End-Systolic Pressure-Diameter Relation of the Left Ventricle during Transient and Sustained Elevations of Blood Pressure

Edson Antonio Bregagnollo, Katashi Okoshi, Beatriz Bojikian Matsubara, Paulo José Ferreira Tucci

Botucatu, SP - Brazil

Objective – *To assess the effect of transient and sustained variations in cardiac load on the values of the end-systolic pressure-diameter relation (ESPDR) of the left ventricle.*

Methods – *We studied 13 dogs under general anesthesia and autonomic blockade. Variations of cardiac loads were done by elevation of blood pressure by mechanical constriction of the aorta. Two protocols were used in each animal: gradual peaking and decreasing pressure variation, the "transient arterial hypertension protocol" (TAH), and a quick and 10 min sustained elevation, the "sustained arterial hypertension protocol"(SAH). Then, we compared the ESDR in these two situations.*

Results – *Acute elevation of arterial pressure, being it "transitory" or "sustained", did not alter the heart frequency and increased similarly the preload and afterload. However, they acted differently in end systolic pressure-diameter relation. It was greater in the SAH than TAH protocol, 21.0±7.3mmHg/mm vs. 9.2±1.2mmHg/mm (p<0.05).*

Conclusion – *The left ventricular ESPDR values determined during sustained pressure elevations were higher than those found during transient pressure elevations. The time-dependent activation of myocardial contractility associated with the Frank-Starling mechanism is the major factor in inotropic stimulation during sustained elevations of blood pressure, determining an increase in the ESPDR values.*

Keywords: end-systolic pressure-diameter relations, cardiac inotropism, arterial hypertension

Studies by Suga et al in the '70s have shown that in preparations of isolated ejecting hearts the values of left ventricular pressure-volume relations (P/V) taken in isochronic points of heartbeats occurring in different load conditions have a linear relation. As time passes, from the start of the ventricular contraction, these linear relations constitute a set of straight lines with progressively increasing inclinations, reaching a maximum value at the end of systole. Considering that this approach showed alterations in the elastic characteristics of the ventricular chamber with respect to time, the investigators applied the concept of the pressure-diameter relation varying in time to the ventricle [1-5]. According to Suga et al [1-4], the inclination of the straight line determined by the P/V relations at the end of systole did not change with wide variations in pre- and afterload, but was, however, extremely sensitive to alterations in the contractile state. Based on these observations, these authors proposed the use of the inclination of this straight line as an index of myocardial contractility called the end-systolic pressure-diameter relation. Later, other authors [6-8] also validated the end-systolic pressure-diameter relation as a safe method for evaluating the inotropic state of the cardiac muscle. On the other hand, several studies on intact hearts [9-15] have shown that the P/V relations at the end of systole may depend on the conditions of the cardiac load. Therefore, the end-systolic P/V relations of ejecting heartbeats do not coincide with those observed in isovolumetric beats.

Another point to be considered is that studies about myocardial contractility performed on isolated cardiac muscles [16-20], isolated hearts [21,22], and in situ hearts [23] have shown a constant interaction between the length of the cardiac fiber at rest and the contractile state of the myocardium.

Due to these conflicts found in the literature, this study aimed to verify if in the in situ heart the cardiac load conditions modify the values of end-systolic pressure-diameter relation. We assessed whether the end-systolic pressure-diameter relation values determined during transient elevations of blood pressure were equivalent to those determined during sustained elevations of blood pressure when time-dependent cardiac adjustments had already be-

en completed. These cardiac adjustments are triggered by arterial hypertension and result from the constant interaction between the preload and afterload present in the in situ heart [24].

Methods

Thirteen male dogs with body weights ranging from 20 to 35kg underwent anesthesia with intravenous chloralose (60mg/kg) and urethane (600mg/kg). After anesthesia, the animals were put in the dorsal decubitus position, intubated, and mechanically ventilated with the Takaoka ™ ventilator, at 16 cycles per minute. The femoral vein was dissected and cannulated for drug administration and volume repositioning.

