A PERSONAL VIEW

Understanding preload and preload reserve within the conceptual framework of a limited range of possible left ventricular end-diastolic volumes

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Peverill RE. Understanding preload and preload reserve within the conceptual framework of a limited range of possible left ventricular end-diastolic volumes. Adv Physiol Educ 44: 414–422, 2020; doi: 10.1152/advan.00043.2020.—Preload has been variously defined, but if there is to be a direct relationship with activity of the Frank-Starling mechanism in its action to increase the force and extent of contraction, preload must directly reflect myocardial stretch. The Frank-Starling mechanism is activated during any stretch of a cardiac chamber beyond its resting size, which is present immediately before contraction. Every left ventricle has an intrinsic and limited range of possible volumes at end diastole. There is a curvilinear relationship between left ventricular (LV) end-diastolic pressure (LVEDP) and LV end-diastolic volume (LVEDV), and, at maximal or near maximal LVEDV, there will be a high LVEDP. Within the possible range, the LVEDV will be determined by the extent of filling, any change in LVEDV will result in changed activity of the Frank-Starling mechanism, and change in LVEDV might, therefore, be considered to represent change in preload. On the other hand, it is the difference between the current and the maximal possible LVEDV (or the preload reserve) that may be of the most clinical relevance. There is a reciprocal relationship between preload and preload reserve, with minor or absent LV preload reserve indicating that there will be either minimal or no increase in stroke volume following intravenous fluid administration. As left atrial pressure can remain within the normal range when the LVEDP is elevated, it is LVEDP, and not left atrial pressure, that provides the most reliable guide to preload reserve in an individual at a specific period in time.

Frank-Starling mechanism; left ventricle; preload; preload reserve

INTRODUCTION

Preload refers to a concept that is not only central to the understanding of cardiac and circulation physiology, but that is also a vital, practical consideration in clinical practice when intravenous fluid resuscitation is being considered. However, despite this fundamental importance, and the common use of the term, there has been no consistent definition of preload used in either the teaching, clinical, or research settings. Thus, in the physiology, cardiology, and critical care literature, cardiac preload has been variably defined as a pressure, a volume, or, less commonly, as end-diastolic wall stress, a divergence in definitions that has been the subject of previous discussion (38, 41, 50). In four well-known physiology textbooks, preload was considered to be left ventricular (LV) end-diastolic volume (LVEDV) in one (43), the LV end-diastolic pressure (LVEDP) in two (27, 45), and there was no clear differentiation between LVEDV and LVEDP in another (34). The definitions or interpretations of preload in cardiology textbooks have generally emphasized the importance of LVEDV, but isolated statements from these books may still be considered confusing about whether preload should be thought of as a volume or a pressure, e.g., “The preload reflects the venous filling pressure that fills the left atrium, which in turn fills the left ventricle during diastole” (44). There is also confusion about which pressure, e.g., “In the clinical setting, end-diastolic pressure and pulmonary capillary wedge pressure are used frequently as measures of preload” (30). Preload has often not been specifically defined when the term is used in the critical care literature, but, when defined, definitions have also been variable: for example, “Preload is defined as the myocardial fiber length at end diastole” and then in the next sentence of the same article, “At the organ level, preload may theoretically be assessed by measuring LV end-diastolic volume” (62). A single measure of LVEDV has also been used as to represent preload in scientific studies (14). The notion of preload as end-diastolic wall stress has received consideration in both the physiological and critical care literature, but there has also been disagreement regarding the appropriateness of a wall stress definition of preload (13, 41, 50).

