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Left ventricular end-systolic stress/diameter relation as a contractility index and as a predictor of survival. Independence of preload after normalization for end-diastolic diameter

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Abstract The independence of the slope of the left ventricular (LV) end-systolic stress/end systolic diameter (ESS/ESD) relation of preload (PL) after normalization for end-diastolic diameter (EDD), and the reliability of both the original and the normalized slope as contractility and prognostic indices, were assessed. We studied echocardiographically, hemodynamically, and with carotid pulse tracing, 25 normal subjects, 18 patients with coronary artery disease having a normal ejection fraction (EF), and 30 patients with idiopathic dilated cardiomyopathy (DCM). The arterial pressure was changed with intravenous infusion of phenylephrine. To investigate the effect of PL on the ESS/ESD slope, in 12 normals the PL was decreased with intravenous infusion of 40 mg of furosemide and increased with 1 l isotonic NaCl. The studied population was followed up for 18–61 months. The mean values of the slope after furosemide and after NaCl differed significantly but when the above values were divided by the EDD the differences were nullified. The mean values of the slope differed highly significantly between the three groups. The normalized slope increased the sensitivity in the discrimination. During the follow-up period 10 patients with DCM died. The original and the normalized slopes separated the deceased and survivors significantly ($P < 0.002$ for both indices) as compared to EF ($P < 0.05$). The ESS/ESD slope is a very sensitive contractility index and is also superior to EF as a prognostic parameter. The normalization of the slope eliminates its dependence on PL and improves the sensitivity in assessing decreased contractility, although it slightly decreases its prognostic value.

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Introduction

Contractility can be defined as the ability of the heart to generate force at a given preload. Maintenance versus loss of contractility is a key determinant of outcome for most cardiac diseases.[1] It is therefore not surprising that so much effort over the last 35 years has been directed toward trying to measure this property clinically.

The assessment of myocardial contractility in clinical practice is difficult because all the currently used indices are influenced more or less by the loading conditions.[2,3] Isovolumic and ejection phase indices, the most established clinical measurements of contractile function, are affected significantly by changes in preload (PL) and afterload (AL).[2–4] The new contractility indices derived from end-systole and combining hemodynamic and mechanical properties of the heart have significant advantages. Specifically, the slope of the end-systolic force/length relation was found to have great sensitivity because it is independent of PL and incorporates AL.[5–7] Previous studies, however, have shown that the slope is influenced by PL.[8–10]

This study was undertaken to evaluate the independence of the end-systolic stress/end-systolic diameter (ESS/ESD) slope, as expression of the end-systolic force/length relation from PL after normalization for end-diastolic diameter, as well as the accuracy of both the original ESS/ESD slope and that normalized for EDD, in assessing the contractile state and prognosis.

Patients and methods

Study population

Seventy-three subjects were included in this study. Twenty-five subjects (15 males and 10 females, aged 50 ± 11 years)