After median sternotomy, the aorta was dissected and repaired with a cardiac band immediately after the emergence of the left subclavian artery. The pericardium was opened, and the margins of the incision were fixed in the anterior chest wall to maintain the heart in a stable position. To obtain left ventricular pressures, a catheter of the Odman-Ledin type (length: 4cm; internal diameter: 1.4mm) was inserted into the left ventricular cavity through a puncture in the apical region. After the surgical procedures, the dogs underwent heparinization (5000 IU/kg, intravenously). A manometric system comprising a P23ID Stathan transducer coupled with a 4RFO Funbec amplifier was used for recording the left ventricular pressures. The dynamic characteristics of this system had already been assessed in our laboratory and were considered adequate for the assessments performed [25]. The horizontal plane passing through the middle of the left ventricular cavity was used as reference zero. The M-mode echocardiogram of the left ventricular cavity was performed with a 5-MHz transducer located on the free wall of the right ventricle, and the ultrasound beam was directed perpendicularly to the interventricular septum and immediately below the mitral valve plane. This arrangement was used for determining the variations in the greatest left ventricular cross-sectional diameter, according to the recommendations of the ISFC/WHO [26].

To avoid the influence of the fluctuation of the autonomic activity upon the cardiac inotropism, the dogs underwent a parasympathetic (atropine: 0.5mg/kg, intravenously) and beta-adrenergic (oxprenolol: 3mg/kg, intravenously) blockade. The efficacy of this blockade had previously been tested in our laboratory [27]. Before applying the experimental protocols, a 10-minute period was awaited for evaluating the stability of the preparation.

In all animals studied, two experimental protocols were applied. The transient and sustained arterial hypertension protocols are schematically represented in figure 1. In both protocols, blood pressure was elevated pulling the cardiac band repairing the aorta. In the transient arterial hypertension protocol, tension was gradually exerted to create an aortic constriction capable of progressively increasing blood pressure to approximately 50mmHg above the basal levels (To condition) during 4 to 6 heartbeats. At the time
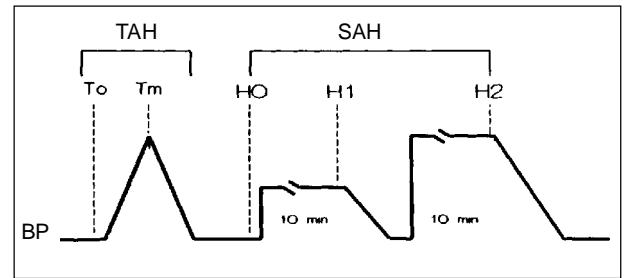

Fig. 1 – Sketch of the experimental protocols: BP- blood pressure; TAH- transient arterial hypertension; SAH- sustained arterial hypertension; To and Tm: basal and maximum BP condition in the TAH protocol; H_0 H_1 e H_2- basal, hypertensive 1 and hypertensive 2 conditions of the SAH protocol, respectively.

blood pressure reached the desired maximum value (Tm condition), the aortic constriction was gradually released to bring blood pressure to basal levels. During these procedures, simultaneous recordings of the electrocardiographic II lead of the left ventricle were taken, as were the recordings of the left ventricular pressure curve and echocardiogram for further determination of the values of the end-systolic pressure-diameter relation (fig. 2). In the sustained arterial hypertension protocol after recording the variables at the basal level (Ho), the blood pressure was elevated by the same maneuver in two steps. In the first step, an aortic constriction was established to increase blood pressure by approximately 25mmHg and to sustain it elevated for 10 minutes (hypertensive condition 1 – H1). The aortic constriction was then released and the cardiac band again tensioned to establish an aortic constriction to increase blood pressure to approximately 50mmHg above the Ho levels for 10 minutes (hypertensive condition 2: H2). In the experimental conditions Ho, H1, and H2, simultaneous recordings of the left ventricular electrocardiographic II lead, pressure curve and echocardiogram were also performed for further determination of the values of the end-systolic pressure-diameter relation (fig. 3). All recordings were obtained after 10 minutes of expiratory apnea to eliminate interferences of respiration upon pressure and cardiac dimensions.

