

# Effects of diazepam, midazolam, propofol and etomidate in myocardial contractility and coronary blood flow: comparative analysis in isolated rat's hearts

*Análise comparativa dos efeitos do diazepam, midazolam, propofol e etomidato na contratilidade miocárdica e no fluxo coronariano: estudo em corações isolados de ratos*

Carlos Geraldo Sobral de MEDEIROS, José Carlos Dorsa Vieira PONTES, Otoni Moreira GOMES, Luiz Paulo Rangel Gomes da SILVA

RBCCV 44205-684

## Abstract

**Objective:** The effects on myocardial contractility ( $dT/dt_{max}$ ) and coronary blood flow of common drugs used in clinical practice (diazepam, midazolam, propofol and etomidate) were studied.

**Method:** Fifty Wistar rat hearts were divided into five groups of ten and perfused using the Langendorff method with Krebs-Henseleit solution (K-H), with the perfusion pressure stable at 90 cm H<sub>2</sub>O and the temperature at 37.0 ± 0.5 °C. With the exception of Group I (control), they were submitted to single one-minute infusions of diazepam (50 micrograms) – Group II; midazolam (25 micrograms) – Group III; propofol (25 and 50 micrograms) – Group IV and etomidate (25 micrograms) – Group V. The drugs were diluted in 0.1 mL of K-H solution and the coronary blood flow rate and perfusion pressure controlled during infusion. The heart rate (beats per minute), myocardial tension (grams) and coronary blood flow (millimeters per minute) were measured at 1, 3, 5, 10, 15, 20, 25 and 30 minutes. The myocardial contractility was obtained by calculating the first derived tension/time ( $dT/dt_{max}$ ), at each time interval.

**Results:** The heart rate showed variations in Groups I, III and IV. A variation in the myocardial tension was seen in all

groups except Group I and alterations in the coronary blood flow were seen in all groups except Group IV during the experiment. The myocardial contractility decreased in all groups, except for Group I.

**Conclusion:** The assayed drugs diminished the myocardial contractility ( $p < 0.05$ ); the variations of the coronary blood flow were not directly correlated to those that occurred with the myocardial contractility.

**Descriptors:** Myocardial contraction. Diazepam. Midazolam. Propofol. Etomidate.

## Resumo:

**Objetivo:** Avaliar o efeito, na contratilidade miocárdica e no fluxo coronariano, de drogas comumente utilizadas na prática clínica (diazepam, midazolam, propofol e etomidato).

**Método:** Foram estudados 50 corações isolados de ratos Wistar divididos em cinco grupos de dez, em preparação de Langendorff com líquido de perfusão de Krebs-Henseleit (K-H), mantendo-se constantes a pressão de perfusão (90 centímetros de água) e a temperatura (37° + 0,5 graus Celsius). Com exceção do Grupo I (Controle), foram feitas infusões

Work performed in the Cardiology and Cardiovascular experimental laboratories of the São Francisco de Assis Cardiovascular Foundation / Heart service - Servcor, in Belo Horizonte, Brazil and of the post graduation course of Cardiovascular Surgery of the Cardiothoracic Department in the Center of Biological Sciences and Health of the Federal University of Mato Grosso do Sul, Campo Grande, Brazil  
Correspondence address: Carlos Geraldo Sobral de Medeiros. Avenida Presidente Vargas, 866, Bairro Santo Antônio. CEP: 79.100-670 / Campo Grande, MS.  
E-mail: cgsobral@terra.com.br Phone/Fax (0xx67)384-6180.

Article received in September, 2003  
Article accepted in May, 2004

únicas, em um minuto, de diazepam (50 microgramas) - Grupo II; midazolam (25 microgramas) - Grupo III; propofol (25 e 50 microgramas) - Grupo IV e etomidato (25 microgramas) - Grupo V. Cada dose foi diluída e administrada em 0,1 mililitro de K-H, mantendo-se o fluxo e a pressão de perfusão coronarianos do sistema, durante sua infusão. Aferiu-se a frequência cardíaca em batimentos por minuto (BPM), a tensão miocárdica em gramas (g), e o fluxo coronariano em mililitros por minuto (ml/min) em 1, 3, 5, 10, 15, 20, 25 e 30 minutos; a contratilidade miocárdica foi avaliada pelo cálculo da primeira derivada tensão/tempo (dT/dtmax), naquelas marcas.

