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Myocardial Effects of Desflurane in Hamsters with Hypertrophic Cardiomyopathy

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Background: **The effects of desflurane on myocardial contraction and relaxation in diseased myocardium have not been completely understood.**

Methods: **The effects of desflurane (1.8 to 9.4 vol%) in left ventricular papillary muscles of healthy hamsters and those with genetically induced cardiomyopathy (strain BIO 14.6) were investigated *in vitro* (29°C, *p*H 7.40, Ca^{2+} 2.5 mM; stimulation frequency, 3/min) under low (isotony) and high (isometry) load. Data are mean percentages of baseline ± SD.**

Results: **Desflurane induced no significant inotropic effect in healthy muscles (maximum unloaded shortening velocity and isometric active force at 9.4 vol%: 97 ± 9% and 92 ± 20%, respectively). In contrast, in cardiomyopathic muscles, desflurane induced a moderate negative inotropic effect (maximum unloaded shortening velocity and active force at 9.4 vol%: 84 ± 19% and 75 ± 25%, respectively). The negative inotropic effect was more pronounced than that in healthy muscles under low ($P < 0.05$) but not high load, and even when concentrations were corrected for minimum alveolar concentrations in each strain. Adrenoceptor blockade or pretreatment with reserpine did not modify the inotropic effect of desflurane, suggesting the absence of intramyocardial catecholamine release. However, tyramine also did not induce any significant catecholamine release in hamster myocardium. In both strains, desflurane induced no significant lusitropic effect under low or high load.**

Conclusions: **Desflurane had no inotropic effect in healthy muscles and a moderate negative inotropic effect in cardiomyopathic muscles. The absence of desflurane-induced intramyocardial catecholamine release was related to hamster myocardium characteristics. (Key words: Catecholamines; contractility; halogenated anesthetics; heart; sympathetic nervous system.)**

DESFLURANE induces a similar moderate depression of cardiac function as isoflurane *in vivo*[1,2] but induces a decrease in systemic vascular resistance that is less pronounced than that of isoflurane and may contribute to its maintenance of higher mean arterial pressure.[2,3] During rapid increases in inspired concentration, desflurane can induce a sympathetic activation.[4–6] When compared with isoflurane in rat myocardium, desflurane induced a moderate positive inotropic effect related to intramyocardial catecholamine release.[7] Indeed, after adrenoceptor blockade or pretreatment by reserpine, desflurane induced a negative inotropic effect that was not significantly different from that of isoflurane.[7] The intramyocardial catecholamine release is distinct from the increase in sympathetic activity observed *in vivo* because it occurs at low concentrations and not during a rapid increase in desflurane concentration.[7]

Most previous studies of the cardiovascular effects of desflurane have been done in healthy myocardium,[1–3,7,8] and the effects of desflurane in diseased myocardium are still being debated.[9–11] Indeed, because desflurane can induce sympathetic activation, intramyocardial catecholamine release, or both, it is difficult to precisely assess its myocardial effects *in vivo*. Furthermore, previous studies have reported that the negative inotropic effects of halogenated anesthetics are more pronounced in ischemic myocardium,[12] pacing-induced cardiomyopathy,[13] and hypertrophic cardiomyopathy.[14]

The various strains of Syrian hamsters with hereditary

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cardiomyopathy offer an opportunity to investigate the effects of anesthetic agents on intrinsic myocardial contractility.[14–16] Contractility, cellular biochemistry, molecular biology, and pathophysiology have been studied extensively in this model, the time course of heart failure is well known, and impairment in contractility results primarily from cardiac muscle cell disease, and thus may be more relevant to clinical cardiomyopathies.[14–16] Therefore we did an *in vitro* study to compare the inotropic (contraction phase) and lusitropic (relaxation phase) effects of desflurane on left ventricular papillary muscles from healthy hamsters and those with hypertrophic cardiomyopathy.

