DESCRIPTION OF AN ANIMAL MODEL OF ACUTE CARDIAC FAILURE: *IN VIVO* EXPERIMENTS IN SHEEP

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Abstract: **The purposes of this work were to, a) describe an acute animal model of severe cardiac failure induced by high doses of halothane, b) analyze the effects of these overdoses of halothane on arterial wall dynamics and c) characterize the cardiovascular effects of halothane through the autonomic nervous system. Measurements were performed in six sheep before and after halothane administration (4%). A significative decrease was observed in mean aortic flow ($P<0.05$) and diameter ($P<0.01$) in heart failure with respect to control state (from 2.64±0.95 $L.min^{-1}$ and 17.32±1.86 mm to 1.69±0.58 $L.min^{-1}$ and 15.33±1.71 mm; respectively). A significantly decrease was observed in mean ($P<0.005$), systolic ($P<0.01$) and diastolic ($P<0.005$) aortic pressure in heart failure (from 85.90±19.49 mmHg, 93.52±18.07 mmHg and 78.86±20.12 mmHg to 49.12±21.77 mmHg, 55.54±20.71 mmHg and 43.48±21.21 mmHg; respectively). Heart rate in control group (127.73±11.20 bpm) was significantly ($P<0.05$) higher than that observed in heart failure (107.15±13.53 bpm).**

Keywords: **cardiac failure, halothane, left ventricular dysfunction.**

I. INTRODUCTION

Despite the use of new drugs and modern circulatory assist devices to treat left ventricular dysfunction, heart failure mortality and the number of hospitalizations have shown a progressive and dramatic increase of epidemic proportions (Fang *et al*., 2008). In this sense, new pharmacological options should be incorporated, and the development of new circulatory assistance devices is a technological area in continuous development in the treatment of left ventricular dysfunction. Consequently, a great number of animal models of heart failure have been developed in order to study both, the modifications induced by new drugs and the effects produced by modern devices and techniques thought to improve the deteriorated hemodynamic state of these patients (Hongo *et al.*, 1997; Doggrell and Brown, 1998; Muders and Elsner, 2000).

Each animal model has its own advantages and disadvantages depending on the animal utilized and the technique employed to induce heart failure. The ideal model should mimic, as closely as possible the human syndrome, be easy to reproduce in the same or different species, inexpensive and capable of exhibiting prolonged steady states that allow cardiac function measurements (Hongo *et al.*, 1997). The mentioned characteristics and others more specific are originated from the fact that these experimental treatments are numerous and have many requirements.

Cardiac failure is the last stage of almost all cardiopathies, consequently the animal models available have different etiologies and levels of hemodynamic impairment. Some of them have acute evolution, while others have chronic features. For instance, animal models of right ventricular failure have been developed showing both, acute (Jett *et al.*, 1983; Cabrera Fischer *et al.*, 1985) and chronic characteristics (Doggrell and Brown, 1998; Hasenfuss, 1998; Muders and Elsner, 2000; Vanoli *et al.*, 2004).

Halothane is a volatile liquid used to maintain the anaesthesia during a surgical procedure. Since it has a relatively high blood/gas coefficient, the induction is relatively low. Besides it is very soluble in lipids and other biological tissues, therefore, the recovery from this type of anaesthetic agent depends on the duration of administration (Zhou and Liu, 2001; Bergadano *et al.*, 2003). Furthermore, halothane has a very strong negative inotropic compound effect, as was reported in the last decades in studies were cardiac function during anaesthesia was analyzed (Hamilton *et al.*, 1966; Sinnet *et al.*, 1981; Schotten *et al.*, 2001).