**Resultados:** A frequência cardíaca apresentou variações nos

## INTRODUCTION

In 1966, CHAI & WANG [1] evidenced a myocardial depressant action on the heart beat and arterial pressure after venous infusion of diazepam in anesthetized cats. They concluded that such effects resulted from the drug's action on mechanisms central to cardiovascular control.

PRINDLE et al. [2], in 1970, however did not observe these depressant actions related to the use of diazepam in isolated papillary cat muscles. In the same year, ABEL et al. [3], using a canine model, reported an improvement in the contractile force of the myocardium after the use of diazepam and credited this effect on an increase in the coronary blood flow, a fact that was later contested by DANIELL [4].

GONZALES et al. [5], in 1990, using isolated rat hearts, observed different responses of the myocardial contractility (increase or reduction), near to concentrations of administered diazepam or midazolam. MARTY & NITENBERG [6], in the same year, contested that myocardial depression determined by midazolam could cause the hypotensor effect observed after its use, rekindling an old controversy about the action of the benzodiazepinic agents on the myocardial contractility.

HERNÁNDEZ [7], in 1991, MEDEIROS et al. [8], in 1995 and PONTES [9], in 1994, demonstrated using isolated rat hearts, inhibition of the myocardial contractility after the infusion of diazepam, midazolam and propofol, reaffirming previously reported concepts.

Confirmation that propofol causes hypotension by reducing myocardial contractility [10] was later contested and this effect was credited to the dose utilized, to the speed of infusion, to reductions of the peripheral vascular resistance, to the heart rate and/or the coronary flow [11, 12].

Etomidate, a carboxylated imidazol, is a powerful hypnotic agent, without analgesic action. On the central nervous system, it causes effects similar to barbiturates, acting on the GABAergic system thus, facilitating the inhibitory action of this neurotransmitter.

AGUIAR-MOHARRO et al. [13], in 1986, and NOCITE [14], in 1988, considered the effects of etomidate on the

Grupos I, III e IV. Em relação à tensão miocárdica, apenas o Grupo I não sofreu declínio; o fluxo coronariano, exceto no Grupo IV, apresentou variações para menos, ao longo do estudo; a contratilidade miocárdica decresceu em todos os grupos estudados, exceto no Grupo I.

**Conclusão:** As drogas ensaiadas diminuíram a contratilidade miocárdica ( $p < 0,05$ ); as alterações do fluxo coronariano não se relacionaram com as variações da contratilidade miocárdica ( $p > 0,05$ ).

**Descritores:** Contração miocárdica. Diazepam. Midazolam. Propofol. Etomidato.

cardio-circulatory system as minimum or absent, consisting of a reduction in the oxygen consumption by the myocardium and a slight reduction of the peripheral vascular resistance. A virtual absence of action of the drug on the heart motivated its widespread use in patients suffering from cardiovascular diseases submitted to surgical procedures.

On the other hand, KOMAI et al. [15], in 1985, and PRICE et al. [16] in 1992 reported a clear depressant action of etomidate on the myocardium.

The myocardial depressant effects caused by the aforementioned drugs, harm the performance of the left ventricle, and may increase the morbid-mortality of patients who undergo surgical procedures, chiefly cardiovascular disease sufferers who require this type of therapy.

This work aims at comparatively evaluating the effects of the benzodiazepinic agents (diazepam and midazolam), propofol and etomidate on the myocardial contractility and coronary flow in isolated rat hearts.

## METHOD

Fifty albino Wistar rats originating in the animal house of the São Francisco de Assis Cardiovascular Foundation / Heart Service - ServCor, Belo Horizonte, Minas Gerais, Brazil and the animal house of the Center for Biological Sciences of the Federal University of Mato Grosso do Sul, Campo Grande, Brazil were studied.

After anesthetizing the animals by the inhalation of sulfuric ether in a closed campanula, thoracotomy was performed, 500 units of sodium heparin were injected in the posterior vena cava, aortic cannulation was made using a metallic 18 F cannula taking care not to damage the aortic valve and finally, drainage of the left ventricle followed by the introduction of a plastic 22 F catheter through the left atrium leaving at the apex of the chamber without damaging any of the important coronary arteries. Subsequently, the hearts were excised and connected to a LANGENDORFF system [17], and for coronary perfusion a solution of KREBS-HENSELEIT / K-H [18] was utilized. Gas was incorporated into this solution using a mixture of 95% oxygen (O<sub>2</sub>) and

5% carbon dioxide (CO<sub>2</sub>), maintaining the temperature stable at 37 ± 0.5 °C using a heat exchanger (Comex Products Médicos Ltda. Belo Horizonte, Brazil) and the perfusion pressure at 90-100 cm H<sub>2</sub>O.

