Ejection Fraction Revisited

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Clinical Use

THE USE OF EJECTION FRACTION (EF), the ratio of the stroke volume (SV) to ventricular end-diastolic volume (Vad), is well accepted as a clinically useful quantitative measurement of ventricular performance.1–5 Because EF is a ratio, calculation of absolute volumes is not necessary. The use of EF to evaluate left ventricular function became common with the widespread introduction of left ventricular catheterization and angiography.6–9 In 1974, Cohn et al. concluded that EF was “probably the most useful of the . . . single hemodynamic measurements in assessing . . . deranged LV [left ventricular] function and the outlook for patients undergoing cardiac surgery.”8 In 1975, Moraski et al. reported that EF was reduced in patients with one- to three-vessel disease independent of a prior myocardial infarction and was further reduced after myocardial infarction.7 They concluded that EF was a more sensitive measurement of left ventricular function than left ventricular end-diastolic volume (Vad).

Although still requiring relatively bulky equipment, radionuclide angiography eliminated the need for left ventricular catheterization but lost morphologic and geometric precision in establishing changes in ventricular volumes. Portable systems have allowed this technique to be used during operation.10,11 For multiple or serial determinations without risk of radiation exposure, the introduction of echocardiography is now almost universally used as part of a complete cardiac evaluation. Echocardiography was initially limited to M-mode studies but rapidly evolved to two-dimensional techniques using transducers positioned on the chest wall, directly on the heart with the chest open, or increasingly during operations with a transesophageal transducer.12–16 Although the presence of ventricular asynergy may reduce the validity

<table>
<thead>
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<th>ABBREVIATIONS</th>
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<tr>
<td>Eₐₑ = effective arterial elastance</td>
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<td>Eₛₑ = end-systolic elastance using corner points of the left</td>
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<td>ventricular ESPVR</td>
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<td>EF = ejection fraction</td>
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<td>EFₛₑ = o = EF obtained by calculation of SV/(Vad – Vₛₑ)</td>
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<td>Eₘₐₓ = the maximum elastance (minimum compliance) of the</td>
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<td>ventricle during systole</td>
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<td>EDPVR = end-diastolic pressure–volume relationship</td>
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<td>ESPVR = end-systolic pressure–volume relationship</td>
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<tr>
<td>HR = heart rate</td>
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<td>LV = left ventricle</td>
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<tr>
<td>Pₛₑ = end-systolic pressure</td>
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<tr>
<td>MAP = mean arterial pressure</td>
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<td>P-V = pressure–volume</td>
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<td>Q = mean arterial flow</td>
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<td>R = total arterial resistance</td>
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<td>RV = right ventricle</td>
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<td>SV = stroke volume</td>
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<td>T = the time for a single cardiac cycle</td>
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<tr>
<td>Vad = ventricular end-diastolic volume</td>
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<td>Vₛₑ = ventricular end-systolic volume</td>
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<td>V₀ = the zero-volume intercept of the end-systolic pres</td>
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<td>sure–volume line</td>
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<td>Vₛₑ = 0 = Vₛₑ intercept of the line relating SV to Vad</td>
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<td>when SV = 0</td>
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of echocardiographic determinations of EF, new ventricular dyskinesia or akinesia during operation usually indicates an acute ischemic event. The recent addition of Doppler flow determination to the same transducer head allows concurrent evaluation of valvular competence necessary to correctly interpret EF because either atrioventricular (tricuspid or mitral) or arterial (pulmonic or aortic) valvular incompetence can lead to an increase in EF that may falsely be interpreted as reflecting normal ventricular function. Dodge and Baxley reported in 1969 that most patients with valvular heart disease had a normal EF and that reduction in EF suggests the presence of myocardial disease.

Although EF is clearly afterload-dependent, and arguably preload-dependent, the measurement of left ventricular EF in the absence of valvular incompetence (either mitral or aortic) is used because it is relatively easy to obtain by imaging techniques. Combined with reasonable clinical judgment, the use of left ventricular EF has become established as a good clinical estimate of left ventricular function, most convincingly in the anesthetic preoperative evaluation of patients for surgical procedures. As early as 1975, Nelson et al. found in 144 medically treated patients that EF was the best prognostic guide in patients followed 14 months. In a 1982 study of 20,088 medically treated patients with significant coronary artery disease, a left ventricular EF less than 0.35 indicated a significantly worse 4-yr survival rate regardless of the number of vessels involved. In the concurrent study of 6,630 patients surgically treated with coronary artery bypass grafting, although operative mortality tended to increase as EF decreased, it was not statistically significant. Similarly, EF was found in another study to be the best predictor of survival in 318 medically treated patients and the second best indicator after the presence of ventricular arrhythmias in 1,131 surgically treated patients with coronary artery disease.

