Effects of lercanidipine on coronary reactivity and myocardial remodeling in transition to heart failure in cardiomyopathic hamsters

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ABSTRACT

AIM: Lercanidipine is a new vasoselective dihydropyridine calcium channel blocker with a short plasma half-life, long duration of action, and demonstrated cardioprotective properties. We hypothesized that it might be effective at attenuating the adverse impact observed on the coronary compartment and myocardium in the transition phase to heart failure in the UM-X7.1 cardiomyopathic (CM) hamster. **METHODS:** The effects of 4-month exposure to lercanidipine 3 and 10 mg/kg (daily oral administration) were evaluated in 150-day-old CM hamsters and in age-matched normal hamsters. Coronary reactivity (reactive hyperemia to 30-s coronary occlusion) and the response to the administration of acetylcholine (100 nmol/L) and sodium nitroprusside (1 μmol/L) were assessed monthly, using the isolated perfused heart model. The left ventricular chamber dilatation index and wall thickness, myocardial fibrosis and myocardial capillary density (papillary muscle) were estimated in selected subgroups at monthly intervals. **RESULTS:** High-dose lercanidipine had beneficial effects on coronary dysfunctions: at month 4 of the treatment period, reactive hyperemia to short duration ischemia was improved, as was the endothelium-dependent vasodilator response (acetylcholine=68 %±16 % *vs* 11 %±5 % in untreated CM hamsters, $P<0.05$) and endothelium-independent vasodilator response (sodium nitroprusside=36 %±5 % *vs* 22 %±12 % in untreated CM hamsters, $P<0.05$). Capillary density averaged 10 879±474 capillaries per mm^2 in papillary muscle from normal hamsters; this value did not change over time in normal hamsters and was not affected during the transition phase to heart failure in CM hamsters. Lercanidipine preserved myocardial capillary density in these conditions. Chronic exposure to lercanidipine had no impact on myocardial remodeling observed in CM hamsters. **CONCLUSION:** Lercanidipine had a beneficial impact on the coronary compartment in the transition phase to heart failure in a model of dilated cardiomyopathy.

INTRODUCTION

Lercanidipine, a new vasoselective dihydropyridine calcium channel blocker with a short plasma half-life and long duration of action[1], is an effective antihypertensive agent[2]. In addition, lercanidipine is devoid of

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significant negative chronotropic and inotropic cardiac repercussions and possesses strong coronary vasodilator properties[3] along with significant anti-ischemic effects[4]. Recent evidence[5] indicates that lercanidipine has a beneficial influence on vascular remodeling of renal arterial tree of SHR, but its protective role on vascular dysfunction in the transition to heart failure remains to be determined.

Vascular dysfunctions and remodeling are considered hallmarks of chronic heart failure; both conditions appear to play a significant role in disease progression[6]. In animal models of cardiomyopathy, development of the disease is associated with necrotic foci, myocytolysis and collagen accumulation, and the early alterations are prevented by early administration of calcium channel blockers[7].

To assess the chronic effects of lercanidipine in the transition phase to heart failure, we selected the UM-X7.1 cardiomyopathic (CM) hamster as a valuable model for the investigation of pathological processes associated with the development of heart failure[8]. Hamsters (150-day-old) were treated daily with lercanidipine for 4 months. Coronary reactivity, cardiac remodeling (left ventricular dilatation index and wall thickness, fibrosis), and coronary capillary density were evaluated at monthly intervals.

MATERIALS AND METHODS

Experimental protocol In this study, normal golden Syrian hamsters (Charles River, St-Constant, Qc, Canada) and UM-X7.1 CM hamsters (Université de Montréal) were cared for in accordance with the guidelines of the Canadian Council on Animal Care (1993). They were housed under identical conditions (24 °C and 12:12-h light/dark cycle) with free access to laboratory chow and tap water. Males and females were used in all groups, and CM hamsters of the same litter were distributed in all experimental groups. This protocol involved a total of 160 hamsters: 40 normal golden Syrian hamsters (NOR), 40 vehicle-treated CM hamsters (CMH_U), 40 CM hamsters treated daily with 3 mg/kg lercanidipine (CMH_L) and 40 CM hamsters treated daily with 10 mg/kg lercanidipine (CMH_H). There are no available reports on the pharmacokinetics of lercanidipine in hamsters. Experiments were performed to establish dose levels necessary to match plasma concentrations considered to be clinically therapeutic and those corresponding to 2 times higher than therapeutic concentrations. Lercanidipine and the vehicle were administered by gavage (0.11 to 0.24 mL). All animals were weighed daily, and their dosage was adjusted for body weight changes. The treatment period was initiated when the animals were 150-day-old and lasted 120 d. To assess the effects of lercanidipine at selected time periods during the transition phase to heart failure, 10 animals per group were sacrificed 30, 60, 90 and 120 d after the beginning of the treatment period (ie, at age 180, 210, 240 and 270 d).

