ventricle at the end of systole.

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Glossary of Pressure-Volume Terms Cont.

END-SYSTOLIC PRESSURE VOLUME RELATIONSHIP (ESPVR)

The ESPVR describes the maximal pressure that can be developed by the ventricle at any given cardiac chamber volume. This implies that the PV loop cannot cross over the line defining ESPVR for any given contractile state.

END-SYSTOLIC VOLUME (ESV)

Volume in the ventricle at the end of systole.

E(T)

Time Varying volume elastance provides means to discriminate end systole from the end of ejection as they might not happen at the same time. Normal LV ejects every shortly after end systole.

EXCITATION-CONTRACTION COUPLING

The cellular relationship between electrical stimulus and contraction which is primarily influenced by Na^+, K^+ and Ca^{2+} ions and the neural, hormonal and exogenous agents which influence their behavior in the cell.

FRANKLIN-STARLING CURVE

"The heart will pump what it receives"-Starling's law of the heart

SV vs EDP: Afterload dependent measure of inotropy where an increase in inotropy shifts the curve up and to the left; a decrease in inotropy shifts the curve down and to the right.

HEART RATE (HR)

Number of times the heart beats per minute.

ISOVOLUMIC RELAXATION CONSTANT (TAU)

Tau represents the exponential decay of the ventricular pressure during isovolumic relaxation. Several studies have shown that Tau is a preload independent measure of isovolumic relaxation.

LUSITROPY

The relaxation properties of the heart during the diastolic phase.

MYOCARDIAL OXYGEN CONSUMPTION (MVO_2)

Amount of oxygen consumed by the heart as a measure of energy consumption. MVO_2 is dependently correlated with cardiac total mechanical energy (TME).

POTENTIAL ENERGY (PE)

Elastic potential energy of the heart is defined by the area between the ESPVR and EDPVR curves to the left of the PV loop. PE = ESP(ESV-V0)/2 -EDP(EDV-V0)/4 where V0 is the theoretical volume when no pressure is generated.

PRELOAD

Preload is described as the stretching of a single cardiac myocyte immediately prior to contraction and is, therefore, related to the sarcomere length. Since sarcomere length cannot be determined in the intact heart, other indices of preload such as ventricular end diastolic volume or pressure are used.

PRELOAD RECRUITABLE STROKE WORK (PRSW)

PRSW is determined by the linear regression of stroke work with the end diastolic volume. The slope of the PRSW relationship is a highly linear index of myocardial contractility that is insensitive to preload and afterload.

PRESSURE-VOLUME AREA (PVA)

The PVA represents the total mechanical energy (TME) generated by ventricular contraction. This is equal to the sum of the stroke work (SW), encompassed within the PV loop, and the elastic potential energy (PE).

PRESSURE-VOLUME LOOP (PV LOOP)

Graph of pressure (y-axis) and volume (x-axis) of a ventricle over a single cardiac cycle. Several loops are often shown superimposed upon one another.

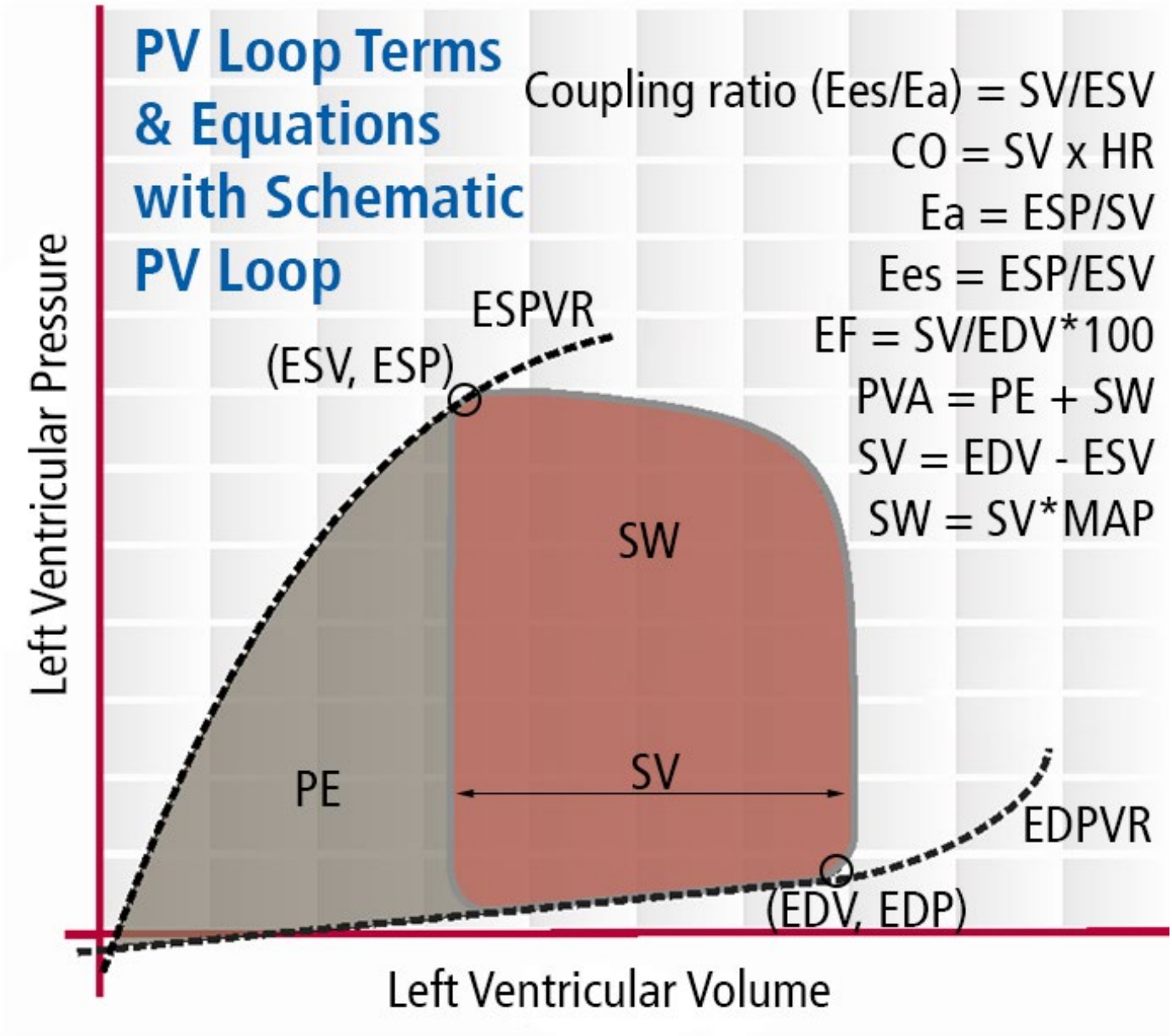
Glossary of Pressure-Volume Terms Cont.

STROKE VOLUME (SV)

Stroke volume is the volume of blood ejected by a ventricle in a single contraction. It is the difference between the end diastolic volume (EDV) and the end systolic volume (ESV).

STROKE WORK (SW)

Ventricular stroke work is defined as the work performed by the left or right ventricle to eject the stroke volume into the aorta or pulmonary artery, respectively. The area enclosed by the PV loop is an estimation of the ventricular stroke work.



Pressure-Volume Conductance Theory of Operation

Deriving ventricular volume from a Conductance Catheter is based on a very simple electrical principle: 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 (G_x) is actually a combination of blood conductance (G_b) and muscle or parallel conductance (G_p).

In 1981, Dr. Baan *et. al.* proposed a relationship between time-varying measurements of total conductance (G_x) to time-varying changes in ventricular volume (Vol) (1). This volume formula takes into account the distance between the recording electrodes (L), blood resistivity (ρ), and the parallel conductance (G_p). It also takes into account the non-uniform nature of the electrical field with the field correction factor, alpha (α).

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 (2).