In previous works, the authors have used high doses of halothane (3% and 4 %) in mongrel dogs and in sheep obtaining severe left ventricular dysfunction that was used to test experimental circulatory assistance devices (Cabrera Fischer *et al.*, 1991; Cabrera Fischer *et al.*, 2002; Cabrera Fischer *et al.*, 2004; Risk *et al.*, 2004). However a complete description of the acute left ventricular failure induced by halothane 4% including hemodynamic changes, arterial wall function and heart rate variability have never been reported. In our published works we used different models of acute heart failure including those surgically induced (Cabrera Fischer *et al.*, 1985) or pharmacologically obtained such as the administration of beta blockers (Cabrera Fischer *et al.*, 1999). Nevertheless, we considered that the analysis of the characteristics that define a reliable model of acute heart failure exposed in experiments performed in a group of sheep using high doses of halothane could contribute to the knowledge of the halothane induced animal model of heart failure that we propose.

The purposes of this work, performed in a new group of experimental animals, were, a) to describe from a hemodynamic point of view an acute animal model of severe cardiac failure induced by halothane 4%, b) to analyze the effects of these overdoses of halothane on arterial wall dynamics and c) to characterize, in this model, the cardiovascular effects of this anaesthetic administration through the autonomic nervous system activity.

II. METHODS

The experimental protocol of this animal research had been approved, previous to the experiments, by the Research and Development Council of the Favaloro University and Universidad de la República. The experiments were performed in accordance with the National Institutes of Health Guidelines for the care and use of laboratory animals (NIH, 1996). In this study, six adult healthy Corriedale sheep weighing 30 to 35 kg and aged between 12 to 16 months were included. Before surgery, all animals were quarantined, vaccinated, treated for skin and intestinal parasites. Each animal was fasted overnight and anaesthetized with sodium thiopentone (20 mg/kg, intravenously) and maintained with halothane (1 %). Respiratory mechanical assistance using a ventilator was employed in all animals (Neumovent 910, Tecme S. A., Cordoba, Argentina). We used a pulse oximeter in order to monitor respiratory function in all animals (Pulse Oximeter 515A, Novametrix Medical Systems Inc., Wallingford, USA). Respiratory parameters were maintained among physiological ranges: arterial pCO_2 at 35-45 mmHg, pH at 7.35-7.4, and pO_2 above 80 mmHg.

A. Measurement devices positioning

At the level of the fourth intercostal space, a left lateral thoracotomy was performed. Positioning of an ultrasonic flowmeter (Model T206, Transonic Systems Inc., 16A/20A Probes, Ithaca, New York, USA) was achieved in the ascending aorta. Besides, a pair of ultrasonic crystals (5 MHz) was sutured to the upper third of the descending aorta in order to measure instantaneous external diameter, which was obtained using a sonomicrometer (Triton Biosciences Inc., Alameda, Calif., USA). The sonomicrometer converts the transit time of the ultrasonic signal into distance. By observing the screen of an oscilloscope (Model 465B, Tektronix, Beaverton, Oregon, USA), the optimal position of the ultrasonic dimension gauges was confirmed. A pressure microtransducer (Millar microtip catheter) with its tip located immediately distal to the aortic arch was placed through the femoral artery near the ultrasonic crystals (Cabrera Fischer *et al.*, 2002; Cabrera Fischer *et al.*, 2008). In all cases, the operator confirmed that the quality of biological signals was optimal (See Fig. 1).

Heparin 300 units.kg^{-1} was given to all animals. Besides, flush solutions were heparinized. An electrical heating blanket was used to maintain the temperature of the animals at 37.5 ºC (Cabrera Fischer *et al.*, 2004).

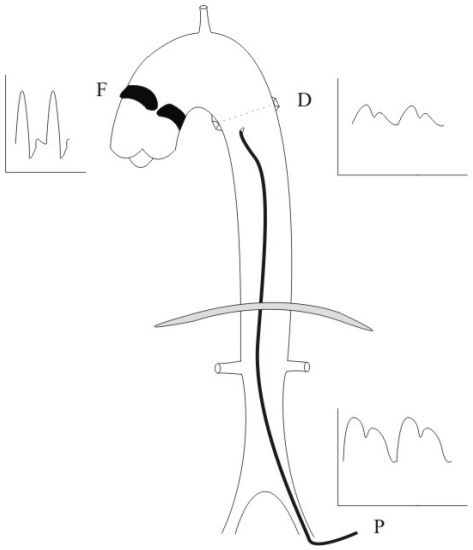

Figure 1. A microtip catheter, which measures blood pressure (P), is positioned in the upper third of the descending aorta through the left femoral artery. Nearby, aortic diameter (D) signals were obtained through a pair of ultrasonic crystals. Aortic blood flow was monitored using an ultrasonic flowmeter (F) placed around ascending aorta.