Materials and Methods

Twenty-eight healthy Syrian hamsters (strain F1B) and 19 cardiomyopathic Syrian hamsters (strain BIO 14.6) were used (Bio Breeders, Fitchburg, MA). 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. All healthy and cardiomyopathic hamsters were aged 6 months. Body weight and heart weight were determined at the moment the animals were killed, and the heart weight:body weight ratio was calculated. The degree of cardiac hypertrophy was determined by dividing the heart weight:body weight value of each cardiomyopathic hamster by the mean heart weight:body weight value in healthy hamsters.[14]

Experimental Protocol

As previously described,[14] left ventricular papillary muscles were suspended vertically in a 200-ml jacketed reservoir with Krebs-Henseleit bicarbonate buffer solution containing 118 mM NaCl, 4.7 mM KCl, 1.2 mM $MgSO_4$, 1.1 mM KH_2PO_4, 25 mM $NaHCO_3$, 2.5 mM $CaCl_2$, and 4.5 mM glucose, and maintained at 29°C. Muscles were field stimulated at 3 pulses/min with rectangular wave pulses lasting 5 ms just above threshold. The bathing solution was bubbled with 95% oxygen and 5% carbon dioxide, resulting in a *p*H of 7.40. After a 90-min stabilization period at the initial muscle length at the apex of the length-active isometric tension curve (L_{max}), papillary muscles recovered their optimal mechanical performance.

Because we previously showed that desflurane induces intramyocardial catecholamine release in rat myocardium,[7] we looked for a similar effect in hamster myocardium by additional experiments. α- and β-adrenoceptors were blocked with phentolamine (1 μM) and propranolol (1 μM), which were added to the bathing solution at the end of the stabilization period. Then desflurane was studied in separate groups of papillary muscles in healthy hamsters. The inotropic effect of desflurane was also studied in healthy hamsters pretreated with reserpine (10 mg/kg injected intraperitonally twice 48 and 24 h before killing). Indeed, reserpine was shown to induce an almost complete depletion of intramyocardial catecholamine stores in the rat.[7,17] To verify this point, catecholamine release was induced by tyramine (1 mM), which was added to the bathing solution. However, pretreatment of healthy and cardiomyopathic hamsters with reserpine or α- and β-adrenoceptor blockade with phentolamine (1 μM) and propranolol (1 μM) did not significantly decrease the positive inotropic effect of tyramine (fig. 1). We conclude that tyramine has a positive inotropic effect in hamster myocardium, which is not mediated by intramyocardial catecholamine release.

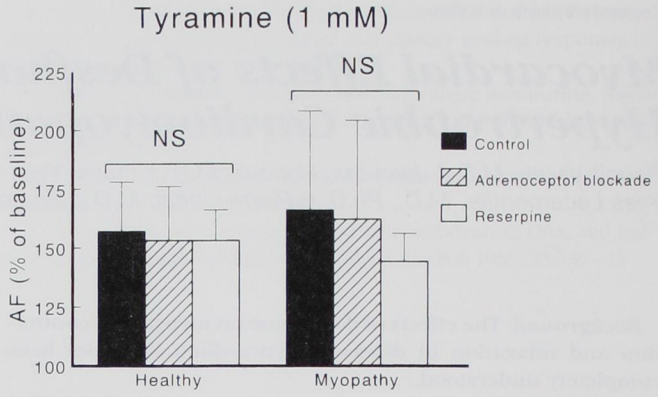

Fig. 1. Effect of tyramine (1 mM) on isometric active force (AF) normalized per cross-sectional are of left ventricular papillary muscles from healthy and cardiomyopathic hamsters. α- and β-adrenoceptor blockade with propranolol (1 μM) and phentolamine (1 μM), or pretreatment with reserpine (10 mg/kg) did not significantly modify the positive inotropic effect of tyramine in both strains. Data are mean ± SD (n = 6 in each group).