BAAN'S EQUATION

$$Vol = \frac{1}{\alpha}\rho L^2(G_x - G_p)$$

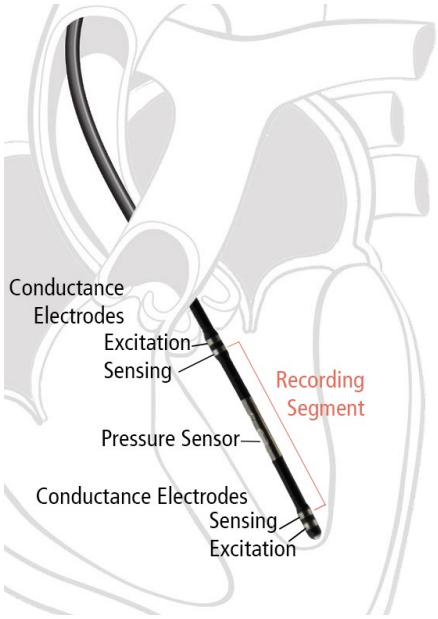
ρ = Blood resistivity

L = Measuring electrode distance

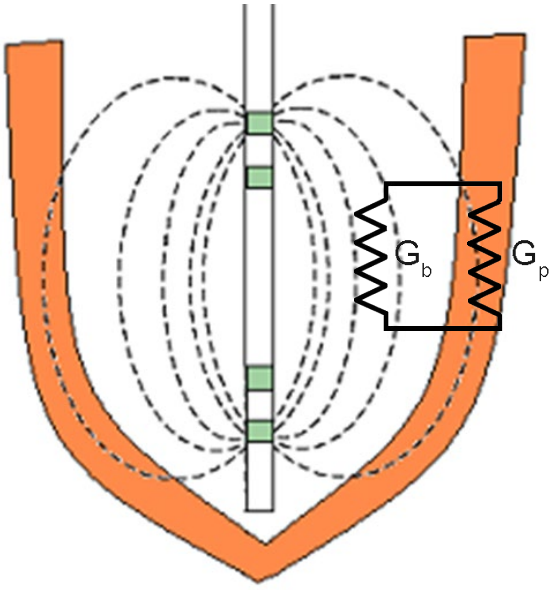
α = Baan's SV correction factor = $(\frac{SV_{conductance}}{SV_{reference}})$

G_x = Measured total conductance

G_p = Baan's parallel/muscle conductance (assumed to be negated by hypertonic saline injection)



Conductance excitation electrodes create an electric field while sensing electrodes measure the voltage change, which allows for the calculation of resistance and conductance.



Conductance uses a circuit model where both blood (G_b) and cardiac muscle (G_m) are conductive and measured together as a single conductance value (G_x) and phase components are ignored.

Pressure-Volume Conductance Theory of Operation Cont.

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 (3). Moreover, if the PV Catheter is positioned off-center in the LV, reported alpha ranges from 0.07 to 0.37 in mice (3). For more in depth discussion about alpha, please see article by Steendijk *et. al.* (4).

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 (see previous page) or by cuvette calibration. Both of these methods give a single constant value for alpha. Parallel or muscle conductance (G_p) 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.

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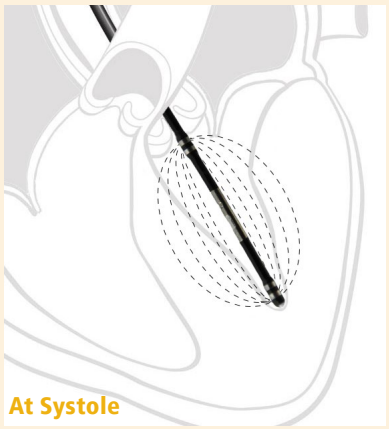
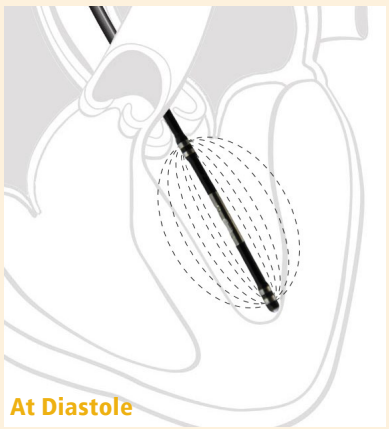
IMPACT OF PHYSIOLOGY ON CONDUCTANCE MEASUREMENTS

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.


At Systole


At Diastole

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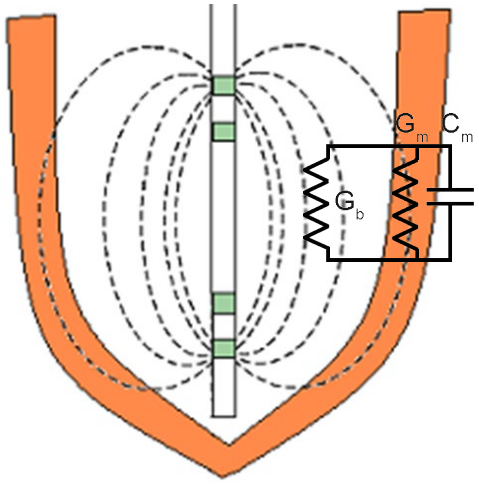
Pressure-Volume Admittance Theory of Operation

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.

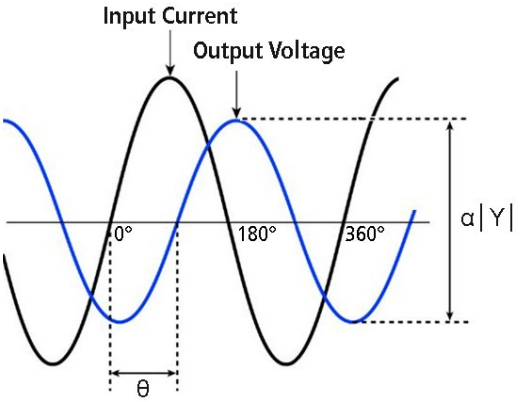
The capacitive property of muscle causes a time (phase) delay in measured signal (see graph at bottom right). By tracking this delay known as the phase angle in real time and mathematically relating it to the resistance of the myocardial tissue, the ADV500 System allows continuous, non-invasive tracking of muscle/parallel conductance (G_m) throughout the heartbeat (1). 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 (α), is assumed to be constant despite the non-linear nature of the electrical field (2). 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, gamma (γ), thus improving accuracy over a wider volume range.

To measure blood volume in real time values are needed for myocardial conductivity and permittivity (for σ/ε ratio/heart type), blood resistivity (ρ), and reference stroke volume (SV). Default values for 'Heart Type' (S/E ratio) are provided and most commonly used (3). However, researchers can study this value using a tetrapolar surface probe provided with the ADV500. Stroke volume can be measured via other technologies.



Admittance uses a circuit model where blood is conductive (G_b) and cardiac muscle is both conductive (G_m) and capacitive (C_m).



The output voltage shows a "delay" compared to the input voltage signal used to generate the electric field. The signal delay, caused by myocardial capacitance, is measured in terms of degrees and is referred to as "Phase angle θ." The admittance magnitude (conductance) is impacted by both the blood and muscle.

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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(2) Wei CL, et. al. "Nonlinear conductance-volume relationship for murine conductance catheter measurement system." IEEE Trans Biomed Eng 2005. 52:1654-61.

(3) Raghavan K, et. al. "Electrical conductivity and permittivity of murine myocardium." IEEE Trans Biomed Eng. 2009. 56:2044-53.

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Comparing Conductance vs Admittance

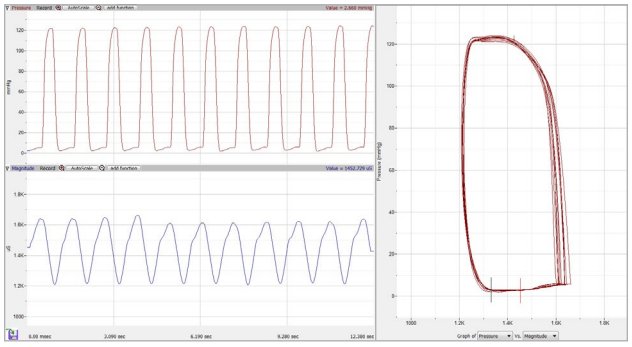
The Scisense ADV500 Pressure-Volume System is capable of being used in either Conductance or Admittance mode. Both methods have value depending on what the researcher is looking to observe.