B. Hemodynamic measurements and heart failure

To monitor the hemodynamic state, surface electrocardiogram and mean aortic flow were visualized along the experiments. Instantaneous electrocardiogram, diameter and pressure signals obtained during the experiments were electronically amplified (Model 4600 Conditioner Cage Gould Inc., Cleveland, Ohio, USA) (Cabrera Fischer *et al.*, 2002; Cabrera Fischer *et al.*, 2008).

Data acquisition was performed using an acquisition board (PCI 1200, National Instruments, Austin, Texas, USA), using LabView 8.0 (National Instruments, Austin, Texas, USA) for Windows program, specifically developed in our Dynamic Circulatory Assistance Laboratory. The electrocardiogram, aortic diameter, flow and pressure signals were electronically stored during the administration of halothane at 1% (control state) and after cardiac depression obtained through a rapid and sustained administration of halothane 4% (heart failure state). Data acquisition in cardiac failure was performed after systolic aortic pressure decrease remained at least 5 minutes in steady state. Storage of all waves in control state and during halothane 4% administration was performed continuously during 15 minutes in each experiment. In all cases, the sampling frequency was set at 500 Hz with four acquisition channels.

As can be seen in Fig. 2, the time needed to obtain the maximum cardiac depression with halothane 4 % is about 10 to 12 minutes. The experiment corresponding to this figure was performed in a preliminary test performed in an animal instrumented in a similar way as was described above, besides a secondary left ventricular solid pressure sensor (Millar microtip catheter) was positioned in the left ventricle through the left atrium.

After each experiment, sheep were euthanized with an overdose of sodium thiopentone. In compliance with the "Principle of laboratory animal care" published by the National Institutes of Health (NIH, 1985) all animals received human care.

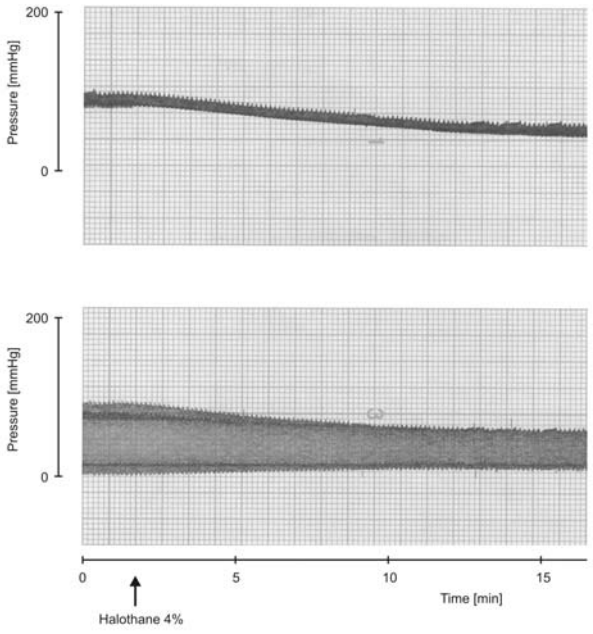

Figure 2. Aortic (upper panel) and left ventricular (lower panel) pressures were recorded in an anaesthetized animal before and after cardiac failure induction using high doses of halothane (4%). Initially halothane administration was 1% (before arrow). As can be noted 10 to 12 minutes of halothane 4% are needed to reach a steady state of a notorious circulatory depression.

C. Data analysis

The following biomechanical parameters were calculated in the six animals included in this study in control state (before halothane 4% administration) and heart failure (15 minutes during halothane 4% administration).

