

Myocardial and Coronary Effects of Propofol in Rabbits with Compensated Cardiac Hypertrophy

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Background: Myocardial effects of propofol have been previously investigated but most studies have been performed in healthy hearts. This study compared the cardiac effects of propofol on isolated normal and hypertrophic rabbits hearts.

Methods: The effects of propofol (10–1,000 μM) on myocardial contractility, relaxation, coronary flow and oxygen consumption were investigated in hearts from rabbits with pressure overload-induced left ventricular hypertrophy (LVH group, $n = 20$) after aortic abdominal banding and from sham-operated control rabbits (SHAM group, $n = 10$), using an isolated and erythrocyte-perfused heart model. In addition, to assess the myocardial and coronary effects of propofol in more severe LVH, hearts with a degree of hypertrophy greater than 140% were selected (severe LVH group, $n = 7$).

Results: The cardiac hypertrophy model induced significant left ventricular hypertrophy ($136 \pm 21\%$, $P < 0.05$). The pressure-volume relation showed normal systolic function but an altered diastolic compliance in hypertrophic hearts. Propofol only decreased myocardial contractility and relaxation at supratherapeutic concentrations ($\geq 300 \mu\text{M}$) in SHAM and LVH groups. The decrease in myocardial performances was not significantly different in SHAM and LVH groups. Propofol induced a significant increase in coronary blood flow which was not significantly different between groups. In severe LVH group, the degree of hypertrophy reached to $157 \pm 23\%$. Similarly, the effects of concentrations of propofol were not significantly different from the SHAM group.

Conclusions: Propofol only decreased myocardial function at supratherapeutic concentrations. The myocardial and coronary effects of propofol were not significantly modified in cardiac hypertrophy.

NUMEROUS studies have demonstrated that propofol is devoid of significant inotropic effect in most species including humans, at least at therapeutic concentrations and in healthy myocardium.^{1–3} Because propofol is being used with an increasing frequency in cardiovascular surgical patients, assessment of the myocardial effects of propofol in the context of cardiac disease may be espe-

cially useful. To date, the effects of propofol on diseased myocardium remain a subject of controversy. Clinical studies have suggested that propofol does not induce significant inotropic effects in patients with coronary artery disease.^{4,5} *In vivo* and in dogs with dilated cardiomyopathy, Pagel *et al.*⁶ observed that the cardiac effects of propofol were not enhanced. However, the precise effects of propofol on intrinsic myocardial properties are difficult to assess *in vivo* because of changes in sympathetic nervous system activity, heart rate, and loading conditions. Thus, *in vitro* studies with isolated hearts remain a helpful approach to evaluate the myocardial effects of propofol. Riou *et al.*⁷ observed that propofol induced no significant inotropic effect in normal and cardiomyopathic hamsters. In contrast, in isolated cardiomyocytes from pigs with pacing-induced dilated cardiomyopathy, propofol induced a more pronounced negative inotropic effect than in healthy myocytes.⁸

Hypertension is frequently observed in anesthetized adult patients and frequently induces cardiac hypertrophy.⁹ The attractive pharmacokinetic properties of propofol and the use of new anesthetic techniques, such as the target-controlled infusion technique, explain that propofol is being used with an increasing frequency. Nevertheless, no previous study has reported the cardiac effects of propofol in compensated cardiac hypertrophy. Thus, we performed an *in vitro* study to compare the myocardial and coronary effects of propofol on normal hearts and those with left ventricular hypertrophy (LVH) induced by a pressure overload in rabbits, using an isolated and erythrocyte-perfused heart model.^{1,10}

Material and Methods

We used adult New Zealand albino female rabbits (weight, 2.8–3.0 kg) aged 14 weeks at the time of the surgical procedure. Care of the animals conformed to the recommendations of the Helsinki Declaration, and the study was performed in accordance with the regulations of the official edict of the French Ministry of Agriculture.

Production of Left Ventricular Hypertrophy

Long-term overload pressure-induced LVH was induced by abdominal aorta stenosis (LVH group, $n = 20$), as previously described.¹¹ Anesthesia was induced with intravenous administration of 0.07 mg/kg flunitrazepam (Roche, Neuilly-sur-Seine, France) and 1.5 mg/kg, then $7 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ etomidate (Janssen-Cilag, Issy-les Mou-

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lineaux, France), and the suprarenal abdominal aorta was surgically isolated. A piece of catheter (OD, 2.42 mm; Biotrol, Paris, France) and the isolated aorta portion were ligated together, and the catheter was immediately removed. This procedure induces an aortic diameter reduction of approximately 45%.^{11,12} The laparotomy was repaired in two layers. Sham-operated animals (SHAM group, $n = 10$) were subjected to the same procedure except that the aorta stenosis was not performed. This experimental model induces a cardiac hypertrophy with preserved systolic function.¹¹ The hearts were studied 12 weeks after the surgical procedure. Body weight (BW), heart weight (HW), and left ventricular weight (LVW) were determined at the end of the study. HW-to-BW and LVW-to-BW ratios were calculated. The degree of ventricular hypertrophy was determined by dividing the LVW-to-BW value of each operated rabbit by the mean LVW-to-BW value in sham-operated rabbits.⁷