Conductance

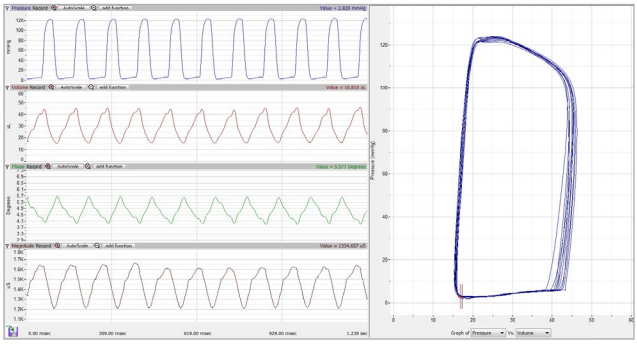
- Measures voltage magnitude
  - Harder to determine position of Catheter in ventricle
- Uses Baan's equation to determine volume
- Parallel conductance (G_p) is assumed constant
  - Parallel conductance determined from hypertonic saline injection after the experiment
- Field Correction Factor is assumed constant (alpha)
  - Requires empirical reference stroke volume to derive α or an approximation (typically 1) can be used
- Volume calculation is done post experiment with no chance to correct for protocol or surgical errors.
- Tends to overestimate volume due to constant nature of α as observed with echocardiography.
- Traditional technique with a solid body of papers that validate the basic principle of conductance catheter volumetry.

Admittance

- Measures voltage magnitude and phase angle
  - Phase angle useful in locating Catheter in ventricle
- Uses Wei's equation to determine volume
- Muscle conductance (G_m) varies throughout cardiac cycle
  - Parallel conductance determined from phase shift in real-time (no hypertonic saline injection required)
  - Requires sigma/epsilon ratio (conductivity/ permittivity) of heart muscle. Default values are commonly used, or can be measured using tetrapolar Calibration Probe.
- Field Correction Factor is non-linear (gamma)
  - Requires empirical reference stroke volume to derive gamma (γ)
- Volume calculation is in real time. Corrections to experimental protocol or surgery can be made before experiment is concluded.
- Closer approximation to absolute systolic and diastolic volume as observed with echocardiography.
- Innovative technology that builds directly on the foundation of conductance catheter volumetry.



Conductance method measures pressure and magnitude in real-time, creating pressure-magnitude loops. Volume can only be calculated post-experiment.



Admittance method measures pressure, volume, phase and magnitude in real-time, creating pressure-volume loops.

Cardiac Volume Measurement Methods

Determining the ideal volume measurement technique for heart hemodynamic studies

There are a variety of techniques which can be used to determine common hemodynamic parameters in the research setting. Choosing the best method requires careful consideration of both the technology and the experimental protocol. Four well-established cardiac volume measurement techniques (echocardiography, pressure-volume catheterization, computer tomography (CT) and cardiac magnetic resonance (CMR)) are compared below. Advantages of the Pressure-Volume Catheter method include the relatively low start-up and maintenance costs, and the ability to measure both load dependent and load independent parameters, including contractility.

PRESSURE-VOLUME CATHETER TECHNOLOGY...

- does not use radiation
- no need for a special technician
- high temporal resolution
- good data reproducibility
- low maintenance cost
- low initial price for the system
- no need for ECG gating
- very good volume data reproducibility

	ECHOCARDIOGRAPHY (TRANSTHORACIC)	PV CATHETER (ADMITTANCE)	CARDIAC COMPUTER TOMOGRAPHY (CT)	CARDIAC MAGNETIC RESONANCE (CMR)
REQUIRED HARDWARE	Echo unit & probes	PV unit & catheters	Sectional X-ray for computer reconstruction	Common CMR magnets (6.3-7 Tesla)
SPECIALIZED TECHNICIAN	Often, but not always	No	Yes in most US states	Yes in most US states
PORTABILITY	Unit on wheels	Light & portable	Heavy & stationary	Not portable
MEASUREMENT TECHNOLOGY	Sound waves	Admittance via tetra-polar catheter	Radiation transmission through tissue	Magnetic properties of tissue
USE OF RADIATION	No	No	Ionizing radiation	No
SPECIFICALLY DESIGNED CRADLES FOR ANIMALS	No	No	Yes	Yes
EXAMINATION TIME	5 - 10 min	30 min	20 - 30 min	1 - 3 hrs
USE IN PUBLICATIONS	Very common	Increasingly common	Common	Moderately common
SPATIAL RESOLUTION (AXIAL, LATERAL)	50 μm^2 (2D echo)	Not applicable	100 μm^3 (3D microCT)	200-300 μm^2 (in plane); 1 mm thick
TEMPORAL RESOLUTION	Low	Very high, captures live transient events	Low	High
CONTRAST RESOLUTION	Limited	Not applicable	High	Very high
SIGNAL TO NOISE RATIO	Acceptable	Acceptable	High	Acceptable
COMMON ARTIFACTS (STREAKS & BLUR)	Caused by breathing (need synchronization) can be limited by cardiac gating	Caused by breathing, can be controlled by a ventilator	Caused by breathing (need synchronization), can be limited by cardiac gating	Caused by breathing (need synchronization), can be limited by cardiac gating
MODEL-BASED ESTIMATION (GEOMETRIC)	Volumetry relies on geometric assumptions	PV system corrects geometric assumptions live	Volumetry relies on geometric assumptions	Volumetry relies on geometric assumptions

Cardiac Volume Measurement Methods Cont.

	ECHOCARDIOGRAPHY (TRANSTHORACIC)	PV CATHETER (ADMITTANCE)	CARDIAC COMPUTER TOMOGRAPHY (CT)	CARDIAC MAGNETIC RESONANCE (CMR)
REPRODUCIBILITY OF VOLUME DATA	Good	Good	Poor	Poor
REAL TIME/ POST PROCESSING	Volume calculations are based on geometric formulas. Need post-processing	Volume calculations are done in Real-Time. DO NOT need post processing	Volume calculations are based on geometric formulas. Need post processing	Volume calculations are based on geometric formulas. Need post processing
ECG GATING	Reconstruction of images based on gating	Not necessary to use cardiac gating	Reconstruction of images based on gating	Limited by cardiac ECG triggering, respiratory gating
RESPIRATORY GATING	Compulsory	Optional	Compulsory	Compulsory
INTER-USER VARIABILITY	High	Very Low	High	High
VERSATILITY/ OTHER INFORMATION FROM SCAN	Real-time, increases with use of Doppler or 3D echo	Collects multiple parameters (ESPVR, EDPVR, PVA, PRSW, Et, Ea, dp/dt min/ max)	Quantitative measure of tissue density can be used to examine myocardial viability. Ability to produce 3D	High tissue contrast, No contrast agent necessary, ability to acquire 3D
ACCURACY OF VOLUME ESTIMATE	Usually over estimates EDV based on histomorphometry	Usually good EDV estimation based on histomorphometry	Usually over estimates EDV based on histomorphometry	Usually over estimates EDV based on histomorphometry
CONTRACTILITY	Basic (EF%, FS%); load dependent	Excellent with IVC occlusion; load independent	Basic (EF%, FS%); load dependent	Basic (EF%, FS%); load dependent
PRELOAD/ AFTERLOAD DETECTION	Difficult (probe positioning)	Excellent with IVC occlusion	Difficult	Difficult
INVASIVENESS	Moderate	High	Moderate	Moderate
LONGITUDINAL STUDIES	Yes	No	Yes	Yes
INITIAL PRICE OF SYSTEM	High	Low	High	High
PRICE FOR EXPERIMENT	Low	Moderate	High (rental & technician fees)	Very High (rental & longer tech time)
MAINTENANCE COSTS	Low	Low	High	Very high
APPLICATION FIELDS	Cardiovascular (cavity size, valve function etc.), Fluid around heart (pericardial effusion) Cancer (chest tumor biology etc.), Developmental biology (CV morphogenesis), Gene therapy (cardiac sonoporation).	Cardiovascular (left and right cavitary pressure-volume, resistance in the lungs, cardiovascular pressure-volume coupling, cardiac elastance) Isolated working heart (left ventricle pressure-volume).	Cardiovascular (cavity size, valve function, coronary artery calcification etc.), Cancer (chest tumor biology), Developmental biology (CV morphogenesis).	Cardiovascular (cavity size, valve function etc.), Fluid around heart (pericardial effusion) Cancer (chest tumor biology etc.), Developmental biology (CV morphogenesis).