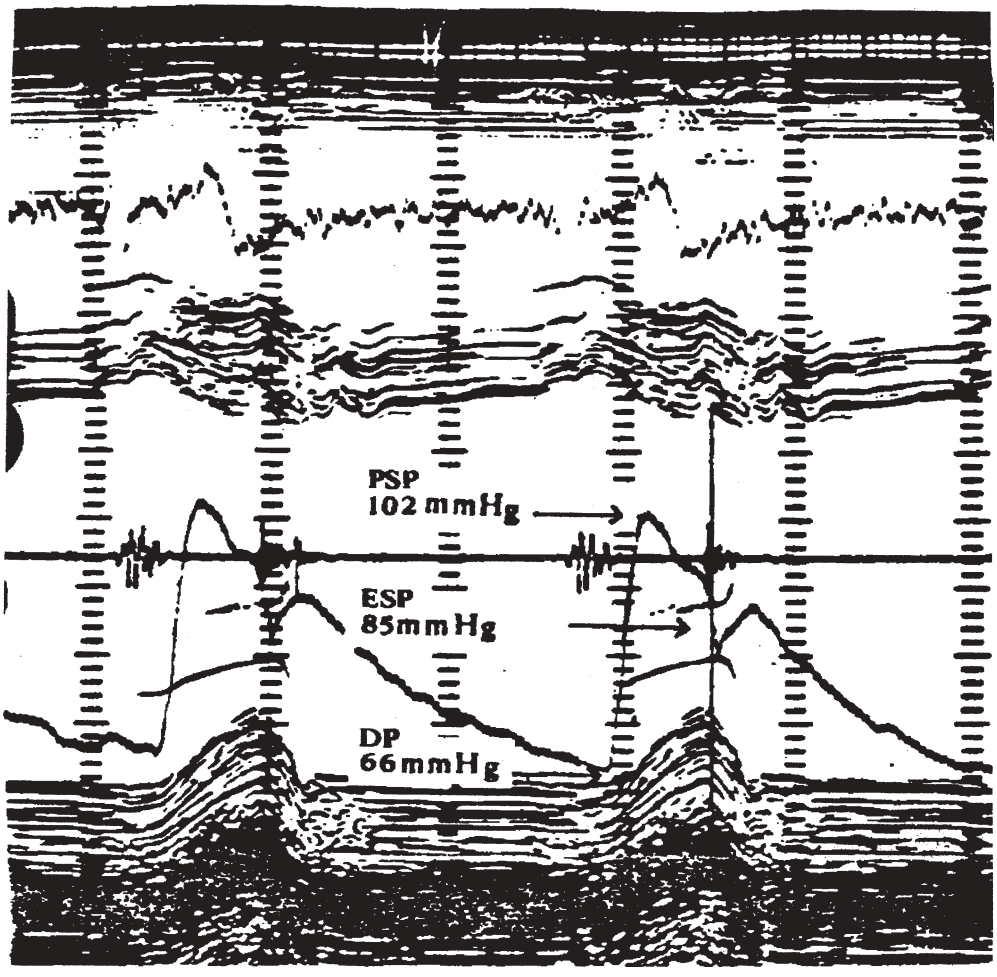

Fig. 1. M-mode echocardiogram of the left ventricular cavity at the level of the chordae tendineae. Above the interventricular septum (the right ventricular cavity) the electrocardiogram is seen and in the *middle* of the figure the phonocardiogram and the carotid artery tracing, standardized according to the method of Stefadouros et al.[13] The *vertical line* passing through the second sound shows the point of the carotid artery tracing corresponding to 30 ms before the incision, at which time end-systolic pressure, end-systolic diameter, and posterior wall thickness were measured

evaluated for chest pain who had normal findings in coronary angiography were considered as the control group (group I, N). Consecutive patient groups consisted of 18 (13 males and 5 females, aged 51 ± 7.5 years) patients with coronary artery disease, normal left ventricular (LV) ejection fraction (EF), and no wall motion abnormalities (group II, CAD), and 30 patients (21 males and 9 females, aged 55.4 ± 14 years) with idiopathic dilated cardiomyopathy (group III, DCM). Of the patients with CAD, 3 had one-vessel disease, 9 had two-vessel disease, and 6 patients three-vessel disease of those with DCM, 9 patients were classified into NYHA class II, 16 into class III, and 5 into class IV. There was no significant difference in systolic pressure or heart rate among the three groups at baseline. The study protocol was approved by the Institutional Committee on Human Research, and informed consent was obtained from all subjects.

