Standardized Ejection Fraction as a Parameter of Overall Ventricular Pump Function

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To evaluate the pump function of the ventricle, a parameter which (i) incorporates systolic and diastolic function and (ii) separates the heart from preload and afterload is needed. This study utilized ejection fraction (EF), calculated from the end-systolic (ES) and end-diastolic (ED) pressure–volume relationship (PVR) using an arbitrary set of loading conditions. Ten isolated canine hearts with a balloon placed inside the left ventricle were used to determine the ESPV and EDV. An end-diastolic volume (EDV) at a pressure of 15 mmHg and an end-systolic volume (ESV) at 70 mmHg were obtained from the ESPV and EDV, respectively. EF was calculated as (EDV – ESV)/EDV. With low-dose (8 μg/min) and high-dose (40 μg/min) dobutamine infusion, the EF increased from 0.25±0.16 to 0.33±0.13 and 0.57±0.08 (p<0.01), respectively, in conjunction with increases in end-systolic elastance from 3.11±0.83 to 3.48±1.08 and 5.38±1.91 mmHg/ml (p<0.01). It was thus concluded that because the estimation of EF separates the heart from preload and afterload, this method may facilitate comparing overall pump function of hearts beating under different loading conditions. (Jpn Circ J 2000; 64: 510–515)

Key Words: Ejection fraction; Pressure–volume relationship; Ventricular mechanics

Although assessing ventricular function is a major issue in cardiovascular research, it is still difficult to describe ventricular pump function by using a single parameter. Several load-independent parameters have been proposed to characterize ventricular function, such as end-systolic elastance or preload-recruitable stroke work. However, those indices only reflect the systolic function of the ventricle and evaluation of diastolic function must be performed separately. In order to assess overall ventricular pump function by one parameter, that parameter should (i) be independent of loading condition and (ii) incorporate both systolic and diastolic functions.

Ejection fraction (EF) is a frequently used parameter of ventricular function in clinical practice, but because of its afterload-dependent nature, the use of EF for the precise assessment of ventricular function has been limited. If it was possible to predict EF under a given loading condition, then hearts beating under different conditions would become comparable. Provided that the end-systolic pressure–volume relationship (ESPVR) and the end-diastolic PVR (EDPVR) are available, EF can be estimated by defining end-systolic pressure (ESP) and end-diastolic pressure (EDP) as a set of loading conditions. Because the calculation of EF incorporates both the ESPVR and EDPVR, the calculation should reflect systolic and diastolic function. In addition, because of the load-independent nature of the ESPVR and EDPVR, the calculated EF should also be load independent.

The purpose of this study was to present a method of predicting EF under a given set of loading conditions from the measured ESPV and EDPV. The response of the estimated EF to dobutamine infusion was examined in an isolated canine heart preparation. The clinical implications of the application of the parameter will be discussed.

Methods

Concept of Estimating Standardized EF

Fig 1 shows the basic concept of estimating the standardized EF. Once the ESPV and EDPV were measured, an end-diastolic volume (EDV) was obtained from the EDPV at an arbitrarily chosen ESP of 15 mmHg. Similarly, an end-systolic volume (ESV) was obtained from the ESPV at an arbitrarily chosen ESP of 70 mmHg. Stroke volume (SV) was estimated as: EDV – ESV and EF was calculated as: SV/EDV. Under loading conditions of an ESP of 15 mmHg and an ESP of 70 mmHg, SV and EF were defined uniquely for the given ESPV and EDPV. The method enables estimation of SV and EF when the ESPV and EDPV are available.

Preparation

Ten mongrel dogs, weighing 20–27 kg, were used. The investigation conformed with the ‘Guide for the Care and Use of Laboratory Animals’ published by the US National Institutes of Health (NIH Publication No.85-23, revised 1996). The dogs were anesthetized with sodium pentobarbital (30 mg/kg iv), intubated and connected to a respirator (Servo 900B, Siemens-Elema, Sweden). A plastic catheter was inserted in the right femoral artery to monitor arterial pressure and to sample arterial blood gas. The chest was opened through a midline incision to expose the innominate artery and aortic arch. The pericardium was opened longitudinally and the azygos vein was ligated and divided.