It will be argued in this review that a direct linear relationship between preload and activity of the Frank-Starling mechanism underlies the importance of the concept of preload, and that definitions of preload based on a single measure of any of LV volume, pressure, or wall stress preclude such a direct relationship. The main themes of this review are as follows. 1) There is an intrinsic (and limited) range of possible LVEDVs for any ventricle, and the extent of LV chamber stretch within this range is the only variable that provides a direct linear relationship with the Frank-Starling mechanism. 2) LVEDP and left atrial (LA) pressure, or its practical alternative of pulmonary arterial wedge pressure (PAWP), can only be presumed to be equivalent in young, healthy hearts and should not be used interchangeably in other settings, and none of these pressures are linearly related to LV stretch. 3) Preload reserve is the maximal increase in LVEDV that is possible during an attempt to increase cardiac filling, its absence is best predicted by a high LVEDP (and even more specifically by a high transmural LVEDP), and estimation of whether there is preload reserve is the most vital consideration when fluid administration is being considered. The above concepts are of fundamental importance for a practical understanding of preload, preload...
reserve, and the Frank-Starling mechanism by students of physiology, cardiologists, emergency physicians, and intensivists and also provide a foundation for decision making regarding fluid resuscitation in all clinical disciplines.

An understanding of the concepts that relate to preload and its importance for understanding heart function benefits from a historical perspective, and such a perspective can be found in complementary reviews that describe the early contributions to the formulation and understanding of what has become commonly known as the Frank-Starling mechanism (26, 33, 42, 64). It was experiments in the early 19th century in skeletal muscle that first showed that progressive stretching of a resting muscle before contraction results in not only an increase in resting tension, but also greater tension development and energy production during contraction (33). That this principle also applied to cardiac muscle was demonstrated in the late 19th century by a number of investigators who showed that the force of contraction, stroke volume (SV), and stroke work (SW) all increase as a result of a larger ventricular size just before contraction (33, 64). In his Linacre Lecture in 1915, Starling stated, “The law of the heart is thus the same as the law of muscular tissue generally, that the energy of contraction, however measured, is a function of the length of the muscle fiber” (58). Our understanding of the Frank-Starling mechanism has been further refined by numerous experiments over the last 100 yr, encompassing studies using isolated cardiac myocytes, strips of cardiac muscle, isolated heart preparations, intact animals, and also studies in anesthetized and conscious humans.

**Stretch in Cardiac Muscle Experiments**

The properties of myocardial contraction can be studied in vitro by mounting a mammalian papillary muscle, trabeculae, or strip of atrial myocardium in an oxygenated, physiological salt solution (19, 56). The cardiac muscle is attached at each of its ends using equipment that enables the measurement of muscle tension at rest and during contraction. When the cardiac muscle is stimulated while held at a fixed length, the resulting contraction is termed isometric, and evaluation of contraction relies on both the timing and magnitude of the active tension. When the stimulated cardiac muscle is allowed to shorten, the resultant contraction is termed isotonic, and evaluation of contraction in shortening cardiac muscle can also include measurement of the amplitude of motion and the minimum muscle length (at the end of contraction), as well as of the developed tension.

**Preload** was the term originally used for a weight attached to one end of the muscle preparation that was used to stretch the muscle before contraction (57). To normalize for the variation in thickness of the muscle preparation, the force generated by the weight was divided by the cross-sectional area of the muscle to give a resting muscle tension (g/cm²). While it was the muscle tension just before contraction that was considered to be preload in the classical experiments, the vital importance of muscle length was also recognized. Any cardiac muscle preparation (down to the level of the cardiomyocyte) will have a resting or slack length (Lrest), this being the length of the unstretched preparation when it is fully relaxed (32). Passive stretch of the cardiac muscle before contraction results in increased force of the subsequent contraction, and the precontraction muscle length at which the subsequent isometric force is maximal has been termed Lmax (32). Thus there is an intrinsic range of possible muscle lengths for a particular muscle ranging from that at Lrest to that at Lmax. At muscle lengths less than Lmax, both the resting tension and the subsequent active tension are less than maximal. The relation between muscle length and active tension is not linear, and small decreases in length below Lmax can result in a substantial decline in both passive and actively developed tension. On the other hand, experiments done at Lmax need to be differentiated from the situation in the normal heart, which in most cases is not functioning at its maximum volume.

