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Indices of Myocardial Contractility

Anusak Kijawornrat

Abstract

Myocardial contractility is defined as the velocity of cycling of heavy meromyosin cross-bridges. Contractility may be defined also as the velocity of myocardial fiber shortening or change in ventricular dimension during contraction when the fiber shortens or the ventricle contracts against no load. In the clinic; however, myocardial contractility may be estimated by some parameters of systolic function adjusted for the degree of stretch on the fibers (the preload) just before contraction begins and the hindrance to ejection of blood (the afterload). Excitation-contraction coupling is a physicochemical process during which electrophysiological changes (initiated by depolarization of the cell) translate to mechanical changes (manifested as a combination of contraction and generation of tension). The result of this process is a combination of the ejection of blood out of the ventricle into and through the arterial tree and of the generation of pressure. Many indices have been used in both humans and experimental animals to assess cardiovascular function: (1) V_{\max} (the maximal velocity of fiber shortening estimated from the imaginary conditions of the fiber shortening against no load), (2) parameters (ESPVR, PRSW, Ees) obtained from the left ventricular pressure-volume relationship, (3) $dLVP/dt_{\max}$ (maximal rate of rise of left ventricular pressure), (4) QA interval (time between onset of electrical activity in the ventricle to initial elevation of arterial pressure), (5) ejection fraction (ratio of stroke volume to preload). However, some (3, 4 and 5) of these indices must be used with caution for estimating contractility since they are also influenced by other factors (e.g. preload, afterload, stiffness of the arterial tree). Parameters of the pressure-volume loop are considered the gold standard for measuring contractility, lusitrope, myocardial energetics and ventricular-vascular coupling.

Keywords: $dLVP/dt_{\max}$, ejection fraction, myocardial contractility, pressure-volume relationship, QA interval, V_{\max}

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บทคัดย่อ

ดัชนีตรวจความสามารถในการหดตัวของกล้ามเนื้อหัวใจ

อนุศักดิ์ กิจถาวรรัตน์

ความสามารถในการหดตัวของกล้ามเนื้อหัวใจ คือ ความเร็วในการหมุนของเมอโรโมออสซินหนักในกระบวนการ cross-bridges หรือความเร็วในการหดตัวของใยกล้ามเนื้อหัวใจ หรือการเปลี่ยนแปลงขนาดของหัวใจห้องล่างขณะที่หัวใจหดตัวในภาวะที่ไม่มีน้ำหนักรีด ในทางคลินิกความสามารถในการหดตัวของกล้ามเนื้อหัวใจอาจประมาณค่าได้จากดัชนีของการหดตัวของหัวใจที่ปรับมาตรฐานกับระดับการยืดของใยกล้ามเนื้อหัวใจก่อนการหดตัว (พรีโหลด) และอุปสรรคในการสูบฉีดเลือด (ออฟเตอร์โหลด) เอ็กไซเตชัน-คอนแทรกชัน คัปปลิง เป็นกระบวนการทางฟิสิกส์และเคมีร่วมกันซึ่งการเปลี่ยนแปลงทางไฟฟ้าสรีรวิทยาเปลี่ยนเป็นการหดตัวของกล้ามเนื้อ ผลของกระบวนการดังกล่าวทำให้เกิดการการสูบฉีดเลือดจากหัวใจห้องล่างสู่หลอดเลือดแดงและเป็นตัวกำหนดความดันเลือด ในสัตว์ทดลองและในคนมีการใช้ดัชนีสำหรับตรวจการทำงานของหัวใจหลายชนิด เช่น 1) วีแม็กซ์ เป็นการบันทึกความเร็วในการหดตัวของใยกล้ามเนื้อในภาวะที่ไม่มีน้ำหนักรีด 2) ดัชนี (ESPVR, PRSW, Ees) ที่ได้จากการหาความสัมพันธ์ระหว่างความดันและปริมาตรของเลือดในหัวใจห้องล่างซ้าย 3) $dLVP/dt_{max}$ เป็นอัตราเร็วสูงสุดของการเพิ่มความดันเลือดในหัวใจห้องล่างซ้าย 4) ระยะคิวเอ เป็นช่วงเวลาจากจุดเริ่มต้นของ Q wave บนภาพคลื่นไฟฟ้าหัวใจจนถึงจุดเริ่มต้นของความดันเลือดแดง และ 5) อีเจ็คชันแฟรคชัน เป็นสัดส่วนของปริมาณเลือดที่ถูกบีบออกจากหัวใจในแต่ละครั้งต่อพรีโหลด อย่างไรก็ตามในการใช้ดัชนีที่ 3, 4 และ 5 ต้องมีความระมัดระวังในการใช้เนื่องจากมีปัจจัยอื่นๆ ที่ไม่ใช่แค่ความสามารถในการหดตัวของหัวใจที่มีผลต่อดัชนีดังกล่าว (เช่น พรีโหลด ออฟเตอร์โหลด และความแข็งของหลอดเลือดแดง) ดัชนีที่ได้จากการหาความสัมพันธ์ระหว่างความดันและปริมาตรของเลือดในหัวใจห้องล่างซ้ายถือว่าเป็นดัชนีมาตรฐานในการตรวจความสามารถในการหดตัวของหัวใจ ความสามารถในการคลายตัว พลังงานของกล้ามเนื้อหัวใจ และการคัปปลิงระหว่างหัวใจห้องล่างและหลอดเลือด

คำสำคัญ: $dLVP/dt_{max}$ อีเจ็คชันแฟรคชัน ความสามารถในการหดตัวของหัวใจ ความสัมพันธ์ระหว่างความดันและปริมาตรของเลือด ระยะคิวเอ วีแม็กซ์

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Introduction

Overview of the cardiovascular system and its properties

Cardiovascular system is essential for multicellular organisms to sustain their intracellular environment (milieu interior) with optimal (i.e. suitable for good health) amounts of oxygen, carbon dioxide, pH, substrates for oxidation, waste products from metabolism. Since all of these factors either come from (e.g. oxygen, substrates) or are discharged to (e.g. carbon dioxide, waste products of metabolism) the external environment, and since only a very few cells of the body have direct (e.g. skin, sclera, tympanic membrane, mucous membranes) or semi-direct (e.g. GI tract, lung, kidney) contact with the external environment, the multicellular organism has evolved with a cardiovascular system that brings each of the approximately one quadrillion cells into intimate contact with the external environment. This system consists of the heart, arteries, veins, capillaries, and the blood within.