Understanding Afterload

Afterload is the mean tension produced by a chamber of the heart in order to contract. It can also be considered as the 'load' against which the heart must eject blood. Afterload is composed of these major parameters: myocardial wall stress, arterial blood pressure, arterial resistance and arterial impedance. A more mathematically precise model of wall stress accounting for afterload comes from a modification of the LaPlace Law which states that wall tension (T) is proportional to the pressure (P) times radius (r) for thin-walled spheres or cylinders. Therefore, wall stress is wall tension divided by wall thickness.

$$\sigma \propto \frac{P \times r}{2h}$$

σ = ventricular wall stress

P = ventricular pressure

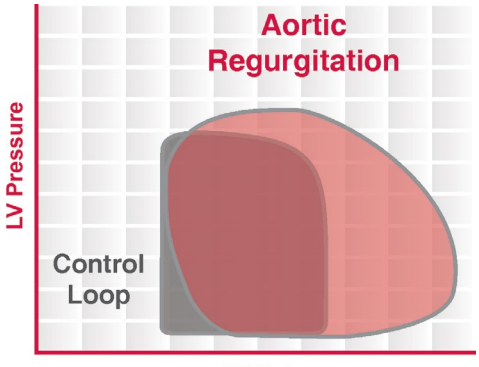
r = ventricular radius

h = wall thickness

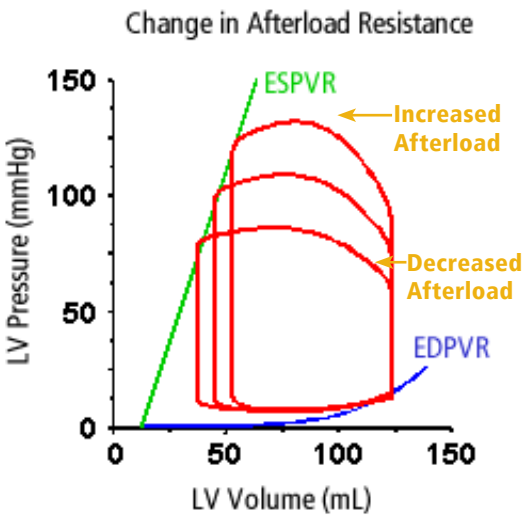
From this relationship it is apparent that wall stress (afterload) increases when the aortic or arterial pressure increases, ventricular radius increases (ventricular dilation), or wall thickness decreases.

Overall, wall stress is contractility dependent and is not constant during the contraction. LV cavity pressure, wall thickness and curvature vary with preload.

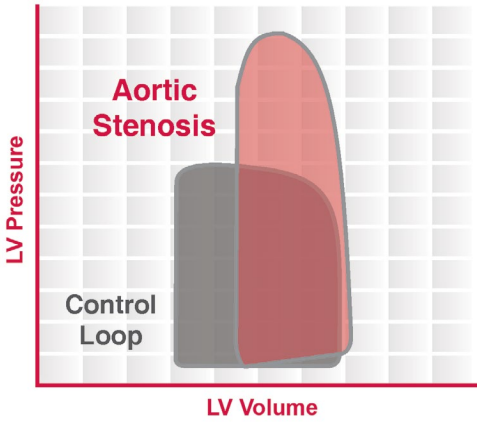
As mammals posses closed cardiovascular circuits, arterial blood pressure, resistance or impedance will have impact on the heart. Left ventricular afterload is affected by various disease conditions. Hypertension increases the afterload since the LV has to work harder to overcome the elevated arterial peripheral resistance and decreased compliance. Aortic valve diseases like aortic stenosis and insufficiency (regurgitation) also increase the afterload whereas mitral valve regurgitation decreases the afterload. Long-term afterload increases can lead to decreased stroke volume and deleterious cardiac remodeling.



Schematic drawing of healthy (control) and disease state (aortic regurgitation) LV PV loops



Different PV loops are obtained with different preloads, modeled by constant contractility (ESPVR and EDPVR boundaries) and afterload. Image courtesy of Burkhoff D, Boston 2013, Transonic lectures



Schematic drawing of healthy (control) and disease state (aortic stenosis) LV PV loops

Understanding Afterload Cont.

Afterload cannot be measured directly, but several methods for assessing afterload indirectly are available. This is normally accomplished by characterizing the interaction between the heart and the arterial system.

ECHOCARDIOGRAPHY

Echocardiography (both transthoracic and transesophageal) gives reliable measures of end systolic surface areas and wall thickness. In combination with ventricular pressure measurement this allows for the calculation of ventricular wall stress as described previously. Additionally, long axis Doppler echocardiography can measure decreases in stroke volume (SV) during the period of increased afterload.

COMBINED PRESSURE AND FLOW

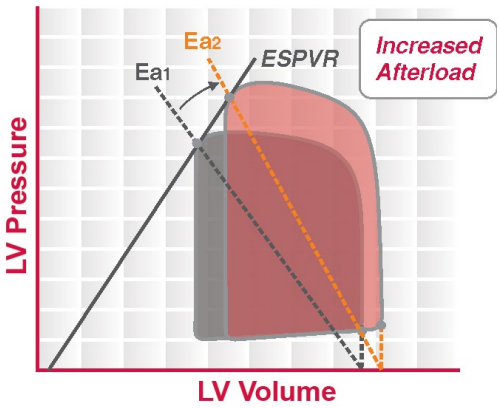
Combination of pressure and flow measurement (transit-time ultrasound Flowprobe and Pressure Catheter) can be used to determine afterload. Using flow as a measurement of cardiac output (CO) and both mean arterial pressure (MAP) and central venous pressure (CVP) can help to determine total peripheral resistance (TPR). Most investigators however omit CVP due to its minimal influence on the total, therefore:

TPR= (MAP /CO) = (MAP /SV*HR)

PRESSURE-VOLUME LOOPS

Pressure-volume loops characterize afterload by total mechanical load on the ventricle during the ejection. During many temporary or chronic (e.g. peripheral vascular hypertension) disease states the PV loops move to the right while both ESP and peak chamber pressure increases and SV decreases. As the ESP increases changes of arterial elastance Ea (the ratio of ventricular chamber end-systolic pressure to stroke volume i.e. Ea=ESP/SV) will takes place along with increase of chambers afterload. To compensate for this peripheral vascular resistance change, necessary adjustment of heart rate (increase) will take place.

On a cellular level, during increased afterload, heart muscle cells have to increase their metabolism while starting to use an oxidative phosphorylation pathway to obtain more ATP to handle calcium homeostasis and, ultimately, to contract. As this increase persists and excitation-contraction mechanisms are stretched to the maximum, it leads to depletion of calcium, and energy homeostasis. Moreover, an increase in oxygen consumption will be characterized by an increase in PVA (pressure volume area) at the beginning of afterload challenge.



Schematic drawing of healthy (control) and disease state (increased afterload) LV PV loops

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transonic
THE MEASURE OF BETTER RESULTS.