Perfusate Preparation

The perfusion medium was reconstituted by mixing human erythrocytes and a modified Krebs-Henseleit bicarbonate buffer containing 118 mM NaCl, 5.9 mM K^+ , 2.5 mM free Ca^{++} , 0.5 mM $MgSO_4$, 1.17 mM NaH_2PO_4 , 28 mM $NaHCO_3$, 11 mM glucose, 0.9 mM lactate, and 0.5% bovine serum albumin. The human erythrocytes were stored at 4°C in our laboratory for no more longer than 1 week. They were centrifuged and washed with saline (Cell-Saver 3+; Haemonetics, Braintree, MA). The mixture allowed us to obtain a hemoglobin value of approximately 8 g/dl. The reconstituted blood was filtered, then continuously oxygenated with a gas mixture comprising 20% O_2 , 5% CO_2 , and 75% N_2 using a membrane oxygenator (Optima; Cobe Cardiovascular, Arvada, CO). After rewarming to 37°C, electrolyte concentrations were adjusted to achieve physiologic concentrations and sodium bicarbonate was added to obtain a pH between 7.35 and 7.45.

Heart Preparation

After the rabbits were anesthetized with ether, thoracotomy was performed, and the heart and aorta arch were excised and rapidly placed in cold (4°C) isotonic saline solution. Under immersion, the pericardium was quickly removed and the aorta was prepared for the cannulation. The heart was mounted on an aortic cannula, and retrograde perfusion was begun according to the Langendorff technique with a constant hydrostatic perfusion pressure of 80 mmHg. As previously described,^{13,14} the apparatus was modified to enable the continuous recording of coronary blood flow (CBF). The column used to set the perfusion pressure was replaced by a syringe with a plunger containing mercury and attached to a displacement transducer that controlled the speed of the peristaltic coronary pump reflecting the CBF. Coronary driving pressure was computed from the

signal pressure obtained from a small catheter that was positioned above the aortic valves and connected to a pressure transducer. Whenever possible, the heart rate was maintained constant during each experiment by an atrial pacing. Nevertheless, when the heart developed arrhythmia during pacing or when spontaneous heart rate was greater than 150 beats/min, heart was not paced. The coronary sinus was drained by a small catheter inserted into the pulmonary artery. A cannulated fluid-filled balloon connected to a pressure transducer by a rigid catheter was inserted into the left ventricle through a left atrial incision. A 2-ml graduated syringe was connected on this pressure transducer and allowed to increase the intraventricular volume, which was noted for each experiment. Left ventricular end-systolic pressure (LVESP), left ventricular end-diastolic pressure (LVEDP), and heart rate were recorded, and the maximal positive (dP/dt_{max}) and negative (dP/dt_{min}) left ventricular pressure derivatives were electronically derived from the left ventricular pressure signal. Because intraventricular volume and heart rate were held constant, dP/dt_{max} and dP/dt_{min} reflected inotropic and lusitropic properties, respectively. The entire apparatus was enclosed in a thermostatic chamber at 37.5°C.

Blood Gas and Electrolyte Measurements

Arterial (P_{aO_2}) and venous (P_{vO_2}) coronary oxygen tension, arterial (P_{aCO_2}) and venous (P_{vCO_2}) coronary carbon dioxide tension, and pH were measured with standard electrodes at 37°C, and the arterial hemoglobin concentration and arterial (S_{aO_2}) and venous (S_{vO_2}) coronary oxygen saturation were measured with a hemoximeter (BG3 System and Model IL 482; Instrumentation Laboratory, Saint-Mandé, France). Arterial (Ca_{O_2}) and venous (C_{vO_2}) coronary oxygen content and myocardial oxygen consumption (M_{vO_2}) were derived from the standard formulas. At the onset of each experiment, a sample of the reconstituted blood was withdrawn to determine the concentration of main electrolytes (Na^+ , K^+ , Cl^- , $NaHCO_3$, and Ca^{++}).

Experimental Protocol

Ventricular Function. To further characterize the model of cardiac hypertrophy, we performed an evaluation of the systolic and diastolic function in the SHAM group ($n = 6$) and in the LVH group ($n = 5$), as previously reported in isolated rabbit heart preparation.¹⁵⁻¹⁷ The left ventricular volume was increased by steps of 0.1–0.2 ml, and LVEDP and LVESP were measured 2–3 min thereafter. The unstressed volume of latex balloons was evaluated at 1.8–2 ml. *Total left ventricular volume* (LVV) was defined as the sum of the volume of saline solution instilled and walls of the balloon associated with the portion of the catheter in the left ventricular cavity. The latter volume was measured between 0.28 and 0.38 ml. The

Table 1. Characteristics of Sham-operated Rabbits (SHAM) and Those with Left Ventricular Hypertrophy (LVH₁ and LVH₂)

	SHAM (n = 10)	LVH ₁ (n = 10)	LVH ₂ (n = 10)
BW (kg)	3.3 ± 0.2	3.3 ± 0.2	3.4 ± 0.3
LVW (g)	5.0 ± 0.4	6.8 ± 1.5*	7.0 ± 0.5*
HW (g)	8.3 ± 0.9	11.1 ± 2.7*	11.4 ± 1.3*
HW/BW (10 ⁻³)	2.54 ± 0.20	3.37 ± 0.76*	3.43 ± 0.35*
LVW/BW (10 ⁻³)	1.53 ± 0.09	2.06 ± 0.41*	2.10 ± 0.22*
Left ventricular hypertrophy (%)	100	134 ± 27*	137 ± 15*

Data are mean ± SD.