The principal task of the heart is to generate the pressure difference that drives blood from arteries to veins through the microcirculation (capillaries), and from the left and right ventricles into the initial portion of the aorta and pulmonary trunk. The heart has five so-called physiological properties that allow it to function:

1. Chronotrope is the ability of a region of the heart—the SA node—to discharge a wave of depolarization at a certain and variable rate to sustain the heart beat.
2. Dromotrope is the ability of various structures (e.g. atrial myocardium, internodal pathways, AV conduction system, ventricular myocardium) in the heart to conduct waves of depolarization.
3. Bathmotrope refers to excitability or the ability to respond to a stimulus.
4. Inotrope is the ability of the heart muscle, once depolarized, to contract and to generate a combination of tension and shortening.
5. Lusitrope is the ability of the heart, once contracted and having ejected blood, to refill.

The following will be a review of the myocardial contractility—the inotropic state. The inotropic state is an important physiological property of the heart, and when it is either decreased or increased, significant morbidity and/or mortality may be expected. Therefore, it is important to measure contractility and, when it is altered, to attempt to return it to levels that might reduce morbidity and/or mortality. It is enigmatic that although everyone knows of the importance of inotrope—and the purpose of this missive is to define and discuss how to measure it—there is virtually no consensus on what change in inotrope is meaningful for patients.

When contractility is too low, the heart may not be able pump enough blood at a sufficient pressure to serve the needs of the organism. When contractility is too high, the heart may consume so much oxygen in which an oxygen debt leads to an energetic imbalance.

A failing heart is a heart with reduced contractility. Heart failure is a clinical entity—syndrome—in which an organism manifests signs and symptoms because of a failing heart and a pathological interaction with the blood vessels (Katz and Konstam, 2008). However, many organisms with a failing heart are not in heart failure but may be at risk for heart failure.

Definition of contractility

Myocardial contractility may be defined simply and most precisely as the velocity of cycling of heavy meromyosin heads (cross-bridges). It is cycling of those cross-bridges, emanating from the thick myosin filament and attaching to the thin actin filament, that actually generates tension and or shortening (Hamlin and del Rio, 2010). This cycling is the most fundamental unit of contraction. Rate of hydrolysis of ATP and the amount of Ca^{++} available to bind to troponin-C are often used as surrogates for contractility. However, the energy from hydrolysis of ATP fuel contraction and binding of Ca^{++} to troponin-C displaces tropomyosin to allow cycling, but not actually, directly measures contractility (Hamlin and del Rio, 2010).

Excitation-Contraction (EC) coupling

A completed review of cardiac excitation-contraction coupling is presented by several authors (Hamlin and del Rio, 2010; Bers, 2002; Jafri, 2012). Contraction of the myocardium resides in the cycling of heavy meromyosin heads, but the process is fueled by energy from the hydrolysis of ATP and initiated when the cell is stimulated allowing Na^+ to enter and depolarize it. The total process, from stimulation to contraction, is termed excitation-contraction (EC) coupling. The following is a sequence of the steps constituting EC coupling:

Step 1: The stimulus to initiate the process is anything that will drastically increase the permeability of the cell membrane to Na^+ . Although a cell may be stimulated mechanically (as by pricking with a pin) or pharmacologically (as with a drop of aconitine), the usual/normal stimulus is the passage of current

across the cell membrane (Negulyaev et al., 1990). The current flux is produced by voltage differences between neighboring regions that possess differing concentrations of ions.

Step 2: Once the permeability of the cell membrane to Na^+ has increased, Na^+ rushes into the cell down its concentration gradient (~ 140 mEq/L outside to ~ 4 mEq/L inside) and its electrical gradient (because the inside of the resting cell is electrically negative (~ -80 mV). This entry of Na^+ depolarizes the cell to $\sim +15$ mV.

Step 3: Depolarization of the cell opens up the voltage-gated, L-type, Ca^{++} channel; Ca^{++} enters the cell, and a small portion of Ca^{++} binds to troponin-C (Tc) but the major portion binds to the ryanodine channel (RyR) in the sarcoplasmic reticulum (SR).

Step 4: When Ca^{++} binds to the RyR channel, the channel opens, and Ca^{++} exits the SR and binds to Tc.

Step 5: When Ca^{++} binds to Tc, the Tc tugs on tropomyosin (TM) and removes TM from a position between the heavy meromyosin crossbridge and a site on actin to which the heavy meromyosin head may attach. When the heavy meromyosin heads (that contains ATPase) attach to the binding sites on actin, ATP is hydrolyzed and energy is released which fuels cycling of the heavy meromyosin.

Step 6: Heavy meromyosin heads, and the necks connecting the heads to myosin, constitute the molecular motor which, when fueled with energy from ATP, produces the cycling (Precisely why cycling occurs is not known, but it probably involves changes in molecular geometry of the heavy meromyosin head and the neck.).

Step 7: Swinging of heavy meromyosin heads and tugging on the actin filament is translated to tugging on the Z band (to which the actin filament is attached), and that tugging are translated to a combination of sarcomere shortening or generation of active tension.