Study protocol

All subjects underwent complete hemodynamic and angiographic studies. In all cases the LV ESS/ESD relation was studied noninvasively using simultaneous recordings of echocardiogram, phonocardiogram, standardized carotid pulse tracing, and a common cuff sphygmomanometer. The blood pressure was initially measured three or four times at rest until its level was stabilized and the subjects were premedicated with atropine, 0.01 mg/kg, to abolish reflex cardiac slowing.[11] Then, an incremental infusion of phenylephrine, starting with 0.04 mg/min and up to 0.12 mg/min, was initiated and the blood pressure was gradually raised 4–10 levels. Levels of arterial blood pressure greater than 40 mmHg from the resting value were excluded from the study in order to avoid the Anrep effect.[12] At each level the blood pressure was measured and the recordings were repeated. From all of these tracings the following measurements were made. The end-systolic pressure (ESP) was measured from the carotid pulse tracing, which was standardized according to the method of Stefadouros et al., so that the zenith of the curve corresponded to peak systolic blood pressure and the nadir to the diastolic blood pressure, the height of the curve being graded accordingly. The ESP was measured at the level corresponding to 30 ms before the dicrotic notch.[13] The end-systolic and end-diastolic diameter (ESD and EDD) and the end-systolic thickness of the posterior wall (h) of the LV were measured from the M-mode echocardiogram, guided by the two-dimensional image at the level of the chordae tendinae (Fig. 1). From the above measurements the meridianal LV end-systolic wall stress

(ESS) was calculated according to the formula: ESS = ESP·ESD·1.35/4h·(1 + h/ESD).[12,14] The slope of the ESS/ESD relation was calculated as the coefficient of regression of the values of the ESS and the corresponding values of the ESD at each level of blood pressure according to the least-square method. The relation of he ESS/ESD was linear for each subject with a high coefficient of correlation (r = 0.94–0.99). The intraobserver and interobserver mean percent error (absolute difference between two observations divided by the mean and expressed in percentage) was determined for the LV dimensions and the end-systolic thickness of the posterior wall (h) in 30 randomly selected patients (8 with CAD, 12 with DCM, 10 controls) and were 4.2% and 4.6% for EDD, 4.4% and 4.8% for ESD, and 5.2% and 5.6% for h, respectively.

To investigate the effect of PL on the slope of the ESS/ESD relation, the above index was estimated before and after alternations of PL in 12 normal subjects. The PL was decreased with an intravenous injection of 40 mg of furosemide and was increased with a rapid infusion of 11 of isotonic NaCl. Phenylephrine infusion was performed at each of three different PL levels, i.e., baseline, furosemide administration, and saline infusion, and the ESS/ESD slope was calculated as described above. To decrease the effect of preload on the sensitivity of the slope in discriminating the abnormal from the normal LV function, the original values of the slopes were "normalized" by division by the initial EDD. The studied population was followed up for a period of 18–61 months (median value 36 months).

Statistical methods

All values are expressed as mean ± 1 standard deviation. Frequency data were compared using chi-square analysis and continuous variables between two groups using the unpaired t-test. Comparisons between the three groups were performed using one-way analysis of variance followed by the Scheffé test. A P value of less than 0.05 was considered statistically significant. Simple linear regression (least-square method) was used to fit each subject's data to an ESS/ESD equation. Survival analysis was performed using Kaplan–Meier estimates (log-rank test) to examine for differences between survivors and deceased in the whole patient population for the studied parameters.

Results

Dependence of the ESS/ESD slope on PL

The EDD, which reflects PL, decreased after the injection of furosemide from 4.82 ± 0.39 to 4.4 ± 0.43 cm (P < 0.05) and increased after the infusion of NaCl from 4.80 ± 0.35 to 5.26 ± 0.52 cm (P < 0.05). The ESD following the changes increased from 3.05 ± 0.33 cm in the "low" PL to 3.39 ± 0.35 cm (P < 0.05) in the "high" PL. This change was not the result of a corresponding change of end-systolic force, as the mean ESS changed marginally from 53.32 ± 14.4 g/cm^2 in the "low" PL to 55.79 ± 13.1 g/cm^2 in the "high" PL. Also, the correlation of ESD and ESS was low (r = 0.386). The calculation of the ESS/ESD slope showed that the high coefficient of correlation at baseline remained similarly high after PL changes (Fig. 2). The mean value of the slope, ESS/ESD, at the "low" PL was 116.2 ± 11.7 and at the "high" PL 128.4 ± 13.4 g/cm^3 (P < 0.05). When the above values were divided by the EDD the differences were nullified. The "normalized" mean slope of ESS/ESD at the "low" PL was 26.3 ± 5.5 and at the "high" PL 25.9 ± 5.8 g/cm^4 (P not significant). The results indicate that both the ESD and the slope of the ESS/ESD relation are mildly but significantly dependent on PL. However, when the values of the slope are divided by EDD they become truly independent of PL.