On the right side, echocardiography and radionuclide angiography have been used, with thermodilution techniques developed that, if adequately validated, may make measurement of right ventricular EF possible in large numbers of patients.

**Relationship of Stroke Volume to End-diastolic Volume**

A straight line characterizing the relationship between V\text{ed} and SV has been empirically observed in normal humans (fig. 1) and autonomically blocked dogs. Figure 2 diagrams possible relationships between V\text{ed} and SV based on these empirical observations. Line a, which runs through the origin, has a slope equal to EF. The slope of line b may be the same as line a; however, because EF is the slope of the line connecting any point and the origin, only line a represents a constant EF, whereas EF is different at each V\text{ed} for line b. The slope of line b is not equal to EF. EF would be equal to the slope of the line between the origin and any SV producing a low EF (dashed line c) and a large SV producing a high EF (dashed line d).

If the intercept through the abscissa of the line relating SV to V\text{ed} is not at zero V\text{ed} (line b), we have called this intercept volume V\text{sv0}, the end-diastolic volume at which SV becomes zero. If the definition of EF were modified by subtracting V\text{sv0} from V\text{ed} in the denominator of the EF calculation, one might argue that a degree of preload independence is obtained and the resulting EF\text{sv0} (i.e., SV/(V\text{ed} - V\text{sv0})) becomes sensitive to afterload and contractility because these will each affect SV and end-systolic volume. If the afterload is relatively constant, then the slope of the line is proportional to contractility. In both normal humans and dogs, V\text{sv0} is small compared with V\text{ed}, and hence little is gained by accounting for V\text{sv0}. This may not be true under pathologic conditions in which V\text{sv0} would be large, e.g., high afterload or low contractility, when the highest V\text{ed} at which isovolumic contraction (SV = 0) first occurs is large.

In normal humans, although EF varies with large alterations in V\text{ed}, the changes usually remain well within clinically normal values. It is this type of data that is used to justify the frequently stated relative preload independence of EF. Because EF is empirically observed to be constant over a wide range of preloads, this observation can be used to predict how an increase in preload (e.g., volume-loading) would distribute increases in SV and end-systolic volume (V\text{es}) affecting cardiac output.

**FIG. 1.** Relationship of SV to LV end-diastolic volume in normal humans, from Nixon et al. Preload was varied from baseline condition by lower body negative pressure (LBNP) and head-up tilting (TILT). There is a straight-line relationship, with its intercept close to the origin and a slope of 0.6. Thus, EF is relatively constant over the wide range of preloads studied. (Reproduced with permission from the American Heart Association, from Circulation 65:908–703, 1982.)
dominantly dilates with little increase in SV (insensitive to volume-loading).

In contrast, Mangano et al.\textsuperscript{29} in studies of patients immediately after cardiopulmonary bypass, observed a clear decrease in EF as $V_{ed}$ was rapidly increased by acute volume-loading with the use of the bypass cannula (i.e., a preload dependence). Some decrease in ventricular contractility and alteration in afterload probably existed in this early postbypass period. To what degree these two factors individually contributed to the decrease in EF is unclear. This illustrates the conventionally accepted wisdom that selective assessment of either right or left ventricular contractility is not obtained with EF because of the load-dependence of the measurement.

**Measurement of Ventricular Function**

In the search for a measure of ventricular function that is independent of all loading conditions (i.e., preload and afterload), Sagawa et al.\textsuperscript{30} analyzed the pressure–volume (P-V) relationship of an isolated left ventricle (LV) with constant coronary perfusion pressure and the ability to independently control both preload and afterload.\textsuperscript{30} Preload in this analysis is defined as the $V_{ed}$ regardless of the end-diastolic pressure. Afterload can be defined as the ventricular pressure at end-systole. In this now classic study, they defined a parameter, $E_{max}$, the maximum elastance (minimum compliance) of the ventricle during systole that can be used to give a quantitative measure of the inotropic state (contractility) of the ventricle independent of loading conditions. The time of maximum elastance is used to define end-systole.