Understanding Preload

Preload is known as the load imposed on the ventricle at the end of diastole. Preload and its relationship to wall stress can be described by LaPlace's Law as pressure at the end diastole times radius of chamber at the end diastole divided by 2 times thickness of the chamber wall thickness at the end diastole.

$$\sigma \propto \frac{P \times r}{2h}$$

σ = ventricular wall stress

P = ventricular pressure

r = ventricular radius

h = wall thickness

On a cellular level, preload is defined as the maximum degree of myocardial fiber stretch or tension (stress) before ventricular contraction, determined by the mean sarcomere length at the end of diastole. Since sarcomere length cannot be determined in the intact heart, other indices of preload such as ventricular end diastolic volume (EDV) or pressure (EDP) are used. In general, EDV offers a better estimation of preload than EDP.

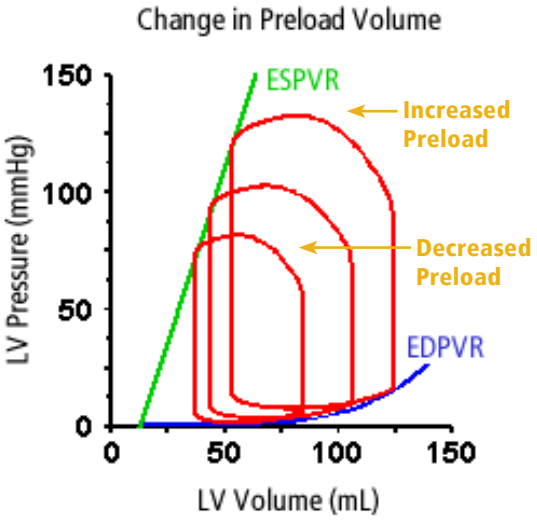
The relationship between the changes in preload and stroke volume depends on the morphology and Frank-Starling curve, which are determined by the contractile capacity of the heart and the ventricular afterload. Increasing preload increases stroke volume by a non-linear relationship. Cardiac preload can also be described as the passive filling properties of ventricles.

FACTORS CAUSING PRELOAD (EDV) INCREASE

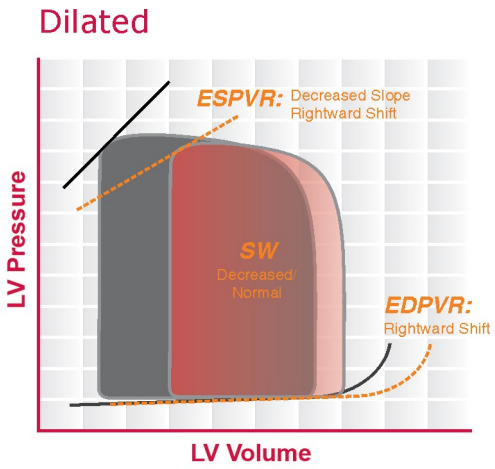
- Increased ventricular compliance
- Venoconstriction
- Increased venous return (skeletal muscle activity and respiratory activity during physical activity or position and gravity)
- Decreased heart rate (increased filling time)
- Neuro-endocrine stimulation of venous tone
- Increased blood volume (e.g. post-transfusion)

FACTORS CAUSING PRELOAD (EDV) DECREASE

- Compliance of ventricle decreases or stiffness increases (multiple muscle diseases leading to hypertrophy, post-tissue graft implantation, etc.)
- Increased heart rate (reduced filling time)
- Venodilation (peripheral or central) causing blood to pool in legs, abdomen, liver etc.
- Atrial arrhythmias (impaired contraction)



Different PV loops are obtained with different preloads, modeled by constant contractility (ESPVR and EDPVR boundaries) and afterload. Image courtesy of Burkhoff D, Boston 2013, Transonic lectures



Schematic drawing. During dilated cardiomyopathy, due to damage of the myocardium chambers, remodeling increases both ED and ES volumes (PV loop moves to the right). Frank-Starling curves shifts down and to the right due to a decrease in contractility. During this dysfunction, stroke volume is also reduced and preload increases as a consequence. LV EDP is near normal at low volumes but becomes elevated at high diastolic volumes as the myocardium is rendered non-compliant by hypertrophy, fibrosis or ischemia.

Understanding Preload Cont.

Preload can be measured by a variety of methods.

THERMODILUTION

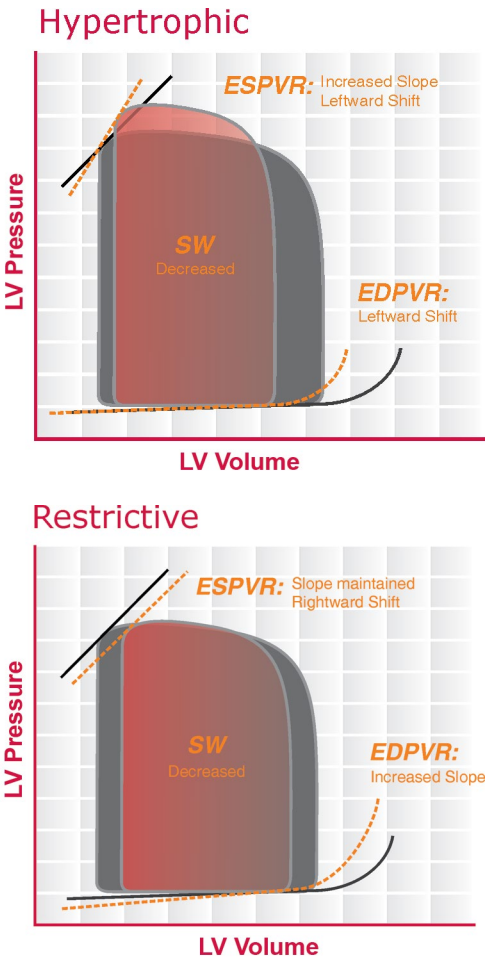
Thermodilution can be used to obtain a global EDV index to evaluate biventricular preload. Alternatively, right ventricle EDV can be obtained using a pulmonary artery catheter with a rapid response thermistor in the right ventricle.

ECHOCARDIOGRAPHY

Echocardiography (both transthoracic and transesophageal) gives reliable measures of end diastolic surface areas. End-diastolic volume can then be calculated using Simpson's method or a similar approach. Long axis Doppler echocardiography can measure increases in stroke volume (SV) during the period of increased preload.

PRESSURE-VOLUME LOOPS

Pressure-volume loops give a direct measurement of end diastolic volume as derived by admittance technology. At the same time, PV loops have the advantage of also providing information on heart contractility (load independent) based on the end systolic and end diastolic pressure volume relationships (ESPVR and EDPVR).



Schematic drawings of both left ventricular hypertrophy and restrictive cardiomyopathy exhibit a reduced end diastolic volume (EDV). As the LV becomes more stiff and less or non-compliant, PV loop leftward shift occurs.

In hypertrophic cardiomyopathy, further myocardial wall remodeling leads to concentric hypertrophy and heart failure. Decreasing of all load parameters (e.g. EDV, SV and EF) occurs as compliance of the ventricle further decreases and stiffness of the chamber increases. When preload rapidly decreases, chamber pressure increases leading to steeper ESPVR.

During restrictive cardiomyopathy, stiffening of the myocardium occurs due to myocarditis leading to reduction of all load based parameters (e.g. EDV, SV, EF). While ESPVR might be unchanged at the beginning, diastolic dysfunction becomes obvious as characterized by an EDPVR shift indicative of heart failure.

Understanding Contractility: Cardiac Inotropy

Cardiac contractility is the intrinsic ability of heart muscle to generate force and to shorten, ideally independent of changes in heart rate (HR), preload or afterload. In that respect, cardiac chamber pressure-volume measurement is the most reliable index for assessing myocardial contractility in the intact circulation, being almost unaffected by changes in preload and afterload.