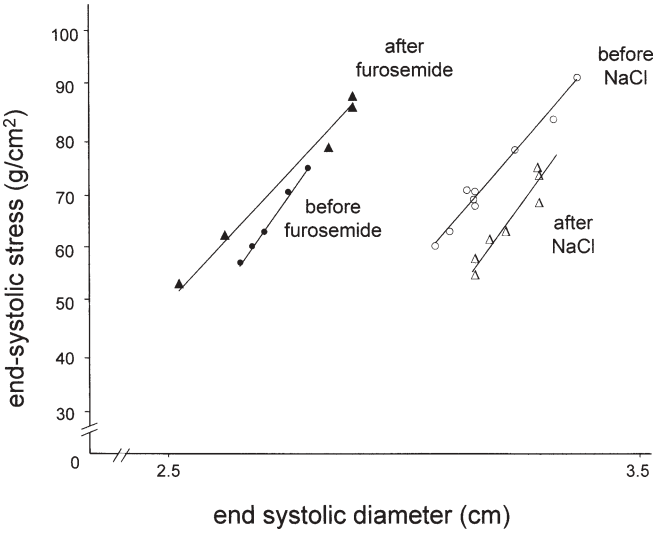

Fig. 2. Values of the ESS/ESD slope before and after NaCl infusion (*left*) and before and after furosemide administration (*right*)

Table 1. Baseline hemodynamic and echocardiographic characteristics of the study population

Parameter	Control	CAD	DCM
CI (l/min/m^2)	3.39 ± 0.50	3.15 ± 0.58	2.18 ± 0.6*
LVEDP (mm/Hg)	10 ± 4	10.3 ± 4.5	23 ± 6*
EF%	64 ± 4	61 ± 7.5	31.6 ± 11*
EDD (cm)	5.1 ± 0.5	5.3 ± 0.45	6.9 ± 0.8*
ESD (cm)	3.38 ± 0.43	3.52 ± 0.46	5.5 ± 0.9*
PWLV (cm)	1.44 ± 0.13	1.43 ± 0.15	1.26 ± 0.15*

CAD, coronary artery disease; DCM, dilated cardiomyopathy; CI, cardiac index; LVEDP, left ventricular end-diastolic pressure; EF, ejection fraction; EDD, end-diastolic diameter; ESD, end-systolic diameter; PWLV, posterior wall end-systolic thickness
*P < 0.001 vs CAD and controls

Sensitivity of the indices in differentiating the three groups of patients

The hemodynamic and echocardiographic findings of the study population are listed in Table 1. As shown in Fig. 3, the mean value of the slope of the ESS/ESD relation of the