Coronary reactivity At the end of the treatment periods selected, the animals were killed by a blow to the head, and the thorax was opened. The heart was then cooled, cannulated via the ascending aorta, excised and perfused with modified Krebs-Ringer buffer consisting (in mmol/L) of NaCl 119, KCl 4.8, $CaCl_2$ 1.3, KH_2PO_4 1.2, $MgSO_4$ 1.2, $NaHCO_3$ 25, and glucose 15. The buffer solution was bubbled with a gas mixture (95 % O_2 and 5 % CO_2) and maintained at pH 7.4 and 37 °C. Coronary perfusion pressure was kept constant at 140 cm H_2O (1 cm H_2O=98.1 Pascal). After 30-min stabilization, coronary reactivity to the endothelium-dependent mediator acetylcholine (100 nmol/L, 2-min infusion) and to the endothelium-independent mediator sodium nitroprusside (1 μmol/L, 2-min infusion) was assessed. Each infusion was followed by a 5- to 10-min washout period to allow coronary flow to return to baseline. In all experiments, short-duration ischemia induced by occlusion of coronary inflow for 30 s and the resultant reactive hyperemia were reproduced before infusion of the vasodilators. All functional data were retrieved on a multichannel recorder (Model 2400S, Gould Electronics, Cleveland, OH).

Cardiac morphometry After decerebration and thoracotomy, the hearts were cooled, cannulated *in situ* via the ascending aorta, and perfused retrogradely with warm oxygenated Krebs-Ringer solution. Necrotic foci readily visible to the naked eye were evaluated overall. The hearts were then perfused with a freshly-prepared 4 % paraformaldehyde solution (NaOH 7.7 g/L, $NaHPO_4$ 33.6 g/L, paraformaldehyde 40 g/L) via the aortic cannula at 100 mmHg perfusion pressure for at least 5 min. The hearts were arrested in diastole with a high-potassium solution. After perfusion with the paraformaldehyde solution, they were fixed in 10 % buffered formalin for 12 h and kept refrigerated. Each heart was then cut half way (middle) between the base and apex, and 2 to 3 slices were inserted in a cassette for continued fixing, dehydration and embedding in paraffin. These

representative 3- to 5-μm cross sections were stained with Masson trichrome and mounted on slides for projection. Disseminated necrotic lesions throughout the heart muscle were assessed quantitatively as described previously[8]. Microscopic readings of necrotic foci were rated by an independent observer according to an arbitrary scale of 0-3, a maximum score of 3 indicating that damage exceeded 50 % of the entire myocardium, whereas a score of 2 corresponded to moderate changes, a score of 1 represented mild changes, and 0, no damage. In the present study, there was no significant change in the overall score of necrotic foci from the hearts of untreated CM hamsters compared to CM hamsters treated with low- or high-dose lercanidipine (data not shown). To quantitatively estimate left ventricular fibrosis, each slide was scanned (AGFA Duoscan T1200, AGFA-Gevaert NV, Morstel, Germany), and the image was processed numerically with Adobe Photoshop 5.02 and a computer program developed at the Université de Montréal (G Tremblay, personal communication). The latter program allows us to discriminate between normal tissue (red staining) and fibrotic tissue (blue staining). Fibrosis results are expressed as percent of the total left ventricular area scanned.

Left ventricular dimensions Slides were viewed on a video screen at 10×magnification. Endocardial and epicardial circumferences were measured with a planimeter digital image analyzer (Sigma Scan Pro System, Software Labtronics Inc, Guelph, Ont, Canada). The left ventricular dilatation index was computed as the ratio of the left ventricular cavity area over the left ventricular area[9]. Left ventricular wall thickness was measured at 3 different sites, and the average was calculated.