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After giving heparin (5 mg/kg iv), a 12F Argyle tube (Sherwood Medical, St Louis, MO, USA) was inserted into the ascending aorta through the innominate artery and 800–1000 ml of blood was removed. High potassium crystallloid cardioplegia was administered through the same tube and the aortic arch was clamped. The inferior vena cava and the left atrial appendage were opened to decompress the heart.

After removing the heart, it was placed in an isolated heart preparation. A latex balloon filled with water was placed inside the left ventricle and connected to a column through which a catheter tip micro-manometer (MPC-350, Millar, Houston, TX, USA) was passed into the balloon. The balloon’s volume was controlled with a syringe connected to the column. The zero drift of the pressure transducer was within 0.5 mmHg throughout the experiment. A small catheter was inserted through a stab wound at the apex to drain Thebesian flow. The heart was perfused with blood oxygenated by a membrane oxygenator (ECMO 0600, SciMed Life Systems, Inc, Minneapolis, MN, USA) and pumped with a centrifugal pump (Biopump, Bio-medicus, Inc, Eden Prairie, MN, USA). The following were added to a liter of blood: albumin (20%, 100 ml), gentamicin (40 mg), clyndamycin (100 mg), methylprednisolone (100 mg), glucose (1800 mg) and insulin (20 U/L).

The potassium and calcium concentrations were adjusted in the range of 4.5–5.5 mmol/L and 0.8–1.0 mmol/L, respectively. The temperature was kept at 36°C with a heat exchanger (DI078E, Electromedics, Englewood, CO, USA).

The right side of the heart was closed (the vena cava and the pulmonary artery were tied off) so as to drain all the coronary sinus effluent into a tube placed in the right atrium. A catheter was inserted through the left subclavian artery to monitor the perfusion pressure, which was maintained at 100 mmHg. The heart was defibrillated after reperfusion, then a pair of pacing electrodes was placed on the right ventricle, and the heart was paced at a rate of 120 beats/min.

**Data Acquisition and Analysis**

The left ventricular pressure was digitized on-line (12 bits, 200 samples/s), stored on a hard disk, and analyzed off-line using a DOS-based personal computer and programs developed in our laboratory, based on a commercially available acquisition and analysis software package (ASYST, Asyst Software Technologies, Rochester, NY, USA).

For each beat, ESP (which is the same as peak systolic pressure in isovolumic contraction) and EDP (which was defined as minimum pressure) were determined. The data were obtained at several volumes.

**ESPVR and Systolic Parameters**

ESPVR, which was originally thought to be linear, was expressed as its slope (Ees) and volume axis intercept (Vo). An increase in contractility caused an increase in Ees and a decrease in Vo. Burkhoff et al showed that ESPVR is curvilinear and that the degree of curvilinearity is related to contractility. We thus calculated ESPVR by fitting the ESPs obtained at several volumes to a quadratic function:

\[
ESP = a_{ES}V^2 + b_{ES}V + c_{ES}
\]

where V is the ventricular volume and a_{ES}, b_{ES} and c_{ES} are the regression coefficients. The averaged correlation coefficient for all the experiments was 0.998±0.004. In this equation, a_{ES} served as a quantitative measure of the curvilinearity of the ESPVR. For an ESPVR that is concave to the volume axis, a_{ES} has a negative value, which implies increased contractility. If the ESPVR is linear, then a_{ES} has a value of zero.

