Reactivity to endothelium-dependent and -independent vasoactive substances is maintained in coronary resistance vessels of the failing hamster heart

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Received 7 March 1996; accepted 23 October 1996

Abstract

Objectives: Several studies suggest that regulation of coronary vasomotion is abnormal in heart failure, but controversies exist as to whether an altered endothelium-dependent dilation of the coronary vasculature contributes to these abnormalities. In the present study we evaluated the coronary reactivity to endothelium-dependent and -independent vasoactive substances in a model of chronic heart failure.

Methods: Isolated hearts from > 200-day-old cardiomyopathic hamsters (UM-X7.1) and age-matched normal Syrian hamsters were mounted on a Langendorff apparatus and retrogradely perfused at constant pressure (100 mmHg). Heart rate, left ventricular developed pressure (LVP) and coronary flow (CF) were measured. A first group of normal and failing hearts were challenged with increasing doses of acetylcholine (Ach), 1–1000 nM, and sodium nitroprusside (SNP), 0.01–10 μM. A second group was challenged with Ach (100 nM) and SNP (1 μM) before and during infusion of the NO synthase inhibitor, N^G^-nitro-L-arginine methyl ester (L-NAME). Finally, normal and failing hearts were challenged with Ach (100 nM) before and during infusion of indomethacin (10 μM) or tetraethylammonium (1 nM).

Results: Myocardial contractility and coronary flow were significantly impaired in failing hearts (LVP = 32 ± 5 vs. 50 ± 4 mmHg in normal hearts; CF = 4.7 ± 0.6 vs. 6.7 ± 0.6 ml/min in normal hearts). Coronary flow increases with increasing doses of Ach (EC_{50} = 84 ± 15 nM for failing hearts and 100 ± 3 nM for normal hearts, P = ns). At concentrations exceeding the EC_{50}, failing hearts were more sensitive to the coronary dilator effects of Ach. The reduction in coronary flow elicited by L-NAME was similar in normal (-41 ± 2%) and failing hearts (-40 ± 3%), in both normal and failing hearts, the acetylcholine vasodilator response was not significantly affected by L-NAME. Indomethacin infusion resulted in a slight increase in coronary flow and significantly reduced the coronary dilator effects of acetylcholine. Tetraethylammonium had no significant effects on basal coronary perfusion of normal and failing hearts. However, in the latter group, acetylcholine vasodilator response was significantly attenuated. Conclusion: Results obtained in isolated failing hamster hearts allow us to conclude that (1) significant coronary dysfunctions are present in this model of chronic heart failure, (2) neither the NO-synthase nor the cyclo-oxygenase pathway contributes to these coronary dysfunctions, and (3) an adequate coronary vasodilator response appears to be present in this model of chronic heart failure.

Keywords: Heart failure; Coronary blood flow; Endothelium; Acetylcholine; L-NAME; Indomethacin; Nitrates; Tetraethylammonium

1. Introduction

Several studies have suggested that regulation of coronary vasomotion is abnormal in heart failure. A reduced basal coronary perfusion along with coronary vasospasm have been reported in patients with chronic heart failure [1–4]. In experimental models of heart failure, a reduced myocardial endo/epi blood flow ratio suggests a compromised subendocardial coronary supply in this condition [5,6] and reduction in basal coronary perfusion has been consistently reported in isolated failing cardiomyopathic hamster hearts [7,8]. In addition, coronary flow reserve has been shown to be depressed in response to dipyridamole and adenosine and blunted reactive hyperemic responses to brief coronary artery occlusion have been documented in this condition [5,6,9,10].