Myocardial capillary density Slides were first projected on a screen at 40×magnification to identify the fiber area perpendicular to the section. The selected section (trabeculae) was magnified at 1000×, and each field was transferred to a digitizing image system analyzer (NIH Image 1.61). Individual capillary space and total tissue area were measured by optimal contrast using Image software. Vessels were excluded when the lumen area was over 50 mm^2. The total number of capillaries, capillary density per unit total tissue area (number/mm^2), and the ratio of total capillary lumen area over total tissue area were estimated.

Drugs Lercanidipine, a generous gift from Recordati SpA. (Milan, Italy), was dissolved in a mixture of PEG:H_2O (50:50). Fresh solutions were prepared weekly, protected from light and kept refrigerated. All other drugs and chemicals were of the highest quality (Sigma Aldrich Canada Ltd, Oakville, Ont, Canada), and solutions were prepared on the day of the experiment.

Statistics Data are expressed as mean±SEM. One-way analysis of variance and the Student's *t*-test were used to determine significant changes. The Dunnett *t*-test was utilized for multiple comparisons. Statistical significance was set at $P<0.05$.

RESULTS

Mortality was low in all groups during the study period. One normal hamster had to be sacrificed because of exaggerated weight loss and physical discomfort, 2 untreated CM hamsters were sacrificed (1 because of wet tail development, and the other for end-stage cardiac failure with evidence of physical distress), 2 deaths were recorded in the low-dose lercanidipine CM hamster group (1 because of septicemia, and the other from an unknown cause), and 2 animals from the high-dose lercanidipine CM hamster group were found dead (1 because of end-stage heart failure revealed at autopsy, and second from an unknown cause).

Mean body weights at the beginning of the study for the different groups were as follows: normal hamsters=192±3 g, untreated CM hamsters=133±2 g, CM hamsters receiving low-dose lercanidipine=128±2 g and CM hamsters receiving high-dose lercanidipine=135±2 g. Body weight was significantly lower in all CM hamster groups compared with in normal hamsters at the beginning of the study period. Body weight and heart weight changes during the study period are presented in Tab 1. Over time, body weight remained lower in untreated CM hamsters as well as in low- and high-dose lercanidipine-treated CM hamsters. After the first month of the treatment period, heart weight was found to be lower in all 3 CM hamster groups. At month 3 of the study period, this difference was no longer detectable. As shown in Tab 1, the ratio of heart weight to body weight was consistently higher in the 3 CM hamster groups without any noticeable difference among them.

A typical response to endothelium-dependent (acetylcholine) and endothelium-independent (sodium nitroprusside) vasodilators is illustrated in Fig 1. Brief coronary dilatation, observed in the presence of acetylcholine (Fig 1A), contrasted with the more stable response elicited by sodium nitroprusside (Fig 1B). As

Tab 1. Body weight (BW), heart weight (HW), and HW / BW ratio of the different groups during the 4-month study period. *n*=3-5. Mean±SEM. $^{b}P<0.05$ *vs* NOR.

	Month 1	Month 2	Month 3	Month 4
Body weight (g)				
NOR	204±6	192±8	188±6	187±4
CMH_U	130±4^{b}	136±5^{b}	136±5^{b}	143±6^{b}
CMH_L	135±4^{b}	128±3^{b}	134±3^{b}	130±4^{b}
CMH_H	132±3^{b}	147±3^{b}	135±3^{b}	130±5^{b}
Heart weight (mg)				
NOR	986±61	1059±38	1036±65	1081±43
CMH_U	762±25^{b}	875±39^{b}	975±62	1057±87
CMH_L	736±44^{b}	854±30^{b}	942±37	1069±66
CMH_H	781±24^{b}	999±40	949±47	1031±70
Heart weight/body weight (mg/g)				
NOR	4.9±0.3	5.6±0.1	5.6±0.4	5.8±0.3
CMH_U	5.9±0.3^{b}	6.5±0.3^{b}	7.1±0.3^{b}	7.4±0.5^{b}
CMH_L	5.4±0.2^{b}	6.7±0.2^{b}	7.0±0.2^{b}	8.2±0.4^{b}
CMH_H	6.0±0.3^{b}	6.8±0.2^{b}	7.0±0.3^{b}	7.8±0.4^{b}

NOR=Normal hamsters, CMH_U=Untreated cardiomyopathic hamsters; CMH_L=Low-dose lercanidipine-treated cardiomyopathic hamsters; CMH_H=High-dose lercanidipine-treated cardiomyopathic hamsters.