The hearts, after being perfused for 15 minutes for recovery and stabilization of their activities (stabilization period) were connected to a system to measure contractility (Force Displacement Transducer, Model FT 03 – GRASS Instrument Company) with the apexes connected by a system of pulleys with microbearings.

The readings of the myocardial tension and the heart rate were processed using a biomonitor (BESE/Bioengenharia DH 073) and prints from a matrix printer (Epson LQ-1070) were later analyzed in a comparative study. Coronary flow was measured by the volume per minute flowing out of the heart chambers and collected in a graduated glass flask.

The fifty hearts were distributed in five groups of ten hearts as follows: Group I (control) - After the initial measurements, the hearts were perfused for 30 minutes and the studied parameters were measured at 1, 3, 5, 10, 15, 20, 25 and 30 minutes. Group II (diazepam) – after the initial measurements they received a single dose of 50 micrograms (mcg) of diazepam diluted in 0.1 milliliter (mL) of K-H solution, immediately injected to the cannula inserted in the aorta over 1 minute. The flow of the perfusion system continued during this period. The studied parameters were measured at 1, 3, 5, 10, 15, 20, 25 and 30 minutes after infusion of the drug. Group III (midazolam) – The procedure only differed

from the previous group with the substitution of diazepam for a single 25-mcg dose of midazolam. Group IV (propofol) - after the initial measurements 25 mcg of propofol (Group IV<sub>25</sub>) or 50 mcg of propofol (Group IV<sub>50</sub>) were injected into the cannula inserted in the hearts. The studied parameters were measured at 1, 3, 5, 10 and 15 minutes after infusion of the drug. Group V (etomidate) – After the initial measurements the hearts received 50 mcg of etomidate and the studied parameters were measured at 1, 3, 5, 10, 15, 20, 25 and 30 minutes.

The studied parameters included variations in the heart rate (beats per minute - bpm), myocardial tension (g), maximum speed of myocardial fiber shortening – dT/dt<sub>max</sub> (grams per second – g/sec) and coronary flow (milliliters per minute (mL/min). The results were evaluated using variance analysis and the student t-test was applied. A p-value of 0.05 was considered significant.

## RESULTS

### Heart rate

As can be seen in Table 1, the heart rate diminished significantly in Groups I, III and IV, but the same variations were not seen in Groups II and V. Group I (control), the reduction was more accentuated in the 5<sup>th</sup> (p=0.04) and 15<sup>th</sup> minutes (p=0.007). In Group II (midazolam), the most significant drops occurred in the 10<sup>th</sup> (p=0.009) and 25<sup>th</sup> minutes (p=0.021). In Group IV (propofol) at a dose of 25 mcg the significant drop of this parameter was observed in

Table 1. Variation of the heart rate (bpm) - mean results

GROUP	t <sub>0</sub>	PERIOD (min)							
		1	3	5	10	15	20	25	30
I	270 (29.22)	270 (29.22)	270 (29.22)	260 (21.79)	258 (23.63)	247 (23.34)	243 (20.28)	240 (17.78)	240 (17.78)
				[0.04]		[0.007]			
II*	311 (25.44)	304 (22.73)	307 (19.85)	307 (19.85)	294 (30.34)	289 (33.22)	286 (29.83)	280 (24.92)	273 (38.27)
III	305 (41.00)	311 (40.11)	303 (43.47)	294 (43.56)	282 (46.93)	279 (46.56)	277 (47.44)	267 (46.61)	261 (48.03)
			[0.04]	[0.04]	[0.009]			[0.02]	[0.04]
IV 25	317 (33.68)	297 (32.77)	286 (29.84)	283 (29.66)	264 (21.57)	260 (24.80)	-	-	-
		[0.008]	[0.01]		[0.0008]				
IV 50	317 (33.68)	256 (25.17)	259 (14.94)	255 (19.35)	249 (20.87)	237 (18.21)	-	-	-
		[0.0002]			[0.04]	[0.002]			
V*	228 (35.00)	213 (38.00)	228 (32.00)	230 (33.00)	227 (37.00)	227 (37.00)	221 (34.00)	221 (34.00)	221 (32.00)

( ) Standard deviation; [ ] p-values < 0.05; \* There were no statistically significant variations

the 1<sup>st</sup> minute (p=0.008), 3<sup>rd</sup> (p=0.019) and 10<sup>th</sup> (p=0.0008) minutes. When 50 mcg of propofol was employed the most significant reductions occurred in the 1<sup>st</sup> (p=0.002), 10<sup>th</sup> (0.04) and 15<sup>th</sup> (p=0.002) minutes.