Although extremely attractive in its conceptual construction, both for understanding and teaching ventricular function, the practical clinical application of the analysis by Sagawa et al.\textsuperscript{30} has been limited mainly by the following factors: 1) Easily applicable in vivo technology to make instantaneous multiple measures of absolute ventricular volumes over a period of time (e.g., the conductance catheter technique)\textsuperscript{27} is not widely available. 2) The analysis requires placement of a high-fidelity intraventricular pressure sensor. In addition, if the influence of respiration on ventricular performance is to be appropriately included, some measure of ventricular surface pressure must be obtained to calculate a true transmural pressure. 3) It becomes necessary to substantially alter ventricular loading conditions by mechanical obstruction of venous and/or arterial vessels, acute alterations in total blood volume, or pharmacologic manipulation of the peripheral vasculature without affecting reflexes that could alter the baseline inotropic state. 4) Right ventricular ejection normally continues after maximal elastance has been reached be-

![Diagram](http://anesthesiology.pubs.asahq.org/pdfaccess.ashx?url=/data/journals/jasa/931345/)
cause of a low pulmonary vascular resistance, and hence neither the peak pressure nor the pressure at pulmonary valve closure reflects the relevant systolic pressure at the moment of maximum ventricular elastance originally defined in the LV\cite{28,29} and shown to be applicable to the right ventricle (RV).\cite{28,29}

Technologic advances allowing accurate measurements of right and left ventricular P-V relationships throughout a cardiac cycle should ultimately be developed and validated. An example of such novel techniques is illustrated by the use of the volume conductance catheter by Kass et al. to determine the online P-V relationships of the LV during coronary angioplasty.\cite{36} However, until this or other techniques for determining P-V relationships are easily applicable, EF will continue to be the single most commonly used clinical quantitative measurement of ventricular pump performance. It is thus reasonable to review those factors determining EF and the relationships between EF and ventricular P-V relationships.

**Using Ventricular Pressure–Volume Relationships to Define Ejection Fraction**

Sagawa et al. have established the concept of ventricular P-V relationships as a powerful tool to better understand both systolic and diastolic ventricular function\cite{31} (fig. 3). The concept of an end-systolic P-V relationship (ESPVR) is based on two observations: 1) The upper left corners of P-V loops obtained with varying loading conditions reach a rather straight line when the inotropic state is constant; and 2) this linear relation is fairly independent of the mode of contraction (e.g., isovolumic or ejecting) but changes slope when inotropic state is altered. Under normal circumstances, the line joining the upper left corner of a left ventricular P-V loop is quite close to a line defining the maximal elastance (equivalent to the maximal stiffness or minimal compliance) during a series of variably loaded ventricular contractions.

Figure 4 illustrates the multiple isochronous points derived from such series of both isovolumic and ejecting contractions. In this example, maximum elastance (E\text{max}) is reached 160 ms after the beginning of contraction, regardless of the extremes in loading conditions. The diastolic properties of the ventricle are described by the end-diastolic P-V relationship (EDPVR) represented by the dotted 0-ms line. These two lines (ESPVR and EDPVR) defining the end-systolic and end-diastolic P-V relationships of a ventricle can be used to characterize the mechanical properties of a ventricle as time-varying elastance. Quite simply, the ventricle is considered as a chamber whose stiffness changes over time in a prescribed and periodic manner.

As with any model that simplifies a complex system to provide a theoretic foundation to improve understanding, there are a number of limitations that offer insight into the complexity of the entire system. Linearity of the ESPVR, although useful for our analyses, may become nonlinear in the intact in vivo system.\cite{32-35} Similarly, small differences in the time to end-systole may occur with changes in preload.\cite{31,36,37} This has led many to use the points at the upper left corner of the left ventricular ESPVR to define end-systolic elastance (E\text{es}) rather than E\text{max}. We shall use the term E\text{max} because it is applicable across a wider range of conditions that may affect both the RVs and LVs.\cite{31} Finally, there can be a degree of afterload dependency that may be related to a rapid change in afterload in the preceding beats.\cite{38-42}

Defining EF in terms of the ventricular P-V relationships as illustrated in figure 3 can provide significant insights in understanding the physiologic basis of EF. By doing this, EF can be related to changes in five parameters: V\text{ed}, ventricular end-diastolic volume (preload); V\text{es}, end-systolic volume; P\text{es}, end-systolic pressure (afterload); E\text{max} (contractility), the slope of the ESPVR; and V\text{0}, the zero-volume intercept of the end-systolic P-V line whose slope defines E\text{max}.