The recordings of the left ventricular echocardiogram, pressure curve, and electrocardiogram were calibrated with the aid of a computed system comprising a version 3 Digi-
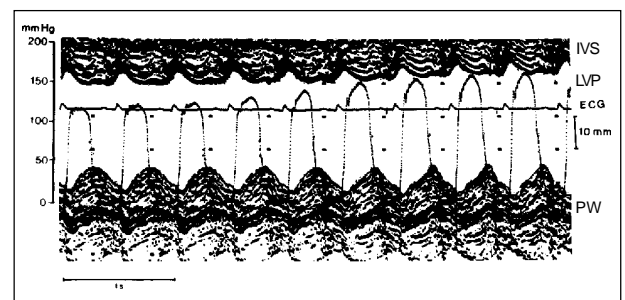

Fig. 2 – Tracing of the simultaneous electrocardiographic recording (ECG); left ventricular pressure (LVP) and left ventricular echocardiogram (IVS- interventricular septum; PW- posterior wall) obtained during transient elevations of blood pressure.
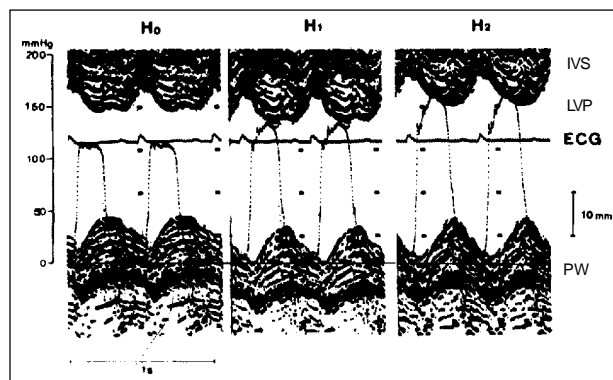
Fig. 3 – Tracing of the simultaneous electrocardiographic recording (ECG); left ventricular pressure (LVP) and left ventricular echocardiogram (IVS- interventricular septum; PW- posterior wall) obtained during sustained elevations of blood pressure.

graph Renoir digitizing table, a PC-286 Itautec computer, and software designed by the Fundação para o Desenvolvimento Tecnológico e Engenharia (FDTE) of the Escola Politécnica of the Universidade de São Paulo. In this program, during the entire cardiac cycle, the following parameters were calculated every five miliseconds: left ventricular pressure (P); left ventricular cross-sectional diameter (D); thickness of the left ventricular posterior wall (h); and also the instantaneous mathematical relation between the values of P and D. The P values were projected in the axis of the ordinates and the D values in the axis of the abscissas of the Cartesian system of axes. This allowed the graphic representation of the cardiac cycles by P/D loops. The time that the P/D relation reached the maximum value was considered the end of systole [28] and was marked with an X in the P/D loop, and its values were taken as end-systolic pressure (ESP) and diameter (ESD). In each experimental situation, the ESP and ESD values of heartbeats occurring in different load conditions were taken as coordinates for obtaining the straight lines of simple linear regression [29]. The angular coefficient of the straight lines obtained defined the values of the end-systolic pressure-diameter relation in each experimental condition. In the transient arterial hypertension protocol, the end-systolic pressure-diameter relation values (ESPDR-TE) were obtained from 4 or 5 cardiac cycles occurring in different load conditions during a transient elevation in blood pressure. In the sustained arterial hypertension protocol, the end-systolic pressure-diameter relation values (ESPDR-SE) were obtained from the linear relations between the end-systolic points of heartbeats occurring during blood pressure stability at the end of the Ho, H1, and H2 conditions. In each experimental condition, the mean values of ESP and ESD considering 5 consecutive cardiac cycles were used as coordinates for determining the straight lines of simple linear regression whose angular coefficient defined the ESPDR-SE value for each dog studied. For each simple linear regression, the Pearson correlation coefficient (r) was calculated between the points used for determining the respective straight lines. In the transient and sustained arterial hypertension protocols, in addition to the