**Myocardial tension**

In relation to the behavior of the myocardial tension detailed in Table 2, there was no significant variation in Group I (control). In Group II (diazepam), there was a great variation in the 1<sup>st</sup> minute (p=0.003) and again in the 20<sup>th</sup> (p=0.034), 25<sup>th</sup> (p=0.011) and 30<sup>th</sup> (p=0.04) minutes. In Group III (midazolam) variations were seen from the 3<sup>rd</sup> (p=0.003) minute and in the 5<sup>th</sup> (p=0.04), 10<sup>th</sup> (p=0.01), 15<sup>th</sup> (p=0.001), 25<sup>th</sup> (p=0.004) and 30<sup>th</sup> (p=0.03) minutes. In Group IV (propofol) at 25 mcg significant variations were observed in the 1<sup>st</sup> (p=0.005), 3<sup>rd</sup> (p=0.03) and 5<sup>th</sup> (p=0.01) minutes. When 50 mcg of propofol was applied important variations occurred starting in the 1<sup>st</sup> minute (p=0.003) and remaining at the same level until the end of the observations. In Group V (etomidate) variations were seen in the 1<sup>st</sup> (p=0.001), 3<sup>rd</sup> (p=0.003), 5<sup>th</sup> (p=0.01), 10<sup>th</sup> (p=0.02) and 20<sup>th</sup> (p=0.03) minutes.

**Maximum speed of myocardial fiber shortening dT/dt<sub>max</sub>**  
The behaviors of the dT/dt<sub>max</sub> are shown in Table 3. No

variation was seen in Group I (control). In the other groups, reductions of this parameter were recorded very similar to the changes seen in myocardial tension. Group II (diazepam) presented with an important drop in the 1<sup>st</sup> minute (p=0.03) and again in the 20<sup>th</sup> (p=0.03), 25<sup>th</sup> (p=0.01) and 30<sup>th</sup> (p=0.04) minutes. In Group III (midazolam) a fall was observed in the 3<sup>rd</sup> (p=0.006), 5<sup>th</sup> (p=0.04), 10<sup>th</sup> (p=0.01), 15<sup>th</sup> (p=0.001), 20<sup>th</sup> (p=0.01), 25<sup>th</sup> (p=0.03) and 30<sup>th</sup> (p=0.03) minutes. In Group IV (propofol) at 25 mcg, a decrease occurred in the 1<sup>st</sup> (p=0.0001), 3<sup>rd</sup> (p=0.03) and 5<sup>th</sup> (p=0.01) minutes and then remained at this lower level without further variations in the 10<sup>th</sup> and 15<sup>th</sup> minutes. At a dose of 50 mcg, there was a reduction in the 1<sup>st</sup> (p=0.0008) and 5<sup>th</sup> (p=0.02) minutes. In Group V (etomidate) significant drops were evidenced in the 1<sup>st</sup> (p=0.00005), 3<sup>rd</sup> (p=0.0001), 5<sup>th</sup> (p=0.003), 10<sup>th</sup> (p=0.01) and 20<sup>th</sup> (p=0.03) minutes.

**Coronary flow**

The coronary blood flow, as can be seen in Table 4, presented with a statistically significant reduction in all the studied groups except Group V (etomidate) where the observed changes were not significant during the experiment. In Group I (control) this variation was evidenced from the 15<sup>th</sup> minute (p=0.007) and again another significant decrease in the 25<sup>th</sup> (p=0.02) minute. In Group II (diazepam)