Contractility is regulated by many mechanisms:

- The parasympathetic and sympathetic nervous systems through catecholamines (circulating, delivered) control contractile force and ensure the coupling between heart performance and peripheral circulation. Catecholamines increase contractile force by the β adrenoceptor-adenylyl cyclase system or by stimulation of α-receptors. Through protein phosphorylation of L-type calcium channels, increase of calcium influx and activation of ryanodine receptors (RyRs) occur to further increase the sarcoplasmatic reticulum calcium release. At the same time, other processes speed up calcium accumulation in the sarcoplasmatic reticulum to allow faster cardiomyocyte relaxation. Parasympathetic action (vagus nerve) has a beneficial effect on cardiac contractility by improving hemodynamics, including decreasing HR and pressure. Vagus nerve stimulation also effectively suppresses arrhythmias, including premature ventricular contractions (2).
- Stroke volume is critically dependent on inotropy. When sarcomere length increases or during preload augmentation, contractile force and stroke volume increases correspondingly, based on the Frank-Starling mechanism.
- Myocardial force development is HR dependent (Bowditch effect). In healthy myocardium the effect is expressed as an increase of heart rate by cardiac pacing that is able to a produce progressive increase in the force of contraction for a few beats (isometric force development) and then remains at a higher plateau (Positive Staircase effect). Functionally, with increasing HR, more calcium enters the cardiomyocyte and is accumulated into the sarcoplasmatic reticulum, while becoming accessible for release in the next contraction, resulting in increased contractile force. The inverse effect occurs when HR is decreased (Negative Staircase).
- Increase in afterload causes an increase in ventricular contractility (inotropy) due to the activation of catecholamines. This effect allows the myocardium to compensate for an increased end-systolic volume and decreased stroke volume that occurs when aortic blood pressure increases. It is called the Anrep effect. Without this effect in place, an increase in aortic blood pressure would create a drop in stroke volume that would compromise circulation to peripheral and visceral tissues.

CONTRACTILITY AND HEART FAILURE

MYOCARDIUM	RT (mN/mm²)	PDF (mN/mm²)	WORK (%)
Non-failing	11.2±1.3	14.5±4.4	136±11
Failing	16.3±1.5	12.7±4.5	74±7

Resting tension (RT) and work are significantly different. Peak developed force (PDF) is not (1).

During heart failure, changes in the gene expression occur (from the adult to fetal pattern) leading to lowering of systolic calcium release and diastolic calcium reuptake. These molecular changes lead to physiological (heart function/hemodynamic) alterations that heavily influence inotropy. Studies in isolated myocardium have shown that increasing contraction rate does not increase contraction force or work in failing myocardium as it does in normal myocardium. However, the Frank-Starling mechanism is still intact in failing myocardium. This does not translate to increased work with increased sarcomere length due to the higher resting tension of failing cardiac muscle. Additionally, failing myocardium has reduced extent of shortening as compared to non-failing myocardium. When cardiac muscle length is increased close to its maximum (maximal stretch) in non-failing myocardium the maximal myocardial work increases with accompanied isometric force development as compared to failing myocardium where the myocardial work is decreasing when cardiac muscle is stretched to its maximum length (1).

Understanding Contractility: Cardiac Inotropy Cont.

Positive Inotropic Agents (Increase Contractility)

TYPE OF AGENT	MECHANISM/ EFFECTS	EXAMPLE AGENT(S)
Calcium	Increases available calcium for binding.	Calcium
Calcium Sensitizer	Increases myocyte calcium sensitivity and binding to cardiac troponin C in a calcium-dependent manner.	Levosimendan
Cardiac Myosin Activators	Targets and activates myocardial ATPase and improves energy utilization. This enhances effective myosin cross-bridge formation and duration.	Omecamtiv
Beta Agonists	Stimulates adenylyl cyclase activity and opening of calcium channels.	Dobutamine, Isoproterenol, Xamoterol
Intrinsic Catecholamines	Increases heart rate, blood pressure and glucose levels.	Dopamine, Epinephrine (adrenaline), Norepinephrine (noradrenaline)
Cardiac Glycosides	Competes with K^+ ions for the same binding site on the Na^+/K^+ ATP-ase pump in cardiomyocytes and decreases its function. This causes an increase in the level of Na^+ in cardiomyocytes, which leads to a rise in the level of intracellular Ca^{2+} because the Na^+/Ca^{2+} exchanger on the plasma membrane depends on a constant inward Na^+ gradient to pump out Ca^{2+}.	Digitalis, Digoxin, Ouabain
Phosphodiesterase-3 Inhibitors	Protects cyclic AMP from its degradation, increases inotropy. Decreases afterload by vasodilatation	Milrinone, Amrinone, Enoximone, Papaverine
Insulin	Exerts Ca^{2+} dependent and independent positive inotropic effects through a phosphatidylinositol-3-kinase (PI3K) dependent pathway.	Insulin
Glucagon	Stimulates the cardiac Ca^{2+} current by activation of adenylyl cyclase and inhibition of phosphodiesterase.	Glucagon

Negative Inotropic Agents (Decrease Contractility)

TYPE OF AGENT	MECHANISM/ EFFECTS	EXAMPLE AGENT(S)
Beta Blockers	Block the action of endogenous catecholamines by interfering with the binding of adrenaline and noradrenaline to their receptors.	Acebutolol, Bisoprolol, Propranolol, Atenolol
Calcium Channel Blockers	Block voltage-gated calcium channels in cardiac muscle.	Verapamil, Diltiazem
Class IA Antiarrhythmic (fast channel blockers)	Block open Na^+ channels, prolonging cardiac action (affecting QRS complex). This results in slowed conduction and ultimately the decreased rate of rise of the action potential.	Quinidine, Procainamid
Class IB Antiarrhythmic	Na^+ channel blockers cause a reduction of the rate of rise of intracellular Na^+.	Lidocaine
Class IC Antiarrhythmic	Na^+ channel blockers	Flecainide, Propafenon
Class III Antiarrhythmic	Have β-like and K^+-like actions, increasing the refractory period via Na^+ and K^+ channel effects, and slowing intracardiac conduction of the cardiac action potential.	Amiodarone

Understanding Contractility: Cardiac Inotropy Cont.

FACTORS AFFECTING THE LEVEL OF INOTROPIC (CONTRACTILE) STATE

Intrinsic

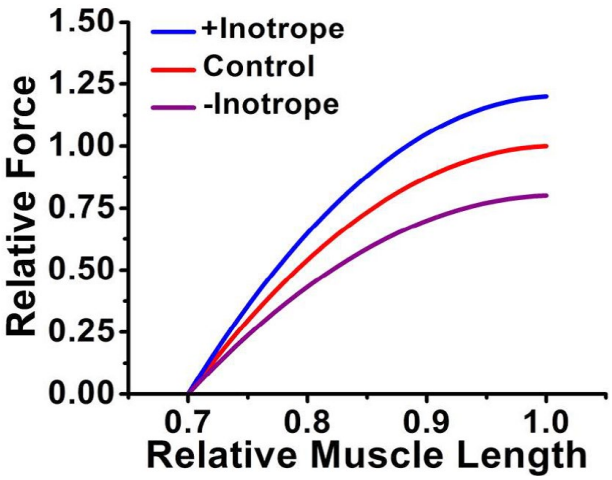
- Affinity of myocardium for calcium changes (insufficient blood flow, ischemia)
- Damage of heart muscle (alteration of numbers of contractile units)
- Calcium release and re-uptake
- Hormones (Glucagon, Insulin)
- Temperature

Extrinsic

- Pharmacological agents (β-agonist, β-blockers, isoflurane)
- Release of norepinephrine into myocardium when postganglionic sympathetic axis is activated
- Release of acetylcholine when parasympathetic axis is activated
- Increase of extracellular calcium concentration

ASSESSMENT OF CELLULAR CONTRACTILITY

- Intact myocardial cells are phenotypically different based on their sarcomere length, as they are localized in different cell sheets of heart. Inside (sub-endocardial) cell layer is stiffer as compared to outside (sub-epicardial) (3).
- Cell sheets localized at sub-endocardium react on pre-load force activation better, as they have longer end-diastolic sarcomere length (4).
- Phenotypic differences might further guide contraction of the whole heart. As during systole, earlier pre-contraction of sub-endocardium might be beneficial for the sub-epicarial, less-stiffer layer (5).
- Importantly, cells from the RV base and apex are narrower as compared to LV at these locations as measured in guinea pigs. This might limit their force-generation, but as they are longer, it might be an advantage to their length-change potential (6).