From figure 3, it is evident that:

\[ P_{es} = E_{max}(V_{es} - V_{0}) \]
Since $V_{es} = V_{ed} - SV$, then:

$$P_{es} = E_{max}(V_{ed} - SV - V_0) \tag{7}$$

$$SV = V_{ed} - P_{es}/E_{max} - V_0 \tag{8}$$

Dividing both sides by $V_{ed}$:

$$EF = 1 - (P_{es}/V_{ed})(1/E_{max}) - V_0/V_{ed} \tag{9}$$

From this equation, it is clear that EF is mathematically related to the ratio of afterload ($P_{es}$) to preload ($V_{ed}$); to contractility ($E_{max}$); and to the ratio of the systolic zero intercept volume ($V_0$) to total end-diastolic volume ($V_{ed}$).

Let us consider this equation in detail.

**Preload ($V_{ed}$)**

With the use of equation 9, the interaction between preload and EF at different afterloads ($P_{es}$) with a constant $E_{max}$ and $V_0$ is illustrated in figure 5. As $V_{ed}$ increases, there is a rapid hyperbolic increase in EF. The EF at a given $V_{ed}$ decreases as afterload increases, the differences being greatest at low preloads. This figure demonstrates that EF is certainly not entirely preload independent, but, over a wide range of ventricular volumes expected in adults with normal contractility ($E_{max} 3-7$), an EF greater than 0.55 would still be observed. With afterload constant, hypovolemia would result in an EF less than 0.55, such that a low EF could reflect hypovolemia with normal contractility. Of more importance, it is the ratio of afterload ($P_{es}$) to preload ($V_{ed}$) that influences EF. Equation 9 states that, for a given $E_{max}$, if $V_0 = 0$ then:

$$EF = 1 - (P_{es}/V_{ed})(1/E_{max}) \tag{9A}$$

If afterload is doubled, doubling preload will maintain EF constant, whereas the inability to increase preload (limited by systemic venous return or ventricular compliance) will reduce EF. Equation 9A also states that, for a given afterload, if $E_{max}$ decreases by 50%, preload must double to maintain EF constant.

**Zero-volume Intercept of the End-systolic Pressure-Volume Line**

As $V_0$ increases, EF decreases at a given $V_{ed}$, $P_{es}$, and $E_{max}$ (fig. 6). Any factor that increases $V_0$ with $E_{max}$ and afterload constant will decrease EF. A recent elegant theoretic analysis of ventricular function by Kass et al. supported the preload independence of EF except at minimal end-diastolic volumes. However, the relationship between $V_{ed}$ and EF was based on constant $E_{max}$ and $P_{es}$ and a $V_0$ of only 2 ml. If $V_0$ were to increase substantially, EF would no longer be preload-independent.
Because our understanding of what $V_0$ means physiologically is limited, whether the clinical implications of a process that influences $V_0$ will produce useful information for clinical decision-making is unclear. Under the theoretic conditions in which a large increase in $V_0$ could occur with no change in $E_{\text{max}}$, i.e., a rightward shift of the P-V loop, most clinicians would interpret such ventricular dilatation as evidence of dysfunction despite an unchanged $E_{\text{max}}$ (fig. 7). This can occur with a stunned myocardium or after an infarct, with the remaining ventricular muscle maintaining normal function.\textsuperscript{30,31,44,45} In this situation, a depressed EF may be more consistent with clinical intuition than a normal or only mildly depressed $E_{\text{max}}$. The clinical usefulness of EF may rest in part on an increased $V_0$ associated with a pathologic process that may have a quantitatively small effect on $E_{\text{max}}$ but produce a decrease in EF.