If shortening is prohibited by loading conditions, then all cycling is translated to tension only. Under impossible (impossible since the muscle or sarcomere must contract against at least its own mass) conditions of no load, then no tension will be developed and all tugging is translated to shortening. The physiological status of the muscle can be described by the velocity tension curve in which the maximal velocity of shortening is defined as contractility.

Step 8: The cell then repolarizes (i.e. returns towards the resting potential of ~ -80 mV) when K^+ exits through a number of specific ion channels (e.g. I_{TO} , I_{Kr} , I_{KS}) whose conductances increase. Simultaneous to the repolarization, Ca^{++} is released from Tc and a small amount (i.e. $\sim 30\%$) exits the cell via the $\text{Na}^+/\text{Ca}^{++}$ exchanger, but the greatest amount (i.e. $\sim 70\%$) is resequenced into the SR through the sarcoendoplasmic reticulum Ca^{++} (SERCa) channel. The removal of Ca^{++} from Tc allows TM to reorient itself to prevent interaction between the heavy meromyosin heads and actin binding sites (Bers,

2002).

Step 9: After repolarization and return to normal Ca^{++} distribution, (1) the cell relaxes and returns to normal, resting geometry generating neither motion nor active tension, (2) there is an ionic exchange of Na^+ and K^+ across the sarcolemma to reestablish ionic balance, and (3) ATP is replenished by mitochondrial metabolism.

Methods of measuring contractility

The primary purpose of this paper was to review several indices of myocardial contractility by defining the indices, discussing how they are measured, discussing limitations of their uses, and discussing how they are used in experimental animals and humans.

1. V_{\max} : the maximal velocity of fiber shortening estimated from the imaginary conditions of the fiber shortening against no load

A single myocardial fiber, a group of fibers forming a muscle, or a group of muscles forming a cardiac chamber of the heart generate tension or be shorten due to cycling of heavy meromyosin heads. Myocardial contractility is defined as the rate of cycling of those heavy meromyosin heads. Is it possible to establish the rate of cycling from the rate of shortening of a muscle fiber, muscle, or even the entire ventricle? Clearly the rate of shortening depends upon both the rate of cycling of heavy meromyosin heads and the load hindering the shortening. If it was possible to measure rate of shortening without any hindrance to shortening, then the rate of shortening would be determined only by the velocity of cycling of heavy meromyosin heads, and would measure myocardial contractility (Hamlin and del Rio, 2010). The problem is that it is impossible to have a fiber shorten against no hindrance because, even if there appeared to be no hindrance, the fiber would still have to shorten against itself. The method for estimating the maximal velocity of fiber shortening that could occur only against no load is shown (Fig 1) and explained as follows.

A load, too heavy for the muscle to shorten against, is attached to the fiber or muscle. When the fiber or muscle is stimulated with a maximal electric current, it contracts and tries to shorten but it cannot move the heavy load, therefore the velocity of shortening is zero. But it does generate the maximal tension it can. This produces a point that intersects the abscissa showing great tension but intersects the ordinate showing zero velocity. Now as the load is lightened and lightened further, the tension generated is reduced, but the velocity of shortening increases and increases further proportional with the reduction in load. This produces the points (obtained by experimentation) shown as asterisks on the hyperbolic curve. Since these points identify a hyperbola, it then becomes simple extrapolation to extend the curve to the Y-axis intercept (at which the X-axis intercept is zero), which gives the velocity of fiber shortening against no load. This intercept is V_{\max} , the maximal velocity that can occur only at zero load, which is also

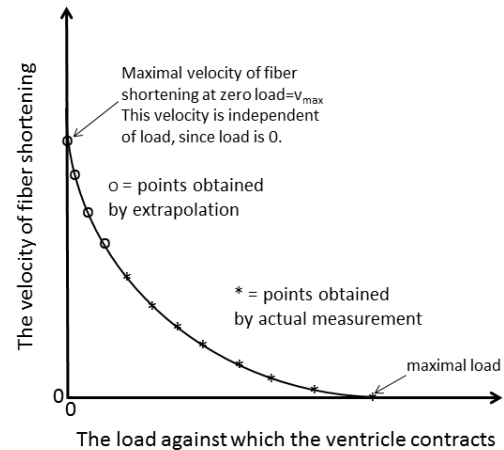


Figure 1 shows the relationship between the load against which the ventricle contracts and the velocity of fiber shortening. V_{\max} is the maximal velocity of fiber shortening at zero load.

the maximal velocity of cycling of heavy meromyosin or myocardial contractility.

This concept originated from studies on skeletal muscle that was not allowed to shorten because of a very high load, and was then allowed to shorten against lower and lower loads (Sonnenblick, 1962). With the assumption that V_{\max} of muscle fibers is equivalent to V_{\max} of the contractile element, V_{\max} has been used, in both physiology laboratories and the clinic, as an index of the inotropic state of cardiac muscle (Hefner and Bowen, 1967; Parmley et al., 1969; Falsetti et al., 1971). Based on the work of Pollack (1970), V_{\max} of the contractile element is not independent of fiber length but increases at least 50% for a 25% increase of fiber length. Therefore, it is unlike that of the muscle fibers. His work indicated that V_{\max} is invalid for estimating cardiac inotrope since a shift of V_{\max} can be attributable to either changing contractility or changing fiber length (Pollack, 1970).

The mean rate of ventricular circumferential fiber shortening (Vcf), as may be approximated by angiography or echocardiography (Ruschhaupt et al., 1983; Karliner et al., 1971), appears to estimate accurately ventricular inotrope for both normal humans and humans with heart diseases. Vcf can be estimated from changes in the minor axis of the left ventricle divided by left ventricular ejection time (the time required for those changes to occur). Mahler and colleagues (1975) performed an experiment in conscious dogs and found that the Vcf was insensitive to volume overload but was sensitive to pressure overload, whereas the opposite effect was found with the dP/dt_{\max} . Data indicate, however, that although Vcf derived from M-mode echocardiography is a useful index of inotrope, it is not truly reflective of the precise change of circumference during systole (Ruschhaupt et al., 1983).