In isotonic muscle experiments, increased preload (and thus a longer precontraction muscle length) leads to increases in the rate of tension development and the velocity of shortening, and also to a larger amplitude of contraction (57). It is important to emphasize (as in my teaching experience it is commonly misunderstood) that, in these experiments, the minimum muscle length (i.e., the muscle length at the end of contraction) does not decrease as a result of an isolated change in preload (8, 57, 59, 63). In other words, the increase in contraction amplitude following an increase in preload is entirely due to the contribution of the increased stretch, and thus increased myocardial length, before the contraction.

A full understanding of myocardial contraction also requires consideration of the load on the myocardium during contraction, most commonly known as the afterload. In papillary muscle experiments, the afterload (sometimes known as the total load, as it also included the preload) was a weight that was lifted by the muscle during isotonic contraction, and similar to preload, this weight was normalized to the cross-sectional diameter of the muscle preparation and expressed as muscle tension (57). The higher the afterload, the longer the time interval between the electrical stimulus and the beginning of muscle shortening, the smaller the amplitude of contraction, and the longer the minimum muscle length at the end of contraction (63). Similar to afterload, changes in contractility lead to changes in both the amplitude of contraction and minimum muscle length, with increased contractility resulting in both a lower minimum muscle length and a larger amplitude of contraction, and decreased contractility having the opposite effects. Thus preload, afterload, and contractility all have independent effects on the amplitude of contraction, and each of these modifiers of contraction can be defined in part by the aspect of the muscle preparation that they do not affect. Thus neither afterload nor contractility have a direct effect on the resting or stretched muscle length before contraction, whereas preload has no direct effect on the minimum muscle length after contraction.

**The Functions of the Frank-Starling Mechanism**

When the cardiac muscle becomes stretched an extra amount, as it does when extra amounts of blood enter the heart chambers, the stretched muscle contracts with a greatly increased force, thereby automatically pumping the extra blood into the arteries [Arthur C. Guyton (25)].

The Frank-Starling mechanism modifies the output of each of the four cardiac chambers on a beat-to-beat basis. Each of the cardiac chambers can increase its output following in-
creased filling, but it is change in LVEDV that is the final and essential part of the pathway that allows the Frank-Starling mechanism to convert an increase in systemic venous return to an increase in the SV ejected into the systemic circulation. The Frank-Starling mechanism is also a vital component of the regulation of the heart and circulatory system because it ensures that the amount of blood pumped out of the left and right ventricles is equal (7). This means that blood does not have the opportunity to accumulate in either the systemic or pulmonary circulations, and, given that there is restriction of total cardiac volume by the pericardium, it acts to prevent progressive volume overload of one ventricle, resulting in compression of the other ventricle. It is important to appreciate that the Frank-Starling mechanism is acting during every cardiac cycle in the normal human heart, as there is always a degree of myocardial stretch before contraction. Thus reductions in intravascular volume, and therefore LV filling and LVEDV, lead to a lower SV and are a reflection of the same mechanism by which increases in LV filling lead to increases in SV (12, 40). Possibly less well recognized is that an increase in LVEDV with resulting activation of the Frank-Starling mechanism can provide an acute compensation for reduction in SV due to diminished contractility or increased afterload. An increase in LVEDV can also provide compensation for a chronic decrease in contraction, but in this case a larger LVEDV may also reflect a positive remodeling process that is independent of the degree of chamber stretch.

**Stretch and the Frank-Starling Mechanism in the Intact Heart**

Specific issues related to the relationships between cardiac pressures, cardiac volumes, myocardial stretch, and cardiac performance have been evaluated in a number of important studies in the intact animal and human, beginning in the 1940s (5, 24, 28, 40, 54, 55). That SW, rather than either SV or cardiac output (CO), was the most appropriate measure of the energy of LV contraction when investigating the “Law of the Heart” was suggested by Sarnoff and Berglund in 1954 (54). In a study performed in anesthetized dogs, a family of LV and right ventricular (RV) function curves was described in which there was a consistent but nonlinear relationship between ventricular SW and mean atrial pressure (54). SW was calculated as the product of SV and the difference between mean arterial and mean atrial pressures. The ventricular function curve (of SW) showed an initial steep rise, but at high atrial pressures the curve flattened off to a plateau. That mean right atrial (RA) or LA pressures may not be identical to RV end-diastolic pressure (RVEDP) or LVEDP, respectively, was considered by the authors, but it was observed that there was a close linear relationship between atrial and end-diastolic pressures on either side of the heart in normal dogs when these pressures were in the low-to-medium range. On the other hand, while a close relationship was found between atrial pressure and the SW of the ventricle on the same side of the heart, such a relationship was not found 1) between RA pressure and LV SW, or between LA pressure and RV SW, 2) between either LA or RA pressure and SV, or 3) between either atrial pressure and CO (54).

