

The load independence of the end-systolic pressure-length relationship of the heart

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Summary

The end-systolic pressure-volume relationship is the state of the art in the measurement of myocardial contractility. This index is load-independent and relatively independent of heart rate. In this study the load-independent character of the end-systolic pressure-length (ESPL) relationship was evaluated in dogs under general anaesthesia. The results indicated that the ESPL is pre- and afterload-independent, since the comparative values of ESPL from afterloaded and reduced pre-load contractions did not differ significantly ($N = 75$; $P = 0,5993$). The application of the ESPL relationship as a means of describing the function of the heart as a muscle as well as a pump is discussed.

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The end-systolic pressure-volume (ESPV) relationship of the heart has been established as an accurate and independent method by which global myocardial contractility can be quantified.¹⁻⁴ Similarly, it has been demonstrated that the end-systolic pressure-length (ESPL) relationship serves as an index of regional myocardial contractility.^{5,6} The linear character of both the ESPV and ESPL relationship makes them useful as a method by which the function of the heart, either as a muscle (contractile properties) or as pump (stroke volume), can be described.

The linear and load-independent nature of the ESPL relationship is demonstrated and its usefulness in describing the function of the heart reviewed.

Subjects and methods

Permission from the Ethical Committee of the Medical Faculty of the University of Stellenbosch was obtained to perform the study and care of the animals was in accordance with national and faculty guidelines.

The experimental protocol has been described in full elsewhere⁷ and only a summary of the techniques employed will be given here.

Fifteen mongrel dogs, mean weight 25,2 kg (range 21,2 - 26,8 kg), were used for the study. The animals were premedicated with morphine 15 mg/kg intramuscularly and anaesthesia was induced with intravenous thiopentone 15 mg/kg. The trachea was intubated and the animals ventilated with oxygen (40%) and nitrogen. The tidal volume was adjusted to the partial arterial carbon dioxide pressure at between 4,7 and 5,2

kPa. Anaesthesia was maintained with halothane or enflurane or isoflurane, which were given in various concentrations to obtain different levels of myocardial depression.⁷ Each vapour was administered to 5 dogs and 5 different predetermined end-tidal concentrations were used for each of the gases.

Normal saline, 5 ml/kg/h, was infused and the temperature of the animals was controlled with the aid of an under-table heating system. The temperature was continuously monitored from a thermister at the tip of the catheter that was floated through the external jugular vein into the pulmonary artery. Cardiac output was determined by the thermodilution method and the heart rate calculated by computer from the left ventricular (LV) pressure recording.

Arterial blood pressure was monitored by a transducer (Statham P23; natural frequency 50,4 Hz) which was connected to a fluid-filled catheter inserted through the internal carotid artery and positioned in the aortic arch. A thoracotomy was performed and the pericardium opened. The heart was suspended in the pericardium and care was taken to avoid obstruction of the venous inflow into the atria. A fluid-filled catheter was inserted into the LV apex through a stab incision and was connected to a pressure transducer (Statham P23 Db; natural frequency 50,8 Hz). From this transducer LV pressure was continuously recorded and, from a magnified calibration, the LV end-diastolic pressure (LVEDP) was registered.

Two piezo-electric crystals were placed in the LV myocardium, 1 cm apart and 1 cm away from the left ascending coronary artery, halfway between the apex and the base of the LV. The signals obtained from the crystals were processed with an ultrasonic apparatus (Schuessler and Assoc., California, USA) and the maximum length between the crystals (L_{max} — at the end of the diastole), minimum length (L_{min} — at the end of the systole) and the regional shortening of the heart ($dL = L_{max} - L_{min}$) were recorded.⁸

The segmental length and the LV pressure recordings were combined on a storage oscilloscope. This allowed the observer to view the function of the heart beat by beat by recording the pressure-length loop from the particular segment of the LV (Fig. 1).⁹

The femoral artery and vein of one of the animal's legs was dissected and occlusion catheters (size 8-14F; Edwards Laboratories, California, USA) were inserted into both. The balloon in the aorta was positioned just distal to the aortic arch and the balloon in the inferior vena cava was positioned between the diaphragm and the right atrium. These were used to change the pre- or afterload during the experiments. The changes in the loading conditions permitted the generation of a number of pressure-length loops (6 - 8) from which the ESPL points could be obtained and used to construct the ESPL (Fig. 2).