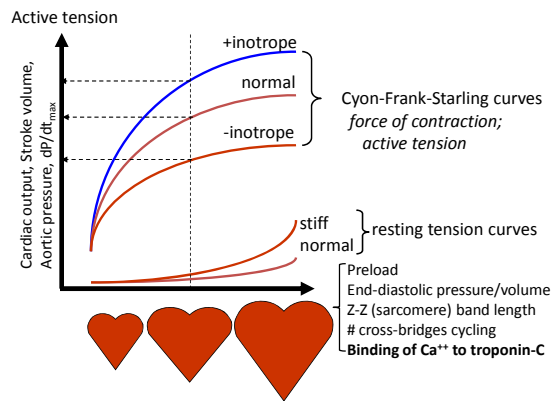


Figure 2 shows Cyon-Frank-Starling curves expressing the “law-of-the-heart”. The parameters of systolic function are plotted against the degree of preload just before the ventricle contracts as shown by the different size of valentine heart.

2. Cyon-Frank-Starling curves:

Myocardial contractility may be measured/inferred/estimated in either the clinic or physiology laboratory from Cyon-Frank-Starling curves expressing the “law-of-the-heart” (Fig 2).

In this plot, parameters (e.g. CO = cardiac output, AoP = aortic pressure, dP/dt_{max} = maximal rate of rise of left ventricular pressure) of systolic function are graphed on the ordinate against the degree of stretch on the myocardial fibers just before they contract graphed on the abscissa. The degree of stretch on fibers forming the wall of the left ventricle is, of course, intimately related to the EDV, and (in the clinic) it is termed the preload (PL). Actually, Cyon, Frank, and Starling stated that systolic function generated by the left ventricle depended upon the level of resting stretch on the fibers if all other factors—in particular hindrance to ejection—remained constant (Cyon, 1866; Frank, 1899; Starling, 1918). The molecular mechanism serving as the basis for this relationship is that the degree of stretch on the fibers just before they contract determines the number of heavy meromyosin cross-bridges that may contact binding sites on Tc, and on the avidity with which Ca^{++} binds to Tc. However, increase in force generation by increasing stretch depends principally on improved binding of Ca^{++} to Tc.

In Fig 2, the vertical, dotted line, originates from a point on the abscissa that represents a degree of stretch (i.e. PL), the number of heavy meromyosin cross-bridges that cycle, and the avidity with which Ca^{++} binds to Tc. The horizontal dotted lines from the curves terminate at points on the ordinate that represent systolic function. The curved lines on the graph represent 3 different states of contractility (inotrope). For each inotropic state, the systolic force increases for increases in preload. For each inotropic state, the systolic force decreases for decreases in preload. Increased force can be generated by either increasing PL or from the same preload but increasing contractility. Similarly, decreased force can be generated by decreasing preload or from the same

preload by decreasing contractility.

Thus, systolic function depends upon both the inotropic state and PL, and attempting to infer the inotropic state by examining systolic events without considering if PL is incorrect (Hamlin and del Rio, 2010).

Contractility may be assessed using Cyon-Frank-Starling curves that require assessment of systolic function and knowledge of preload. Of course heart rate, stiffness of the aorta, compliance of the left ventricle, and many other parameters of cardiovascular function must be held constant to comply with the Cyon-Frank-Starling restriction. Systolic function is then monitored by SV, CO, developed left ventricular pressure (i.e. peak systolic minus end-diastolic), aortic pressure, $dLVP/dt_{max}$, or many other indices, and preload is altered by increasing or decreasing venous return. The plot of systolic function versus preload (degree of stretch on the fibers just before contraction) produces a baseline Cyon-Frank-Starling curve. Often left ventricular end-diastolic pressure (LVEDP) is used as an assessment of preload (PL). However, PL is determined not only by LVEDP, but also by intrapleural pressure (Ppl) and stiffness of the ventricle (ϵLV). Therefore, if EDP is substituted for PL, it must be confirmed—or assumed—that both Ppl and ϵLV were not affected by the intervention. Next, an intervention (drug or disease) that may change contractility is imposed, and another curve of systolic functions versus preloads is generated. The points at equal preloads for the 2 curves are compared. If the points have identical coordinates, there has been no change in contractility; if the points for the second curve are above those for the baseline curve, the intervention was a positive inotrope; if the points for the second curve are below those for the initial curve, the intervention was a negative inotrope.

3. Pressure-Volume (PV) loop, end-systolic pressure-volume relation (ESPVR), and preload recruitable stroke work (PRSW)—time-varying elastance (Ees)

The concept of time-varying elastance (elastance is the reciprocal of compliance or ease of filling) model was established in 1973 by Suga and colleagues (Suga et al., 1973) and has been used as a contractility index in man since 1976 (Weisfeldt, 1976). A small catheter with a high-fidelity micromanometer (Millar instruments, Texas, USA or Scisense, Ontario, Canada) at the tip for measuring the left ventricular pressure and with 4-10 metal rings used for measuring volume (Baan et al., 1984) by electrical impedance is advanced into the ventricle via a carotid artery. A plot (pressure-volume loop) of ventricular pressure (ordinate) versus ventricular volume (abscissa) is generated. In addition, a family of loops is made as the ventricle becomes temporarily smaller due to partial occlusion of venous return. From analysis of this family of loops, maximal information can be gleaned about (1) systolic and diastolic function of the ventricle, (2) how the heart interacts with the arterial tree, and (3) the energetic balance of the heart (i.e. the ratio between oxygen demand and work).