The slope of ESPVR, Ees, was obtained from the slope of the tangential line at the ESP of 70 mmHg from the equation:

\[
Ees = \frac{d(ESP)/dV}{ESP} \bigg|_{ESP = 70 \text{ mmHg}} = \frac{2a_{ES}V + b_{ES}}{ESP = 70 \text{ mmHg}}
\]

We chose an ESP of 70 mmHg to calculate Ees, because it was in the physiologically appropriate range. The volume axis intercept (Vo) and ESV were obtained from equation (1) by giving the value of 0 and 70 mmHg, respectively, for the ESP. The smaller ESV reflects better contractility, as it represents more complete ventricular emptying.

**EDPVR and Diastolic Parameters**

To obtain the EDPVR, the diastolic pressure–volume points were fitted to a cubic function:

\[
EDP = a_{ED}V^3 + b_{ED}V^2 + c_{ED}V + d_{ED}
\]

where a_{ED}, b_{ED}, c_{ED} and d_{ED} are the regression coefficients. Conventionally, the EDPVR has been fitted to an exponential function, but we decided that EDPVR may be better fitted to a cubic function, because of the significant negative pressure values at small volumes (Fig 2). Indeed, the averaged correlation coefficient for all the experiments was 0.996±0.003 for the cubic function. From equation (3), EVD was obtained by choosing a value of 15 mmHg for the EDP. The larger EVD indicates better diastolic function, because it represents better filling with the same EDP.

**SV and EF**

To estimate overall pump function of the ventricle, SV and EF were calculated from the equations:

\[
SV = EVD - ESV
\]

\[
EF = SV/EDV
\]

The estimated SV and EF were obtained using the loading conditions of an ESP of 70 mmHg and an EDP of 15 mmHg.
Table 1 Summary of Functional Parameters

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>DOB(L)</th>
<th>DOB(H)</th>
<th>ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ees (mmHg/ml)</td>
<td>3.2±0.3</td>
<td>3.4±0.1</td>
<td>5.3±1.0</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Vo (ml)</td>
<td>5.4±0.8</td>
<td>4.8±1.0</td>
<td>5.1±0.8</td>
<td>NS</td>
</tr>
<tr>
<td>ESV (ml)</td>
<td>29.5±5.1</td>
<td>26.6±7.6</td>
<td>18.5±5.0</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>EDV (ml)</td>
<td>40.5±10.3</td>
<td>40.0±10.3</td>
<td>43.2±8.9</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>SV (ml)</td>
<td>11.0±2.5</td>
<td>14.0±6.1</td>
<td>24.8±6.0</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>EF</td>
<td>0.26±0.15</td>
<td>0.3±0.11</td>
<td>0.57±0.08</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>aEes (mmHg/ml²)</td>
<td>-0.012±0.029</td>
<td>-0.013±0.026</td>
<td>-0.06±0.051</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Expressed as mean±standard deviation. Ees, end-systolic elastance; ESV, end-systolic volume; EDV, end-diastolic volume; SV, stroke volume; EF, ejection fraction; aEes, second order regression coefficient of the ESPVR as an index of curvilinearity.

*Significantly different (p<0.05) from Control; **significantly different (p<0.05) from DOB(L).

Protocol

The systolic parameters (Ees, ESV, aEes, Vo), the diastolic parameter (EDV) and the overall pump function variables (SV, EF) were compared in 3 different conditions. The control set of measurements were done with no dobutamine infusion. After the control protocol, dobutamine was infused at a rate of 8 μg/min and 5 min later another set of measurements was taken, known as the low-dose dobutamine protocol, DOB(L). The rate of infusion was then increased to 40 μg/min. After again waiting for 5 min, the third set of measurements was recorded (the high-dose dobutamine protocol DOB(H)).

Statistical Analysis

SPSS/PC+ software (SPSS Inc, Chicago, IL, USA) was used for the analyses. The measured variables are expressed as the mean±standard deviation. One-way analysis of variance with repeated treatment was used to test the hypothesis that all 3 measurements are equal. A p value less than 0.05 was used to reject the hypothesis. Once ANOVA showed significant difference among 3 measurements, the Bonferroni t test was used to perform intergroup comparison. Because there were 3 groups, significant difference between 2 groups was assumed if the p value was less than 0.017 (0.05/3).