Although defective endothelial function might contribute to the pathogenesis as well as to the progression and complications of coronary artery disease [11], contro-
versities exist as to whether an altered endothelium-dependent dilation of the coronary vasculature develops in the presence of heart failure. While some studies suggested that coronary endothelium-dependent response is attenuated [12,13], other investigations reported no change or even an increased endothelium-dependent dilator response [14–16]. Such discrepancies might be related to differences in the model of heart failure (acute vs. chronic), to differences in the experimental preparation used (ex vivo vs. in vivo), to differences in vessel sensitivity (conductance vs. resistance vessels), or to regional differences in endothelial function (coronary and peripheral vessels). Since few studies deal with the reactivity of coronary resistance vessels in a model of chronic heart failure, we investigated their reactivity to various vasoactive substances with either endothelium-dependent or -independent mechanisms. Experiments were performed in normal and failing isolated hearts (cardiomyopathic hamsters, UM-X7.1 strain, > 200-day-old). The nitric-oxide synthase inhibitor L-NAME, the cyclo-oxygenase inhibitor indomethacin, the K⁺ channel blocker tetraethylammonium, acetylcholine and sodium nitroprusside were used to study coronary reactivity.

2. Methods

2.1. Experimental model

In the present study, UM-X7.1 cardiomyopathic hamsters [17], > 200-day-old and age-matched normal Syrian hamsters (LVG, Charles River Canada Inc., St-Constant, Que., Canada) were used. Animals were cared for in accordance with the guidelines of the Canadian Council on Animal Care [18]. Animals had free access to Purina laboratory chow and tap water.

2.2. Isolated heart preparation

Following decerebration, the chest was opened, the heart was exposed, cooled and cannulated in situ via the aorta for retrograde perfusion. The heart was then excised, mounted on a perfusion system and perfused using a modified Krebs-Ringer buffer consisting (in mM) of 119 NaCl, 4.8 KCl, 1.3 CaCl₂, 1.2 KH₂PO₄, 1.2 MgSO₄, 25 NaHCO₃, and 15 glucose. The buffer was saturated with a gas mixture (95% O₂ and 5% CO₂) and kept at 37°C and pH 7.4. The perfusion pressure was kept constant at 100 mmHg. All hearts were kept at 37°C throughout the study by placing them in a temperature-controlled chamber. Coronary flow (CF) was monitored continuously with an ultrasonic flow probe connected to a flowmeter (Model T201, Transonic Systems Inc., Ithaca, NY, USA) placed in the perfusion line upstream to the heart. Left ventricular systolic and diastolic pressures were obtained by a saline-filled latex balloon inserted in the left ventricle via the atriun and connected to a pressure transducer (Model P23AC, Statham Instruments Inc., Hato Rey, Puerto Rico). The balloon volume was adjusted to maintain a diastolic pressure of 10 mmHg and this volume was kept constant for the duration of the experiment. Left ventricular developed pressure (LVP) was computed as systolic minus diastolic left ventricular pressure and expressed in mmHg. Heart rate was allowed to change spontaneously and was calculated from the pressure tracing. All physiological measurements were registered on a multichannel recorder (Polygraph Model 5D, Grass Instruments, Quincy, MA, USA).

2.3. Experimental protocols

After a stabilization period of 25–30 min, baseline values of heart rate, LVP and coronary flow were recorded. In the first set of experiments, normal and failing hearts (n = 10 per group) were challenged with increasing doses of acetylcholine (1, 5, 10, 50, 100, 500, 1000 nM) and sodium nitroprusside (0.01, 0.05, 0.1, 0.5, 1.0, 5.0 and 10 μM) in order to determine their EC₅₀. For acetylcholine and nitroprusside, given as 2 min infusion, peak coronary dilator response was used for comparison. In the second set of experiments, normal and failing hearts (n = 10 per group) were challenged with a 20 min infusion of the nitric oxide synthase inhibitor, N²-nitro-L-arginine methyl ester (L-NAME), 30 μM. The concentration of L-NAME (30 μM) was selected on the basis of previous studies and preliminary experiments from this laboratory indicating a stable and maximal vasoconstriction at this dose [19]. In the latter group, a challenge with acetylcholine (100 nM) and sodium nitroprusside (1 μM), given as 2 min infusion, was carried out following 15 min exposure to L-NAME. In a third set of experiments, normal and failing hearts were challenged with indomethacin (10 μM for 20 min) or tetraethylammonium (1 mM infusion for 20 min). Acetylcholine infusion (100 nM) was added following exposure to indomethacin (15 min) or tetraethylammonium (10 min). The concentration of indomethacin used has been shown to inhibit cyclo-oxygenase activity [20,21]. Tetraethylammonium concentration was selected from previous studies [22,23].