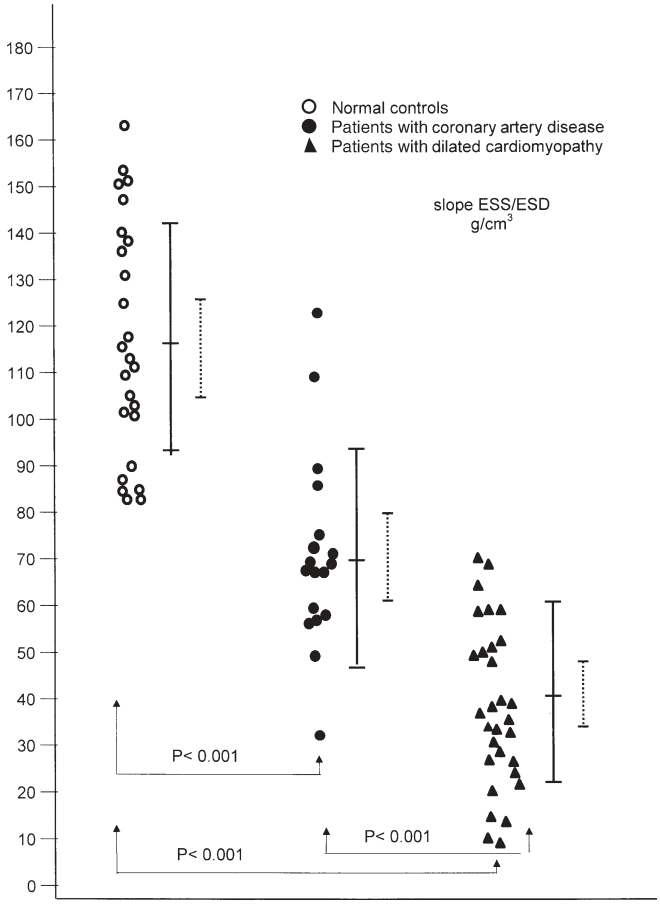

Fig. 3. Distribution of the values of the slope of the end-systolic stress/end-systolic diameter relation. At the *left* of the figure are the normal controls, in the *middle* the coronary artery patients, and at the *right* the patients with dilated cardiomyopathy. The *vertical bars* at the side of each group show the mean values and the standard deviation (*continuous line*), and the 95% confidence limits (*dotted line*)

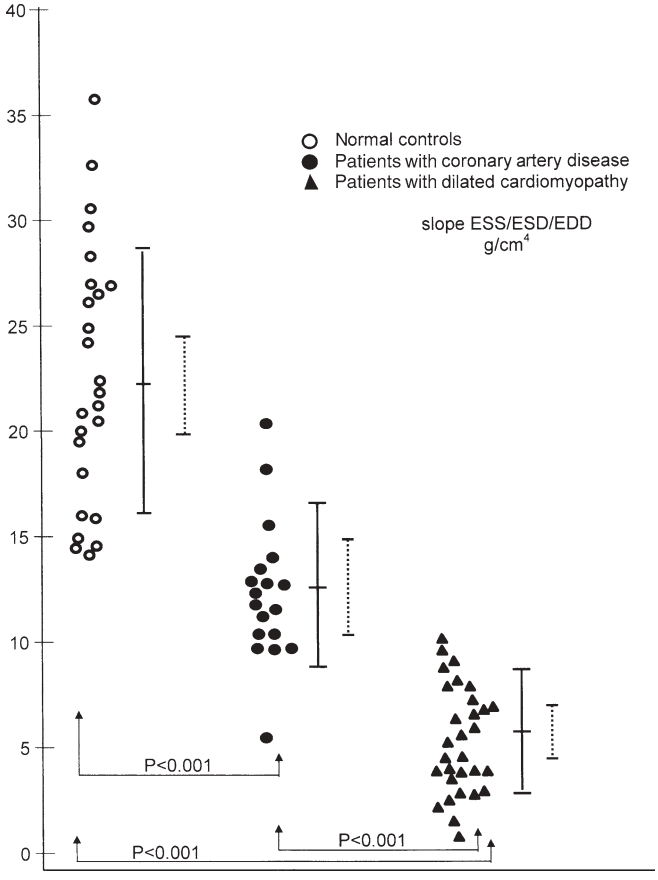

Fig. 4. Distribution of the values of the end-systolic stress/end-systolic diameter slope normalized for end-diastolic diameter. Explanations as for Fig. 2