Determining the Effect of Heart Size on Ees and EF. One of the disadvantages of Ees is its dependence on heart size. The Ees value will be higher in small hearts and lower in large hearts. The present EF estimation was designed to circumvent this shortcoming. To investigate the effect of heart size on Ees and EF in a quantitative manner, multiple regression analyses were performed by incorporating the dobutamine dosage (DOSE=0, 8, 40 μg) and left ventricular weight (LVW) into the regression equations:

\[
Ees = b_{Ees} \text{LVW} + b_{Ees} \text{DOSE} + c_{Ees}
\]

(6)

\[
EF = b_{EF} \text{LVW} + b_{EF} \text{DOSE} + c_{EF}
\]

(7)

The coefficients, b_{Ees} and b_{EF}, respectively, illustrate the effect of LVW on Ees and EF. A p value less than 0.01 was used to test the hypothesis that the coefficients b_{Ees} or b_{EF} were zero, which would imply no dependence on LVW.

Results

Systolic Parameters

The pressure–volume diagrams of the 3 measurements in a representative heart are shown in Fig 2. With dobutamine infusion, the ESP increased at each volume, which resulted in an increase in the slope of ESPVR (Ees). The ESPVR also showed more curvilinearity (concave to the volume axis). Consequently, the ESV in this representative heart decreased. There was a minimal change in Vo. These representative findings are supported by the summarized data in Table 1. Ees increased from 3.12 mmHg/ml of the control protocol to 3.48 mmHg/ml with DOB(L) and to
5.38 mmHg/ml with DOB(H). The infusion of dobutamine enhanced curvilinearity of the ESPVR illustrated by the serial decrease of a_{es}, from -0.0119 mmHg/ml^2 of the control to -0.0130 mmHg/ml^2 and -0.0637 mmHg/ml^2 with DOB(L) and DOB(H), respectively. ESV also decreased from 29.5 ml (control) to 26.1 ml DOB(L) and 18.5 ml DOB(H). There was no significant difference in Vo.

**Diastolic Parameter**

The infusion of dobutamine increased EDV by causing the downward shift of the EDPRV as illustrated in Fig. 2. In that dog, the downward shift of the EDPRV resulted in an increase in EDV from the control value of 30.7 ml to 31.8 ml and 35.5 ml with DOB(L) and DOB(H), respectively. As a group, EDV increased from 40.5 ml of the control protocol to 43.3 ml with DOB(H) (Table I).

**SV and EF**

The estimated pressure–volume loops in a representative dog are shown in Fig. 2. The estimated SV increased markedly with the infusion of dobutamine. EF increased as well in this heart from 0.13 (control) to 0.35 (DOB(L)) and 0.55 (DOB(H)).

The data from 10 hearts are summarized in Table 1. SV increased from 11.0 ml (control) to 14.0 ml (DOB(L)) to 24.8 ml (DOB(H)). EF also increased from 0.26 (control) to 0.33 (DOB(L)) and 0.57 (DOB(H)). The increase in EF with DOB(H) was more than twice that of the control value (128% increase). Ees increased 72% compared with the control value. The sensitivities of the variables to DOB(H) were estimated by the percent change compared with the control value. The sensitivity was highest in EF (128%) followed by SV (118%), Ees (72%), ESV (−37%) and EDV (7%).

**Effect of Heart Size on Ees and EF**

Ees and estimated EF were plotted against LVW (Fig 3). There was a trend in Ees; the smaller the heart the larger the Ees. Multiple regression analyses using equation (6) showed that Ees was dependent on LVW with a slope of b_{Ees} = -3.8 mmHg/ml-100 gLV (p=0.0005) as well as DOSE (slope a_{Ees} = 0.0574 mmHg/ml-g.g, p<0.0001). The overall goodness of fit of equation (6) was judged by an F test with an F value of 20.18, which gave a p value of less than 0.0001. Although there was a significant correlation between EF and DOSE (slope a_{EF} = 0.0078/g.g, p<0.0001) and the overall goodness of fit using equation (7) was significant (F=23.0, p<0.0001), there was no correlation between EF and LVW (p=0.661). The heart shown by the filled diamonds is the same heart shown in Fig 3.