In their important 1954 study, Sarnoff and Berglund (54) referred specifically to previous disagreement about whether it is the volume of the ventricle or the pressure in the ventricle that is most closely associated with the extent of the subsequent ventricular contraction. When the pressure around the ventricles was increased by the production of cardiac tamponade, the ventricular SW of both ventricles fell, despite increased atrial pressures, and thus the ventricular function curves during tamponade showed an apparent suppression. If, however, the effective filling or transmural pressure (pericardial pressure minus atrial pressure) was plotted against SW, no suppression of the ventricular function curves was observed. This observation was also in accord with the view that the work of the ventricle is a function of diastolic fiber length, and that this length is related to the effective end-diastolic pressure. As nonlinear curves have the disadvantage of being difficult to quantify, and the use of pressure as the index of preload introduced susceptibility to such extraneous influences as pericardial pressure and septal shifting, Sarnoff and Berglund speculated that a plot of ventricular SW against ventricular volume (or fiber length) would be closer to a straight line. In a review from the following year, Rushmer (51) also emphasized the importance of cardiac fiber length and thus chamber size, rather than LVEDP, in any investigation of the Frank-Starling mechanism.

Some 30 yr later, Glower et al. (24) investigated the relationship between preload and SW in chronically instrumented dogs, with preload assessed as either end-diastolic segment length or chamber volume. The relationship of SW with varying end-diastolic segment lengths or chamber volumes within individual animals, termed the preload recruitable SW (PRSW) relationship, was highly linear in every study (mean r = 0.97). Previous nonlinear relationships between SW and pressures could thus be explained as being due to the exponential relation between end-diastolic pressure and volume. Glower et al. concluded that avoiding pressure as the measure of preload should minimize the problematic influences of pericardial pressure, septal shifting, or respiratory variations in intrapleural pressure. Linearity of the PRSW relationship also provided a quantification of cardiac performance by a simple slope and x-intercept. It is important to emphasize that the linear relationship between LVEDV and SW that was demonstrated in this study was based on multiple values from individual animals during vena cava occlusion induced reductions in venous return (and thus reductions in LVEDV), and not on single values of LVEDV from individual members of the group. The findings are, therefore, consistent with the notion that change in LVEDV is directly related to change in SW, but does not imply that a single measure of LVEDV can predict SW (24). It is also important that it is change in SW, rather than SV, which has the closest relationship with a change in LVEDV, and that SW is dependent on the induced change in pressure from diastole to systole as well as on the SV. It is clear from a reorganization of the formula for ejection fraction (EF) (SV/LVEDV) to focus on SW (EF × LVEDV) that a single measure of LVEDV can only predict SV if the EF is also known. To complicate this issue further, an increase in afterload can lead to a decrease in EF. Further discussion of the effects of afterload on SV and SW are beyond the scope of this review.

**Stretch and the Sarcomere**

The Frank-Starling mechanism is manifest at the cellular level, within the sarcomere, where active force generation is a function of sarcomere length (22). The mechanisms responsible for length-dependent activation within the sarcomere are still not fully understood, but increased responsiveness to calcium is a likely contributor, and a reduction in interfilament...
lattice spacing has also been considered as a possible mechanism (22). It is now believed that the giant protein titin, which is located in the sarcomere between the Z and M lines, functions as a bidirectional spring and can store energy during stretch of the sarcomere, also plays an important role in length-dependent activation (22).