Administration of Volatile Anesthetic Agents

Desflurane was added to the carbon dioxide and oxygen mixture using a calibrated vaporizer (TEC 6; Ohmeda, Steeton, UK). The gas mixture bubbled continuously in the bathing solution, and the jacketed reservoir was covered with a thin paraffin sheet.[18] Anesthetic concentrations in the gas phase were measured continuously with an infrared calibrated analyzer (Artema MM 206SD, Taema, Antony, France). Desflurane concentra-

tions used were 1.8, 3.7, 5.6, 7.5, and 9.4 vol%. These concentrations are equivalent to 0.5, 1, 1.5, 2, and 2.5 minimum alveolar concentration (MAC) in rodents at 29°C, respectively.[7] A 20-min period of equilibration was allowed between each anesthetic concentration and mechanical parameter recording.

Mechanical Parameters

The electromagnetic lever system has been described before.[19,20] Mechanical parameters at L_{max} were calculated from three twitches. The first twitch was isotonic and loaded with the preload corresponding to L_{max}. We determined maximum shortening velocity ($_{max}Vc$) and maximum lengthening velocity ($_{max}Vr$) from this twitch. The second twitch was abruptly clamped to zero-load just after the electrical stimulus, with a critical damping to slow the first and rapid shortening overshoot resulting from the recoil of series passive elastic components.[21] The maximum unloaded shortening velocity (V_{max}) was determined from this twitch. The third twitch was fully isometric at L_{max}. We determined the maximum isometric active force normalized per cross-sectional area (AF), and the peak of the positive ($+dF \cdot dt^{-1}$) and negative ($-dF \cdot dt^{-1}$) force derivatives normalized per cross-sectional area from this isometric twitch. Because changes in the contraction phase induce coordinated changes in the relaxation phase, variations in contraction and relaxation must be considered simultaneously to quantify drug-induced changes in lusitropy.[18,22] The coefficient R1 = $_{max}Vc/_{max}Vr$ evaluated the lusitropy under low load (isotony). Because of the lower sensitivity of myofilament for calcium when cardiac muscle is markedly shortened under low load, relaxation proceeds more rapidly than contraction, apparently because of the rapid uptake of calcium by the sarcoplasmic reticulum (SR).[23] Thus R1 tests SR uptake function. The coefficient R2 = $(+dF \cdot dt^{-1}/-dF \cdot dt^{-1})$ evaluated the lusitropy under high load (isometry). Because of the higher sensitivity of myofilaments for calcium,[24] the time course of relaxation is determined by calcium unbinding from troponin C rather than by calcium sequestration by the SR. Thus R2 indirectly reflects myofilament calcium sensitivity.

At the end of the study, the muscle cross-sectional area was calculated from the length and weight of papillary muscle, assuming a density of 1.

Statistical Analysis

Data are expressed as mean ± SD. The Student's *t* test was used to compare the two means. Several means were compared using repeated-measures analysis of variance and Newman-Keuls test (concentrations of anesthetic agents expressed as vol%) or multivariate analysis of variance (concentrations of anesthetic agents expressed as multiples of MAC). All probability values were two-tailed, and $P < 0.05$ was required to reject the null hypothesis. Statistical analyses were done on a computer using NCSS 6.0 software (Statistical Solutions Ltd, Cork, Ireland).

Table 1. Mechanical Parameters of Papillary Muscles in Healthy and Cardiomyopathic Hamsters