* $P < 0.05$ versus SHAM.

LVH₁ = left ventricular hypertrophy with a "normal" left ventricular end-diastolic pressure; LVH₂ = left ventricular hypertrophy with a "high" left ventricular end-diastolic pressure (see text for explanation); BW = body weight; LVW = left ventricular weight; HW = heart weight.

slope (E_{\max}) of the isovolumic LVESP-LVV relation, a reliable measure of the contractile performance, was calculated by a linear regression analysis ($LVESP = E_{\max} \cdot (LVV - LVV_0)$, with LVV_0 being the left ventricular volume at an LVESP of 0 mmHg). Fitting of the LVESP-LVV relation as a straight line might induce error because during enhanced and depressed contractile state this relation might be curvilinear.¹⁸ Nevertheless, Goto *et al.*¹⁵ have previously reported that fitting this relation by a linear regression analysis allowed assessment of a reliable evaluation of the systolic function of the rabbit left ventricle. The accuracy of the evaluation of the LVV by the balloon method has been shown to be underestimated by only 2–15%.¹⁹ Because a comparison between different heart sizes was performed, E_{\max} was also normalized by dividing its value by the LVW, as previously described.¹⁷ The analysis of the LVEDP-LVV relation allowed the assessment of the left ventricular compliance by fitting it to an uniexponential relation ($LVEDP = b \cdot e^{k \cdot LVV}$, with b and k being constants).^{16,20} The increase in the LVV was stopped when the LVEDP was greater than 30 mmHg or when it was incompatible with the intrinsic compliance of balloon. To assess whether propofol alters the left ventricular function, we evaluated the pressure-volume relations in absence and in presence of propofol (30 μ M).

Myocardial and Coronary Effects of Propofol. The LVV was adjusted to obtain an LVEDP of approximately 10 mmHg, as previously reported.^{1,10} Then, a 10-min recovery period was allowed for stabilization of ventricular performances and coronary blood flow. After baseline measurements, propofol (Diprivan; AstraZeneca, Rueil-Malmaison, France) was administered just above the aortic cannula. Intracoronary infusions were used to target concentrations of 10, 30, 100, 300 and 1,000 μ M. The peak of the effect of propofol was noted within 5 min. Before and after each propofol infusion, arterial and coronary sinus samples were collected for blood gas analysis. After the end of each infusion of propofol, a recovery period was allowed, to return to baseline values. In preliminary experiments, we noted that, at the same level of LVEDP (*i.e.*, 10 mmHg), hearts with LVH had lower inotropic and lusitropic parameters (LVESP, dP/dt_{\max} , and dP/dt_{\min}) in comparison with the normal

hearts. To compare myocardial and coronary effects of propofol at the same level of inotropy and lusitropy in both types of hearts, we divided the LVH group into two subgroups: LVH₁ (n = 10), LVH with "normal" LVEDP, at the same level as SHAM group (10 mmHg), and LVH₂ (n = 10), LVH with "high" LVEDP by additional volume of saline solution in balloon. The effects of propofol solvent 10% Intralipid (Ivèlip; Baxter, Maurepas, France) on myocardial performances, coronary blood flow, and oxygen myocardial consumption were studied in additional hearts from sham-operated rabbits (n = 3) and from animals with long-term overload pressure-induced LVH (n = 3).

Myocardial and Coronary Effects of Propofol in Severe Left Ventricular Hypertrophy. To assess myocardial and coronary effects of propofol in a more severe LVH, hearts with a degree of hypertrophy greater than 140% were selected from the initial LVH group (severe LVH group, n = 7). Then, the coronary and myocardial effects of increased concentrations of propofol in this group were also compared with the SHAM group.

Statistical Analysis

Data are expressed as mean ± SD. Comparison of two means was performed using the Student *t* test. Comparison of several means was performed using repeated-measures analysis of variance and the Newman-Keuls test. A *P* value less than 0.05 was required to reject the null hypothesis.

Results

There were no significant differences in pH and electrolyte composition of the reconstituted perfusate between the SHAM and LVH groups (pH, 7.38 ± 0.05 ; Na⁺, 137 ± 4 mM; Cl⁻, 105 ± 4 mM; K⁺, 4.8 ± 0.7 mM; NaHCO₃, 25 ± 3 mM; and Ca⁺⁺, 2.0 ± 0.1 mM). Body weight was not significantly different between SHAM and LVH groups, whereas the HW and LVW were significantly greater in rabbits with LVH. Consequently, the HW-to-BW and LVW-to-BW ratios were significantly greater in rabbits with LVH (table 1). No physical signs of