Peterson Modulus

The Peterson modulus (*Ep*) was calculated as:

$$Ep = \frac{(Ps - Pd)}{(Ds - Dd)} \cdot Dd \qquad (1)$$

where *Ps* and *Pd* are the systolic and diastolic values of pressure, respectively, and *Ds* and *Dd* the corresponding systolic and diastolic values of diameter (Nichols and O'Rourke, 1998).

Peripheral vascular resistance

The peripheral vascular resistance (*PVR*) was calculated according to the equation:

$$PVR = \frac{MAP}{MAF} \qquad (2)$$

where *MAP* is the mean aortic pressure and *MAF* the mean aortic blood flow (Nichols and O'Rourke, 1998).

Heart rate and aortic pressure variability study

Data acquisition for heart rate variability study in heart failure state began when pressure and aortic flow reached a steady state of hemodynamic depression (10-12 minutes after halothane 4% administration) and was prolonged to complete 15 minutes. The electrocardiogram was utilized, through R wave identification using a specific detection algorithm, in order to determine the RR interval (Risk *et al.*, 2007). Afterwards, the very few premature beats and artifacts recorded in the experimental sessions were corrected and eliminated. In this way, for each RR interval, we obtained the values of heart rate and mean aortic pressure for the sequence (Risk *et al.*, 2004).

Different signals were constructed and sampled at a constant rate of 4Hz, including heart rate and mean aortic pressure. The variability analysis was performed in both time and frequency domain. The mean and the standard deviation of the biological signals acquired were determined in the time domain. These basic calculations indicate the average value of each variable and the dispersion of the measured values (variability). For analysis in the frequency domain, we employed the power spectral density of the temporal series of the signals.

The heart rate and the mean aortic pressure variability in the frequency domain were achieved with the following spectral measurements: low frequency area (LF), which represents the sympathetic and parasympathetic nervous system activity, between 0.04 and 0.15 Hz; and high frequency area (HF), which represents the parasympathetic nervous system activity, between 0.15 and 0.4 Hz (Risk *et al.*, 2004). A natural logarithm transformation was used to normalize distributions of the LF and HF indexes.

D. Statistical analysis

All above mentioned data were subjected to two-tailed paired student T-tests. A $P<0.05$, was chosen as indicator of statistical significance. Values are expressed as mean ± SD. All statistical analysis was performed using R language (R, 2008).

III. RESULTS

No animal deaths or cardiac arrhythmias occurred during the course of any experimental session in the animals included in this study. All data acquisition performed in control and heart failure state could be included in the data analysis.

Mean aortic flow and diameter were significantly decreased in heart failure with respect to control state (from 2.64±0.95 $L.min^{-1}$ and 17.32±1.86 mm to 1.69±0.58 $L.min^{-1}$ and 15.33±1.71 mm; respectively). See Table 1.

Mean, systolic and diastolic aortic pressure were also significantly decreased in heart failure (from 85.90±19.49 mmHg, 93.52±18.07 mmHg and 78.86±20.12 mmHg to 49.12±21.77 mmHg, 55.54±20.71 mmHg and 43.48±21.21 mmHg; respectively). See Table 1.

Table 1: Hemodynamic data in control and heart failure (n=6).

	Control	Heart Failure
Mean AoF [$L.min^{-1}$]	2.64 ± 0.95	1.69 ± 0.58 $^{\#}$
Mean AoP [mmHg]	85.90 ± 19.49	49.12 ± 21.77 **
Systolic AoP [mmHg]	93.52 ± 18.07	55.54 ± 20.71 *
Diastolic AoP [mmHg]	78.86 ± 20.12	43.48 ± 21.21 **
Mean AoD [mm]	17.32 ± 1.86	15.33 ± 1.71 *
SVR [$mmHg.min.L^{-1}$]	40.00 ± 26.82	35.05 ± 27.46

Values are mean ± SD. AoF: aortic flow. AoP: aortic pressure. AoD: aortic diameter. SVR: systemic vascular resistance. *P* values determined by Paired t-test. $^{\#}P < 0.05$. $^{*}P < 0.01$. $^{**}P < 0.005$.

Table 2: Time domain results in control and heart failure (n=6).