**Afterload ($P_{\text{es}}$)**

Ejection fraction is conventionally described as being an afterload-sensitive measure of ventricular function. This sensitivity is evident in both equation 9 and figure 5, which graphically represents the relationship between EF and $V_{\text{ed}}$ at different afterloads. As afterload increases for a given $V_{\text{ed}}$, the x-intercept increases when EF = 0 (equivalent to $V_{sv} = 0$ in fig. 2). In figure 8, for a given preload and $E_{\text{max}}$, an increase in afterload is seen to decrease EF.

Experimental studies and clinical experience suggest that EF appears to act as if it were a controlled variable because the cardiovascular system normally maintains EF at approximately 0.6. If the EF of each ventricle is constant at a given $E_{\text{max}}$, then the ratio of $P_{\text{es}}/V_{\text{ed}}$ for that ventricle also must be maintained constant. Neural and humoral modulation of venous tone will influence the steady-state $V_{\text{ed}}$ of each ventricle proportional to its compliance. Thus, the ability to acutely and selectively alter the preload of one ventricle without influencing the other is limited. In contrast, the ability to alter the afterload of each ventricle independently offers the cardiovascular system the possibility of maintaining a constant EF, even if $V_{\text{ed}}$ and $E_{\text{max}}$ substantially change in only one ventricle. Endogenous neural and humoral modulation of the systemic arterial resistance are well-recognized mechanisms through which the system theoretically could chronically adapt to a de-
creased left ventricular $V_{ed}$ or decreased left ventricular $E_{max}$ to maintain an EF of approximately 0.6. 47,48

The RV, in contrast, does not have the ability to significantly diminish baseline afterload. Recent data suggest that the normal pulmonary vascular bed is actively vaso-
dilated. 49 However, pathologic processes may lead to fixed increases in pulmonary vascular resistance and thereby pose major problems for the RV. Unacceptable systemic arterial vasodilation is frequently manifested when exogenous pharmacologic manipulation is used to obtain a reduction in pulmonary vascular resistance. 50 This implies that, in contrast to the LV, which has a number of mechanisms available to reduce $P_{a}$ and hence preserve EF, the mechanisms available to the RV are limited when the pulmonary vascular bed is abnormal.

**Contractility ($E_{max}$)**

Although the preceding illustrations demonstrate the sensitivity of EF to preload and afterload, clinically EF is used as a measure of ventricular function, and if this is true, it should be sensitive to $E_{max}$. Figures 8 and 9a illustrate the relationships between EF and $E_{max}$ under conditions of changing afterload and preload. It is clear that, although EF is relatively insensitive to changes in $E_{max}$ when $E_{max}$ is greater than 5, it is quite sensitive to changes that have the greatest clinical relevance, i.e., to changes when $E_{max}$ is small. Regardless of the $V_{0}$, preload ($V_{ed}$), or afterload ($P_{a}$), EF decreases rapidly as $E_{max}$ declines at its lower values. This sensitivity to changes in $E_{max}$ is enhanced with either a decreased preload (e.g., hypovolemia) or increased afterload (e.g., hypertension). This may account for the clinical utility of EF. Over a wide range of preloads and afterloads, a decrease in EF below 0.4 implies either a substantial decrease in ventricular function and/or a substantial abnormality in loading conditions. EF is insensitive to a wide range of changes above and around normal values but is sensitive to small changes when $E_{max}$ is reduced. Thus, the lowest EF would be associated with a high afterload, low preload, and minimal $E_{max}$.

The most striking finding derived from figures 8 and 9a is the lack of sensitivity (low gain) of EF to changes in $E_{max}$ at normal and supernormal values with a reasonable afterload, but the exquisite sensitivity (high gain) of EF to changes in $E_{max}$ when $E_{max}$ is subnormal. EF is sensitive to changes in $E_{max}$ in exactly that region of diminished ventricular contractility that is of most interest to the anesthesiologist. Conversely, the anesthesiologist usually is not interested in distinguishing between ventricles with normal or supernormal function. Thus, part of the usefulness of EF relates directly to its ability to detect small changes in $E_{max}$ when contractility is low.