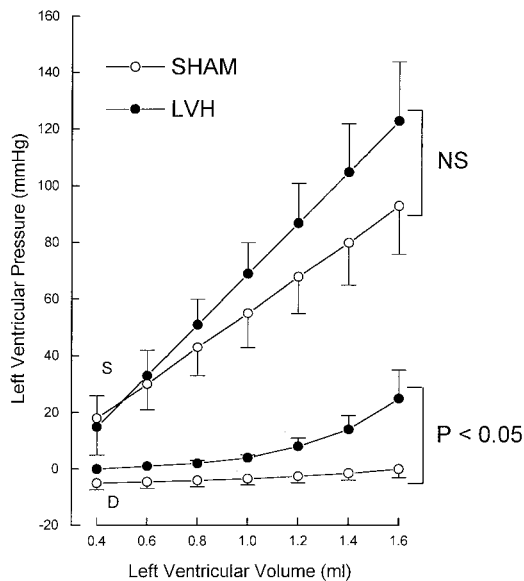


Fig. 1. End-systolic and end-diastolic pressure–volume relations of hearts from sham-operated rabbits (SHAM; $n = 6$) and hearts from rabbits with left ventricular hypertrophy (LVH; $n = 5$). The systolic and end-diastolic pressure–volume relations were obtained by fitting the pressure–volume relation to a linear and an exponential relation, respectively. P values refer to between-group difference. NS = not significant.

congestive heart failure were observed in either the SHAM or the LVH group (*i.e.*, peripheral edema, ascites, pericarditis, or pleural effusion).

Evaluation of Ventricular Function

The analysis of the end-diastolic pressure–volume relation showed a reduced diastolic compliance in the LVH group (fig. 1). The mean r values of fit of the regression line to the end-systolic pressure–volume relation were 0.99 (range, 0.97–1.00) for the LVH group and 0.99 (range, 0.98–1.00) for the SHAM group. The slope of the end-systolic pressure–volume relation (E_{\max}) was not significantly different between SHAM and LVH groups (67 ± 23 vs. 83 ± 38 mmHg/ml, not significant [NS]); similarly, no significant difference in normalized E_{\max} was noted between groups (11.2 ± 5.2 vs. 13.1 ± 4.4 mmHg \cdot ml $^{-1} \cdot$ g $^{-1}$, NS). At the therapeutic concentration (30 μ M), propofol did not significantly modify the left ventricular function (systolic and diastolic) evaluated by the pressure–volume relation in either the SHAM (fig. 2A) or the LVH (fig. 2B) group.

Effect of Propofol on Myocardial Performance

The volumes of saline solution instilled in the intraventricular balloon in LVH₁ and LVH₂ groups were 1.2 ± 0.2 ml and 1.7 ± 0.7 ml, respectively. As expected, LVEDP was significantly greater in the LVH₂ group, and the inotropic (LVESP and dP/dt_{\max}) and lusitropic (dP/dt_{\min}) parameters were significantly lower in the LVH₁ group (table 2). Heart rate was not significantly different between three groups (127 ± 14 beats/min in the SHAM, 115 ± 17

beats/min in the LVH₁, and 123 ± 24 beats/min in the LVH₂ groups). Return to baseline values of myocardial performances was obtained before each perfusion of propofol (data not shown). At concentrations less than 300 μ M, LVESP, dP/dt_{\max} , and dP/dt_{\min} remained unchanged in SHAM, LVH₁, and LVH₂ groups. At concentrations of 300 μ M or more, propofol induced a significant decrease in LVESP, dP/dt_{\max} , and dP/dt_{\min} in all groups. Negative inotropic and lusitropic effects in normal hearts were not significantly different from those in hearts with LVH (table 2). When propofol was administered at a concentration less than 1,000 μ M, LVEDP did not change. In contrast, at the highest concentration of 1,000 μ M, propofol induced a significant increase in LVEDP. Propofol vehicle alone induced nonsignificant myocardial and coronary effects (data not shown).

Effect of Propofol on Coronary Blood Flow

The coronary blood flow normalized by the weight of the left ventricle was significantly lower in hearts with LVH (LVH₁ and LVH₂ groups). Return to baseline values of coronary blood flow was obtained before each perfusion of propofol (data not shown). In normal myocardium, propofol induced an increase in CBF that was significant from a concentration of 100 μ M (table 2). Propofol-induced coronary vasodilation was not significantly different between SHAM, LVH₁, and LVH₂ groups.

Effect of Propofol on Myocardial Oxygen Consumption

The baseline value of MvO_2 was significantly lower in the LVH groups (table 3). Return to baseline values of oxygenation variables was obtained before each infusion of propofol (data not shown). Although there was a trend toward a decrease in MvO_2 by increased concentrations of propofol, this was not statistically significant. Nevertheless, at 300 and 1,000 μ M, propofol induced a significant increase in coronary PvO_2 and CvO_2 (table 3).

Effect of Propofol on Myocardial Performance and Coronary Blood Flow in Severe Left Ventricular Hypertrophy

In the group with severe LVH, the degree of the LVH was $157 \pm 23\%$ (range, 142–207%). Although LVEDP was significantly greater in the group with severe LVH, the baseline inotropic (LVESP and dP/dt_{\max}) and lusitropic (dP/dt_{\min}) parameters were significantly lower in this group (table 4). Coronary blood flow was also significantly lower in the group with severe LVH. There were no significant differences in the myocardial and coronary effects of increased concentrations of propofol between the group with severe LVH and the SHAM group (table 4).