The percentage of the extent by which a strip of myocardium can be stretched from \( L_{\text{rest}} \) is substantially, although not wholly, dependent on the sarcomeres in the individual cardiomyocytes. The resting or slack length of a sarcomere is \( \sim 1.8 \) \( \mu \text{m} \), and the maximum possible length of a stretched sarcomere is \( \sim 2.3 \) \( \mu \text{m} \), reflecting the physiological range for resting sarcomere length and the potential of an \( \sim 28\% \) increase in length from the resting state (21). It is important that sarcomeres of 2.3 \( \mu \text{m} \) (and also myocytes and muscle strips that have been stretched so that their sarcomeres are 2.3 \( \mu \text{m} \)) will have minimal scope for further stretching without this resulting in permanent muscle damage. In other words, there is a length at which the reserve of the sarcomere for further stretching without damage is exhausted. However, the extent by which a cardiac chamber can be stretched from its resting size is not just related to the sarcomeres and the myocardium, but is also limited by the pericardium (23).

**A Limited Range of Possible Ventricular Volumes and the Limitations of a Single LVEDV Measurement as a Surrogate for LV Stretch**

Using the concept of muscle stretch described in muscle strip experiments, stretch from \( L_{\text{rest}} \) to the precontraction muscle length for a strip of myocardium is equivalent to the difference between the resting LV volume (i.e., the volume of the fully relaxed left ventricle with a transmural pressure of zero) and the current LVEDV (see Fig. 1). This is an important concept because LV wall stretch cannot be represented by an absolute LV volume. This also introduces the concept that each left ventricle must have a possible range of volumes, ranging from a LVEDV at zero transmural LVEDP to that at which there is a high LVEDP (25 mmHg or thereabouts). There is a curvilinear relationship between LVEDV and LVEDP, with the curve getting steeper at higher volumes (Fig. 1). A normal left ventricle during rest and with moderate exercise is operating in a volume range well within these limits, but in the presence of cardiac pathology, a ventricle could be operating near its maximal LVEDV (associated with a high LVEDP) at rest.

For a single measurement of LVEDV to be able to reflect stretch of that ventricle, it would have to be apparent where the measured volume was within the ventricle’s possible range of volumes. However, information about the possible range of volumes cannot be easily measured or accurately predicted. Thus there are significant differences in the resting LVEDV between healthy individuals of different sexes and body sizes (e.g., different LVEDVs at a LVEDP of 8 mmHg of two healthy young adults shown in Figs. 1 and 2), but there also can be substantial differences in LVEDV between individuals, even when sex and body size are both taken into consideration (12). Moreover, there are a number of circumstances that can lead to LV remodeling and thus change in LVEDV indepen-

![Fig. 1. Representation of the relationship between left ventricular (LV) end-diastolic volume (LVEDV) and LV end-diastolic pressure (LVEDP) showing the range of possible LV volumes at end diastole for a young, healthy adult male of 1.8-m\(^2\) body surface area during variations in the amount of LV filling. The data points are partly based on published data but also include some assumptions. The closed circles (●) have taken into consideration previously published data in which pulmonary artery wedge pressure (PAWP) was altered by changes in the intravascular volume state (12), with the assumption that PAWP is similar to LVEDP in healthy young adults, at least when pressures are within the normal range (3). The data points at higher values of LVEDP are based on extensive evidence that there is a rapid increase in LVEDP as the ventricle gets close to its maximal LVEDV (6, 46). The points with open circles (○) are not based on published data but are an extrapolation on the basis that there must be a lower limit of LVEDV as the transmural LVEDP approaches zero. The vertical dashed lines highlight the LVEDV at a normal LVEDP (8 mmHg, A), an elevated LVEDP (15 mmHg, B), and at a LVEDP where the LVEDP is near maximal (C). The shorter of the horizontal dotted lines demonstrates the extent of LV chamber stretch (preload) at 8-mmHg LVEDP, and the longer of the horizontal dotted lines demonstrates the larger extent of LV chamber stretch at 15-mmHg LVEDP. The longer horizontal solid line represents the large extent of preload reserve when the LVEDP is 8 mmHg, and the shorter horizontal solid line represents the smaller preload reserve when the LVEDP is 15 mmHg. The range of LVEDV in this individual over the normal range of LVEDP (4–12 mmHg) can be seen to be \( \sim 96–142 \) mL. Near maximal LVEDV is assumed in this case to be when the LVEDV is \( \sim 20 \) mmHg (vertical line C). Preload reserve can be defined as maximum LVEDV − current LVEDV.