controls was 117.4 ± 25.5 g/cm^3, and differed highly significantly from the mean value of the CAD patients (72 ± 21 g/cm^3) and patients with DCM (43.6 ± 18 g/cm^3). The mean value of the slope separated the normal subjects from the DCM patients without overlap. Of the CAD patients only 4 had normal values of the slope although they had a normal EF. The mean value of the "normalized" slope of the controls was 23.2 ± 6 g/cm^4 versus 13.3 ± 3.3 g/cm^4 in the CAD patients and 6.2 ± 2.5 g/cm^4 in the DCM patients. This discrimination between the three groups with the normalized slope showed increased sensitivity. The separation of normal controls from the DCM patients was better than with the original slope, and it is obvious that the gap between the two groups became wider, while only 3 patients with CAD had normal values (Fig. 4). For the total number of patients, therefore, the sensitivity of the original slope was 91%, the specificity 86%, and the predictive value 100%. For the normalized slope the respective values were 94%, 89.3%, and 100%. If we used the simple ratio ESS/ESD and ESS/ESD/EDD there was also a significant difference between CAD and controls ($P < 0.05$) as well as between DCM and controls ($P < 0.001$), but with a significant overlap for both indices.

Prognostic implications

During the follow-up period, 10 cardiac deaths occurred among the patients with DCM but none in CAD patients and controls. Six of the deaths were sudden and four were due to advanced heart failure; 2 occured in class II patients, 5 in class III, and 3 in class IV. The mean age of those who died was 57.3 ± 12.6 years and that of the survivors was 53 ± 14.2 years, which was not a significant difference. The mean value of both the original and the normalized slopes showed a highly significant difference between the deceased and survivors (50.5 ± 17.5 vs 29.7 ± 9.7 g/cm^3 and 7.1 ± 2.4 vs 4.3 ± 1.5 g/cm^4, respectively), $P < 0.002$ for both indices. This is clearly shown from the fact that the confidence intervals of the mean values of both the original and corrected slopes in the two subgroups did not overlap (confidence limits of the survivors were 42.8–58.2 and of the deceased were 23.7–35.7 for the original slope, while they were 6.1–8.1 and 3.36–5.2 for the normalized slope, respectively). In comparison, the mean EF of the survivors and patients who died was 34.6% ± 10.5% and 25.7% ± 10%, respectively. The difference was just significant ($P < 0.05$). The confidence intervals of the mean values of the EF showed a significant overlap (Fig. 5). The simple ratios ESS/ESD and ESS/ESD/EDD were also less sensitive in discriminating between the deceased and