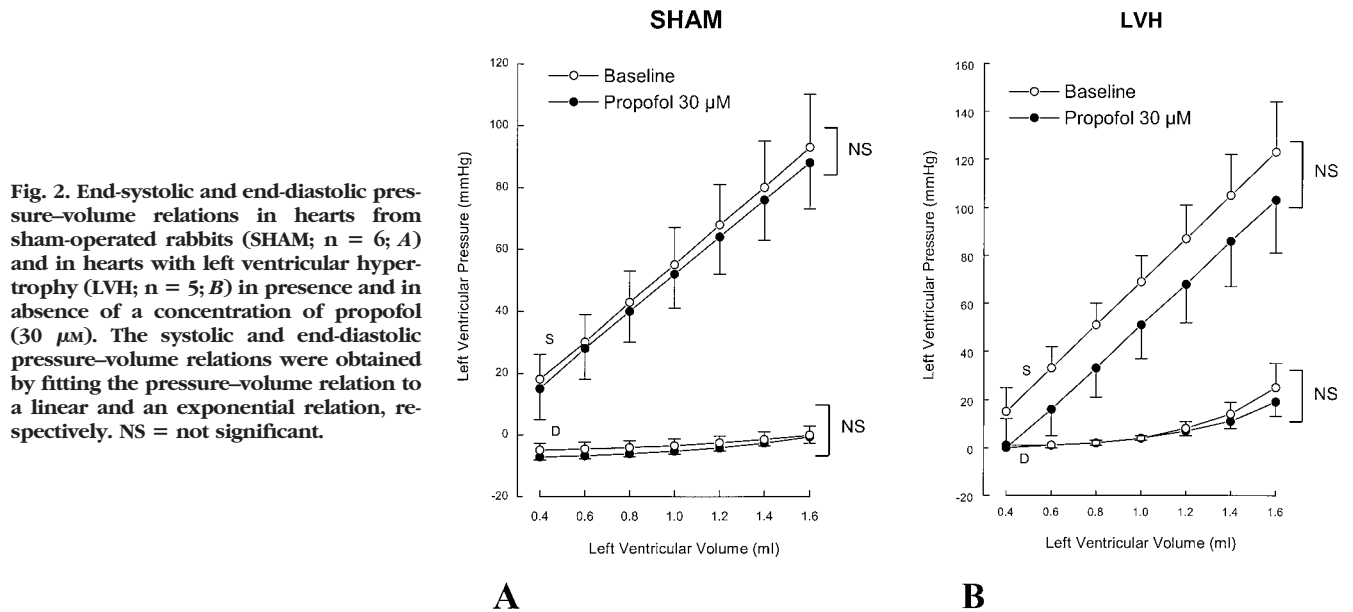


Fig. 2. End-systolic and end-diastolic pressure-volume relations in hearts from sham-operated rabbits (SHAM; $n = 6$; A) and in hearts with left ventricular hypertrophy (LVH; $n = 5$; B) in presence and in absence of a concentration of propofol ($30 \mu\text{M}$). The systolic and end-diastolic pressure-volume relations were obtained by fitting the pressure-volume relation to a linear and an exponential relation, respectively. NS = not significant.

Discussion

In the current study, we observed that (1) in normal myocardium, propofol only induced a significant myocardial depression at concentrations greater than $300 \mu\text{M}$; (2) in compensated cardiac hypertrophy, the negative inotropic and lusitropic effects were not modified, no matter what the LVEDP was; and (3) propofol-induced coronary vasodilation was similar in normal hearts and in hearts with LVH.

Clinical and experimental *in vivo* studies have reported that propofol induces cardiovascular depression. However, most *in vitro* studies in various mammalian species, including the human, concluded that propofol is devoid of significant effects on intrinsic myocardial properties, at least within therapeutic concentrations.^{1-3,6,21-27} The negative inotropic effect observed with propofol in the guinea pig has been attributed to the sensitivity of calcium current and marked reduction

Table 2. Baseline Values and Effects of Propofol on Myocardial Performances and Coronary Blood Flow in the SHAM ($n = 10$) and in the Left Ventricular Hypertrophy Groups, LVH₁ ($n = 10$) and LVH₂ ($n = 10$)

Variables	Baseline Value	Concentrations of Propofol (% of Baseline Value) (μM)					Between-groups Comparison
		10	30	100	300	1,000	
LVEDP (mmHg)							$P < 0.05$
SHAM	10 ± 3	100 ± 2	103 ± 9	99 ± 4	99 ± 3	$109 \pm 15^*$	
LVH ₁	9 ± 2	99 ± 2	100 ± 3	100 ± 6	104 ± 10	$120 \pm 13^*$	
LVH ₂	$15 \pm 2\ddagger$	98 ± 3	99 ± 6	98 ± 5	98 ± 8	$106 \pm 8^*$	
LVESP (mmHg)							NS
SHAM	$120 \pm 22\ddagger$	99 ± 2	99 ± 4	91 ± 7	$80 \pm 13^*$	$53 \pm 15^*$	
LVH ₁	94 ± 18	100 ± 2	100 ± 6	94 ± 9	$74 \pm 23^*$	$51 \pm 16^*$	
LVH ₂	$121 \pm 29\ddagger$	101 ± 3	98 ± 6	92 ± 7	$76 \pm 16^*$	$57 \pm 15^*$	
dP/dt _{max} (mmHg/s)							NS
SHAM	$2,414 \pm 563\ddagger$	98 ± 2	95 ± 6	87 ± 10	$74 \pm 18^*$	$47 \pm 17^*$	
LVH ₁	$1,675 \pm 417$	99 ± 1	99 ± 7	94 ± 9	$73 \pm 25^*$	$44 \pm 17^*$	
LVH ₂	$2,290 \pm 807\ddagger$	101 ± 3	97 ± 7	90 ± 9	$71 \pm 17^*$	$48 \pm 16^*$	
dP/dt _{min} (mmHg/s)							NS
SHAM	$1,565 \pm 278\ddagger$	99 ± 2	98 ± 5	91 ± 7	$80 \pm 13^*$	$49 \pm 15^*$	
LVH ₁	$1,252 \pm 351$	99 ± 2	100 ± 8	95 ± 12	$73 \pm 31^*$	$42 \pm 18^*$	
LVH ₂	$1,532 \pm 544\ddagger$	101 ± 2	98 ± 7	93 ± 10	$74 \pm 22^*$	$48 \pm 20^*$	
CBF ($\text{ml} \cdot \text{min}^{-1} \cdot \text{g}^{-1}$)							NS
SHAM	3.0 ± 0.7	104 ± 3	115 ± 10	$139 \pm 16^*$	$167 \pm 29^*$	$315 \pm 33^*$	
LVH ₁	$2.1 \pm 0.5\ddagger$	108 ± 4	119 ± 11	$156 \pm 35^*$	$223 \pm 64^*$	$381 \pm 97^*$	
LVH ₂	$2.3 \pm 0.9\ddagger$	105 ± 4	113 ± 5	$143 \pm 25^*$	$201 \pm 59^*$	$320 \pm 51^*$	