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The Limitations of LVEDP and LA Pressure as Surrogates for LVEDV and LV Stretch

That there are limitations of LVEDP as a predictor of LVEDV has been recognized for some time. The curvilinear relationship between LVEDP and LVEDV means that, at higher pressures, the LVEDV increases to a lesser extent with the same absolute increase in LVEDP, and the LVEDP versus LVEDV relationship eventually reaches a degree of extreme steepness, at which point further changes in LVEDP are no longer reflected in changes in LVEDV (Fig. 1) (6, 52). Nevertheless, LVEDP does increase with increases in LV filling and LVEDV. While the PAWP, as a surrogate of LA pressure, has been used to estimate LVEDP, there is a major limitation in using LA pressure as a predictor of LVEDP, given that, in any LV pathology, a substantial LA contribution to LV filling can occur, and this can result in a LVEDP that is considerably higher than the mean LA pressure (4, 48, 49). In one comparison of LVEDP and mean LA pressure in patients with LV disease, the LVEDP exceeded the mean LA pressure in all patients, with the pressure difference averaging 9 mmHg and ranging from as low as 1 to as high as 18 mmHg (4). Thus the

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\text{PAWP can still be within the normal range while the LVEDP is considerably elevated. Human studies have shown that neither central venous pressure (CVP) nor PAWP correlate with LVEDP or SV (or indeed with indexed LVEDV or SV), and neither do changes in CVP or PAWP correlate with changes in LVEDV or SV (9–11, 16–18, 20, 29, 31, 36, 37, 39, 53, 60).}
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It is the transmural LVEDP (pressure difference between the left ventricle and the pericardium at end diastole), rather than the standard comparison of LVEDP luminal pressure with atmospheric pressure at a zero-reference level that will be most closely related to the LVEDV (61). Transmural LVEDP can vary independently of the LVEDP during alterations in pericardial pressure, with the most common cause for an increase in pericardial pressure outside of the intensive care unit likely to be an increase in RVEDP (61). In heart failure with reduced EF, the LVEDV can fall in association with a high RVEDP, due to ventricular interaction mediated by the pericardium (2).

The Limitation of End-Diastolic Wall Stress as a Surrogate of LV Stretch

Preload has been defined by some investigators as end-diastolic LV wall stress (tension), which can be calculated (at least for the LV short axis) using the Laplace equation, with variables comprising LVEDP and end-diastolic LV short-axis radius and wall thickness$^1$ (41). One advantage of this approach is that it provides consistency with the definition of

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\text{1 LV wall stress} = \frac{\text{LVEDP pressure \times radius}}{2 \times \text{LV wall thickness}}.
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afterload as being the LV wall stress at end systole. Thus systolic wall stress is the load experienced by the LV wall during ejection, also calculated using the Laplace equation, and, as a measure of afterload, systolic wall stress has the advantages of being directly related to LV end-systolic volume, SV, and oxygen consumption (41). On the other hand, end-diastolic LV wall stress can be said to have a limitation as a definition of LV stretch because calculated wall stress is not linearly related to wall stretch and, therefore, cannot be linearly related to the Frank-Starling mechanism.