The arterial blood gases and pH were checked at regular intervals (IL 613 and IL 283, Instrumentation Laboratories, Lexington, Mass., USA) and, if necessary, corrections were made to the ventilator to ensure optimum physiological conditions.

Pressure transducers were calibrated before the start of the experiments, as well as between each step. Data were recorded by computer and stored directly onto floppy disk. Sampling was done at 200 Hz for 5 seconds.

The aim of this study was to evaluate whether the ESPL ratio (i.e. the contractile state) obtained during an acute mecha-

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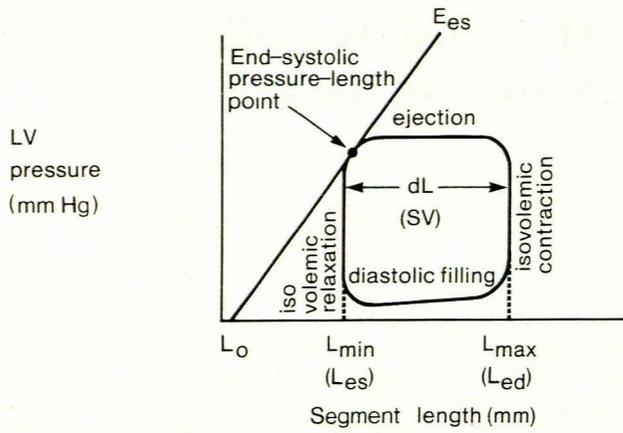


Fig. 1. A pressure-volume diagram of a single cardiac contraction. If a number of loops are generated while the pre- or afterload is changed, the various end-systolic pressure and length points can be used to calculate E_{es} (or ESPL relationship) by linear regression. The slope of this line is an index of myocardial contractility. Shortening of the muscle cannot proceed past this line.

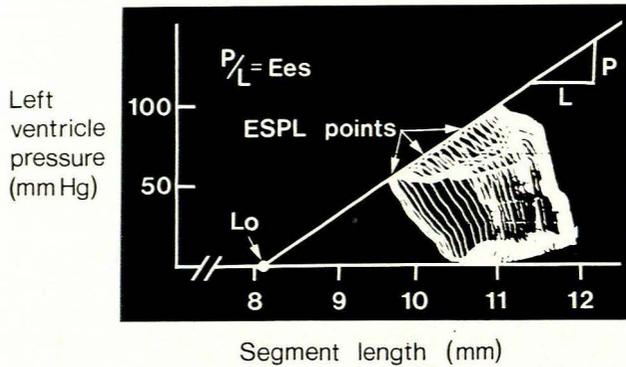


Fig. 2. A number of pressure-length loops generated by changing the afterload. Note the linear character of the end-systolic pressure-length line and the fact that regional shortening of the muscle cannot proceed past this line.

nical increase in afterload or an acute mechanical decrease in preload differed. For statistical analysis the paired *t*-test was initially applied but if the distribution of data proved to be significantly different from normal (Roysten's development of the Shapiro-Francia *W*-test¹⁰), the Wilcoxon signed-rank test was applied.

Calculation of the ESPL relationship

In each animal, a single anaesthetic vapour was used in 5 predetermined concentrations. Twenty-five minutes were allowed for the cardiovascular system to reach stable conditions before the data were recorded at each level of anaesthesia. The exact concentrations utilised have been published elsewhere⁷ and need not be discussed, since this study was devised to compare the values for the ESPL relationship obtained by different methods — irrespective of the level of myocardial contractility. The inhalational agents were only used to give various levels of contractility.

To construct an ESPL relationship that can be used as an index of myocardial contractility, the maximum pressure-length ratio of the ventricle must be recorded. The ratios of pressure and volume vary throughout the cardiac cycle and

this is referred to as the time varying elastance of the ventricle. The maximum ratio for pressure and volume occurs at the end of systole and this particular ratio is termed the ESPL. Since this ratio is a constant, the ESPL relationships of various beats (similar contractility) will be constant and hence this can be discussed with reference to linear mathematics. The slope of the regression analysis obtained from the maximum pressure:volume ratios is the index of myocardial contractility.