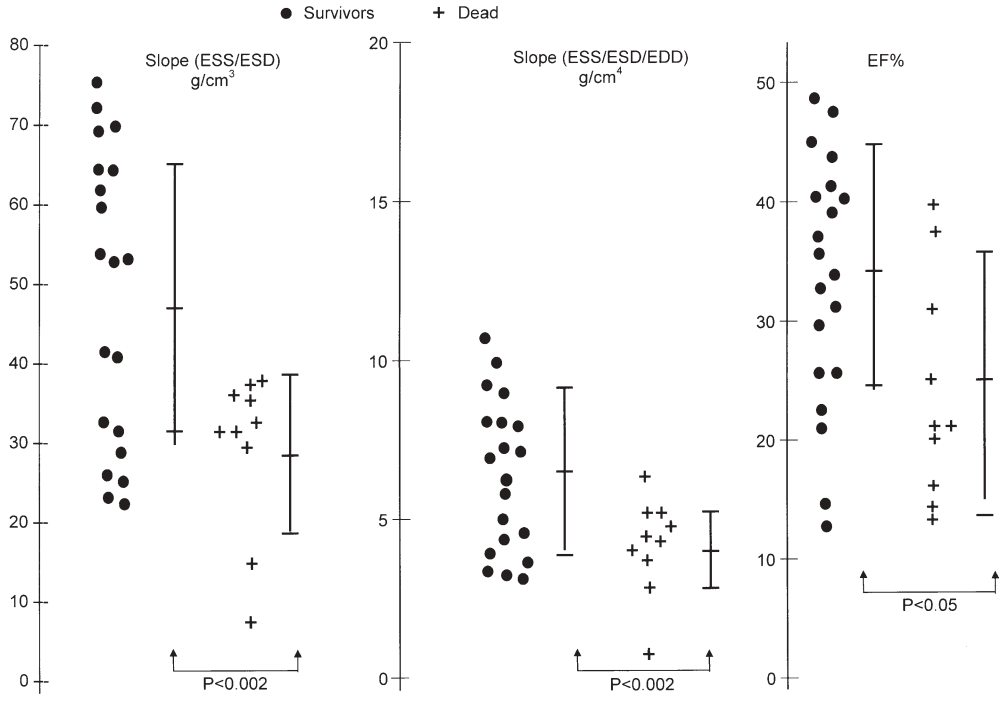

Fig. 5. Distribution of the end-systolic stress/end-systolic diameter slope (*left*) after normalization for end-diastolic diameter (*middle*) and of the ejection fraction (*right*) between survivors (*dark dots*) and deceased (*crosses*), in patients with dilated cardiomyopathy. The *vertical bars* show the mean values and standard deviation

survivors ($P < 0.05$ for both indices) than the original and normalized slope. No patients with an original slope greater than 40 g/cm^3 died during the follow-up period. Below 40 g/cm^3 there were 10 deaths and 7 survivors giving a predictive value of 59% (sensitivity 100%, specificity 65%). Regarding the normalized slope, no patients with a value more than 7.5 g/cm^4 died during the follow-up period. Below 7.5 g/cm^4 there were 10 deaths and 10 survivors, giving a predictive value of 50% (sensitivity 100%, specificity 50%). No level of EF satisfactorily separated the survivors from deceased. Taking an arbitrary level of EF of 30% would yield a sensitivity of 70%, a specificity of 65%, and a predictive value for mortality of 50%. Kaplan–Meier survival analysis of all the patients showed that survival was significantly lower in those with ESS/ESD slope values lower than 40 g/cm^3 (log-rank test for the comparison between survivors and deceased = 4.20, $P = 0.04$). The same analysis showed that survival was also better in the patients with ESS/ESD/EDD values greater than 7.50 g/cm^4 (log-rank test = 10.50, $P = 0.001$).

Discussion

It is well known that contractility is the most significant parameter of cardiac function and influences the prognosis of patients with latent or overt heart failure. It is therefore logical to assume that the contractility indices might be significant predictors of survival.[15–18]

Our findings indicate that the slope of the ESS/ESD relation effectively separated normal subjects from both groups of patients. In addition to the significant difference between group means, the individual values of the slope in all group III patients were below the normal range observed in group I and also, only 4 patients in group II had normal values of the slope. These results show that the slope ESS/ESD is a very sensitive measure of decreased contractility and is more accurate than the EF, despite the significant correlation between the two indices. This possibly occurs because the correlation is exponential and, thus, in the first half of the curve the values of the indices of end-systole remain low, revealing the decreased contractility despite the relatively high value of EF.[19–21] The superiority of the above index versus EF is also evident due to its greater independence from PL and AL as compared to EF. Furthermore, the slope, ESS/ESD, expresses the force and, indirectly, the extent of shortening, whereas the EF expresses only the extent of the shortening.

In accordance with our study, El-Tobgi et al.,[20] using the ESP/ESD slope, separated without overlap normal subjects from patients with CAD and normal EF when segmental akinetic areas were present but not when they were absent. In contrast, when they used the EF as a separating index there was a significant overlap between the two groups and the difference in the mean values was less significant. Ramanatham et al.[22] also demonstrated that the simple ratio peak systolic pressure/end-systolic diameter (PSP/ESD) was superior to the EF. With the ratio PSP/ESD, they significantly separated the control group from patients with CAD without regional asynergy and from those with CAD and regional asynergy. In contrast, the ejection phase indices, as did EF and mean velocity of circumferencial fiber shortening, showed a significant difference only between controls and CAD patients with regional asynergy.