Figure 9b is a three-dimensional representation of the relationships between EF, contractility, and preload, illustrating a complete continuum of the information presented with only four different preloads in figure 9a. A surface is described that defines the changes in EF with changes in $V_{ed}$ and $E_{max}$. A line across the surface defines all conditions with $EF = 0.5$. Figures 8 and 9 also imply

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![Diagram](http://anesthesiology.pubs.asahq.org/pdfaccess.ashx?url=/data/journals/jasa/931345/)
that an improved EF can be obtained by reducing afterload and increasing preload at the same $E_{max}$. The specific therapeutic approach to improving EF must be tailored to each patient and the underlying pathologic process. This can be seen in figure 10, in which four similar curves of EF versus $V_{ed}$ reflect matched decreases in $E_{max}$ with decreases in afterload, such that a "normal" EF is present with a profoundly reduced $E_{max}$; this EF, however, is produced only by significantly reducing the afterload (which may not be possible if the required decrease in $P_{es}$ limits coronary perfusion). An increase in EF implies that something clinically "good" has occurred.

**The Meaning of Ejection Fraction**

Although EF is frequently considered a relatively preload-independent and afterload-dependent clinically useful measure of ventricular function, its meaning is not scientifically satisfying. Considering the dependence of EF on contractility and afterload, the relative constancy of EF over such a wide range of preload conditions is surprising. It is generally accepted that the normal LV has an EF in the range of 0.55–0.75 and over a relatively wide range of steady-state preload conditions tends to remain close to that range.19,25 If, for argument’s sake, EF remains constant and nothing is done to alter $E_{max}$, then this implies that the cardiovascular system alters afterload ($P_{es}$) and preload ($V_{ed}$) to maintain a constant ratio. The cardiovascular system has numerous pathways through which it can alter arterial resistance, compliance, and impedance and an equally large number of ways through which it can vary the venous vascular bed’s resistance and compliance. A paradox then appears because, after autonomic blockade, which presumptively maintains venous and arteriolar tone constant, the cardiovascular system at a constant inotropic state still keeps the ratio of $P_{es}/V_{ed}$ constant so that EF is approximately 0.6 over a wide range of preloads.24

If the inotropic state ($E_{max}$) is allowed to vary, it is clear that the autonomic intact cardiovascular system has a great ability to increase and decrease preload and at least left ventricular afterload (right ventricular afterload normally being quite low), allowing EF to be maintained near 0.5–0.6. This leads to interpretation of EF, not as a measure of ventricular function, but as a measure of the integrated cardiovascular system’s ability to maintain homeostasis, which, again for some reason, can be characterized as an EF of approximately 0.5–0.6.

Thus, the clinical usefulness of EF reflects the fact that, barring valvular incompetence, which allows $P_{es}$ (tricuspid/mitral incompetence) or $V_{ed}$ (pulmonic/aortic incompetence) to escape control of the normal regulatory mechanisms, a “normal” EF reflects the integrated system’s ability to cope, under the conditions at the time of measurement, with abnormalities in preload, afterload, and/or contractility and still maintain an adequate cardiac output. Conversely, an abnormal EF reflects the inability of the entire system, with all the endogenous mechanisms available to it, to compensate, maintaining this “magical goal” of an EF of 0.6. In essence, this restates the concepts of preload–afterload matching enunciated by Ross51 for ventricular failure and combines it with the concept of ventricular–arterial bed interaction described by Sagawa et al.31

For the clinician, EF has become a practically and, we now believe, theoretically extremely useful measurement. Because it is clearly preload- and afterload-dependent, its usefulness as a measure of ventricular function is limited. However, it becomes a highly useful screening measurement for the clinician describing a “sick system” for which additional tests will be required to define the precise cause of the “sickness.” If EF is low, any additional adverse stresses placed on any aspect of the system, preload, afterload, or contractility, may have catastrophic effects if appropriate treatment to manipulate the system is not given. From this perspective, EF becomes a measure, not of ventricular performance, but of the integrated system’s performance in dealing with a pathologic process.

**Why Is the Normal Ejection Fraction Approximately 0.6?**

Why does a normal ventricle choose to maintain an EF of 0.5–0.6 rather than, for example, 0.1 or 0.9? Teleologic
reasoning would suggest that there must be an advantage, perhaps in terms of efficient energy utilization, for the ventricle not to empty completely with each cardiac cycle even as it fulfills its physiologic function of delivering oxygen to the body tissues. Two possibly related but different levels of analysis are apparent, system mechanics and cellular energetics.