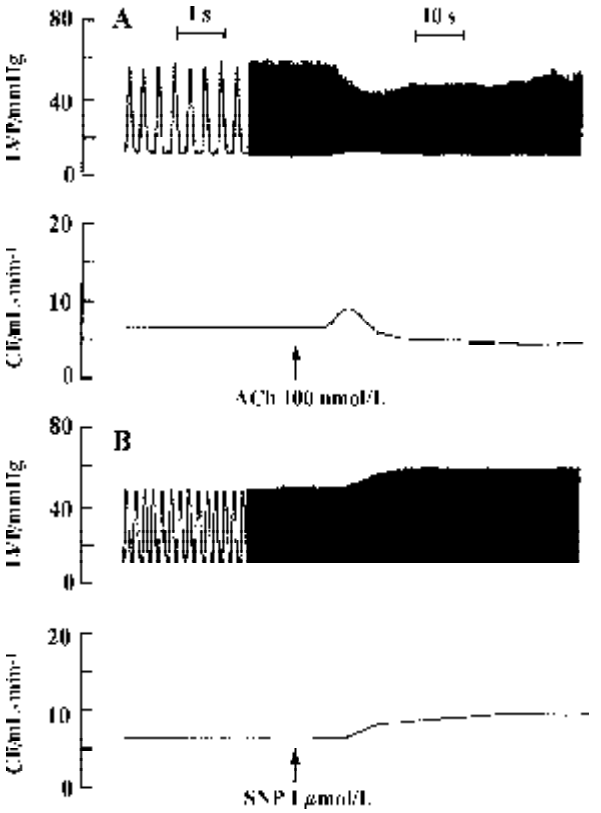

Fig 1. Typical experiment illustrating the coronary response elicited by acetylcholine (A) and sodium nitroprusside (B) in a normal hamster heart. The arrow indicates the beginning of drug infusion. CF=coronary flow; ACh=acetylcholine; SNP=sodium nitroprusside.

shown in Tab 2, the vasodilator response elicited by acetylcholine tended to be lower in untreated CM hamsters compared to normal hearts. In the presence of high-dose lercanidipine, the endothelium-dependent vasodilator response was improved up to the end of the study (CM hamsters aged 270 d). The nitroprusside vasodilator response was significantly affected in CM hamsters at the beginning of the study period, and lercanidipine had a beneficial influence on this attenuated response. The overall beneficial effects of lercanidipine on coronary reactivity at month 4 of the study period are exemplified in Fig 2. In CM hamsters given high-dose lercanidipine, the hyperemic response following brief coronary occlusion (30 s) was significantly increased, and the endothelium-dependent as well as the endothelium-independent vasodilator response were improved.

Fig 3 illustrates representative mid-cross sections of hearts from a normal hamster (Fig 3A) and an untreated CM hamster (Fig 3B) at the end of the study period. In addition to an enlarged cavity and reduced wall thickness, disseminated necrotic foci were present along with fibrosis in CM hamster hearts. The overall morphologic characteristics of hearts from the different groups studied are enumerated in Tab 3. The dilatation index, computed as the ratio of left ventricular endocardial surface over left ventricular epicardial surface, was consistently greater in untreated CM hamsters than that in normal hamsters during the study period. Neither low- nor high-dose lercanidipine treatment improved the left ventricular dilatation index. A significant reduction in left ventricular wall thickness was noted in untreated CM hamster hearts compared to normal hearts, and this parameter was not altered significantly in lercanidipine-treated animals. Estimation of left ventricular fibrosis indicated a significant increase in the untreated CM hamster group at month 1 up to the end of the study period. Lercanidipine did not attenuate the development of myocardial fibrosis. Fig 4 illustrates a typical cross sectional area from a papillary muscle (normal heart), judged by nearly circular capillaries and compact tissue, used to assess capillary density. The

Tab 2. Coronary reactivity of isolated hearts harvested during the 4-month study period. *n*=3-5. Mean±SEM. $^{b}P<0.05$ *vs* NOR. $^{e}P<0.05$ *vs* CMH_U. $^{h}P<0.05$, significant linear trend between the 3 CM hamster groups.