end-systolic pressure-diameter relation, the behavior of the following variables was also assessed: left ventricular systolic (LVSP) and end-diastolic pressures (LVEDP), left ventricular systolic (SD) and diastolic (DD) diameters, systolic (Sh) and diastolic (Dh) thickness of the left ventricular posterior wall, heart rate (HR). In the transient arterial hypertension protocol, the values of these variables at the basal level (To) were compared with those verified when the blood pressure reached the maximum value (Tm). In the sustained arterial hypertension protocol, the values of these variables were compared in the Ho, H1 and H2 conditions. For all variables studied, the values found in the To and Tm conditions of the transient arterial hypertension protocol were compared with those found in the Ho and H2 conditions, respectively, of the sustained arterial hypertension protocol.

Results

Preliminary analyses of descriptive statistics showed that the ESPDR did not have a gaussian distribution. For this reason, the comparisons of the ESPDR-SE and ESPDR-TE values were performed using the Friedman test [30]. For the other variables (LVSP, LVEDP, SD, DD, Sh, Dh, HR), we used the analysis of repetitive measures (Morrison, 1976) complemented by the analysis of confidence intervals for interest contrasts (CI=95%). The differences between the compared values were considered significant when the statistical probability by chance was lower than 5% (p<0.05).

Table I shows the values ($\bar{x}\pm sd$) of the variables analyzed with the use of the transient and sustained arterial hypertension protocols. The statistical analyses used to compare these results allowed us to make the following observations: 1) the heart rate did not significantly vary; 2) the maximum increases in LVSP and LVEDP were similar; 3) the variations in left ventricular SD and DD were statistically different; 4) the alterations in Sh and Dh of the left ventricular posterior wall were similar. These results show that the alterations in cardiac load triggered by elevation in pressure were similar in both protocols, being, however, transient or sustained. Comparison of load conditions (LVSP, LVEDP, SD, DD, Sh, Dh) in basal (To and Ho) and maximum (Tm and H2) conditions in both protocols did not also identify significant differences between them. These observations lead to the conclusion that alterations in cardiac loads triggered by hypertension were similar in the transient and sustained arterial hypertension protocols.

The graphic representation of the cardiac cycles by the P/D loops using the software developed by the FDTE reproduced those reported in the literature [31-33]. Figure 4 illustrates 3 P/D loops obtained in one experiment. In each loop, the time of the cardiac cycle when the P/D relation reaches the maximum value is marked with an X and identifies the end of systole in each cardiac cycle. The linear relation between the end-systolic points is the coordinate that de-

Table I - Values (¯x ± sd) of heart rate (HR); left ventricular systolic (LVSP) and end-diastolic (LVEDP) pressures; left ventricular systolic (SD) and end-diastolic (DD) diameters; systolic (Sh) and diastolic (Dh) thickness of the left ventricular posterior wall in the transient (TAH) and sustained (SAH) arterial hypertension protocols

	TAH		SAH		
	To	Tm	Ho	H1	H2
HR (bpm)	136 ± 22	137 ± 23[a]	136 ± 25[a]	136 ± 23[a]	136 ± 24[a]
LVSP (mmHg)	133 ± 27	180 ± 27[*]	129 ± 25[a]	152 ± 23	182 ± 24[b][**]
LVEDP (mmHg)	7 ± 2	13 ± 2[*]	7 ± 2[a]	10 ± 2	14 ± 3[b][**]
SD (mm)	23.2 ± 4.5	28.1 ± 4.4[*]	21.8 ± 4.9[a]	23.1 ± 4.3	24.8 ± 4.5[b][**]
DD (mm)	32.2 ± 4.3	35.1 ± 5.0[*]	30.9 ± 4.4[a]	32.4 ± 4.4	34.8 ± 4.2[b][**]
Sh (mm)	10.6 ± 1.4	8.4 ± 1.4[*]	10.8 ± 1.0[a]	10.3 ± 1.4	9.6 ± 1.2[b][**]
Dh (mm)	8.3 ± 1.2	7.0 ± 1.2[*]	8.7 ± 0.9[a]	7.7 ± 0.8	7.0 ± 0.7[b][**]