Parameter	Healthy (n = 40)	Cardiomyopathy (n = 28)
Characteristics		
L_{max} (mm)	3.4 ± 1.4	1.8 ± 1.1*
CSA (mm^2)	0.71 ± 0.23	0.89 ± 0.46*
RF/TF	0.20 ± 0.08	0.35 ± 0.15*
Contraction		
V_{max} ($L_{max} \cdot s^{-1}$)	3.37 ± 0.61	2.83 ± 0.86*
$_{max}Vc$ ($L_{max} \cdot s^{-1}$)	2.25 ± 0.41	1.74 ± 0.59*
AF ($mN \cdot mm^{-2}$)	37 ± 24	20 ± 20*
$+dF \cdot dt^{-1}$ ($mN \cdot s^{-1} \cdot mm^{-2}$)	480 ± 275	286 ± 294*
Relaxation		
$_{max}Vr$ ($L_{max} \cdot s^{-1}$)	2.70 ± 0.65	1.69 ± 1.14*
$-dF \cdot dt^{-1}$ ($mN \cdot s^{-1} \cdot mm^{-2}$)	284 ± 176	164 ± 199*
Contraction–relaxation coupling		
R1 (low load)	0.82 ± 0.18	0.96 ± 0.28*
R2 (high load)	1.56 ± 0.34	1.49 ± 0.39

Values are mean ± SD.

L_{max} = initial length; CSA = cross-sectional area; RF/TF = ratio of resting force to total force; V_{max} = maximum unloaded shortening velocity; $_{max}Vc$ = maximum shortening velocity; AF = isometric active force normalized per cross-sectional area (CSA); $+dF \cdot dt^{-1}$ = peak of the positive force derivative normalized per CSA; $_{max}Vr$ = maximum lengthening velocity; $-dF \cdot dt^{-1}$ = peak of the negative force derivative normalized per CSA; R1 = $_{max}Vc/_{max}Vr$; R2 = $(+dF \cdot dt^{-1})/(-dF \cdot dt^{-1})$.

* $P < 0.05$ *versus* healthy muscles.

Results

Body weight was significantly less in cardiomyopathic hamsters than in healthy hamsters (94 ± 17 *vs.* 139 ± 13 g, $P < 0.001$). The heart weight:body weight ratio was significantly greater in cardiomyopathic hamsters (4.24 ± 0.68 *vs.* 3.03 ± 0.26 mg/g, $P < 0.001$), indicating cardiac hypertrophy (140 ± 22%, $P < 0.001$). The intrinsic mechanical performance of papillary muscles from hamsters with cardiomyopathy were significantly lower in isometric (AF, +dF/dt) and isotonic (V_{max}, $_{max}Vc$) conditions (table 1). R1, which tests the lusitropy under low load, was significantly greater in cardiomyopathic than in healthy muscles. In contrast, R2, which tests the lusitropy under high load, was not significantly

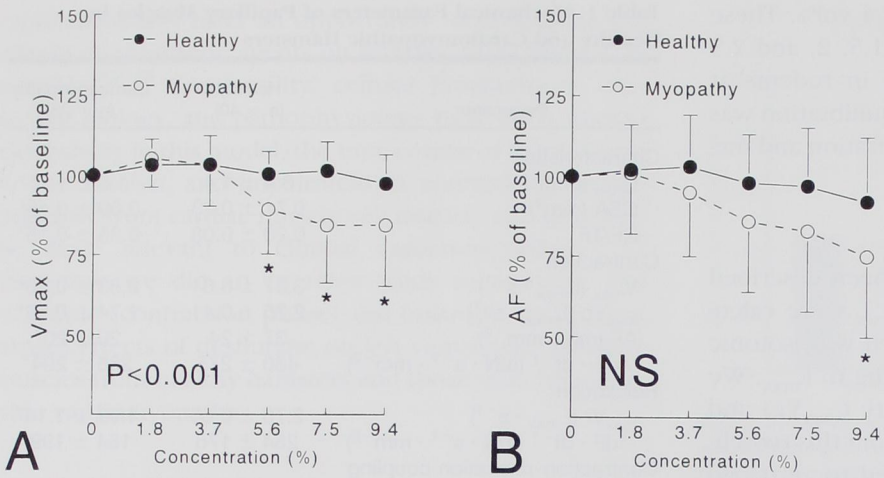

Fig. 2. Comparison of the inotropic effects of desflurane on (*A*) maximum unloaded shortening velocity (V_{max}) and (*B*) isometric active force (AF) normalized per cross-sectional area, in papillary muscles from healthy and cardiomyopathic hamsters. Desflurane concentrations are reported in vol%. Data are mean ± SD (n = 10 in each group). *P* values refer to differences between groups. NS, not significant. *$P < 0.05$ *versus* baseline values.

different between healthy and cardiomyopathic muscles (table 1).