	Month 1	Month 2	Month 3	Month 4
ACh 100 nmol/L (Δ%)				
NOR	9.1±1.5	31.1±15.5	59.1±10.2	36.0±5.9
CMH_U	-0.8±0.8^{b}	8.5±6.2	22.5±13.0	10.6±5.3^{b}
CMH_L	3.7±1.7	15.5±4.4	55.6±16.1	12.2±5.8
CMH_H	2.3±0.9	42.2±18.2^{e}	66.7±10.2^{h}	67.6±16.0^{eh}
SNP 1 μmol/L (Δ%)				
NOR	8.9±1.9	41.6±10.5	50.0±7.8	49.6±6.5
CMH_U	-0.1±1.9^{b}	2.6±2.8^{b}	38.3±6.1	22.0±11.7
CMH_L	0.8±0.8	24.1±3.8	34.9±10.8	15.6±8.0
CMH_H	0.8±1.1	30.3±13.0^{e}	48.4±3.8	36.3±4.9
Hyperemia (mL/min)				
NOR	6.2±0.4	9.9±1.1	8.1±1.0	5.8±0.5
CMH_U	5.9±0.7	6.5±1.0	7.2±0.8	5.6±0.8
CMH_L	6.0±0.7	7.5±0.7	7.5±0.6	6.3±0.4
CMH_H	4.9±0.4	7.3±1.0	7.9±0.2	8.2±0.3^{eh}

Abbreviations as in Tab 1.

Tab 3. Cardiac morphologic characteristics of normal and CM hamster groups during the 4-month study period. *n*=3-5. Mean±SEM. $^{b}P<0.05$ *vs* NOR.

	Month 1	Month 2	Month 3	Month 4
Dilatation Index				
NOR	0.47±0.05	0.51±0.05	0.39±0.04	0.39±0.06
CMH_U	0.63±0.02^{b}	0.57±0.04	0.54±0.04^{b}	0.62±0.03^{b}
CMH_L	0.58±0.04^{b}	0.47±0.04	0.54±0.04^{b}	0.58±0.04^{b}
CMH_H	0.59±0.04^{b}	0.54±0.04	0.50±0.06^{b}	0.61±0.03^{b}
Thickness (cm) ($\times 10^{-2}$)				
NOR	14.65±1.54	13.29±1.38	14.75±1.22	12.75±1.04
CMH_U	8.88±0.78^{b}	8.74±0.64^{b}	10.30±0.63^{b}	9.32±0.54^{b}
CMH_L	8.39±0.52^{b}	10.89±0.68^{b}	10.15±0.90^{b}	8.67±0.71^{b}
CMH_H	9.51±0.97^{b}	10.47±0.64^{b}	10.78±1.26^{b}	8.70±0.85^{b}
Fibrosis (% total left ventricular area)				
NOR	6±1	5±1	8±2	9±1
CMH_U	17±2^{b}	18±2^{b}	17±2^{b}	18±1^{b}
CMH_L	17±1^{b}	15±1^{b}	20±1^{b}	23±2^{b}
CMH_H	16±2^{b}	21±3^{b}	16±2^{b}	23±3^{b}

Abbreviations as in Tab 1.