Table 2. Variation of the myocardial tension (g) – mean results

GROUP	t <sub>0</sub>	PERIOD (min)									
		1	3	5	10	15	20	25	30		
I*	3.20 (0.40)	3.20 (0.40)	3.20 (0.40)	3.12 (0.28)	3.15 (0.27)	3.14 (0.27)	3.12 (0.21)	3.10 (0.19)	3.13 (0.12)		
II	2.43 (0.56)	2.14 (0.63)	2.17 (0.56)	2.10 (0.62)	2.01 (0.60)	1.93 (0.49)	1.85 (0.46)	1.75 (0.47)	1.72 (0.48)		
		[0.003]				[0.05]		[0.01]	[0.004]		
III	2.69 (0.19)	2.66 (0.21)	2.52 (0.27)	2.43 (0.38)	2.31 (0.48)	2.19 (0.51)	2.15 (0.54)	2.05 (0.58)	1.97 (0.60)		
			[0.003]	[0.04]	[0.01]	[0.001]		[0.004]	[0.03]		
IV 25	2.80 (0.39)	2.59 (0.38)	2.51 (0.35)	2.42 (0.35)	2.35 (0.42)	2.32 (0.43)	-	-	-		
		[0.005]	[0.03]	[0.01]							
IV 50	2.80 (0.39)	2.33 (0.44)	2.28 (0.46)	2.34 (0.48)	2.21 (0.49)	2.24 (0.52)	-	-	-		
		[0.003]									
V	2.34 (0.43)	1.82 (0.31)	2.00 (0.32)	2.05 (0.44)	2.03 (0.52)	2.03 (0.52)	1.93 (0.61)	1.93 (0.61)	1.88 (0.61)		
			[0.03]	[0.01]	[0.02]		[0.03]				

( ) Standard deviation; [ ] p-values < 0.05; \* There were no statistically significant variations

Table 3. Variation of the dT/dtmax (g/sec) – mean results

GROUP	t <sub>0</sub>	PERIOD (min)								
		1	3	5	10	15	20	25	30	
I*	39.54 (3.07)	39.57 (3.07)	39.57 (3.07)	39.00 (3.52)	39.37 (3.44)	39.25 (3.39)	39.00 (2.68)	38.75 (2.42)	39.12 (1.56)	
II	30.37 (7.10)	26.75 (7.91)	27.12 (7.10)	26.25 (7.86)	25.12 (7.56)	24.12 (6.15)	23.12 (5.78)	21.87 (5.90)	21.50 (6.03)	
		[0.003]				[0.05]	[0.03]	[0.01]	[0.04]	
III	33.62 (2.39)	33.12 (2.52)	31.50 (3.32)	29.77 (4.79)	28.87 (5.96)	27.37 (6.36)	26.57 (6.90)	25.62 (7.20)	24.62 (7.48)	
			[0.006]	[0.04]	[0.01]	[0.001]	[0.01]	[0.03]	[0.03]	
IV <sub>25</sub>	34.55 (3.86)	31.73 (5.11)	30.78 (4.93)	29.65 (4.79)	29.08 (5.63)	28.50 (5.97)	-	-	-	
		[0.0001]	[0.03]	[0.01]						
IV <sub>50</sub>	34.55 (3.86)	27.88 (5.41)	28.08 (5.10)	28.13 (5.78)	27.50 (6.15)	27.57 (5.86)	-	-	-	
		[0.0008]			[0.02]					
V	34.53 (8.80)	23.07 (6.33)	25.83 (6.92)	26.48 (9.04)	25.57 (9.85)	25.57 (9.85)	26.20(10.76)	26.20(10.76)	26.21(11.20)	
		[0.00005]	[0.0001]	[0.003]	[0.01]	[0.01]	[0.03]			

( ) Standard deviation; [ ] p-values < 0.05; \* There were no statistically significant variations

Table 4. Variation of the Coronary blood flow (mL/min) – mean results

GROUP	t <sub>0</sub>	PERIOD (min)								
		1	3	5	10	15	20	25	30	
I	13.30 (2.86)	13.30 (2.86)	13.30 (2.86)	12.35 (2.96)	12.60 (2.79)	12.10 (2.64)	12.00 (2.70)	11.65 (2.88)	11.50 (2.68)	
						[0.007]		[0.02]		
II	8.85 (2.46)	8.60 (2.32)	8.15 (2.45)	8.15 (2.44)	7.55 (2.45)	7.00 (2.01)	6.85 (2.06)	6.55 (2.22)	6.55 (2.22)	
		[0.04]	[0.001]		[0.0004]	[0.01]		[0.01]		
III	7.20 (0.63)	6.85 (0.71)	6.35 (0.71)	6.10 (0.57)	5.46 (0.76)	5.25 (0.72)	5.10 (0.70)	4.85 (0.58)	4.80 (0.67)	
		[0.01]	[0.0005]	[0.007]	[0.0004]	[0.04]	[0.04]	[0.02]		
IV <sub>25</sub>	9.75 (2.12)	9.00 (1.87)	8.25 (1.51)	7.50 (1.43)	6.15 (0.91)	5.50 (0.58)	-	-	-	
		[0.005]	[0.0008]	[0.001]	[0.0002]	[0.004]				
IV <sub>50</sub>	9.75 (2.12)	5.95 (0.64)	5.85 (0.67)	5.55 (0.64)	5.35 (0.53)	5.10 (0.52)	-	-	-	
		[0.0005]		[0.01]	[0.01]	[0.007]				
V*	10.79 (2.41)	10.71 (2.34)	10.71 (2.34)	10.46 (2.32)	9.96 (2.31)	9.96 (2.31)	9.25 (2.15)	9.25 (2.15)	8.83 (1.61)	