The single pressure-volume loop:

The left ventricle generates a pressure-volume loop (A, B, C, D) for each cycle of contraction (Fig 3). BD occurs during systole; DB occurs during diastole. Isovolumetric phases, during which times pressures change but volumes do not, are BC for systole and DA for diastole; isotonic phase, during which volumes change but pressure changes only slightly, are CD for systole and AB for diastole. BC is produced when the ventricular pressure rises quickly but the volume does not change. This isovolumetric period occurs because the mitral valve is closed (ventricular pressure exceeds atrial pressure) and the aortic valve has not yet open (ventricular pressure has not yet exceeded the pressure in the aorta resulting from the elastic recoil of the aorta). CD is produced when ventricular pressure exceeds aortic pressure and the ventricle pumps a stroke volume (SV) into the proximal portion of the aorta. In fact, stroke volume is equal to the horizontal distance between C and D. During this phase ventricular pressure elevates only slightly, since energy of contraction is transferred to motion rather than tension. DA is the period of relaxation when ventricular pressure falls rapidly, but there is no change in volume. The rapidity with which this pressure falls is related to the rapidity with which Ca^{++} is driven off of Tc and resequestered into the SR through the SERCa channel in the SR membrane (Bers, 2002). Energy for this event comes from further hydrolysis of ATP. During this phase of diastole, the ventricle is closed because the aortic valve is closed (aortic pressure exceeds left ventricular pressure) and the mitral valve has not yet opened (left ventricular pressure still exceeds left atrial pressure). It is important to note that, despite the ventricle relaxing, there is no ventricular filling. However, during AB the left ventricle fills even though there is little change in pressure. The aortic valve remains closed but the mitral valve is open. The slope of AB reflects the property of dynamic stiffness. The steeper the slope (i.e., then greater the pressure required to achieve a given volume), the stiffer the ventricle, since a steep slope indicates that a greater pressure is required to achieve each volume. The end-diastolic pressure volume point (B) reflects static stiffness, since it is stiffness at only a single time. Stiffness is the opposite of lusitrope, therefore analysis of the PV loop is useful for estimating both the dynamic and static components of lusitrope. Since time is not expressed in the PV loop, the loop provides no information about isovolumetric events such as rate of decrease in pressure, the maximal value of which is determined by the rate of resequestration of Ca^{++} from Tc to the SR via the SERCa channel. It is estimated that approximately 50% of the morbidity and mortality from heart disease arise from reduction in lusitrope; therefore, lusitrope is as important a parameter as inotrope (Aurigemma, 2006; Owan et al., 2006).

With respect to valves opening and closing, the mitral valve opens at A and closes at B; the aortic valve opens at C and closes at D. With respect to

Ventricular Pressure-Volume (PV) Loop

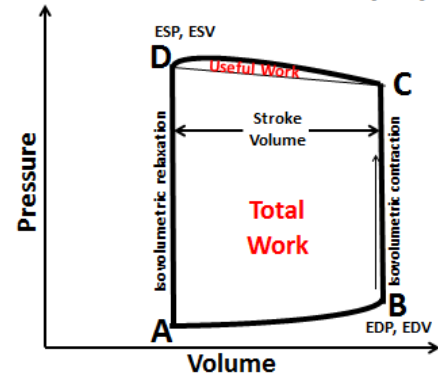


Figure 3 shows Pressure-volume loop of the left ventricle. The mitral valve closes after the onset of systole. This phase is called isovolumetric contraction because the mitral valve is closed and the aortic valve is not yet opened; therefore, the volume is constant. When the aortic valve opens and the pressure in the ventricle meets the aortic pressure (afterload), the ejection phase begins. Aortic valve closes at the point of end-systolic pressure-volume relationship (ESPVR). The next phase is called isovolumetric relaxation since the aortic valve is closed but the mitral valve is not open yet; therefore, the volume is constant again. The mitral valve opens when the left ventricular pressure falls below the pressure in the left atrium. The blood flows from left atrium to the left ventricle, ventricular filling. The filling phase ends at the point of end-diastolic pressure-volume relationship (EDPVR).

ventricular volume, end-diastolic volume occurs at B but remains until C; end-systolic volume occurs at D but remains until A.

The pressure-volume loops proceed with counterclockwise rotation. The area within the counterclockwise component of the pressure-volume loop measures total work performed by the ventricle. Two very important instants are B (the end-diastolic pressure-volume point) that estimates end-diastolic stiffness, and D (the end-systolic pressure-volume point) that measures end-systolic stiffness (elastance) which is used for calculating contractility.

Pressure-volume loops are enormously useful for identifying and understanding the pathophysiology of aortic and mitral regurgitation and of an interventricular septal defect. With all 3 of those lesions, the left ventricle changes volume during what should be isovolumetric phases (when no changes in volume should occur), and the changes and the degree to which they change identify both the lesion and the magnitude of the abnormal blood flow.

A family of pressure-volume loops:

From the family of PV loops (Fig 4), myocardial contractility may be inferred from either the end-systolic pressure-volume relationship (ESPVR) or from preload recruitable stroke work (PRSW). Both methods require obtaining a family of curves generated by recording individual loops during a brief period of decreased venous return leading to reduction in preload. While recording a number of pressure-volume loops, they are normally

“Family” of pressure-volume loops generated by decreasing preloads (PL). [Steepness of E_{ES} (the slope of the end-systolic pressure-volume points (ESPVR) expresses myocardial contractility.]