In previous studies it has been shown that the ESS/ESD slope is mildly but significantly PL-dependent.[8–10] Although it has been suggested that variations of PL are of minor

importance in normal subjects, this study verified the PL dependence; however, when the values of the slope are divided by EDD, the mild dependence on PL is eliminated, and they become truly independent of PL.[23] Thus, the improvement of the normalized slope compared with the simple one is indicated from the greater sensitivity, specificity, and predictive value in the discrimination between normal subjects and the patient groups. Moreover, the normalization of the original slope with the EDD possibly causes "correction" of other parameters affecting the relation end-systolic force–length, such as cavity size and stroke volume, which are proportional to the body surface area.[12,24] The normalization of the slope might be especially applicable in mitral regurgitation where the isovolumic indices are not significant, due to lack of isovolumic contraction,[26,27] and the usefulness of the ejection phase indices is limited, due to low AL and high PL, resulting in increased values.[8] On the other hand, the original slope, ESS/ESD, is decreased but the normalization restores its validity.[8] Consequently, the ESS/ESD slope is better than the previously reported contractility indices because the simple ESS/ESD ratio is AL-dependent, and AL-adjusted ESS/ESD may be independent of AL and superior to the simple ratio.[25] Moreover, the PL-adjusted ESS/ESD/EDD slope should be independent of PL and AL.[1,23,25]

Several parameters assessing LV systolic dysfunction have been used for prognostic purposes.[14–17,25,28] Ejection fraction is the most widely used index of the contractile state and is a powerful predictor of mortality in many but not all studies.[29–33] Notably, in cases with mild or moderate heart failure it is considered one of the best prognostic indices.[30] However, later in the course of heart failure the ejection phase indices are strongly AL-dependent.[34,35]

Previous studies have examined the utility of the end-systolic force–length relation in predicting surgical morbidity and mortality in patients with chronic mitral or aortic regurgitation undergoing valve replacement. Most of them showed that the slope or the simple ratio, ESS/ESV or PSP/ESV, was an excellent and independent predictor for good or unfavorable postoperative results.[36–43]

In our study, the ESS/ESD slope, which is more reliable than the simple ratio ESS/ESD,[1,25] is apparently superior to EF as a prognostic index given that the mean value separates deceased from survivors with clearly greater sensitivity compared with EF. The normalization of the slope with the EDD, despite the increase in sensitivity as the contractility index, does not increase the sensitivity of the original slope as the predictor of survival, although the normalized slope is also superior to EF. In addition, the normalization decreases the specificity and prognostic value. This is possible because normalization of the original slope makes this more sensitive in detecting milder types of LV systolic dysfunction and, consequently, decreases its specificity and prognostic value in death prediction.

Study limitations

Certain limitations of this study must be discussed. The evaluation of left ventricular volumes by only one diameter introduces an error factor. Similarly, measurement of the arterial blood pressure with a common cuff sphygmomanometer and also evaluation of end-systole from the standardized carotid pulse tracing can cause errors. However, evaluation of the LV dimensions by echocardiography constitutes an established practice and the value of the end-systolic diameter as a prognostic index in aortic regurgitation is well known, despite the consequent changes in LV shape.[44,45] In addition, the accuracy of the external measure of arterial pressure and the indirect estimation of end-systole by a standardized carotid pulse tracing have been verified in comparison with invasive measures.[13,46] Moreover, mild dependence of the ESS/ESD slope from the PL has been suggested but the normalization of the EDD nullifies the PL dependence.[8–10,47–50] Also, despite the belief that the force–length relation is linear, several studies showed that the relation is curvilinear.[51,52] However, this occurs in conditions with an extreme increase or decrease in AL.[53] Finally, the small number of patients followed up does not allow us to draw a definite conclusion concerning the prognostic significance of the above indices. Nevertheless, it is logical to assume that these errors and approximations are not so large as to invalidate our study.

Conclusions

Our findings show that the slope of the ESS/ESD relation is a very sensitive index of decreased contractility and also might be a prognostic parameter with a good positive predictive value of survival, clearly superior to EF. The normalization of the ESS/ESD slope for EDD eliminates its dependence from PL and, consequently, improves the sensitivity in the diagnosis of impaired contractility, although it slightly decreases its predictive value in mortality prediction.

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