( ) Standard deviation; [ ] p-values < 0.05; \* There were no statistically significant variations

this drop was significant from the 1<sup>st</sup> minute ( $p = 0.04$ ) with other variations occurring in the 3<sup>rd</sup> ( $p = 0.001$ ), 10<sup>th</sup> ( $p = 0.004$ ), 15<sup>th</sup> ( $p = 0.01$ ) and 25<sup>th</sup> ( $p = 0.01$ ) minutes. In Group III (midazolam) these falls were significant during all the experiment except in the 30<sup>th</sup> minute ( $p = 0.29$ ). In Group IV (propofol) at 25 mcg and 50 mcg, except in the 3<sup>rd</sup> minute using 50 mcg, reductions in the coronary blood flow were seen throughout the experiment ( $p < 0.05$ ).

#### COMMENTS

The injection of 7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one (diazepam) at a dose of 50 mcg, gave significant reductions ( $p < 0.05$ ) of the myocardial tension,  $dT/dt_{max}$  and the coronary flow when compared with the initial values, with a drop to the following respective percentages: 70.84%, 69.21% and 73.50%. It is interesting to stress that these alterations in the performance of the heart occur with a relatively low dose of the drug that, when considering the coronary blood flow at the moment of its infusion (8.85 mL/min), corresponds to 5.64 mcg/mL of diazepam. Thus the concentration is within the range currently used in clinical practice which is between 5 and 32 mcg/mL [19]. The results we obtained with the use of diazepam confirmed the conclusions of CHAI & WANG [1] in 1966, DANIELL [4] in 1975, GONZALES et al. [5] in 1990, MEDEIROS et al. [8] in 1995 and PONTES [9] in 1994. However our results differ from those of PRINDLE et al. [2] and ABEL et al. [3] in 1970, who demonstrated an innocuous action or even a positive inotropic action after the use of the drug.

Infusion of 25 micrograms of 8-chloro-6-(2-fluorophenyl)-1-methyl-4H-imidazo [1,5-a] [1,4] benzodiazepine (midazolam), gave significant alterations ( $p$ -value  $< 0.05$ ) in the heart rate, myocardial tension,  $dT/dt_{max}$  and coronary blood flow, with a reduction to the following percentages compared to the controls: 85.33%, 72.75%, 72.75% and 66.69%. Taking into account the mean coronary blood flow of 7.2 mL/min at the moment of injection of the drug, the employed dose corresponds to 3.74 mcg/mL of midazolam, thus less than the plasma concentration determined by the dose of 0.3 mg/kg which is currently used in anesthesia (0.4 to 2.0 mg/kg) [19]. The data reported here confirm the results obtained by REVES et al. [20] in 1984, MEDEIROS et al. [8] in 1995 and PONTES [9] in 1994, who described myocardial depressant effects caused by the use of midazolam. These results did not agree, on the other hand with those published by MARTY & NITENBERG [6] in 1990, who did not evidence a depressant action in the myocardium that justified the hypertensive effect observed after the use of midazolam.