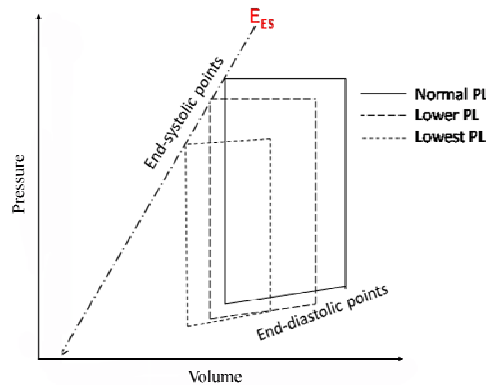


Figure 4 shows a family of pressure-volume loops. A series of loops was obtained by inflation of a balloon in the caudal vena cava to reduce preload. Myocardial contractility is measured as the slope of the lines connecting the end-systolic points on the family of loops.

superimposed except for slight variations in their positions produced, when during inspiration, end-diastolic volume and pressure, peak systolic pressure, and stroke volume decrease. During expiration just the opposite occurs. However, if 6 to 10 heart beats, venous return is diminished by occluding the caudal vena cava, a family of pressure-volume loops is generated in which end-diastolic pressure and volume, stroke volume, and end-systolic pressure and volume decrease according to the Cyon-Frank-Starling law-of-the-heart. During diminished venous return, the centroid of the area of the pressure-volume loop drifts leftward and the area diminishes. Three enormously valuable bits of information about the myocardium can be gleaned from this family of curves: (1) contractility, (2) lusitrope, and (3) energetics.

End systolic pressure volume relationship (ESPVR)

ESPVR identify the end-systolic points of pressure-volume for all loops as the heart becomes smaller due to occlusion of the vena cava. Each point refers to end-systolic elastance because it occurs at end-systole, and the ratio of pressure to volume is elastance. Connect the end-systolic points, and construct a straight line (E_{es}), named the end-systolic pressure volume relationship (ESPVR) that connects the points (Suga et al., 1973; Sunagawa et al., 1983). This line represents time-varying elastance. During some times the points may not fall on the line (i.e. the line may be curvilinear), so it is important to select those points for which the r^2 of the line is > 0.9 . The slope of the line, E_{es} , represents myocardial contractility because it expresses the maximal pressure that can be developed from any/all preloads.

The line that represents time-varying elastance also possesses enormous importance in estimating the energetic balance of the heart (Asanoi

et al., 1996). Energetic balance is the ratio between myocardial oxygen demand to oxygen delivery. Myocardial oxygen demand (MVO_2) is determined principally by heart rate (HR), myocardial contractility (V_{max}), and peak (p) myocardial tension. Whereas peak myocardial tension (T_p) equals aortic diastolic arterial blood pressure ($PAO_{diast.}$) times end-diastolic radius (EDr) or volume (EDV) of the ventricle divided by end-diastolic wall thickness (EDWT) of the ventricle. Delivery of oxygen depends upon lung function, amount and health of hemoglobin (Hb), and coronary blood flow [$Q_{cor} \approx (PAO - PRA) / HR$]. Thus, energetic balance depends upon HR, V_{max} , $PAO_{diast.}$, PRA, Hb, EDV, ESV, SV; V_{max} , EDV, SV, $PAO_{diast.}$ which may be measured from the PV loop and the slope of ESPVR, and other determinates of energetics (e.g. HR, Hb, EDWT) can be measured by other means (e.g. echocardiography).

Though slope of the P-V relation is used as a gold standard for contractility index, there are some potential limitations. Firstly, the end-systolic P-V relation is not always linear. The work of Burkhoff and colleagues (1987) demonstrated that the ESPVR tended to be concave downward at a high E_{max} and upward at a low E_{max} . Secondly, E_{max} must be normalized for different heart size (Suga, 1984). Finally, E_{max} is slightly dependent upon loading conditions (Sugiura et al., 1989). Despite these limitations, the E_{max} concept is still considered the gold standard to characterize the myocardial contractility.

Preload recruitable stroke work (PRSW):

Instead of estimating contractility as the slope of the line produced by graphing end-systolic pressure (ESP) versus end-systolic volume (ESV) during reductions in preload and representing ESPVR, contractility may be estimated even better as the slope of the line produced by graphing stroke work (SW) versus left ventricular end-diastolic volume (EDV) during reductions in preload and representing preload recruitable stroke work (Takeuchi et al., 1992; Takaoka et al., 1995; McClain et al., 1998). From each PV loop, SW is taken as SV (EDV-ESV) times ESP, and preload is taken as EDV. Then, a line is produced by graphing SW versus EDV for all PV loops at differing preloads. The line connecting points of PRSW is superior for estimating contractility than the line connecting points of ESPVR for 2 major reasons. First, the points forming PRSW produce a near straight line. Second, the slope of the PRSW line is independent of the size of the animal, i.e. it is nearly the same for all animals. ESP for all animals is approximately 100 mmHg, whereas ESV varies from 0.25 ml for a mouse with an EDV 0.5 ml to 50 ml for a large dog with an EDV of 100 ml. This produces ratios of ESP: ESV of 100: 0.25 (400) for a mouse and 100: 50 (2) for a dog, and of producing highly variable slopes from the highly variable ESP: ESV ratios. On the other hand, for PRSW based upon ratios of SW: EDV, SW is SV x ESP, EDV is EDV, so the SW: EDV ratio is (SV x ESP): EDV, or SV/EDV x ESP. SV/EDV (approximately 0.5) and ESP

(approximately 100) are fairly constant (approximately 0.5) among species; therefore, the slopes from PRSW have larger r^2 and have similar values among species than for ESPVR.