Sunagawa et al. extended the ventricular P-V analysis to include its interaction with the arterial bed. By plotting a change in SV against the change in \( P_e \), on the same axes used for describing the ventricular \( E_{max} \), a line the slope of which they called \( E_a \) (effective arterial elastance) describes a mechanical characteristic of the arterial bed reflecting the coupling of the ventricle and arterial bed but that is independent of ventricular function (fig. 11). \( E_a \) can also be approximated as \( E_a = R/T = R \times HR \), where \( R \) is total arterial resistance and \( T \) is the time for a single cardiac cycle that is inversely related to the heart rate (HR). This approximation is derived by assuming that \( P_e \) is close to mean arterial pressure (MAP), and hence MAP = \( R \times Q \), where \( Q \) is the mean arterial flow.

Because \( SV \times HR = Q \), then \( P_e \approx R \times SV \times HR \) and hence \( P_e/SV \approx R \times HR \). An argument can be made that \( E_a \) offers better insight than does \( P_e \) alone in understanding the frequently confusing term “afterload.” By plotting \( E_a \) and \( E_{max} \) on the same axes in figure 11 and making a number of simplifying assumptions (i.e., \( V_0 \), downstream arterial and ventricular end-diastolic pressures all equal zero), the two lines must intersect at the one point that satisfies the characteristics of both systems. This point defines the SV. The relationship between EF, \( E_a \), and \( E_{max} \) can be described as follows:

\[
E_a = \frac{P_e}{SV}
\]

Eliminating \( P_e \) from equations 7 and 10 by rearranging each to be equal to \( P_e \), and then setting them equal to each other and solving with respect to SV:

\[
SV = \left( E_{max}/(E_{max} + E_a) \right) (V_{ed} - V_0)
\]

Dividing both sides by \( V_{ed} \):

\[
EF = \left( E_{max}/(E_{max} + E_a) \right) \left(1 - V_0/V_{ed}\right)
\]

If \( V_0 = 0 \), then:

\[
EF = \frac{E_{max}}{E_{max} + E_a}
\]

Of most importance is the appreciation that, as a first approximation by considering only the ventricular and arterial bed elastances as the system parameters, the complex relationships between each ventricle and its respective arterial bed can be simply and directly related to a single number, EF. Equation 12 states that if \( V_0 \) is small, EF is independent of preload and hence offers an explanation for the previously mentioned paradox, in which EF is constant over a wide range of preload despite autonomic blockade. Although EF unquestionably can be affected by the autonomic system’s influence on ventricular contractility and arterial tone, EF is determined by the mechanical coupling of the ventricle and arterial bed. The properties of both \( E_{max} \) and \( E_a \) are essentially independent of preload. \( E_a \) is independent of preload despite being approximated as \( P_e/SV \). This is because \( E_a \) defines the effective elastance of the arterial bed regardless of ventricular loading conditions or contractility. Thus, \( E_a \) is a parameter that represents the property of the arterial system and is, by definition, independent of any ventricular variables. Although changes in preload, afterload, or contractility can influence SV, the measurement of \( E_a \) can be made regardless of how the SV was produced. In the extreme, \( E_a \) can be measured with the use of a pulsatile bypass pump with the ventricle completely eliminated. Thus, \( E_a \) is independent of ventricular preload because it is independent of any aspect of ventricular performance
except a resultant SV, which theoretically does even not require a ventricle if an appropriate pump is available.

Equation 13 states that EF is independent of preload when $V_0 = 0$. If $V_0 > 0$, the intersection of $E_{max}$ with the abscissa would be shifted $V_0$ ml to the right of the origin. Under these conditions, as stated in equation 12, EF becomes preload-dependent. This equation restates the dependence of EF on both $V_0$ and $V_{ed}$ when $V_0$ is greater than 0, an increase in $V_{ed}$ increasing EF and an increase in $V_0$ decreasing EF.