In healthy papillary muscles, desflurane induced no significant inotropic effect under isotonic or isometric conditions (fig. 2). In contrast, in cardiomyopathic muscles, desflurane induced a slight but significant negative inotropic effect, as shown by the decrease in V_{max} and AF (fig. 2). This negative inotropic effect in cardiomyopathic muscles was significantly different from that in healthy muscles, but only in isotonic conditions (fig. 2). Because contractile properties vary from one papillary muscle to another in cardiomyopathic hamsters, papillary muscles were divided into two groups: those with moderate myocardial failure (*i.e.*, baseline AF $>$ 15 mN · mm^{-2}, n = 4) and those with severe myocardial failure (*i.e.*, baseline AF $\leq$ 15 mN · mm^{-2}, n = 6), as previously described.[14] At the highest concentration of desflurane (9.4 vol%), there was no significant difference in the negative inotropic effect of desflurane between papillary muscles with severe myocardial failure (82 ± 20% of baseline) and those with moderate myocardial failure (65 ± 32% of baseline).

Because we previously showed that desflurane induces a positive inotropic effect related to intramyocardial catecholamine release in the rat myocardium,[7] we investigated such an effect in the myocardium of healthy hamsters. We studied the effect of desflurane after α- and β-adrenoceptor blockade and after pretreatment with reserpine to deplete catecholamine stores. The inotropic effect of desflurane in healthy muscles was not significantly modified by adrenoceptor blockade or by pretreatment with reserpine (fig. 3).

Because we have shown that the MAC of desflurane is 7% lower in cardiomyopathic hamsters,[25] we also plotted V_{max} and AF as functions of MAC values determined in each strain (fig. 4). Accordingly, the inotropic effect of desflurane was significantly different between healthy and cardiomyopathy muscles in isotonic but not in isometric conditions.

Desflurane induced no significant lusitropic effects under isotonic or isometric conditions in both healthy and cardiomyopathic papillary muscles (fig. 5).

Discussion

In the current study, we showed that (1) in healthy papillary muscles, desflurane had no significant inotropic effect and did not appear to induce a significant intramyocardial catecholamines release, in contrast to that previously reported in the rat[7]; (2) desflurane had a moderate negative inotropic effect in cardiomyopathic muscles, which was significantly different from that in healthy muscles only in isotonic conditions and even when concentrations were corrected as MAC multiples for each strain; (3) desflurane induced no significant lusitropic effects in both strains.

In humans, desflurane did not significantly modify cardiac index, left ventricular ejection fraction, and velocity of left ventricular circumferential fiber shortening, suggesting that desflurane may produce less depression in myocardial contractility than other halogenated agents.[2] In dogs fitted with instruments for long-term monitoring, desflurane caused less decrease in arterial pressure, systemic resistance, and cardiac function than isoflurane did.[8,26] These differences between isoflurane and desflurane were abolished with pharmacologic autonomic nervous system blockade, suggesting that desflurane may

produce less depression in sympathetic tone and autonomic reflexes than does isoflurane. Gueugniaud *et al.*[7] showed that desflurane induces a slight positive inotropic effect in rat myocardium compared with isoflurane, which might be related to intramyocardial catecholamine release. After adrenoceptor blockade or pretreatment with reserpine, they observed that desflurane induced a negative inotropic effect comparable to that induced by isoflurane.[7] In contrast to that observed in rat myocardium, adrenoceptor blockade or pretreatment with reserpine did not significantly modify the inotropic effect of desflurane in hamster myocardium, suggesting the absence of intramyocardial catecholamine release.