An increase in inotropy is associated with an increase in the strength of contraction (force) for the same stretch or preload (muscle length). A decrease in inotropy decreases contraction strength (1). Changes in the inotropic state of the myocardium produce changes in performance (force development, extent of shortening) independent of preload and afterload.

Image courtesy of Burkhoff D, Boston 2013, Transonic lectures

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THE MEASURE OF BETTER RESULTS.

Understanding Lusitropy

Lusitropy describes the relaxation properties of the heart during the diastolic phase. Left Ventricle (LV) relaxation begins during late ejection and continues throughout an early rapid filling and ends fully relaxed by diastasis, before the atrial systole begins. Diastolic (lusitropic) properties can be described by both active relaxation and passive diastolic properties.

This active relaxation during diastole is a spatially non-uniform process, based on different rates and amounts of untwisting during periods of isovolumic ventricular relaxation (IVR). Twisting of the myocardial tissue leads to storage of potential energy that is freed in early ventricular diastole during untwisting. As the LV wall is composed of helically woven muscle layers and sheets, including extracellular matrix, all are assembled in interwoven layers such that fiber orientation is modified both transmurally and along the long axis of the ventricle (1). This LV geometric arrangement generates the spatially and temporally unique relaxation pattern accounting for unique, heart specific lusitropic patterns (1). Additionally, since LV and RV share the common septum, direct diastolic ventricular interaction is important to consider lusitropy when assessing the diastolic properties.

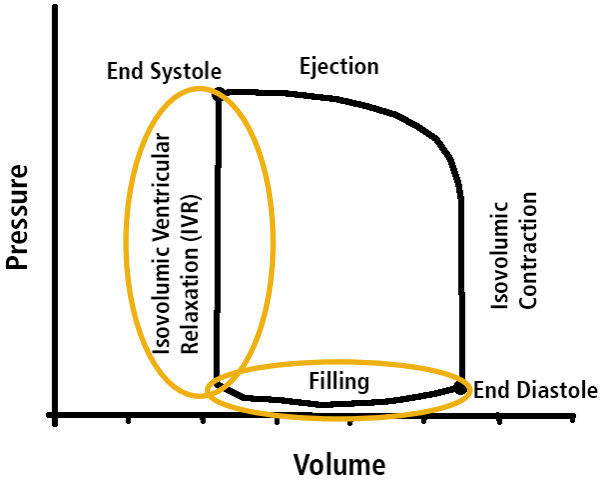

Fig. 1: Simplified sketch of LV PV loop. Diastolic phase includes isovolumic ventricular relaxation (IVR) and filling.

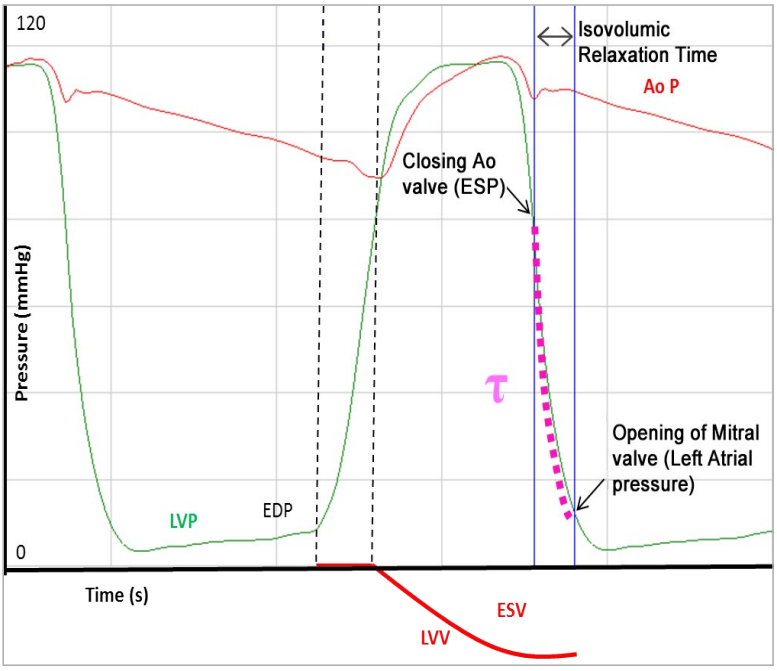

Fig. 2: The decay of LV pressure during the isovolumic ventricular relaxation (IVR) of diastole follows a roughly exponential time course. Active relaxation can be characterized by Tau, the segment of pressure contour between aortic valve closure and the mitral valve opening.

It is important to note that Tau has multiple methods of expression. Tau was originally used by Weiss to describe the IVR of LV (3). Raff and Glantz proposed an alternative method to express Tau, referred to as Tau Glantz (4). The latest IVR Tau logistic was proposed and described in 1995 by Dr. Suga in Japan (5).

Understanding Lusitropy Cont.

ACTIVE RELAXATION PROPERTIES

- Indexed by Tau (isovolumic relaxation time, also known as time of pressure decay) IVR is from aortic valve closure to mitral valve opening
- dP/dt_{min} (is not as precise when compared to Tau, since dP/dt_{min} depends on the peak aortic pressure and timing of aortic valve closure) (2)
- Impacted by heart rate (HR)
- On cellular level, relaxation is energy consuming process requiring ATP as release of calcium from sarcomere requires SERCA (sarco-endoplasmatic reticulum Ca-ATPase) for its re-uptake.

An increase in Tau indicates impairment of active properties of diastolic relaxation. Isovolumic relaxation and Tau are influenced by:

- Left atrial - left ventricle pressure gradient
- LV elastic recoil
- Chamber relaxation
- Mitral orifice area
- Heart rate
- Energy supply (Tau increases during MI and post-ischemia)
- Beta-stimulus (Tau decreases with β-adrenergic stimulation)

During many LV disease states (i.e. LV hypertrophy, LV ischemia, diabetic cardiomyopathy etc.) active relaxation is delayed.

When active relaxation is inadequate in early diastole, LV chamber relaxation might become incomplete at the end of diastole.

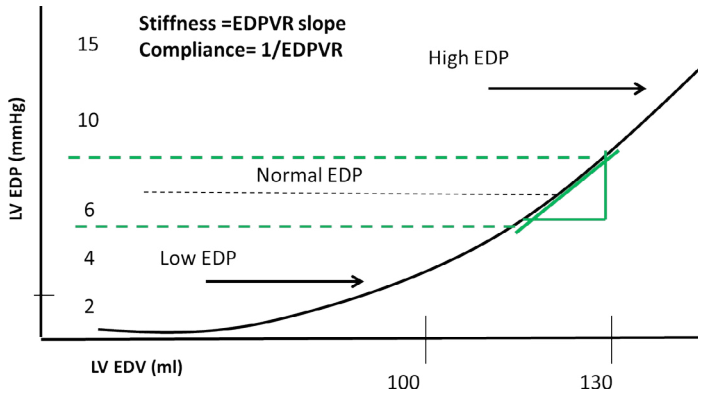

Fig. 3: Schematic drawing. EDPVR represents the relation between EDP and EDV, at the stage of the cardiac cycle that is marked by A-V (mitral) valve closure. The non-linear curve represents diastolic stiffness with the exponential fit EDP=A*exp (k*EDV), where k is diastolic stiffness constant. Since the EDPVR is nonlinear, the compliance varies with volume; compliance is greatest at low volume and smallest at high volumes.