**Discussion**

We have presented a method of estimating EF from measured ESPVR and EDPVR by giving ESP and EDP, which we used with an isolated isovolumically contracting heart preparation. The estimated EF sensitively responded to dobutamine infusion and the value was independent of heart size. Because the estimation of EF incorporates the ESPVR and EDPVR, it represents the overall pump function of the ventricle; and because the ESPVR and EDPVR are independent of loading conditions, the estimated EF is assumed to be load independent as well. The estimation is based on the vast amount of evidence showing that when contractility is held constant, the ESPVR and EDPVR are relatively unaltered regardless of the mode of contraction. To the best of our knowledge, there has been no load-independent parameter that incorporates ESPVR and EDPVR into a single variable. One possible exception is preload–recruitable stroke work (EDV–stroke work relationship) because stroke work is influenced by ESPVR and EDPVR. However, the influence of EDPVR on stroke work is small compared with that of ESPVR, and for this reason preload–recruitable stroke work is considered as a parameter of systolic ventricular function.

The standardized EF will be useful in the clinical setting where ESPVR, EDPVR, and the loading conditions vary independently. Partial left ventriculotomy (Batista procedure) for dilated cardiomyopathy provides a good example as prediction of ventricular performance after this procedure has been a subject of debate because resection of the left ventricular free wall causes a shift to the left of the ESPVR (improved contractility) and the EDPVR (impaired diastolic compliance). Because ESPVR and EDPVR can be predicted from the preparative data and the amount of left ventricular mass to be resected the standardized EF and SV can be calculated. From the latter, we can calculate if the heart can provide adequate output to maintain systemic circulation after the operation, which is crucial information for determining the operative indication. Individual analysis
of the ESPVR and EDPVR does not answer the question as to whether the heart function is good or bad. Integration of the ESPVR and EDPVR is important, which is achieved with the introduction of a standardised EF and SV.

It should be mentioned that our purpose was to present a parameter of the overall pump function of the ventricle. On some occasions, the overall pump function does not reflect myocardial contractile function; for example, impaired ventricular function in cardiac tamponade is due to an extrinsic force, which shifts the ESPVR to the left panel. Sometimes, the ESPVR is altered without any change in myocardial contractility. The right ventricular ESPVR shifts to the right when the left ventricle is unloaded. The mechanism of the shift to the right of the right ventricular ESPVR is the loss of the systolic contribution of the left ventricle through the septum or resetting of regional preload in the right ventricular free wall But it has nothing to do with myocardial contractility itself. The standardised EF should reflect these extrinsic factors applied to the ventricle in addition to myocardial contractility.

Because EF and SV are widely used variables in various clinical situations, our estimation will allow the load independent parameters to be related to the more conventional variables such as cardiac output or stroke work. From the estimated SV, cardiac output (= SV × heart rate) or stroke work (= SV × (ESP – EDP)) are readily calculated. These calculations will help predict how the heart will perform under a given loading condition.

Although Ees is a widely accepted parameter of contractility, one of its disadvantages is that it varies inversely with heart size. EF is essentially a normalized SV with respect to EDV. Our standardised EF is independent of heart size, as shown by multiple regression analyses (Fig 3). Therefore the estimated EF can be used to compare overall pump function between hearts of differing sizes.

Burkhoff et al showed that the ESPVR, which had been originally thought to be linear, is curvilinear. Therefore, it cannot be expressed as 2 parameters: the slope (Ees) and intercept (Vo) of the ESPVR. Our estimation of EF, however, is not at all compromised by the fact that the ESPVR is curvilinear, because we utilized the ESPVR only to identify one end-systolic point.