To- basal level of the TAH protocol; Tm- time of maximum systolic pressure in the TAH protocol; Ho- basal level of the SAH protocol; H1- hypertensive condition 1 of the SAH protocol; H2- hypertensive condition 2 of the SAH protocol; a- with no statistical significance (p>0.05) in regard to the To condition of the TAH protocol; b- with no statistical significance (p>0.05) in regard to the Tm condition of the TAH protocol; * significantly different (p<0.05) from To; **: significantly different from Ho. N = 13 dogs.

termines the straight line whose angular coefficient defines the end-systolic pressure-diameter relation value.

Table II shows the individual values and the medians of ESPDR and the Pearson correlation coefficients (r) between the end-systolic points of the cardiac cycles that defined the straight lines determining ESPDR in all dogs studied. Obtaining the ESPDR index assumes the existence of linearity between the end-systolic points used for determining each of these straight lines. In our study, r values ranged from 0.913 to 0.999. Our results are similar to those reported by other authors [34-36]. Therefore, we consider that the linearity condition between the end-systolic points used to obtain the straight lines determining the ESPDR values was met. Statistical analyses regarding ESPDR showed that the ESPDR-SE values are significantly higher than those of the ESPDR-TE (p<0.05). Given that the variation in cardiac load was similar for both protocols, it is evident that transient and sustained elevations in blood pressure result in different ESPDR values.

Table II - Values of left ventricular end-systolic pressure-diameter relation (ESPDR) obtained in the transient arterial hypertension protocol (ESPDR-TE) and in the sustained arterial hypertension protocol (ESPDR-SE). The Pearson correlation coefficients (r) of the straight lines determining the ESPDR values are also shown.

Dog Nº	ESPDR-TE (mmHg/mm)	r	ESPDR-SE (mmHg/mm)	r
1	8.7	0.997	30.5	0.927
2	9.2	0.993	16.7	0.983
3	8.9	0.913	11.8	0.998
4	7.6	0.997	17.9	0.999
5	9.8	0.948	38.0	0.974
6	11.1	0.979	15.6	0.932
7	7.3	0.978	18.8	0.936
8	7.4	0.983	16.1	0.946
9	7.8	0.993	23.0	0.998
10	9.6	0.959	24.0	0.917
11	6.3	0.952	13.6	0.998
12	10.9	0.949	19.8	0.996
13	11.1	0.989	27.1	0.971
Median	8.9	—	18.8*	—
¯x	8.9	0.959	21.0*	0.967
sd	1.5	0.031	7.3	0.031

MmHg/mm- millimeters of mercury/millimeter; *: significantly different (p<0.05) from ESPDR-TE. Values of ESPDR-TE and ESPDR-SE obtained with an increase of 50 mmHg in blood pressure.

Discussion

In this study, the values of the variables indicating the preload (DD; LVEDP; Dh) and afterload (SD; LVSP; Sh) conditions significantly increased, and they were equivalent when blood pressure reached its maximum value (Tm and H2). Therefore, the fundamental characteristic differentiating transient and sustained arterial hypertension protocols was the duration of pressure elevation. Therefore, the ESPDR results allow us to consider that the most significant finding of this study was that transient and sustained blood pressure elevations are followed by time-dependent cardiac adjustments capable of increasing the ESPDR values.