The positive inotropic of tyramine we observed in hamster myocardium was comparable to that previously reported in the rat myocardium,[7] and that observed in the current study in cardiomyopathic hamster myocardium. This result confirms those reported by Feng *et al.*,[27] who showed that the effect of tyramine was not decreased in rats with congestive heart failure. However, the positive effect of tyramine was not abolished after adrenoceptor blockade or pretreatment with reserpine, suggesting that tyramine induced no significant catecholamine release. Species differences among rodents could explain this discrepancy, because the effect of chemical sympathectomy is more prominent in rats than in guinea pigs.[28] Our results explain why we failed to demonstrate a desflurane-induced release of intramyocardial catecholamines in the hamster, as previously noted in the rat.[7] Because we demonstrated species differences in the myocardial effects of desflurane and because few data are available concerning species differences in intracardiac autonomic neurons,[29] further studies are needed to investigate the effects of desflurane in human myocardium.

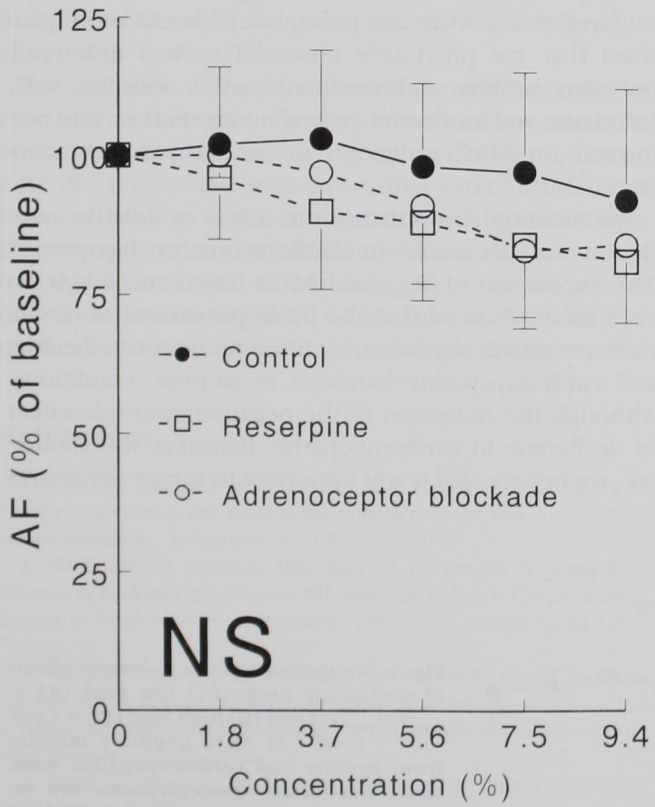

Fig. 3. Comparison of the inotropic effects of desflurane in papillary muscles from healthy hamsters, on isometric active force (AF) normalized per cross-sectional area; in control conditions (n = 10), after α- and β-adrenoceptor blockade (n = 6, propranolol 1 μM and phentolamine 1 μM), or after pretreatment with reserpine (n = 6, 10 mg/kg). Desflurane concentrations are reported in vol%. Data are mean ± SD. *P* values refer to differences between groups. NS, not significant.

We observed a moderate inotropic effect of desflurane in the hamster, compared with that observed in the rat, pending appropriate blockade of intramyocardial catecholamine release. Because we used the same experimental model, only species differences could explain these differences. Indeed, the inotropic effects of desflurane in healthy and cardiomyopathic muscles were similar to those previously described with isoflurane.[14]

R1 tests the lusitropic state under low load and reflects the rapid uptake of calcium by the SR.[18,22] In both healthy and cardiomyopathic papillary muscles, desflurane induced no significant lusitropic effect under low load (fig. 4). This result was consistent with the known weak interference of desflurane with the SR in rodent myocardium.[7] R2 tests the lusitropic state under high load and thus reflects myofilament calcium sensitivity.[18,22] Our study showed that desflurane did not significantly modify R2 in healthy or in cardiomyopathic muscles (fig. 4). These results corresponded with those of Gueugniaud *et al.*[7] in rat myocardium. Thus desflurane seems to be devoid of any lusitropic effect in healthy and cardiomyopathic papillary muscles.