For each step in the experiment, the aortic balloon was first inflated to partially occlude the aorta. This was done over 5 - 8 heart beats. By doing this, the configuration of the pressure-length loops obtained varied and a number of ESPL points were obtained (Fig. 3). Similarly, by inflating the balloon in the inferior vena cava, the preload of the heart was reduced over 5 - 8 beats and the resultant changes in configuration allowed for the collection of a number of ESPL points (Fig. 4).

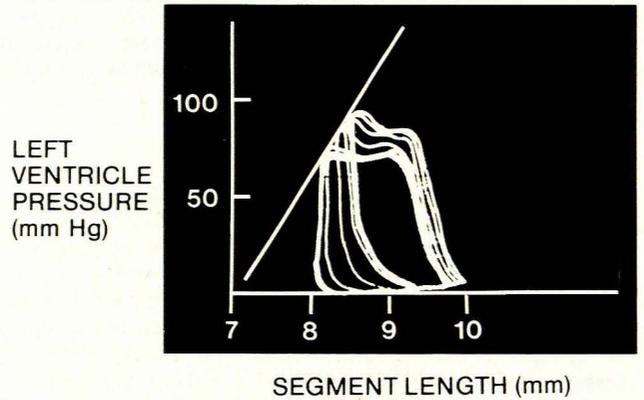


Fig. 3. In this experiment the aortic afterload was increased with an intra-aortic balloon inflated over 5 - 6 s. The end-diastolic volume increased (right lower corner of the loops) and the ventricular pressure increased as the ejection of the stroke volume proceeded. The linear character of the ESPL relationship is again obvious.

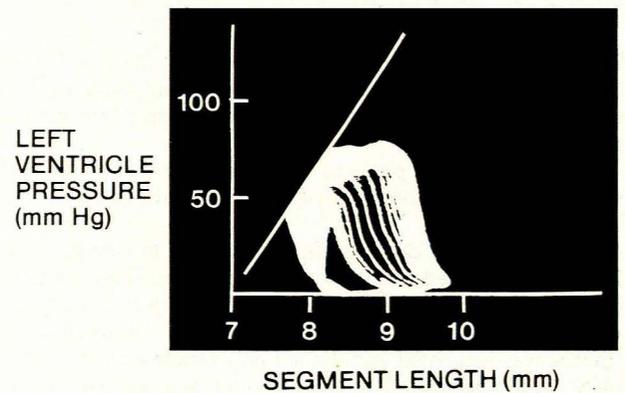


Fig. 4. A number of pressure-length loops generated by decreasing the preload with a balloon in the inferior vena cava. Again note the linear character of the ESPL relationship.

The maximum ESPL ratio for each beat was sought by the computer and registered. These various pressure and length points obtained were then subjected to linear regression (least squares method) and the slope of the ESPL line was recorded. By simple mathematical manipulation, the intercept of this line on the length (*x* axis) could be obtained and this was also recorded (Fig. 2).

Results

Because the concentrations of the anaesthetic gases were pre-determined and equal, data from the various experiments were pooled.

In order to demonstrate the range of myocardial contractility registered, the mean \pm SEM for the minimum and maximum values for the ESPL ratios are given below:

	Minimum (mmHg/mm)	Maximum (mmHg/mm)
Halothane	137,07 \pm 16,58	29,18 \pm 4,15
Enflurane	142,06 \pm 38,55	28,16 \pm 2,46
Isoflurane	225,01 \pm 100,50	27,88 \pm 2,51

If the initial values for ESPL ratio (i.e. at the lowest inhaled gas concentration used) represented 100%, the ESPL ratio decreased by 78% for halothane, 80% for enflurane and 87% for isoflurane.

The increase in the afterload is reflected by the increase in mean arterial pressure of 50,80 \pm 18,05% above control values. The inflation of the balloon in the inferior vena cava resulted in a reduction in the preload as reflected by the decrease in the LVEDP of 20,15 \pm 5,12%.