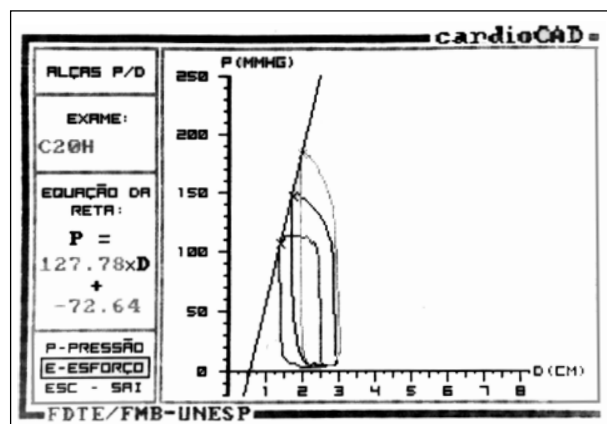In experimental conditions, the viscoelastic myocardial

Fig. 4 – Graphic representation of the pressure/diameter loops obtained during the experiments. The end-systolic points are marked with an X. The linear relation between these points determines the straight line whose angular coefficient defines the ESPDR value. P- pressure in millimeters of mercury; D- diameter in centimeters.

accommodations, the alterations in afterload, and the accentuation in cardiac inotropism should be considered as factors potentially capable of interfering with and modifying the ESPDR values during pressure elevations.

In regard to viscoelastic accommodations, some studies [37-39] that assessed these properties in in situ hearts applying pressure or volume overloads within physiological limits did not identify alterations in left ventricular P/V relations compatible with viscoelastic accommodations. Time-dependent deviations of left ventricular P/V relations in dogs were shown only when marked pressure (LVSP>200mmHg) or volume (LVEDP>25mmHg) overloads were induced [40]. Way et al [41] assessed the influence of viscoelastic myocardial accommodations upon P/V relations in in situ hearts of dogs undergoing beta-adrenergic blockade and thoracotomy. In that study, the authors did not find alterations in the ESPDR values when elevation or reduction in the blood pressure occurred within 4 to 6 heartbeats and LVEDP was normal or increased. In our study, variations in cardiac load did not reach the values reported [40] as capable of triggering significant changes in the P/V relations depending on viscoelastic accommodations. According to the literature [40,41], the deviations resulting from viscoelastic accommodations tend to reduce ESPDR values, which opposes the variations observed in our study. Therefore, if elevations in blood pressure were accompanied by viscoelastic myocardial accommodations, they worked reducing the increases in the ESPDR promoted by other dominating factors.

Given that in this study the ESPDR was determined during primary changes in afterload, we should consider that the differences in the ejecting ventricular pattern during blood pressure elevation might have interfered with the results obtained. Several studies assessing the behavior of ESPDR during afterload elevations in preparations of isolated [42,43] and in situ [44,45] hearts concluded that this contractility index does not significantly change during pressure elevations. Freeman et al [45] assessed the ESPDR values in preparations of in situ heart, where the heart ejected blood into the native aorta or into a rigid arterial system. In this last study, the authors showed that acute changes in vascular compliance do not significantly change the ESPDR values. Taking all this evidence in the literature into consideration, it seems reasonable to conclude that the afterload level and characteristics do not directly interfere with the assessments of ESPDR and, therefore, in our study, changes in the ESPDR values did not depend on changes in pressure levels. Given that in the in situ heart a constant interaction between preload and afterload [24] exists and that the ESPDR-SE values were significantly more elevated than those of ESPDR-TE (table II), it is clear that sustained blood pressure elevations triggered time-dependent cardiac adjustments that stressed cardiac inotropism. Analyzing cardiac adaptations during pressure elevations in such conditions, the variations in heart rate, the changes in the coronary perfusion pressure (CPP), and the changes in the ventricular volume depending on the interaction between pre- and afterload deserve to be highlighted.

In regard to heart rate, several studies [3,36,46,47] report an increase in ESPDR values associated with an elevation in the heart rate. Data analysis related to heart rate (table I) shows stability of the cardiac automatism during the experiments. These results assure that heart rate did not play a role in the oscillations of inotropism and, therefore, the ESPDR values did not result from fluctuations in heart rate.