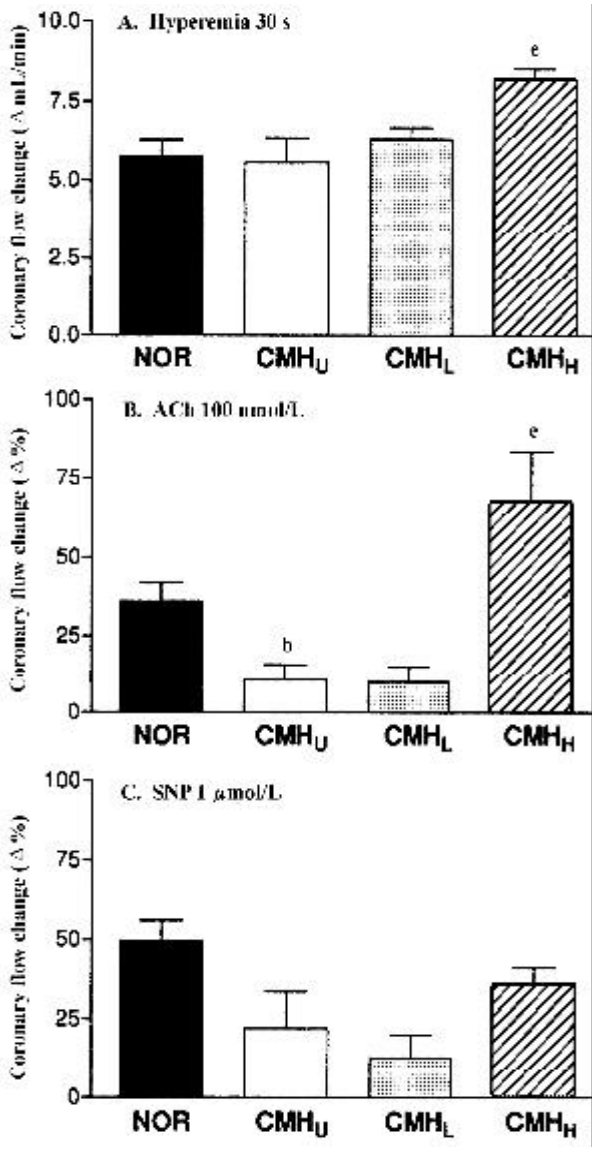

Fig 2. Coronary reactivity in the different groups at month 4 of the study period. *n*=3-5 per group. Mean±SEM. $^{b}P<0.05$ *vs* NOR. $^{e}P<0.05$ *vs* untreated CMH. NOR=normal hamsters; CMH_U=untreated cardiomyopathic hamsters; CMH_L=cardiomyopathic hamsters treated with low-dose lercanidipine; CMH_H=cardiomyopathic hamsters treated with high-dose lercanidipine.

computed results on capillary density in the different groups during the study period are presented in Tab 4. Mean capillary density was 10 879±474 capillaries per mm^2 in heart papillary muscle from normal hamsters at month 1, and this value did not change significantly during the follow-up period. A similar finding was made in untreated CM hamster hearts. Lercanidipine slightly but significanlty increased capillary density after the first month of the study period. Thereafter, the values were similar to those reported in normal and untreated CM

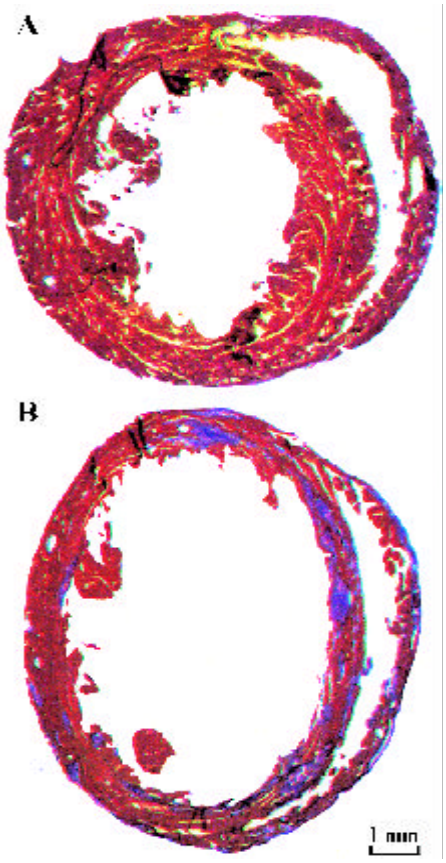

Fig 3. Photomicrographs of representative mid-cross sections of hearts from 270-day-old normal hamster (A) and 270-day-old untreated CM hamster (B). Paraffin-embedded 3-μm section stained with Masson trichrome.