The calculation of each ESPL ratio was performed on a mean of 6,75 pairs of datapoints (range 5 - 9). A correlation was performed for the end-systolic pressure and volume points for each of the various experimental steps. The mean of these correlations were:

afterloaded ESPL ratio: $r = 0,994 \pm 0,12$ ($N = 75$; $P < 0,001$)
 preload change ESPL ratio: $r = 0,995 \pm 0,12$ ($N = 75$; $P < 0,001$)

Comparison of the afterloaded ESPL ratios and the preload reduced ESPL ratios, demonstrated that there was no difference between the two methods (paired t -test $P = 0,9183$). However, since the values appeared not to be normally distributed (Roysten's development of the Shapiro-Francia W -test; $W = 0,8725$), the Wilcoxon signed-rank test was applied. Again no difference between the two methods could be demonstrated ($P = 0,5293$; $U = 0,6290$).

The correlation between the ESPL ratio for the afterloaded contractions (y) and the reduced preload ESPL ratio (x) yielded (Fig. 5):

ESPL (preload) = $-0,1611 (\pm 0,9211)$. ESPL (afterload) + 1,001 ($\pm 0,009$)
 $F = 10280,50$, d.f. = 1,72, $r = 0,997$, SEE = 4,5205.

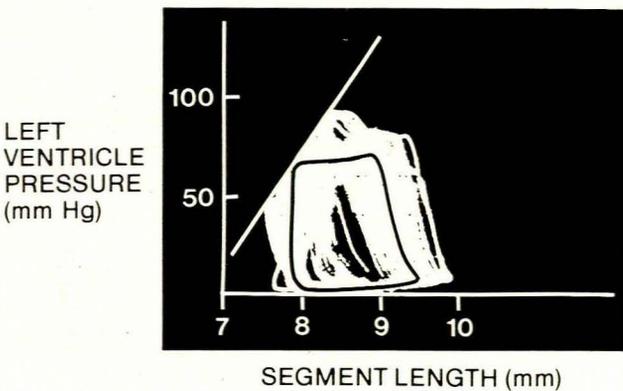


Fig. 5. The load-independence of the ESPL relationship is demonstrated. The dark loop (centre) was the control loop. Initially the preload was reduced and the ESPL points below the control loop were generated. Thereafter the preload was restored and the afterload increased immediately as indicated by the ESPL points above the control loop. There is no difference in the slope of the decreased preload ESPL relationship and the afterloaded ESPL relationship.

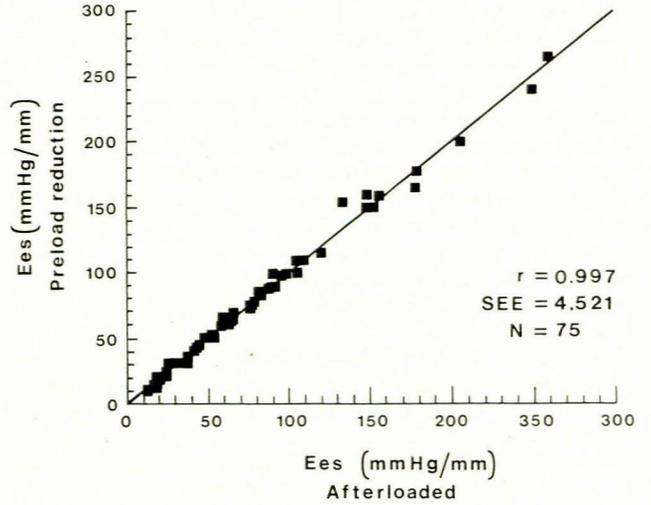


Fig. 6. A correlation between the ESPL relationships generated by reducing the preload and increasing the afterload. The regression line does not differ from the line of identity thus confirming the load-independence of the ESPL as an index of myocardial contractility.

This line was not different from the line of identity when subjected to analysis of co-variance (Fig. 6).

Discussion

There are two significant findings in this study: (i) the maximum pressure-length relationship has a linear character; and (ii) the ESPL is independent of the pre- and afterload. These results support results previously reported for the ESPV relationship.¹¹ Results we obtained pertain to segmental myocardial function as opposed to the ESPV relationship, which is applied to global myocardial function.