	Control	Heart Failure
Heart Rate [bpm]	127.73 ± 11.20	107.15 ± 13.53 *
SD RR [ms]	2.08 ± 0.72	2.32 ± 0.65
SD AoP [mmHg]	0.95 ± 0.29	0.86 ± 0.35

Values are mean ± SD. RR: temporal interval between R waves. AoP: mean aortic pressure. *P* values determined by Paired t-test. * $P < 0.05$.

Table 3: Frequency domain results in control and heart failure (n=6).

	Control	Heart Failure
LF RR [ms^2]	6.16 ± 0.93	7.65 ± 1.45 *
HF RR [ms^2]	7.09 ± 0.80	7.32 ± 0.41
LF AoP [$mmHg^2$]	2.48 ± 1.25	3.66 ± 0.74
HF AoP [$mmHg^2$]	6.23 ± 0.72	5.95 ± 0.81

Values are mean ± SD. RR: temporal interval between R waves. AoP: mean aortic pressure. LF: low frequency spectral area. HF: high frequency spectral area. *P* values determined by Paired t-test. * $P < 0.05$.

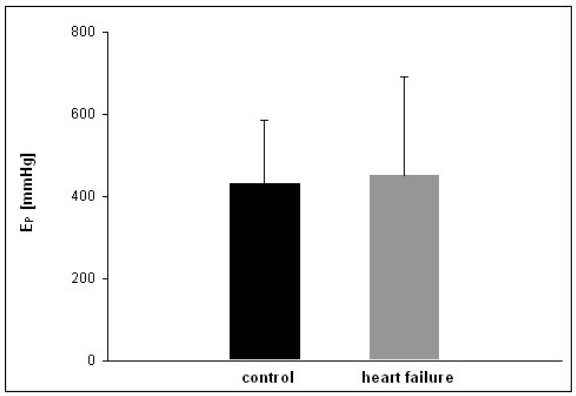

Figure 3. Peterson Modulus (Ep) calculated through pressure and diameter wave analysis, in control state (during halothane 1% administration) and after heart failure induction (during halothane 4% administration), showing non significative differences.

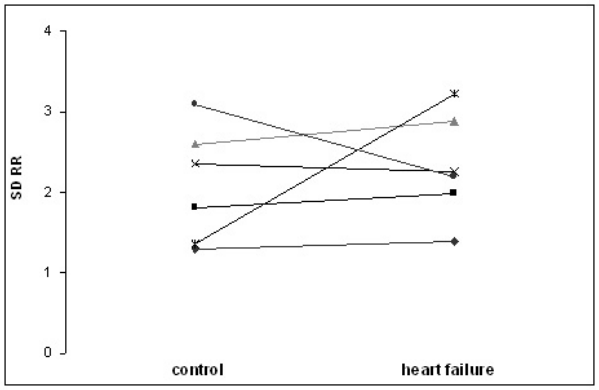

Figure 4. Standard deviation (SD) of temporal interval between R waves (RR) for each and all animals in both, control state (during halothane 1% administration) and after heart failure induction (during halothane 4% administration).

Systemic vascular resistance was not significantly decreased by sustained administration of halothane 4% (from 40.00±26.82 mmHg.min.$L^{-1}$to 35.05±27.46 mmHg.min.L^{-1}).

Heart rate in control group (127.73±11.20 bpm) was significantly (P<0.05) higher than that observed in heart failure (107.15±13.53 bpm). See Table 2.

Calculated values of Peterson Modulus showed a very little increase (statistically non significative) during induced heart failure (from 432.35±153.31 mmHg to 452.43±240.33 mmHg; respectively) (see Fig. 3).

The variability analysis in the time domain revealed that mean values of SD obtained from RR intervals and mean aortic pressure showed non-significant changes during halothane 4% administration with respect to control state (Table 2 and Fig. 4). In the frequency domain, low frequency spectral area values obtained from RR intervals were significantly increased (P<0.05) in heart failure with respect to control state (from 6.16±0.93 ms^2 to 7.65±1.45 ms^2) while high frequency spectral area of RR intervals showed non-significant changes after halothane 4% administration. Low and high frequency spectral area analysis of mean aortic pressure showed non-significant changes in heart failure with respect to control state. See Table 3.