**Preload Reserve**

Volume administration into the venous circulation can only directly lead to an increase in LV output via an increase in RV end-diastolic volume and then, in turn, via an increase in LVEDV. However, as discussed above, there are finite limits to the volume of any cardiac chamber (as there are for the length of a sarcomere and the length of a strip of myocardium). The limits of LVEDV are dependent on LV structure, the pericardium and, at higher than normal intravascular volumes and right heart pressures, can also be dependent on RVEDP due to ventricular interaction in the setting of an intact pericardium (1, 15). Within these limits there will be an achievable maximal limit of LVEDV (LVEDV\text{max}), where attempts to increase chamber filling result in a large increase in chamber pressure but only a minor increase in volume (Fig. 1), fluid starts to move out of the circulation into the tissues, or both processes could occur at the same time. The difference between the effective LVEDV\text{max} and the current LVEDV can be thought of as the preload reserve, and the preload reserve of an individual at a specific time will be dependent on the intrinsic LVEDV\text{max} and the extent of LV filling at that time. LV filling will be affected by the metabolic requirements of the individual and the effect of this on venous return, the intravascular volume and its location within the circulation, the heart rate, and the atrial contribution to filling. The presence of preload reserve indicates that there is potential for fluid administration to increase the LVEDV and lead to increases in SV and, more specifically, to increases in SW. When attempts to increase LVEDV lead to minor or absent increases in LVEDV and large increases in LVEDP, then preload reserve can be said to be exhausted, this being a more physiologically accurate description for what has also been previously described as “failure of the Frank-Starling mechanism” (35).

Preload reserve also cannot be predicted by a single measurement of LVEDV, given that it is the difference between the current LVEDV and LVEDV\text{max} and thus requires prior information about the LVEDV\text{max}.

**A Definition of Preload That Is Not an Absolute Volume, a Pressure, or Wall Stress**

When used in the clinical setting, the term preload is generally considered to be the stimulus that directly activates the Frank-Starling mechanism, and, therefore, having a definition of preload that encompasses this relationship would seem to be a justifiable aim. There can be no change in the force or extent of LV contraction via the Frank-Starling mechanism, and thus no change in SV or SW, without a preceding change of LVEDV in the same direction. Any increase in stretch of myocardial fibers of the LV chamber is expected to be accompanied by increased stretch at the cardiomyocyte level, and also increased stretch of the sarcomeres within the cardiomyocytes, with stretch at all these levels considered to be essential for an increase in the force of contraction of the left ventricle. This fundamental link of stretch (at all levels of cardiac structure) with the Frank-Starling mechanism provides a strong rationale for including the notion of chamber stretch in a clinical definition of preload, and limitations of a single measure of LVEDV, a left heart pressure, or end-diastolic wall stress for the purpose of measuring chamber stretch have already been discussed.

An important limitation of using LV stretch as a definition of preload for clinical purposes is that there is then no practical means of directly measuring preload in a living individual, given that the transmural pressure of the relaxed ventricle is always greater than zero, and, therefore, a resting LV volume does not occur naturally in the intact organism. On the other hand, while an absolute single value of LVEDV cannot reflect LV stretch, change in LVEDV will always reflect change in stretch. Moreover, it is estimation of the presence of preload reserve (representing the potential for wall stretch) rather than preload that could be considered to be the most important aim in clinical circumstances where volume infusion is being considered.

If LV preload is defined as stretch of the LV cavity, then preload is not linearly related to the LVEDP. Nevertheless, in the absence of an increase in pericardial pressure or the presence of acute ischemia or infarction, LVEDP (either measured or estimated) provides useful information about where a current LVEDV lies within the range of possible LVEDVs for a given ventricle and also allows prediction of whether there is preload reserve, arguably the most important information for clinical purposes. Thus there is guidance available regarding the presence of preload reserve and the potential for volume responsiveness when the LVEDP is either low, normal, or high. A low LVEDP, or a LVEDP in the normal range (4–12 mmHg), suggests the presence of preload reserve and, therefore, the likelihood of responsiveness to intravascular volume infusion, whereas a LVEDP >20 mmHg, and possibly >15 mmHg, indicates minimal preload reserve and, therefore, minimal volume responsiveness (Fig. 1). While LVEDP and mean LA pressure are often both grouped together under the term “filling pressures” (47), it has been mentioned previously in this review that the magnitude of LVEDP and mean LA pressure are often not the same. In the absence of mitral valve disease, a high PAWP predicts a high LVEDP and the absence of preload reserve; however, a normal PAWP is not a reliable predictor that the LVEDP is not elevated, and thus a PAWP at the upper limit of the normal range does not indicate the presence of preload reserve.