Data are mean \pm SD.

* $P < 0.05$ versus baseline value. † $P < 0.05$ versus left-ventricular hypertrophy with a "normal" left ventricular end-diastolic pressure (LVH₁; baseline value only). ‡ $P < 0.05$ versus sham-operated group (SHAM; baseline value only).

LVEDP = left ventricular end-diastolic pressure; LVH₂ = left ventricular hypertrophy with a "high" LVEDP (see text for explanation); LVESP = left ventricular end-systolic pressure; NS = not significant; dP/dt_{max}, dP/dt_{min} = maximal positive- and negative-pressure derivatives; CBF = coronary blood flow.

Table 3. Baseline Values and Effects of Propofol on Myocardial Oxygen Consumption in Healthy Hearts (n = 10) and in Those with Left Ventricular Hypertrophy, LVH₁ (n = 8) and LVH₂ (n = 9)

Variables	Baseline Value	Concentrations of Propofol (μM)					Between-groups Comparison
		10	30	100	300	1,000	
Hemoglobin (g/dl)							NS
SHAM	8.3 ± 0.5	8.3 ± 0.5	8.3 ± 0.5	8.3 ± 0.5	8.3 ± 0.5	8.3 ± 0.5	
LVH ₁	8.0 ± 0.5	8.0 ± 0.5	8.0 ± 0.5	8.0 ± 0.5	8.0 ± 0.5	8.0 ± 0.5	
LVH ₂	8.2 ± 0.5	8.2 ± 0.5	8.2 ± 0.5	8.2 ± 0.5	8.2 ± 0.5	8.2 ± 0.5	
Pao ₂ (mmHg)							NS
SHAM	147 ± 8	147 ± 8	148 ± 13	150 ± 14	150 ± 19	145 ± 25	
LVH ₁	147 ± 23	147 ± 22	151 ± 22	147 ± 16	151 ± 17	150 ± 21	
LVH ₂	147 ± 22	147 ± 22	146 ± 22	145 ± 24	142 ± 20	141 ± 26	
Pvo ₂ (mmHg)							NS
SHAM	32 ± 3	32 ± 4	35 ± 5	39 ± 5	48 ± 7*	64 ± 16*	
LVH ₁	31 ± 6	31 ± 6	33 ± 6	38 ± 7	48 ± 19*	59 ± 19*	
LVH ₂	29 ± 4	29 ± 4	31 ± 4	34 ± 5	41 ± 9*	55 ± 12*	
Cvo ₂ (ml/dl)							NS
SHAM	8.4 ± 0.8	8.6 ± 0.8	9.0 ± 0.8	9.5 ± 0.8*	10.3 ± 0.3*	10.8 ± 0.4*	
LVH ₁	8.1 ± 0.8†	8.2 ± 0.9	8.5 ± 0.8	9.2 ± 1.0	9.6 ± 1.0*	10.3 ± 0.7*	
LVH ₂	8.0 ± 0.8†	8.2 ± 0.8	8.6 ± 0.8	9.1 ± 0.7*	9.8 ± 0.7*	10.5 ± 0.7*	
Mvo ₂ (ml · min ⁻¹ · 100 g ⁻¹)							NS
SHAM	9.1 ± 2.6	9.1 ± 2.8	8.6 ± 3.2	8.2 ± 2.6	5.9 ± 2.1	5.8 ± 2.9	
LVH ₁	6.3 ± 2.0†	6.6 ± 2.3	6.6 ± 2.4	6.2 ± 2.4	6.2 ± 3.4	5.2 ± 2.9	
LVH ₂	7.4 ± 3.8†	7.5 ± 4.0	7.0 ± 3.6	6.7 ± 3.2	6.0 ± 2.8	4.9 ± 1.8	

Data are mean ± SD.

* $P < 0.05$ versus baseline value. † $P < 0.05$ versus sham-operated group (SHAM; baseline value only).