Our method relies on the fact that ESPVR is minimally altered with ejection, although we could not elucidate this issue because an isolated 'ejecting' heart preparation was not available, so this is a limitation of the present experimental study. The effect of ejection on ESPVR has been extensively studied, and it has been shown that it had a negative effect on ESP13,14 Sugii et al15 and Hunter16 both studied the effect of ejection on the ESPVR with physiologically loaded isolated canine heart preparation and showed that the effect of ejection depends on EF (ie, with a large EF, the effect was negative). In other words, the ESP obtained from the ESPVR of an ejecting heart was smaller than the ESP of the ESPVR from the isovolumically contracting heart, when the EF of the ejecting heart was large. Whereas, with a small EF the effect of ejection was positive. The crossover point from positive to negative varied between an EF of 0.36 and 0.67, according to Hunter's study. To estimate the error of our standardized EF, Hunter's results were incorporated into our data (Fig 4).

SV and EF were recalculated according to Hunter's study using a quadratic function (the crossover point was set at an EF of 0.50 and a maximal pressure difference of 8 mmHg at an EF of 0.25). With DOB(H), the EF obtained from the ESPVR and EDPVR of an isovolumically contracting heart was 0.04 larger and the SV was 1.2 ml larger than the EF estimated from the ESPVR obtained from the quadratic function incorporating the result of Hunter's study, whereas in DOB(L) our estimation obtained from isovolumically contracting heart was 0.07 smaller for EF and 2.3 ml smaller for SV, which implied substantial underestimation. The simulation discussed herein indicates a limitation of obtaining a standardized EF from isovolumically contracting heart (ie, underestimation of SV and EF for low EF). However, the estimation works very well for an EF between 0.40 and 0.60. Because our aim was to establish a simple method for this estimation, we did not incorporate the effect of ejection on the ESPVR.

The loading conditions (EDP of 15 mmHg and ESP of 70 mmHg) were set arbitrarily to facilitate the comparison of results obtained from other isolated heart preparation studies. Most of the isolated 'working' heart preparations were loaded with a filling pressure of 15–20 cmH2O and an ejection pressure head of 100 cmH2O, or 74 mmHg. Loading conditions could have been used for our estimation.

The preceding discussion elucidates an inherent limitation of the standardised EF. If 2 hearts have a different ESPVR and EDPVR, but the same ESV at an ESP of 70 mmHg, and the same EDV at an EDP of 15 mmHg, the
calculated standardized EF will be identical. Thus careful selection of the values of EDP and ESP is important. To obtain clinically meaningful values, the mean value of EDP and ESP from normal subjects should be used as the set of loading conditions.

The other way to overcome these limitations is to generalize the concept by drawing a three-dimensional surface of the EF defined by the ESPVR and EDPPVR above the plane of the ESP and EDP (Fig 5). The procedure incorporates all possible combinations of ESP and EDP, and the obtained EF surface will be uniquely defined. We can thus state that if 2 hearts had an identical EF surface, the ventricular function will be exactly the same, except for heart size. As has been theoretically predicted, the lower the ESP and the higher the EDP, the larger the EF. Our estimation is identical to finding an intersection between the EF surface and a vertical line passing the ESP—EDP plane at an ESP of 15 mmHg and an EDP of 70 mmHg. The effect of dobutamine infusion is appreciated as the upward shift of this EF surface. Miskyn et al showed similar EF—afterload relationship using end-systolic myocardial stress as a parameter of afterload. Calculation of myocardial stress, however, is complicated, whereas our method utilizing ESP as a parameter of afterload is simple and readily available, especially in clinical settings.

In conclusion, we present a method of estimating EF from the ESPVR and EDPPVR. The obtained parameter, standardized EF, can be used as a parameter of overall pump function of the ventricle. Because of the nature of the ESPVR and EDPPVR, the standardized EF is load independent. Further study is needed to test the load independence of the standardized EF in the in-situ heart. Because the estimated EF does not require heart size normalization, our method will facilitate comparing hearts varying in size beating under different loading conditions.

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References