2.4. Statistical analysis

Data in Tables and Figures are expressed as means ± s.e.m. Differences between groups were assessed using the analysis of variance (ANOVA) and the Student t-test for paired or unpaired data according to the statistical comparison. Correction for multiple comparisons was made when appropriate. Differences were considered significant at P < 0.05.

2.5. Drugs

Acetylcholine bromide, L-NAME, indomethacin and tetraethylammonium were purchased from Sigma Chemical Co. (St Louis, MO, USA). Sodium nitroprusside (Nipride) was obtained from Hoffmann-La Roche (Mississauga, Ont., Canada) and PGF₂α (Prostin) from The Upjohn Company (Montreal, Que., Canada). Stock solutions were prepared
for L-NAME, indomethacin and tetraethylammonium and kept refrigerated. All other solutions and dilutions were prepared daily. Solutions were infused via a side-arm of the aortic cannula at 1/100th of the coronary flow and concentrations are expressed as final molar concentrations detailed in the paper.

3. Results

Normal control hamsters, > 200-day-old, had a mean body weight of 181 ± 5 g whereas cardiomyopathic ham-

### Table 1
Baseline hemodynamics from normal and failing hamster hearts

<table>
<thead>
<tr>
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<th>Normal hearts</th>
<th>Failing hearts</th>
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</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>154 ± 20</td>
<td>164 ± 12</td>
</tr>
<tr>
<td>Left ventricular pressure (mmHg)</td>
<td>50 ± 4</td>
<td>32 ± 5 *</td>
</tr>
<tr>
<td>Coronary flow (ml/min)</td>
<td>6.7 ± 0.6</td>
<td>4.7 ± 0.6 *</td>
</tr>
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Mean ± SEM (9–10 isolated hearts per group).
* P < 0.05 vs. normal hearts.

### Table 2
Chronotropic and inotropic effects of acetylcholine and sodium nitroprusside in normal and failing hearts

<table>
<thead>
<tr>
<th></th>
<th>Normal hearts</th>
<th>Failing hearts</th>
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<tbody>
<tr>
<td><strong>Acetylcholine (ACh)</strong></td>
<td></td>
<td></td>
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<tr>
<td>Heart rate (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACh 50 nM</td>
<td>8 ± 13 *</td>
<td>-2 ± 5</td>
</tr>
<tr>
<td>ACh 100 nM</td>
<td>-3 ± 3</td>
<td>-13 ± 6</td>
</tr>
<tr>
<td>ACh 500 nM</td>
<td>-30 ± 13 *</td>
<td>-35 ± 12 *</td>
</tr>
<tr>
<td>LVP (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACh 50 nM</td>
<td>-13 ± 6</td>
<td>-4 ± 4</td>
</tr>
<tr>
<td>ACh 100 nM</td>
<td>18 ± 5 *</td>
<td>6 ± 4</td>
</tr>
<tr>
<td>ACh 500 nM</td>
<td>-17 ± 12</td>
<td>-1 ± 11</td>
</tr>
</tbody>
</table>

**Sodium nitroprusside (SNP)**

<table>
<thead>
<tr>
<th>Heart rate (%)</th>
<th>Normal hearts</th>
<th>Failing hearts</th>
</tr>
</thead>
<tbody>
<tr>
<td>SNP 0.5 µM</td>
<td>0.2 ± 4</td>
<td>-3 ± 7</td>
</tr>
<tr>
<td>SNP 1.0 µM</td>
<td>-0.3 ± 6</td>
<td>5 ± 7</td>
</tr>
<tr>
<td>SNP 5.0 µM</td>
<td>-1.5 ± 10</td>
<td>6 ± 12</td>
</tr>
<tr>
<td>LVP (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SNP 0.5 µM</td>
<td>16 ± 6</td>
<td>16 ± 7</td>
</tr>
<tr>
<td>SNP 1.0 µM</td>
<td>17 ± 6</td>
<td>20 ± 6</td>
</tr>
<tr>
<td>SNP 5.0 µM</td>
<td>24 ± 7</td>
<td>36 ± 10 *</td>
</tr>
</tbody>
</table>

* Mean ± s.e.m. (8–10 isolated hearts per group). Data are expressed as percent change from baseline before drug administration. Doses of ACh and SNP represent the EC_{50}, EC_{75} and EC_{90} computed from the dose–response curve of their coronary dilator effects.