In cardiomyopathic muscles, desflurane induced a moderate negative inotropic effect, which was significantly different from healthy muscles for V_{max} (fig. 2). These results accord with those of previous studies, which showed that the negative inotropic effects of halogenated anesthetics are more pronounced in diseased myocardium.[12–14] However, the cardiovascular effects of desflurane in diseased myocardium remain controversial. Thomson *et al.*[10] did not find any significant difference in morbidity and mortality rates between desflurane and isoflurane in patients undergoing coronary

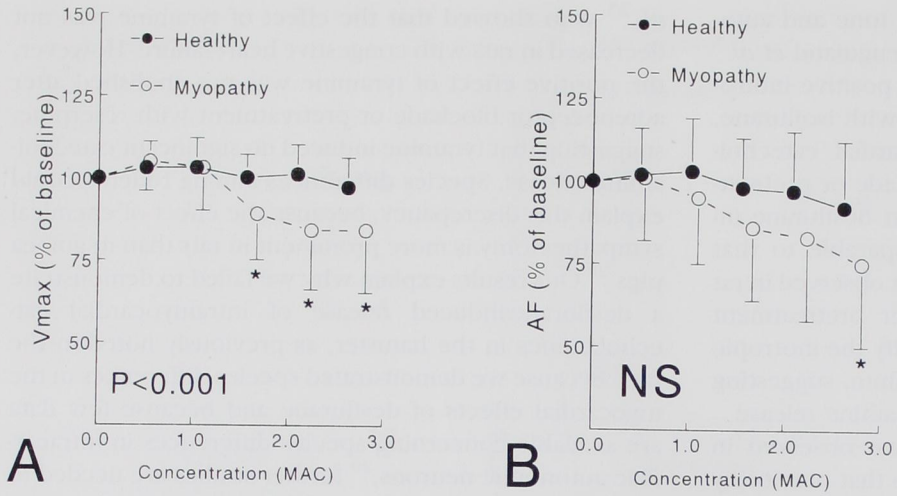

Fig. 4. Comparison of the inotropic effects of desflurane on (*A*) maximum unloaded shortening velocity (V_{max}) and (*B*) isometric active force (AF) normalized per cross-sectional area, in papillary muscles from healthy and cardiomyopathic hamsters. Desflurane concentrations are reported as minimum alveolar concentration multiples in each strain. Data are mean ± SD (n = 10 in each group). *P* values refer to difference between groups. NS, not significant. **P* < 0.05 *versus* baseline values.

artery bypass graft surgery, and Pagel *et al.*[11] found that desflurane and isoflurane had similar moderate beneficial actions on left ventricular function in the presence of severe abnormalities in systolic and diastolic functions during myocardial ischemia in dogs. Our study did not allow us to determine precisely the mechanism(s) by which desflurane induced a significant negative inotropic effect in cardiomyopathic and not in healthy muscles. Because we observed no significant differences between groups in R1 (assessing SR function) and R2 (assessing calcium myofilament sensitivity), it is likely that this difference was related to the desflurane effect on calcium inward. Modifications of conductance, the number density of voltage-sensitive calcium channel, and of sarcolemmal calcium ATPase have been reported in cardiomyopathic hamsters.[29–31] Li *et al.*[32] found that calcium current (I_{Ca}) is reduced and action potential duration is increased in cardiomyopathic hamsters. These differences may explain different susceptibility to halogenated anesthetics whose negative inotropic effect is related mainly to a decrease in I_{Ca}. Further studies are required to elucidate this point, but it should be emphasized that we previously observed such a difference between healthy and cardiomyopathic muscles with halothane and isoflurane (when no correction was performed for MAC reduction in cardiomyopathic hamsters).[14]