Coronary artery perfusion may affect the heart contractile capacity due to biochemical or physical reasons. Biochemical influences that may result from CPP are those traditionally linked to ischemia. In experimental conditions, a specific pattern of myocardial ischemia has to be considered: the one related to the Anrep effect. This effect consists of the fluctuation of inotropism following sudden elevations in ventricular systolic pressure [48-50]. This sudden elevation in ventricular pressure causes the subendocardial vessels to collapse with ischemia and depression of the local muscular contraction. Then, a quick normalization of blood flow and recovery of the inotropic state occur due to the feedback coronary mechanism. These inotropic oscillations linked to the Anrep effect are established in a few seconds. On the other hand, it was recently proposed that elevations in CPP might intensify the influx of calcium for the myocytes, constituting another interfering factor with myocardial inotropism [51]. It is worth adding that the relations between perfusion pressure and ventricular performance are simultaneously established with the variation in pressure, being complete after a few heartbeats.

Physical influences of CPP on left ventricular performance were shown in situations where metabolic factors could be considered as nonparticipating [52-55]. CPP is admitted to influence ventricular mechanical action modulating the length of fibers overlapping the coronary arteries [52-55] and interfering with the dimensions of the ventricular wall [54]. Either by one reason or another, coronary perfusion may regulate fiber length independently from the cavity volume.

The effects of CPP on ESPDR values have already been assessed in different studies [42,55,56]. In those studies, it was shown that ESPDR is not sensitive to variations in CPP when the perfusion pressure is >60mmHg. In our study, LVSP (left ventricular systolic pressure) was always >100mmHg and, therefore, no reason exists for supposing that CPP had effects on the results obtained.

In the in situ heart, variations in the ventricular volume occurring during hypertension are established due to forces of interaction between the pre- and afterloads [24,57,58]. The increases in afterload are followed by a reduction in the ejected volume in the subsequent systoles, and the amount of residual blood remaining in the ventricular cavity causes dilation in the chamber. This functional sequence is one of the classic vias for activating the Frank-Starling mechanism [59]. The research [18-21] that analyzed the physiological bases of this mechanism confirmed that the accentuation of the contractile capacity caused by myocardial stretching includes changes in the cellular kinetics of the calcium ion as well as in the affinity of its ligation with contractile proteins. Therefore, among the subcellular adjustments caused by myocardial

stretching, adaptations of the biochemical process of contraction exist, characterizing an inotropic intervention. The subcellular rearrangements linked to myocardial stretching begin simultaneously with variations in the cellular length, being completed after a few minutes [20,21,55]. In our study, it was evident that the elevations in blood pressure were accompanied by significant increases in left ventricular diastolic dimensions, characterizing, therefore, a maneuver of increase in the ventricular volume with consequent myocardial stretching. Currently, it is understood that during a sustained elevation of pressure levels for 10 minutes, as occurred in the sustained arterial hypertension protocol, cardiac accommodations associated with hypertension have already been completed making, in this way, the occurrence of inotropism activation possible. The existence of a linear relation between the values of left ventricular diastolic dimensions and the first temporal derivative (dP/dT) with a strong relation to the contractile state [60] has already been reported.

Considering data available the results observed in our study, it may be concluded that the ESPDR values determined in the sustained arterial hypertension protocol are higher than those verified in the transient arterial hypertension protocol. The major mechanism most probably involved in inotropic activation is the time-dependent activation caused by adaptations of the biochemical process of contraction, characterizing an inotropic intervention. The subcellular rearrangements related to myocardial stretching begin simultaneously with variations in length and are completed in a few minutes [19-23]. This interpretation in accordance with data available in the literature about cardiac accommodations during pressure elevations justifies the use of ESPDR as an index of myocardial contractility in stable physiological conditions. It is worth clarifying that data from this study do not allow the assessment of the relative contribution of coronary perfusion pressure and ventricular volume for the increases in the ESPDR values when this inotropic index is determined during sustained arterial hypertensions.

Acknowledgments

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