$E_a$ varies as the ratio $P_{es}/SV$. If $E_a$ is now considered the effective afterload, then it may remain constant as decreases in SV incur proportionate decreases in $P_{es}$ under conditions in which vascular tone remains constant. This point of view allows a useful interpretation of the previously discussed study by Mangano et al., who observed a decrease in EF after an increase in preload in patients immediately after cardiopulmonary bypass. By using $E_a$ rather than either $P_{es}$ or systolic wall tension as a measure of afterload, their data (from table 1 in Mangano et al.) can be transformed with two assumptions, that the patients had a surface area of 1.8 m² and that $V_0 = 0$. (As discussed above, any increase in $V_0$ would decrease EF.) Their data originally presented in a normalized form then can easily be given absolute values for end-diastolic, end-systolic, and stroke volumes. $E_a$ is calculated as the reported systemic vascular resistance $\times$ HR; this calculated $E_a$ can be used to calculate $P_{es}$, because $E_a \times SV = P_{es}$. When this is done for both the control and posttransfusion states and then plotted, as in figure 12, $E_{max}$ for each condition is determined by the line between the origin and $P_{es}$. Although there is a decrease in $E_a$ after the increase in preload, the far more impressive observation is the decrease in $E_{max}$. With the use of this format, the cause for the decrease in EF is a decrease in contractility and not an increase in afterload.

The rectangular area derived from perpendicular segments as drawn in figure 11 from the intersection of the $E_a$ and $E_{max}$ lines defines an area that approximates stroke work (pressure $\times$ volume). It can be shown that the maximum stroke work will occur when the slopes are equal. Rigorous approaches to this concept have been published. From equation 13, when $V_0 = 0$, EF will approach 1 as $E_a$ approaches 0, whereas if $E_{max} = E_a$, then EF = 0.5, the condition in which maximum stroke work occurs. To the extent $V_0 > 0$, as would be expected in vivo, the calculated EF that would fulfill the criteria for maximum stroke work would be less than 0.5. Experimental confirmation that maximum stroke work occurs when $E_a = E_{max}$ has been obtained for the isolated ventricle. Burkhoff and Sagawa extended this analysis to include mechanical efficiency, which they defined as the ratio of external work done by the ventricle to ventricular oxygen consumption. This approach results in maximum mechanical efficiency occurring when $E_a$ is approximately half of $E_{max}$. From equation 13, this results in EF = 0.67. This result not only agrees with the EF found in completely healthy unanesthetized subjects, but also suggests that the cardiovascular system normally maintains the arterial bed in a state of relaxation relative to the state that corresponds with maximal stroke work, choosing maximal efficiency over maximal stroke work. Although these concepts are extremely attractive, the identity of a "receptor" for either stroke work or maximum mechanical efficiency is unclear.

At the cellular level, the evolving understanding of the relationship between muscle fiber length and calcium activity governing fiber shortening, particularly because it may offer a reason for Starling's Law of the Heart, may ultimately provide insight into EF. If a cardiac muscle fiber increases its affinity for calcium as it is stretched and decreases its affinity as it shortens, then shortening might occur as a percentage of end-diastolic length rather than as a fixed amount of shortening at varying end-diastolic lengths. Whether the empiric observation that a normal EF of 0.6 can be explained by those studying the molecular
biology of cardiac muscle’s interaction with the systemic venous and arterial vascular beds remains to be seen.

Conclusions

EF is the single most commonly used clinical quantitative measure of ventricular performance because of the technical ease in making the measurements and because of the clinically demonstrated usefulness of EF as a predictor of a patient’s cardiovascular response to stress. We have examined the influence of changes in loading conditions and contractility on EF based on an evaluation with respect to ventricular P-V relationships. We conclude that, although EF is both preload- and afterload-dependent, it serves the clinician well in its sensitivity to changes in contractility when ventricular function is reduced. EF is also maximally sensitive to changes in either afterload or preload when ventricular function is minimal. The empiric observations of EF under normal conditions lead to the provocative question of why the cardiovascular system maintains an EF of 0.6. An attractive rationale defines EF in terms of the elasance of the ventricular and arterial systems, an EF of 0.67 optimizing mechanical efficiency. Thus, EF, although a relatively simple measure that is intuitively easily comprehended, is an extremely complex parameter describing the entire cardiovascular system and requires additional study. EF appears to be a highly efficient and integrated measure of the entire cardiovascular system’s ability to cope with abnormalities in any or all of the three critical variables that determine ventricular performance—preload, afterload, and contractility.

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References


47. Kirchheim HR: Systemic arterial baroreceptor reflexes. Physiol Rev 56:100–176, 1974


55. Lakatta EG: Starling's law of the heart is explained by an intimate interaction of muscle length and myofilament calcium activation. J Am Coll Cardiol 10:1157–1164, 1987