NS = not significant; LVH₁ = left ventricular hypertrophy with a "normal" left ventricular end-diastolic pressure; LVH₂ = left ventricular hypertrophy with a "high" left ventricular end-diastolic pressure (see text for explanation); Pao₂, Pvo₂ = coronary arterial and venous oxygen pressure; Cvo₂ = coronary venous oxygen content; Mvo₂ = myocardial oxygen consumption.

in action potential duration.²³ Nevertheless, most of these studies have been performed in healthy myocardium. In diseased myocardium, the effect of propofol remains controversial.⁴⁻⁸ Hebbar *et al.*⁸ reported a more pronounced negative inotropic effect of propofol during congestive heart failure. In contrast, Riou *et al.*⁷ and

Pagel *et al.*⁶ reported that propofol in pathologic hearts (genetically induced hypertrophic cardiomyopathy and pacing-induced dilated cardiomyopathy, respectively) did not induce more accentuated myocardial effects.

In vivo assessment of the effects of propofol on the myocardial intrinsic properties remains difficult because

Table 4. Baseline Values and Effects of Propofol on Myocardial Performances and Coronary Blood Flow in the SHAM (n = 10) and in the Severe Left Ventricular Hypertrophy Groups (Severe LVH, n = 7)

Variables	Baseline Value	Concentrations of Propofol (% of Baseline Value) (μM)					Between-groups Comparison
		10	30	100	300	1,000	
LVEDP (mmHg)							NS
SHAM	10 ± 3	100 ± 2	103 ± 9	99 ± 4	99 ± 3	109 ± 15*	
Severe LVH	14 ± 2†	101 ± 1	101 ± 2	100 ± 1	102 ± 5	108 ± 8*	
LVESP (mmHg)							NS
SHAM	120 ± 22	99 ± 2	99 ± 4	91 ± 7	80 ± 13*	53 ± 15*	
Severe LVH	106 ± 35†	100 ± 2	100 ± 6	94 ± 9	74 ± 23*	51 ± 16*	
dP/dt _{max} (mmHg/s)							NS
SHAM	2,414 ± 563	98 ± 2	95 ± 6	87 ± 10	74 ± 18*	47 ± 17*	
Severe LVH	1,770 ± 689†	102 ± 2	97 ± 7	90 ± 6	66 ± 16*	45 ± 16*	
dP/dt _{min} (mmHg/s)							NS
SHAM	1,565 ± 278	99 ± 2	98 ± 5	91 ± 7	80 ± 13*	49 ± 15*	
Severe LVH	1,299 ± 513†	101 ± 3	97 ± 8	91 ± 9	66 ± 21*	42 ± 19*	
CBF (ml · min ⁻¹ · g ⁻¹)							NS
SHAM	3.0 ± 0.7	104 ± 3	115 ± 10	139 ± 16*	167 ± 29*	315 ± 33*	
Severe LVH	2.1 ± 1.0†	105 ± 5	114 ± 5	146 ± 30*	209 ± 71*	326 ± 61*	

Data are mean ± SD.

* $P < 0.05$ versus baseline value. † $P < 0.05$ versus sham-operated group (SHAM; baseline value only).

NS = not significant; LVEDP = left ventricular end-diastolic pressure; LVESP = left ventricular end-systolic pressure; dP/dt_{max}, dP/dt_{min} = maximal positive- and negative-pressure derivatives; CBF = coronary blood flow.

of concomitant changes in preload and afterload, systemic vascular resistances, and sympathetic activity. Isolated and erythrocyte-perfused heart allowed a precise assessment of intrinsic myocardial contractility and coronary circulation. Indeed, the ventricular volume and the heart rate are maintained constant, and influences of the autonomic nervous system are abolished. Thus, dP/dt_{\max} and dP/dt_{\min} are reliable estimates of the inotropic and lusitropic properties, respectively. The presence of erythrocytes in the perfusate is a clear advantage. This medium does provides physiologic values of P_{aO_2} and Ca_{O_2} and preserves myocardial metabolism.^{28,29} Indeed, Mouren *et al.*¹ have demonstrated that the myocardial effects of propofol depend on the type of perfusate: a marked negative inotropic effect was observed using Krebs-Henseleit solution, which is known to be associated with poor oxygen transport and altered cardiac function,²⁹ compared with erythrocyte-containing solution. The poor oxygen transport capacities of the Krebs-Henseleit solution has even been reported to induce regional ischemia in hypertrophic heart.³⁰ Moreover, a high P_{aO_2} , which is required when using a Krebs-Henseleit solution, induces a coronary vasoconstriction that may interfere with the drug effects on coronary circulation.³¹

In the current study, we used an experimental model of compensated cardiac hypertrophy induced by pressure overload over a 12-week period. The degree of hypertrophy induced in our study ($136 \pm 21\%$) was consistent with previous studies using the same model and reported a mean cardiac hypertrophy of 127% ¹¹ and 136% .³² These authors reported noncardiac abnormalities associated with cardiac hypertrophy, including skeletal and diaphragmatic muscle abnormalities, without any physical signs of congestive heart failure, but they did not perform accurate evaluation of myocardial performance.¹¹ Our results showed a preserved state of contractility as indicated by the absence of significant difference in indexed E_{\max} between SHAM and LVH groups but an alteration of the diastolic compliance in the LVH group (fig. 1). These results explain significant differences in the inotropic and lusitropic baseline values between SHAM and LVH₁ groups. In the latter group, by altered diastolic compliance, the value of 10 mmHg LVEDP corresponded to a lower ventricular load than in the SHAM group. Consequently, SHAM and LVH₁ groups showed different inotropic and lusitropic baseline values (table 2). The additional insufflated volume allowed normalization of inotropic and lusitropic variables in the LVH₂ group by the Starling law at the expense of a significant increase in the LVEDP. We also observed diminished coronary blood flow and myocardial consumption (tables 2 and 3), as previously reported in cardiac hypertrophy.^{33,34} Consequently, we considered that this experimental model appropriately mimics compensated cardiac hypertrophy before the occurrence of