IV. DISCUSSION

An acute model of heart failure should mimic as closely as possible a well-defined cardiovascular lesion that determines a measurable and significant level of circulatory impairment. It is desirable that hemodynamics changes include low cardiac output and systolic left ventricular and arterial pressures. The ideal model should be technically easy to reproduce and cheap (Doggrell and Brown, 1998). Is important to take into account the time dependency of certain cardiovascular parameters and especially in acute pathological states in which cardiac failure has not allow to completely developed compensatory mechanism. The model above described was conceived to be use in test destined to probe the performance of left ventricular assist devices usually indicated in acute heart failure.

As myocardial depression is the commonest finding in patients in cardiac failure, to the best of our knowledge, halothane would be the best choice since it is an inexpensive volatile anaesthetic drug that can be administered continuously allowing expectable and stable pharmacological effects. The myocardial depression produced by inspired halothane has been shown to be higher than that observed using enfluorane (Van Trigt *et al.,* 1984), sevoflurane (Coetzee *et al.,* 2000; Schotten *et al.,* 2001) or isoflurane (Marano *et al.,* 1997; Schotten *et al.,* 2001). Furthermore, the levels of halothane administration can be easily regulated allowing changes in the left ventricular level of depression.

The first objective of our work was to describe hemodynamic changes that results from halothane 4% administration. As can be seen in Fig. 2, a quickly and remarkable decrease of systolic and diastolic aortic pressures is observed as a consequence of left ventricular depression characterized by both, a decrease of systolic and an increase of diastolic pressures. Furthermore, significant decrease of cardiac output were also confirmed (Table 1). These findings are coincident with those previously reported by our group (Cabrera Fischer *et al.,* 1991; Cabrera Fischer *et al.,* 2002; Cabrera Fischer *et al.,* 2004; Risk *et al.,* 2004). In this animal model of acute circulatory failure, peripheral vascular resistance showed non-significant changes after halothane 4% administration.

The second aim of this study was to analyze the effects of halothane 4% administration on aortic wall

stiffness. The Peterson modulus showed that, in this model of cardiac depression, a non significative increase of aortic stiffness is observed. This change is different from that reported for in vivo experiments using volatile anaesthetics, such as isoflurane and halothane in therapeutic doses. In the work of Hettrick *et al.* (1996), they found increases in aortic wall distensibility that they attributes to arterial pressure decreases. However, is important to take into account that in our experiments we administered doses much higher than that used in experimental dogs by these authors. We hypothesized, that compensatory mechanisms would be involved in the observed non significative increased of aortic stiffness, perhaps as a results of the arterial blood pressure significative decrease shown.

With respect to the third aim of this work, we think that the observed decrease in heart rate during cardiac failure state (Table 2), suggests a diminution either of the sympathetic tone or an increase of the parasympathetic tone, or both mechanisms acting together (Table 2 and Fig. 4).

A more detailed analysis in the frequency domain showed an increased area under the spectrum in the low frequency band, and together with an increased in the high frequency (in this case non-significant), suggests a predominant parasympathetic activity during heart failure (Table 3), therefore the decrease in the heart rate observed in Table 2 is explained. The non-significant changes in blood pressure variability suggest a stable regulation.

Previous works showed an effect of halothane in the heart rate regulation of the autonomic system (Constant *et al.*, 1999) and a decrease of the baroreflex function (Duke *et al.*, 1977), in terms of a lack of heart rate response to a diminished blood pressure. In our model we verified a decrease in the blood pressure associated with a reduction in heart rate. These findings suggest that the baroreflex function is abolished, since the normal response should be a compensatory tachycardia due to the decrease in blood pressure.