The importance of the ESPV and ESPL relationship lies in the fact that this is a load-independent method by which myocardial contractility can be described. This is in contrast with some of the other indices of contractility often employed, e.g. ejection fraction¹² and the rate of rise in LV pressure during isovolaemic contraction (dp/dt_{max}),¹³ which are load-dependent, influenced by heart rate, normal conduction and normal heart anatomy. Furthermore, the ESPL relationship is a useful method to describe the function of the heart as a pump and the concept of pressure-volume relations then becomes a unifying concept that can quantify both the function of the heart as a pump and at the same time define myocardial contractility.

The ESPL relationship can briefly be discussed with reference to the experimental work of Taylor *et al.*,¹⁴ who demonstrated that muscle shortening of the contracting heart is always terminated at some predetermined point. This observation could be applied to isometric contraction, freely ejecting hearts and afterloaded contractions. The predetermined point (or pressure-volume ratio) at which shortening stops is similar irrespective of the method of contraction. Also fundamental to the concept of the ESPL relationship is the demonstration of a change in the elastance of the ventricle with time after the start of the systole.¹⁵ The pressure-volume relationship (elastance) of the heart increases up to a maximum point during systole and thereafter declines during the isovolaemic relaxation period of the cardiac cycle (Fig. 1). The maximum pressure-volume relationship occurs at the end of systole hence the term end-systolic pressure-volume relationship (ESPL relationship, commonly abbreviated as E_{es}).

Linear regression mathematics applied to the time varying elastance of the heart can be used to develop the theory of the ESPL relationship (Figs 1 and 2):

$$P_{es} = E_{es}(V_{es} + P_o) \dots\dots\dots (1)$$

where P_{es} = pressure at the end of the systole; V_{es} = volume at the end of systole; E_{es} = slope of the pressure-volume relationship; and P_o = intercept on the pressure (y) axis.

Equation 1 can be rewritten in order to accommodate the intercept on the volume (x) axis:

$$P_{es} = E_{es}(V_{es} - V_o) \dots\dots\dots (2)$$

where V_o is the volume in the ventricle at the time LV pressure is zero. Solving equation 2 for E_{es} :

$$E_{es} = P_{es}/(V_{es} - V_o) \dots\dots\dots (3)$$

From equation 3 the following assumptions can be made:

(i) the end-diastolic volume (V_{ed}) does not appear in the equation and hence E_{es} , or the measurement of myocardial contractility, is preload-independent; and (ii) if P_{es} changes, it will not affect E_{es} because of the constant relationship between P_{es} and V_{es} . E_{es} is therefore afterload-independent.

Our results confirm the theoretical concepts as discussed above. We have demonstrated that the ESPL relationship is independent of pre- and afterload.

When discussing the ESPL relationship, it is important to state the value for V_o . A change in contractility is indicated by a change of the slope of the ESPL relationship, irrespective of the position of V_o . An increase in V_o may occur in the dilated heart while a decrease in V_o is expected in the hypertrophied LV myocardium.⁶

The function of the heart as a pump can also be discussed with reference to the ESPL relationship:

$$SV = V_{ed} - V_{es} \dots\dots\dots (4)$$

From equation 2:

$$V_{es} = P_{es}/E_{es} + V_o \dots\dots\dots (5)$$

From equation 5 and 4:

$$SV = (V_{ed} - V_o) - P_{es}/E_{es} \dots\dots\dots (6)$$

Equation 6 can be tested against well-known cardiac physiology principles. If the Starling mechanism of the heart is invoked, i.e. if V_{ed} increases SV will increase, all other things being equal. If the afterload is increased, SV will decrease if all the other factors remain constant. In the case of cardiac failure, i.e. a decrease in E_{es} , SV will decrease if other parameters remain constant. Equation 6 can also predict the response of the SV if therapeutic modalities are applied. In the case of cardiac failure, i.e. a decrease in E_{es} , a reduction in afterload (P_{es}) will improve SV.

In summary, we have confirmed the linearity and load-independence of the ESPL relationship as an index of myocardial contractility. The theory of the pressure and volume relations of the heart suggests that it is a useful index to describe the circulation. This theoretical advantage is borne out by everyday clinical practice.

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