We recently showed that the MACs of volatile anesthetics are decreased in cardiomyopathic hamsters.[25] The expression of V_{max} and AF as functions of MAC in each strain showed that the inotropic effects of desflurane remained significantly different between healthy and cardiomyopathic hamsters in isotonic conditions. Although the reduction of the negative inotropic effect of desflurane in cardiomyopathic hamsters was moderate, we believe that it was important to report our results

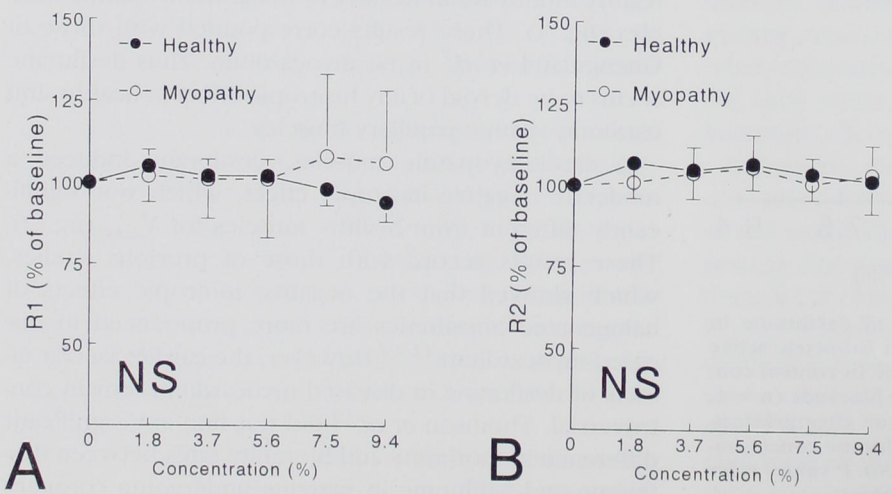

Fig. 5. Comparison of the lusitropic effects of desflurane under (*A*) low load (R1 = $_{max}Vc/_{max}Vr$) and (*B*) high load (R2 = $(+dF \cdot dt^{-1}) / (-dF \cdot dt^{-1})$) in papillary muscles from healthy and cardiomyopathic hamsters. Desflurane concentrations are reported in vol%. Data are mean ± SD (n = 10 in each group). *P* values refer to differences between groups. NS, not significant.

from a pharmacologic perspective (fig. 2) and from a clinically relevant perspective (fig. 4), as previously described.[14]

The following points must be considered in the overall assessment of our results. First, this study was conducted *in vitro* and dealt only with intrinsic myocardial contractility. Changes in cardiac function depend on heart rate, venous return, afterload, and sympathetic nervous system activity. Second, this study was conducted at 29°C and at a low-stimulation frequency; yet papillary muscles must be studied at this temperature because mechanical parameters are not sufficiently stable at 37°C and at a low frequency because high-stimulation frequency induces core hypoxia.[33] Third, although the effects of volatile anesthetics on the myocardium appear to be similar among species (at least in mammalian species), the hamster myocardium differs somewhat in its cardiac behavior from other species, including humans. Fourth, the results obtained in this experimental model of genetically induced cardiomyopathy cannot be generalized to all types of cardiac failure.

In conclusion, in healthy hamster myocardium, desflurane had no inotropic effect under isotonic or isometric conditions; and, in contrast to rat myocardium, desflurane did not induce intramyocardial catecholamine release in healthy hamster myocardium. In cardiomyopathic papillary muscle, desflurane induced a moderate but significant negative inotropic effect. Desflurane induced no lusitropic effect under low or high load in neither healthy nor cardiomyopathic papillary muscles.

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