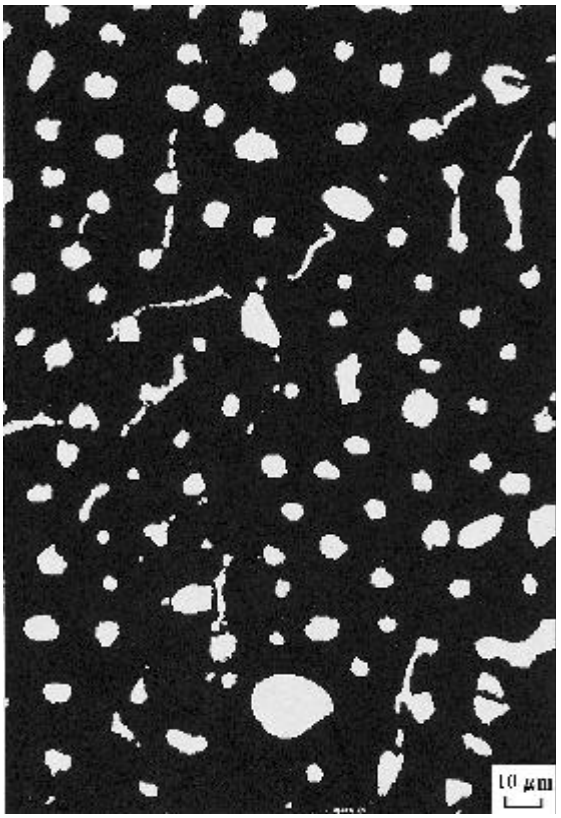

Fig 4. Photomicrograph of cross-sectioned capillaries from a 180-day-old normal hamster heart (papillary muscle). Paraffin-embedded 3-μm section stained with Masson trichrome.

Tab 4. Total capillary density and ratio of total capillary lumen area over total myocardial tissue area in normal and CM hamsters during the study period. *n*=3-5. Mean±SEM. $^{b}P<0.05$ *vs* NOR. $^{e}P<0.05$ *vs* CMH_U.

	Month 1	Month 2	Month 3	Month 4
Capillary density (number/mm^2)				
NOR	10870±747	12980±755	10890±731	12760±515
CMH_U	10330±555	12650±1316	11060±754	12370±1857
CMH_L	14330±881^{b}	10850±549	13010±453	12620±747
CMH_H	14440±808^{b}	12210±702	10890±731	12760±515
Area ratio (μm^2/μm^2×10^{-2})				
NOR	8.2±1.2	6.4±1.0	7.0±0.9	10.0±1.0
CMH_U	5.5±0.9	8.6±1.4	12.2±1.6^{b}	9.7±1.1
CMH_L	9.1±1.7^{e}	9.1±1.0	10.0±1.0	10.6±1.4
CMH_H	11.3±2.3^{e}	10.5±0.9	7.4±0.6^{e}	8.1±0.3

hamster hearts. Tab 4 depicts the ratio of capillary surface over total papillary tissue surface in all groups tested.

DISCUSSION

The Syrian CM hamster is considered a valuable model for the investigation of pathological processes associated with the development of heart failure. In the UM-X7.1 CM hamster, a subline of BIO 14.6 developed at the Université de Montréal in the early 1970s, myocardial necrosis reaches maximum severity by age 90 d. Subsequently, myocardial fibrosis and adverse remodeling lead to end-stage cardiac failure. Genetic defects of membrane structure and function, calcium overload, increased adrenergic tone and coronary dysfunctions are considered as factors contributing to development of the disease. Since the transition phase leading to heart failure observed in UM-X7.1 CM hamsters is similar to that occurring clinically, this model is suitable to assess the effects of chronic drug treatment on both coronary dysfunctions and myocardial remod-

eling associated with the progression to heart failure[8].

The effects of chronic lercanidipine administration on coronary reactivity, cardiac remodeling and myocardial capillary density were assessed during the transition to heart failure in UM-X7.1 CM hamsters. The coronary dysfunctions seen in untreated CM hamsters (impaired endothelium-dependent and endothelium-independent coronary reactivity) were improved in the presence of high-dose lercanidipine. The myocardial remodeling found in CM hamsters, ie, an increased dilatation index, reduced wall thickness, and fibrosis, was not modified by lercanidipine. Myocardial capillary density studies revealed that disease progression did not alter myocardial capillarization. Lercanidipine exposure slightly increased capillary density, but only after the first month of the study period. These results indicate that lercanidipine improved coronary reactivity during the transition to heart failure but not myocardial remodeling.