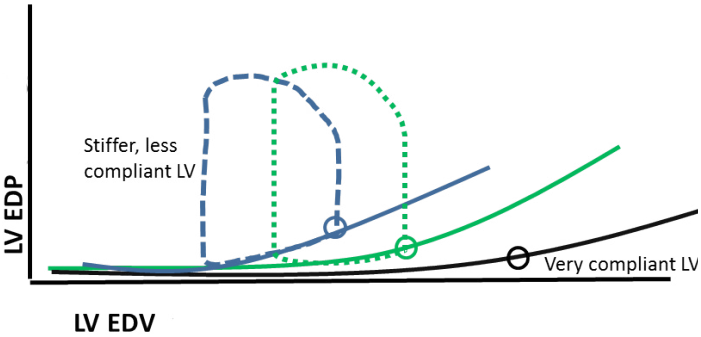

Fig. 4: Schematic drawing. EDPVR changes with lusitropic conditions. Examples of decreasing compliance detected by EDPVR leftward shift (stiffening of LV) include restrictive cardiomyopathy, infiltrative disease (amyloid), and hyperthrophic cardiomyopathies.

Understanding Lusitropy Cont.

PASSIVE DIASTOLIC PROPERTIES

- Compliance (dV/dP, inverse of stiffness): LV compliance is determined by the substantial properties of the cardiac myocytes, cardiac fibroblasts, and other cardiac cells along with their cellular-molecular preparedness to contraction and relaxation.
- Stiffness (dP/dV, inverse of compliance)
- EDPVR: LV end-diastolic pressure-volume relationship provides an indication of LV compliance during the filling phase of cardiac cycle (Fig. 4 & Fig. 6). In late diastole passive properties of LV are more prominent as compared to active relaxation.
- Capacitance: Characterizes diastolic volume at given pressure. LV chamber geometry is important determinant of capacitance and its overall compliance (Fig 5).
- As myocardium is perfused mostly in diastole, stiffness of myocardium plays role in limiting coronary perfusion (7).

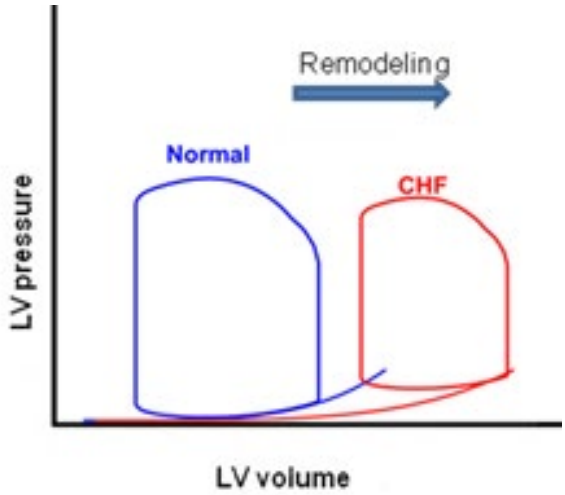

Fig. 5: Schematic drawing. Chronic heart failure (CHF) is seen in the late stages of post-myocardial infarct injury remodeling. Over time the remodeling mechanism persists beyond control and, in the non-injured region, cardiomyocytes hypertrophy and fibroblasts proliferate producing interstitial collagen. As the LV chamber volumes increase (EDV & ESV) the PV loop shifts to the right. However both SV and SW are diminished.

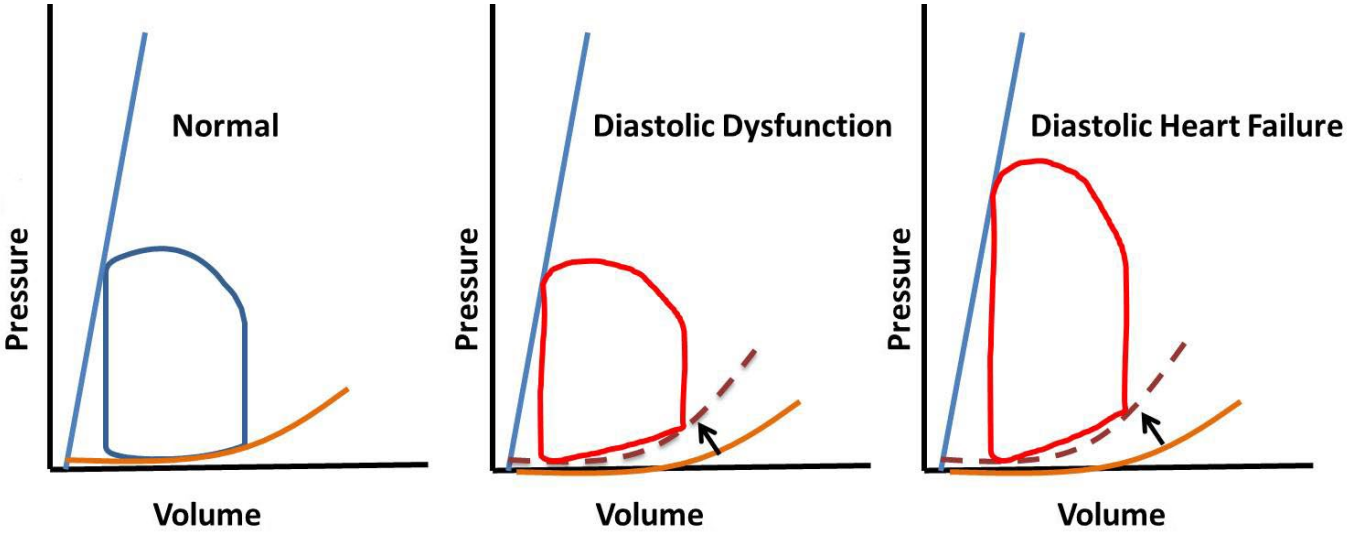

Fig. 6: Schematic drawing. Diastolic dysfunction is a syndrome characterized by impaired ventricular filling resulting from prolonged active LV myocardial relaxation and/or increased passive diastolic LV stiffness. Both indexes can help to determine diagnosis of diastolic dysfunction, and/or diastolic heart failure.

Understanding Lusitropy Cont.

Lusitropy can be further detected by non-invasive measurement of velocities of myocardial tissue using Tissue Doppler Imaging (TDI) echocardiography by Doppler E-wave deceleration time (DT) (Fig. 7). Many subjects with prolonged Tau interval (IVR) show a well delayed E-wave relaxation pattern on echocardiographic exam. However this relationship of Tau and E-wave does not always have good correlation since Tau requires a mathematical fit to the pressure contour (2).

Another method for assessing diastolic indices is speckle tracking echocardiography (STE), where myocardial speckles (small structures) are tracked to determine myocardial velocity and strain (6). Strain is the change in velocities length during a given time period, and it is possible to measure it by STE in the longitudinal, circumferential, transverse, and radial directions to assess regional diastolic function such as interstitial fibrosis in the region to identify myocardial viability.

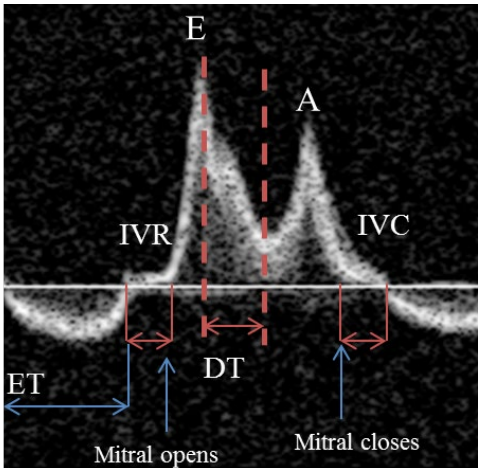

Fig. 7: E-wave deceleration time corresponds to diastolic relaxation properties. E-wave duration that is prolonged and lower in peak value than the A-wave, often represents underlying diastolic dysfunction. (IVC) Isovolumic contraction time, (DT) deceleration time, (IVR) Isovolumic relaxation time, (ET) ejection time.

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