The injection of 25 micrograms of 2,6-diisopropylphenol (propofol) considering a mean coronary blood flow at that

moment (9.75 mL/min), resulted in important alterations ( $p$ -value  $< 0.05$ ) in the heart rate, myocardial tension,  $dT/dt_{max}$  and coronary blood flow, with a reduction to the following percentages compared to the control group: 82.54%, 82.91%, 82.12% and 58.37% respectively. The infusion of 50 micrograms of the same drug, when correlated to the controls measurements diminished even more the aforementioned parameters. After this second dose, the new percentages in respect to the control group were 75.76%, 79.52%, 79.60% and 55.01% respectively. The marked alterations occur with the two doses (25 mcg and 50 mcg) that, when considering the coronary blood flow at the moment of injection as previously mentioned, determined concentrations of 2.57 mcg/mL and 9.09 mcg/mL, much lower than those (24 to 30 mcg/mL) obtained with the use of doses currently employed in clinical practice (1.6 to 2.5 mg/kg) [19]. These results confirm those published by BRÜSSEL et al. [10] in 1989, PUTTICK et al. [21] in 1992, MEDEIROS et al. [8] in 1995 and PONTES [9] in 1994, who reported depressant effects on the myocardium with the use of propofol. On the other hand, the results differ from those presented by GOODCHILD & SERRAO [11] in 1989 and MOUREN et al. [12] in 1994, who did not evidence significant alterations in the myocardial contractility, or did not evidence contractile depression that justified the adverse effects observed in the arterial blood pressure after the injection of the drug.

The infusion of 50 micrograms of [R-(+)-ethyl-1-(1-methyl-benzyl)-1H-imidazol-5-carboxylic-sulfate] (etomidate) gave an important reduction of the values of myocardial tension and  $dT/dt_{max}$  when compared to the control measurements to the following percentages: 80.48% and 72.08% respectively. The dose employed, considering the mean coronary blood flow at the time of the infusion (10.79 mL/min), was the equivalent of 4.61 mcg/mL, a concentration compatible with the doses currently in use in the anesthesia practice [19].

Greater evidence of the myocardial depression caused by this drug resides in the variation of the  $dT/dt_{max}$  where a reduction of 35% occurs within the first minute after injection of the drug ( $p$ -value  $< 0.05$ ), which remains 30% below the control values until the last observation. These results repeated those presented by KOMAI et al. [15], MILDE et al. [22] in 1985, and PRICE et al. [16] in 1992, who confirmed significant myocardial depression after the use of this drug. On the other hand, the results differ from Aguiar-MOHARRO et al [13] in 1986 and DE HERT et al. [23] in 1990, who did not evidence significant alterations in the myocardial contractility after the use of etomidate. KETTLER & SONNATAG [24] in 1974 observed an increase in the coronary blood flow after infusion of etomidate. We did not evidence statistically significant variations in the coronary blood flow or the heart rate after the infusion of this drug

over the period of the observations, as we did not observe a cause/effect relationship between the variations of the coronary blood flow and the myocardial contractility.

Possibly, at lower doses, the clinical use of these drugs does not manifest the harm of their effects on the myocardial contractility, in view of the homeostatic physiological mechanisms arising from the interaction of the cardiac performance and the neuro-humoral system of circulation control, notably the sympathetic activity and adrenergic liberation. This myocardial depressant effect, however, may become much more evident in clinical and experimental situations when other cardio-inhibitory substances are employed as with the solutions utilized in heart surgery for myocardial protection (cardioplegic solutions) thereby justifying the existence of situations such as drunken heart syndrome described by GOMES et al. [25] in 1992 based on experimental investigations.

#### CONCLUSION

It is possible to conclude from this present investigation that:

- All tested drugs significantly reduced the myocardial contractility (p-value < 0.05);
- The reduction in the myocardial contractility determined by propofol at a dose of 50 micrograms was greater than that produced by the same drug at a dose of 25 micrograms, with statistically significant variations (p-value < 0.05);
- The variations of the coronary blood flow determined by the tested drugs do not correlate with the variations observed in the myocardial contractility -  $dT/dt_{max}$  (p-value > 0.05).