It is recognized that coronary dysfunctions are linked to the development of heart failure. Several studies indicate that reduced coronary perfusion, vasospastic episodes, impaired coronary reserve and decreased coronary reactivity to endothelium-dependent mediators are present at an early stage of the disease and contribute to myocardial deterioration[10]. In CM hamsters, altered coronary perfusion as well as increased sensitivity to vasoconstrictors (norepinephrine, angiotensin II, arginine-vasopressin) have been suggested as factors contributing to the development of heart failure. Although several vasodilators, including diltiazem, have been shown to improve cardiac function associated with cardiomyopathy[11], a direct action on the coronary compartment has never been estimated. In addition, other mechanisms may explain the previously-reported beneficial effects, ie, ameliorated coronary reserve via left ventricular relaxation, correction of regional disparities in oxygen demand (improved regional wall motion), reduced dilatation of the left ventricular cavity, or diminished myocardial oxygen demand through a negative inotropic outcome.

In the present study, we provide evidence that lercanidipine has a direct impact on the coronary compartment. Coronary reactivity was improved, as evidenced by the increased reactive hyperemia to brief coronary occlusion in the presence of lercanidipine. Similarly, endothelium-dependent (acetylcholine) and endothelium-independent (sodium nitroprusside) vasodilator responses were enhanced over time in diseased hearts in the presence of lercanidipine. The latter is an attractive new observation. While other dihydropyridines have been shown to improve endothelial function in pathological conditions, such as hypertension and myocardial ischemia, their role in the transition phase leading to heart failure was never addressed. The benefits of lercanidipine are in contrast with the reported detrimental consequences of amlodipine on endothelial function in heart failure[12].

Previous findings suggest that dihydropyridine calcium channel blockers interfere with myocardial remodeling, and chronic exposure to some of these agents may be beneficial in pathological conditions evolving towards heart failure[7] when administered in young (35-day-old) animals, a situation in which the necrotic processes of CHF are still absent. The reason of failure of lercanidipine on myocardial remodeling could be attributed to the time of administration of the compound. At 90 days age, myocardial necrosis in the CM hamster reaches maximum severity. Subsequently, cardiac remodeling develops (150-180 days). Lercanidipine was administered in the late transition phase in which irreversible tissue myolysis, necrosis and fibrosis lead to a final stage of depressed myocardial performance and heart failure. On the other hand, no data are currently available of the effects of 1,4-DHPs administered in the late transition phase of CHF. It remains to be demonstrated that calcium channel blockers that exert cardioprotective actions in the early development stages of cardiomyopathy will be effective in the transition to heart failure.

Another interesting finding of the present study is that lercanidipine did not deteriorate myocardial capillary density of papillary muscle. Interestingly, this contrasts with the recently-reported negative impact of another calcium channel blocker, mibefradil, on capillary density during the transition to heart failure in the same model of dilated cardiomyopathy[13]. Although this aspect is particularly attractive in view of the suspected contribution of repetitive ischemic episodes and coronary vasospasms to the development of the disease[14], the role of calcium channel blockers in the maintenance of adequate capillarization in the presence of myocardial remodeling has not been thoroughly investigated. Previous experiments have reported improvement in capillary density with other dihydropyridines[15,16], but none has addressed the critical transition phase to heart failure. The maintenance of normal capillary density reported in the present study,

compared with the significant reduction associated with mibefradil, suggests that lercanidipine's properties, ie, lipophilicity, vasoselectivity and high membrane partition coefficient, may play a role in such differences.

Limitations of the study The results can not be directly extrapolated to all clinical situations since the UM-X7.1 CM hamster does not correspond to all pathological situations leading to heart failure. Secondly, some data were collected in isolated heart preparations, an experimental model that does not take into account the possible interaction of circulating elements or neurohormones on coronary reactivity. However, this experimental model offers some advantages, since a direct effect on coronary reactivity can be determined adequately.

In conclusion, a 4-month treatment period with lercanidipine in UM-X7.1 CM hamsters during the transition phase to heart failure resulted in a beneficial impact on altered coronary reactivity and myocardial capillary density. These observations suggest that during the transition to heart failure, lercanidipine, a novel lipophilic and vasoselective dihydropyridine calcium channel blocker, exerts a beneficial action on the coronary compartment in a model of dilated cardiomyopathy.

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