4. $dLVP/dt_{max}$

The maximal rate of rise of left ventricular pressure (dP/dt_{max} or $dLVP/dt_{max}$) is obtained by differentiation of the left ventricular pressure pulse. dP/dt_{max} usually occurs at the end of the period of isovolumetric contraction, just before the ventricle begins to eject. In both experimental and clinical settings, dP/dt_{max} can be obtained by placing a micro-tip manometer catheter within the left ventricular cavity and recording both left ventricular pressure and its derivative (Fig 5). When left ventricular pressure is constant (i.e. there is no change in pressure), the derivative is 0; when left ventricular pressure increases, dP/dt is positive; when left ventricular pressure decreases, dP/dt is negative; and the dP/dt_{max} or dP/dt_{min} are measured, the rates of change of pressure are the greatest. dP/dt_{max} is species and heart rate dependent, and varies from 400 mmHg/sec for a guinea pig (Hamlin et al., 2004; Mooney et al., 2012), to 7,000 mmHg/sec for a mouse (Reddy et al., 2007), and is between 1000 and 5000 mmHg/s for dog (Markert et al., 2012). The cost for obtaining dP/dt is relatively low, and the technique is quite simple when compared to the gold standard obtained from pressure-volume loops. Although used frequently, dP/dt_{max} , in fact, may or may not be an index of cardiac contractility, since it is influenced by afterload and preload, and afterload (peak myocardial tension) is influenced by left ventricular radius, pressure and wall thickness that occur at end-diastole just before ejection begins (Katz, 2006). Therefore, the change of dP/dt_{max} reflects the change of contractility only when other factors that might influence it are unchanged. Recently, Hamlin and del Rio (2012) proposed the new term of dP/dt_{max} as "baroinometry". Since it is well-known that dP/dt_{max} is affected by both afterload (i.e. aortic diastolic pressure) and preload (left ventricular end diastolic pressure). dP/dt_{max} may decrease in response to arteriolar dilator drugs even though myocardial contractility has not changed or may have even increased (Hamlin and del Rio, 2012). On the other hand, dP/dt_{max} may increase without an increase in contractility in response to increase venous return via the Cyon-Frank-Starling mechanism (Cyon, 1866; Frank, 1895; Starling, 1918). Schmidt and Hoppe (1978a) demonstrated that the $dLVP/dt_{max}$ was strongly dependent on preload in the canine heart and lung preparation. The authors also showed that the relation between the $dLVP/dt_{max}$ and EDP demonstrated the steepest slope right after isolation and continued to decline once the heart deteriorated. The same authors showed that $dLVP/dt_{max}$, when compared with other indices of cardiac contractility (e.g. V_{max} , VCE_{max}), was more affected by changes in preload than V_{max} . Of course if preload was held constant, then dP/dt_{max} was a sensitive indicator of contractility (Schmidt and Hoppe, 1978b).

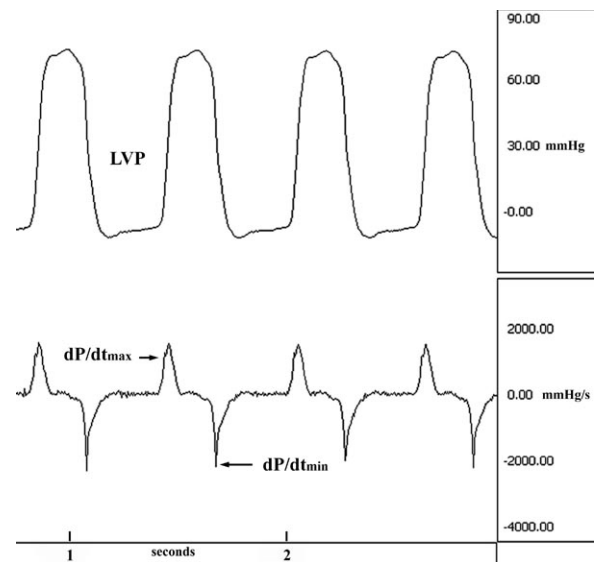


Figure 5 shows left ventricular pressure (LVP; top panel) and its maximum rate of rise of the LVP (dP/dt_{max} ; bottom panel) of the anesthetized dog.

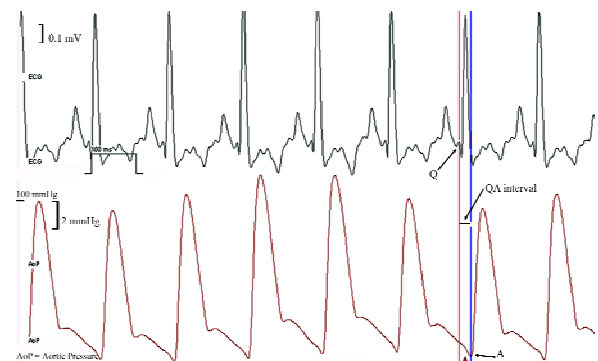


Figure 6 shows a simultaneous ECG (top trace) and arterial pressure pulse (bottom trace) from a guinea pig, demonstrating how QA interval is measured. The QA interval represents time from the beginning of Q wave in the electrocardiogram (ECG) tracing to the beginning of the aortic pressure. It is an indirect measure of the duration of isovolumetric contraction without need for left ventricular pressure measurement.

According to the Bowditch effect (Lakatta, 2004), it is also recognized that dP/dt_{max} , and all other indices of contractility, is influenced by heart rate. That is dP/dt_{max} will increase when the heart rate (frequency) increases and vice versa when heart rate decreases. In the canine heart and lung preparation, increased heart rate by 30 bpm resulted in a 20% rise of $dLVP/dt_{max}$ (Schmidt et al., 1979). Although much work has been done to determine the equation for adjusting dP/dt_{max} to heart rate, Pedraza-Toscano (2006) found that dP/dt_{max} (mmHg/sec) = 1394 (mmHg/sec) + $12.42HR$ (beats/minute) in awake, freely-moving dogs. Recently, a complicated equation that has been used for correcting dP/dt_{max} for heart rate in conscious dogs, minipigs, and cynomolgus macaques has been proposed by Markert and colleagues (2012). The proposed formula was $LVdP/dt_{maxc} = a*(HR)^b*exp(c*HR)$, whereas the parameters (a, b, and c) were estimated using the glm

function in R 2.13.0, which could be downloaded from <http://www.r-project.org/>. By using both positive and negative inotropic agents, the formula demonstrated the inotropic effects of drugs independent from the change of heart rate.