#### BIBLIOGRAPHIC REFERENCES

1. Chai CY, Wang SC. Cardiovascular actions of diazepam in the cat. *J Pharmacol Exp Ther* 1966;154:271-80.
2. Prindle Jr. KH, Gold HK, Cardon PV, Epstein SE. Effects of psychopharmacologic agents on myocardial contractility. *J Pharmacol Exp Ther* 1970;173:133-7.
3. Abel RM, Reis RL, Staroscik RN. The pharmacological basis of coronary and systemic vasodilator actions of diazepam. *Br J Pharmacol* 1970;39:261-74.
4. Daniell HB. Cardiovascular effects of diazepam and chlordiazepoxide. *Eur J Pharmacol* 1975;32:58-65.
5. Gonzales R, Zeeger A, Eigenhuis JJ, Leewin RS, Van Wilgenburg HA comparative study of diazepam and midazolam induced actions on isolated rat hearts. *Eur J Pharmacol* 1990;183:208.
6. Marty J, Nitenberg A. The use of midazolam and flumazenil in cardiovascular diagnostic and therapeutic procedures. *Acta Anaesthesiol Scand Suppl* 1990;92:33-4.
7. Hernández J. The negative inotropic effect of diazepam in rat right ventricular strips. *J Pharm Pharmacol* 1991;43:879-81.
8. Medeiros CGS, Pontes JCDV, Gomes OM. Análise comparativa dos efeitos do diazepam, midazolam e propofol na contratilidade miocárdica: estudo em corações isolados de ratos. *Rev Bras Cir Cardiovasc* 1995;10:198-205.
9. Pontes JCDV. Efeitos do diazepam, midazolam e propofol na resposta contrátil do miocárdio a dopamina e dobutamina: estudo experimental em corações isolados de ratos [Tese de Mestrado]. Belo Horizonte: Curso de Pós-Graduação em Cardiologia e Cirurgia Cardiovascular da Fundação Cardiovascular São Francisco de Assis, 1994.
10. Brüssel T, Theissen JL, Vigfusson G, Lunkenheimer PP, Van Aken H, Lawin PH. Hemodynamic and cardiodynamic effects of propofol and etomidate: negative inotropic properties of propofol. *Anesth Analg* 1989;69:35-40.
11. Goodchild CS, Serrao JM. Cardiovascular effects of propofol in the anaesthetized dog. *Br J Anaesth* 1989;63:87-92.
12. Mouren S, Baron JF, Albo C, Szekely B, Arthaud M, Viras P. Effects of propofol and thiopental on coronary blood flow and myocardial performance in an isolated rabbit heart. *Anesthesiology* 1994;80:634-41.
13. Aguiar-Moharro JA, Gonzalez-Miranda F, Laynez-Cerdena I, Bosa-Ojeda F. Echocardiographic evaluation of various intravenous anesthetic agents. *Rev Esp Anesthesiol Reanim* 1986;33:23-4.
14. Nocite FG. Associação etomidato-fentanil controla alterações circulatórias pós-intubação traqueal em cardiopatas. *Rev Bras Anesthesiol* 1988; 38:219-22.
15. Komai H, De Witt DE, Rusy BF. Negative inotropic effect of etomidate in rabbit papillary muscle. *Anesth Analg* 1985;64:400-4.
16. Price ML, Millar B, Grounds M, Cashman J. Changes in cardiac index and estimated systemic vascular resistance during induction of anaesthesia with thiopentone, methohexitone, propofol and etomidate. *Br J Anaesth* 1992;69:172-6.
17. Döring HJ, Dehnert H. The isolated perfused warm-blooded heart according to LANGENDORFF. West Germany, 1988: Biomesstechnik-Verlag March GmbH, D7806 March.

- 
18. Krebs HA, Henseleit K. Untersuchungen über die Harnstoffbildung im Tierkörper. *Z Physiol Chem* 1932;210:33-66.
  19. Dundee JW, Wyant GM. Etomidato. Propofol. Benzodiazepinas. In: *Anestesia intravenosa*. 2a ed. Rio de Janeiro: Revinter; 1993. p.148-91.
  20. Reves JG, Kissin I, Fournier S. Negative inotropic effects of midazolam. *Anesthesiology* 1984;60:517-8.
  21. Puttick RM, Diedericks J, Sear JW, Glen JB, Foëx P, Ryder WA. Effect of graded infusion rates of propofol on regional and global left ventricular function in the dog. *Br J Anaesth* 1992;69:375-81.
  22. Milde LN, Milde JH, Michenfelder JD. Cerebral functional, metabolic and hemodynamic effects of etomidate in dogs. *Anesthesiology* 1985;63:371-7.
  23. De Hert SG, Vermeyen KM, Adriaensen HF. Influence of thiopental, etomidate and propofol on regional myocardial function in the normal and acute ischemic heart segment in dog. *Anesth Analg* 1990;70:600-7.
  24. Kettler D, Sonntag H. Intravenous anesthetics: coronary blood flow and myocardial oxygen consumption (with special reference to althesine). *Acta Anaesthesiol Belg* 1974;25:384-401.
  25. Gomes OM, Moraes DJ. Síndromes de proteção miocárdicas. *Coração* 1992;2:3-5.