The non significative increase in the Peterson Modulus value during the induced heart failure, suggests an increase in the sympathetic activity, since the sympathetic branch of the autonomic nervous system can regulate the blood vessels' stiffness. In summary, our model of heart failure showed changes in the hemodynamic parameters, as well as they suggest an effect on the autonomic regulation, regarding a lack of baroreflex function; these findings suggests that even in a heart failure condition, the autonomic regulation try to maintain the homeostasis, in other words the blood pressure and cardiac output, regulating both heart rate and vessel's stiffness.

This model of in vivo heart failure is comprehensive since it shows the behavior of different cardiovascular parameters that deal with hemodynamics, arterial function and heart rate variability. From this point of view, it allows to compare not only cardiac depression but also other factors that come into play when acute heart failure is induced. Such description of this model was never reported before.

Comparatively, this halothane model of acute heart failure would have the advantage to determine a severe myocardial depression without the appearance of cardiac arrhythmias, as was evident in the six animals included in this study. This is not a minor point when experiments are aimed to test left ventricular assist devices or pharmacological treatments in acute severe cardiac failure; indeed, at present the most used animal model is the coronary artery ligation that has several disadvantages. Coronary artery ligation is an expensive procedure, technically demanding, associated to a high mortality rate (up to 50%) and collateral circulation determines very important differences in the infarct size. Sometimes it is not possible to find myocardial necrotic areas at autopsy after coronary artery ligation and frequently infarction is not associated to cardiac failure (Hongo *et al.*, 1997; Doggrell and Brown, 1998; Hasenfuss, 1998; Muders and Elsner, 2000; Vanoli *et al.*, 2004).

Cardiac arrhythmias occurring in an animal model of severe cardiac failure constitutes a very important limitation. Indeed, some acute models of heart failure are necessary to test circulatory assist devices such as intra and extra aortic counterpulsation in which the synchronization between heart beats and the technological devices is mandatory (Cabrera Fischer *et al.*, 1991; Cabrera Fischer *et al.*, 2002; Cabrera Fischer *et al.*, 2004; Risk *et al.*, 2004). Fortunately, the model of halothane-induced heart failure seems not to be accompanied by cardiac arrhythmias.

The minimal effects observed both, on the aortic stiffness, systemic vascular resistances and autonomous nervous system would be a desirable characteristic when circulatory mechanical assistance is performed using non pulsatile devices, in which changes in the autonomous nervous systems have been reported (Nishinaka *et al.*, 2001).

The main limitation of this study is technical. The decline in the use of halothane may consequently make it harder to obtain. Moreover, since halothane is not considered an anaesthetic for induction, there is a need to use another anaesthetic to produce the initial effect. Although halothane is relatively cheap, the induction anaesthetic may not be as cheap.

Another limitation of this work is that we did not evaluate left ventricular mechanical properties during cardiac failure induced by a high dosis of halothane, instead, we only used a record of a previous experiment in order to illustrate about this (Fig. 2). The reason is that whenever left ventricular function evaluation through pressure and diameter sensors placement, the pericardium might be damaged to such an extent as to impair nerve fibers. In such a case, the data collected for variability analysis could be distorted since some of the nerve fibers might be cut accidentally. Therefore, in our model, we take special care to maintain an intact heart. The only place were the sensors were positioned was the aortic artery in which a gently dissection was per-

formed in order to position blood flow and diameter sensors. On the other hand, the heart dysfunction observed in this model was extensively evaluated and reported previously by our group; furthermore the original contribution of van Trigt contained very demonstratives left ventricular pressure-diameter loop obtained before and after halothane administration (Van Trigt *et al.,* 1984; Cabrera Fischer *et al.,* 1991; Cabrera Fischer *et al.,* 2002; Cabrera Fischer *et al.,* 2004, Risk *et al.,* 2004).

V. CONCLUSIONS

We conclude that, in this model of heart failure, a hemodynamic depression is confirmed, while control activity of nervous autonomic system remains even after halothane 4% administration. On the other hand, aortic stiffness showed non significative changes. The findings observed in this work, in which unusually high doses of halothane were administered, have not been previously reported and require further clinical and laboratory research in order to study the reversibility of observed changes provoked by halothane administration.

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