There are important implications arising from this perspective of preload and the accompanying concept of preload reserve. Given that preload reserve is the most important determinant of the potential of fluid infusion to increase SV, and the LVEDP is the most reliable indicator of the presence or absence of preload reserve, finding an accurate and reliable noninvasive estimation of LVEDP may be an appropriate aim for future investigations. A second implication is that there may be a case for the reinterpretation of previous experimental and clinical studies in which preload has been considered to be either a pressure or a chamber volume. In particular, a lack of
LV SW response to volume infusion implies that LVEDV has not increased, but there are two possible explanations for this, and these may have different clinical significance: 1) LVEDV could not increase because it was already maximal (i.e., no preload reserve); or 2) preload reserve was present and thus an increase in LVEDV was possible, but the volume infusion did not result in such an increase. With respect to teaching of these concepts, my experience is that the diagram in Fig. 1 provides invaluable assistance when explaining both the nature and importance of the concepts of preload and preload reserve and also why it is that LVEDP provides vital information about the latter.

Conclusions

There has not been a consistent definition of cardiac preload in the domains of either physiology or clinical medicine, and it can be considered to be a limitation of previous definitions that they do not provide a direct link with the Frank-Starling mechanism. Definitions of preload for clinical purposes that are based on pressures have been shown to have limitations, given that LVEDP is not linearly related to LVEDV, and changes in LVEDP are not linearly related to changes in LVEDV, SV, or SW. PAWP has the additional limitation that it can underestimate LVEDP. A left ventricle can be considered to have an intrinsic limited possible range of end-diastolic volumes, with the lower end of the range at a LVEDP of 0 mmHg and the upper end of the normal range at a LVEDP of 25 mmHg or thereabouts. The LVEDV of a specific left ventricle at a particular time is dependent on both its possible range of volumes and the degree of filling. A definition of preload based on a single measurement of LVEDV (or even an indexed LVEDV) has the limitation of giving little indication of where that volume fits within the range of possible LVEDVs for an individual, and thus no useful information about how much stretch of the ventricle is present. In this review, I have argued for an alternative definition of LV preload, this being the extent of stretch of the relaxed left ventricle at end-diastole. In this definition, preload is directly related to the ultrastructural stimulus that underlies the Frank-Starling mechanism. Furthermore, by this definition it would not be expected that any of PAWP, CVP, or LVEDV could accurately describe LV preload, as no measurement of pressures, or a single volume measurement, can directly reflect stretch of the LV myocardium. While assessing stretch of the ventricle has the important practical limitation that it is not directly measurable, acute change in LVEDV does reflect change in preload. The difference between the current and the maximal LVEDV (preload reserve) changes in a reciprocal fashion with preload and is the variable of most importance in the clinical setting when fluid infusion is being considered. A high transmural LVEDP is a reliable indicator of absence of preload reserve, and thus a prediction of absence of volume responsiveness, although LVEDP has the practical limitation that a directly measured LVEDP is not generally available. The more commonly available pressure of PAWP is predictive of a high LVEDP when PAWP is high (in the absence of mitral valve disease), but cannot be used as a reliable predictor of lack of elevation of LVEDP because it can substantially underestimate LVEDP when there is LV disease. A high CVP can also predict lack of fluid responsiveness and has extra significance in some circum-
stances, because a reduction in CVP can lead to a reduction in pericardial pressure and an increase in LV transmural pressure and, in turn, can lead to an increase in LVEDV and SV (2).

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author.

AUTHOR CONTRIBUTIONS

R.E.P. prepared figures; R.E.P. drafted manuscript; R.E.P. edited and revised manuscript; R.E.P. approved final version of manuscript.

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