5. QA Interval

The QA interval was first purposed as an indirect index of myocardial contractility in 1986 as a result of studies on anesthetized dogs (Cambridge and Whiting, 1986). The shorter the QA interval, the greater the contractility. The QA interval is defined as the duration from the onset of the Q wave on the electrocardiogram (ECG) to the initial upstroke on the aortic pressure wave recorded, most often, from a catheter-tip or transducer located in the aorta between the renal and iliac arteries (Fig 6). It is thought that QA interval measures the duration of isovolumetric contraction without need to catheterize the left ventricle, and that this interval relates inversely to contractility.

However, there are numerous factors—other than myocardial contractility—that contribute to the duration of QA: (1) electropressor latency (time between depolarization and completion of excitation-contraction coupling when contraction begins), (2) isovolumetric contraction (time between onset of contraction and beginning of ejection), (3) the amount of pressure the ventricle must generate from the onset of contraction until the onset of ejection, (4) velocity of propagation of the pulse wave down the aorta (determined principally by the stiffness of the aorta), and (5) distance between the ventricle and the point in the aorta where the pulse is being measured. Therefore, it seems that QA interval depends on many factors other than myocardial contractility (Hamlin and del Rio, 2010) and, if it changes in response to a drug or disease, the change may not be attributed to altered contractility, alone, unless potential effects on other determinants are known.

The QA interval has been demonstrated to correlate inversely with other indices of myocardial contractility (i.e. dP/dt_{max}) in rats, guinea pigs, dogs, and monkeys (Gras et al., 2000; Takahara et al., 2001; Tontodonati et al., 2007; Priori et al., 2008; Adeyemi et al., 2009; Norton et al., 2009; Mooney et al., 2012; Saengklub et al., 2012). Mostly, the animals were instrumented with a radiotelemetry device for simultaneous recording of electrocardiograms and pulsatile arterial pressure. In both conscious rat and dog, inverse linear correlation between $LVdP/dt_{max}$ and \log_{10} QA interval was reported (Adeyemi et al., 2009; Norton et al., 2009).

6. Ejection Fraction (EF) and Fractional shortening (FS)

It is well-known that echocardiography is now standard diagnostic non-invasive technique in human cardiologic examinations. The M-mode echocardiography was first described in 1953 by Inge Edler and Hellmuth Hertz (Singh and Goyal, 2007). After that the technique was carried forward and the article about the left ventricular wall thickness,

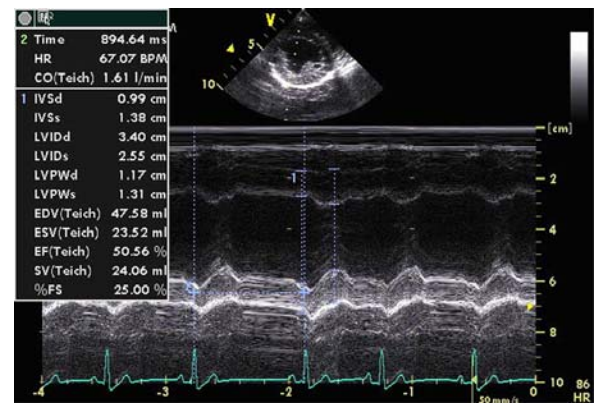


Figure 7 shows an echocardiogram from a dog. In the short-axis view of the left ventricle, an M-mode cursor is placed through a left ventricle, perpendicular to the interventricular septum and left ventricular wall just below the tips of the mitral valves at the largest ventricular chamber size (top panel). Bottom panel shows the M-mode image of left ventricular chamber at the middle of the picture and the electrocardiogram located at the bottom below the left ventricular free wall. Dash lines represent the measurement of the left ventricular dimension and the values are demonstrated in the table on the left side of the picture. (Picture by courtesy of Dr. Pedro Vargas Pinto).

internal dimensions, stroke volume, ejection fraction, and valvular regurgitation was first published in 1968 by Feigenbaum and colleagues (1968). Ejection fraction is defined as the fraction of the end-diastolic volume that is ejected as the stroke volume ($EF = SV/EDV$). It measures how well the heart pumps the blood out which reflects the myocardial contractility. In fact, EF is a mathematic equation and may be obtained from cardiac imaging techniques other than echocardiography (i.e. magnetic resonance imaging, computerized tomography). The EF in both experimental animals and patients is usually obtained from M-mode of left ventricular image of echocardiogram (Fig 7). The proper image is obtained by placing M-mode cursor through the septal and posterior LV wall just above the tip of the mitral leaflets in a parasternal long axis view or placed the M-mode cursor directed between the papillary muscles in a parasternal short axis view at the level just beneath the mitral valve (Schiller et al., 1989). By placing a marker of the LV wall dimension during systole and diastole, the echocardiogram machine will generate the number of EF. In several clinically settings, the EF can be used as a predictor of early and late mortality in patients with coronary bypass and patients with heart failure (Soliman Hamad et al., 2010; Campbell et al., 2012).

As with other myocardial contractility indices, the EF is load-dependent with afterload more influential than preload. Moreover, measurement of EF by m-mode evaluates information of myocardial contractility only along a single line. If the regional wall motion of the LV is abnormal (i.e. subject with coronary artery disease), the M-mode beam may not transit through that region which will interpret EF higher than what actually happen. In addition, the M-mode beam usually transverses the LV in a tangential manner which may not reflect the true minor axis

dimension in some situations (i.e. subject with emphysema or elderly patients) and thus overestimates the true internal dimension (Suga et al., 2000).

Summary/Conclusions

At the present time, data derived from a single PV loop or from a family of PV loops are the closest to ideal index of cardiac contractility due to its less sensitivity to load and frequency. The technique is challenging and will be improved to use in clinical setting in the near future. Other indices (i.e. dP/dt_{max} , ejection fraction, QA interval, and V_{max}) are also usable for the measurement of myocardial contractility with caution of their limitations and assumptions.

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