cardiac failure.³⁵ To assess whether myocardial and coronary effects of propofol were enhanced in a more severe cardiac hypertrophy, we also selected hearts with a degree of cardiac hypertrophy greater than 140%. In this group (the group with severe LVH), baseline values showed a moderate left ventricular systolic and diastolic dysfunction (table 4). Nevertheless, myocardial and coronary effects of propofol were not significantly modified. In the current study, we also compared the pressure-volume relation (systolic and diastolic) in absence and in presence of propofol in SHAM and LVH groups (fig. 2). The concentration of $30 \mu\text{M}$ was chosen for two reasons. First, $30 \mu\text{M}$ is a therapeutic blood concentration during general anesthesia.⁵⁶ Second, we preferred to evaluate a concentration of propofol that did not induce any significant vasodilation, to avoid interference between the coronary vessels and the myocardium performances.³⁷ This concentration of propofol did not induce any significant effect on the pressure-volume relation in either group.

In isolated and erythrocyte-perfused rabbit heart preparation, propofol only induced a significant myocardial depression at a concentration greater than $300 \mu\text{M}$. Our results are consistent with those reported by Kanaya *et al.*²⁴ in rat and Ismail *et al.*²² in dog. In human atrial muscle, Gelissen *et al.*² observed a negative inotropic effect of propofol only at concentrations greater than $100 \mu\text{M}$. The blood concentration of propofol during anesthesia was evaluated between 5 and $80 \mu\text{M}$.³⁶ Propofol is highly bound to serum protein and the unbound fraction may be low. Indeed, the clinical range of the unbound propofol was evaluated at approximately $4 \mu\text{M}$. In our study, protein concentration was relatively low ($< 5 \text{ g/l}$), and the unbound propofol concentration was probably higher. Nevertheless, there are no data to indicate the importance of protein binding during short-term administration of propofol; thus, the precise concentration of propofol at which the heart is exposed during induction of anesthesia remains speculative. Nonetheless, from a pharmacologic point of view, we considered that it was important to encompass the therapeutic and suprathreshold concentrations of propofol when assessing its myocardial and coronary effects. Because rate of the infusion was not modified during propofol-induced coronary vasodilation, the intracoronary concentration of propofol probably slightly decreased. It should be pointed out that the propofol effects occur rapidly (within 1 min), thus probably minimizing this problem.

The myocardial effects of propofol were not significantly modified in compensated cardiac hypertrophy. These results contrast with those of Hebbar *et al.*,⁸ who reported that the myocardial effects of propofol were enhanced in pacing-induced congestive heart failure, but concord with those obtained in hamsters with genetically induced hypertrophic cardiomyopathy.⁷ Hebbar *et al.*⁸ made the hypothesis that the more pronounced

negative inotropic effect of propofol in congestive heart failure was related to alteration in L-type Ca^{++} channels that were previously altered by ventricular remodeling. However, ventricular remodeling is thought to occur also in compensated cardiac hypertrophy.^{35,38} No data are available about the contraction–excitation coupling in the cardiac hypertrophy model used in the current study. In the current study, myocardial effects of propofol were not significantly different in hearts with LVH, even when considering only the rabbits with the most severe cardiac hypertrophy. These findings support that the contraction–excitation coupling was not subject to important remodeling because it was recently reported in other moderate hypertrophy.³⁵ In the current study, propofol induced a potent vasodilatory coronary effect, only at high concentration. This result is consistent with previous *in vitro* studies in various species.^{1,39,40} Using intracoronary artery infusion of propofol in dogs, Ismail *et al.*²² also observed a coronary vasodilation that occurred at suprathreshold concentration without alteration in the endocardium-to-epicardium flow ratio. The precise mechanism of coronary vasodilation remains controversial, but is thought to occur with and without endothelium and to involve calcium channels.^{40,41} In the current study, the infusion of propofol was associated with no significant decrease in myocardial oxygen consumption. Anyway, the coronary effects of propofol were not significantly modified in cardiac hypertrophy. This result is important because cardiac hypertrophy is known to be associated with significant reduction in coronary blood flow, myocardial oxygen consumption, and coronary vascular reserve,^{33,34} as observed in the current study (tables 2 and 3).

The following points must be considered in the assessment of the clinical relevance of our study. First, to study direct myocardial effects of propofol on isolated and erythrocyte-perfused heart model, preload and afterload systems are eliminated. *In vivo*, the cardiovascular depression of propofol is a result of myocardial and systemic vascular effects. Second, the current study was performed in myocardium of rabbit, and species differences cannot be completely ruled out.

In conclusion, propofol induced direct cardiac depressant and vasodilatory coronary effects only at suprathreshold concentrations. In compensated cardiac hypertrophy, a disease frequently observed in anesthetized patients, myocardial and coronary effects of propofol were not significantly modified.

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