* P < 0.05 vs. pre-drug administration within each group.
sters had a significantly lower body weight (136 ± 4 g). At autopsy, all cardiomyopathic hamsters showed evidence of severe heart failure: pulmonary and liver congestion, peripheral edema. Cardiac hypertrophy expressed as heart weight (mg)/body weight (g) was present in all cardiomyopathic hamsters (ratio of heart weight/body weight = 4.61 ± 0.16 in cardiomyopathic hamsters as compared to a ratio of 3.98 ± 0.2 for normal hamsters, P < 0.05). Baseline values of heart rate, left ventricular developed pressure and coronary flow from normal and failing hearts are shown in Table 1. A significant reduction of left ventricular pressure and coronary perfusion was observed in failing hearts.

3.1. Coronary and cardiac effects of acetylcholine and sodium nitroprusside

A typical recording of the effects of a 2 min infusion of acetylcholine on left ventricular pressure and coronary flow, obtained in a normal heart, is shown in Fig. 1A. Within seconds a transient rise in coronary flow was followed by a rapid return towards baseline values while LVP was only slightly affected. Peak coronary dilator response to increasing doses of acetylcholine was measured in normal and failing hearts (Fig. 2A). The computed EC_{50} was similar in normal and failing hearts (100 ± 3 and 84 ± 15 nM, respectively) while, at concentrations exceeding the EC_{50}, failing hearts were more sensitive to the vasodilator effects of acetylcholine. Chronotropic and inotropic effects of acetylcholine using the computed EC_{25}, EC_{50} and EC_{75} of its coronary dilator actions are presented in Table 2. Negative chronotropic effects were observed at high doses only, with no significant difference between normal and failing hearts.

A typical recording of sodium-nitroprusside-induced cardiac and coronary effects, observed in an isolated normal heart, is illustrated in Fig. 1B. A 2 min infusion of sodium nitroprusside elicited a rapid and stable increase in coronary flow. The coronary dilator effects of increasing doses of sodium nitroprusside are illustrated in Fig. 2B. Sodium nitroprusside-induced coronary dilation was similar in normal and failing hearts at all doses studied. The chronotropic and inotropic effects of sodium nitroprusside using doses corresponding to the EC_{25}, EC_{50} and EC_{75} of its coronary dilator effects are shown in Table 2. LVP was increased in normal and failing hearts at high dose only.

3.2. Effects of L-NAME

Effects of 30 μM infusion of L-NAME are shown in Fig. 3A. L-NAME induced a gradual reduction in coronary flow.

![Figure 3](image-url)

Fig. 3. Effects of L-NAME (panel A) and indomethacin (panel B) on coronary flow in normal and failing hearts. Data are expressed as percent change (Δ%) from baseline (mean±s.e.m.). ACh = acetylcholine; SNP = sodium nitroprusside.
flow that stabilized within 10 min. This reduction in coronary flow was similar in normal (−41 ± 2%) and failing hearts (−40 ± 3%). Fig. 4A illustrates the effects of L-NAME on the coronary dilator action of acetylcholine (100 nM, 2 min infusion). In both normal and failing hearts, the acetylcholine response was not significantly affected by L-NAME. The interaction between L-NAME and sodium nitroprusside is illustrated in Fig. 4B. In the presence of L-NAME, sodium nitroprusside-induced coronary dilation was significantly increased in both normal (298 ± 40%) and failing hearts (238 ± 30%).

3.3. Effects of indomethacin

The effects of indomethacin on coronary flow are shown in Fig. 3B. In normal and failing hearts, indomethacin resulted in a slight but significant increase in coronary flow (13–15%). Fig. 5A illustrates the effects of indomethacin on acetylcholine-induced coronary dilation: in the presence of indomethacin, the acetylcholine-induced increase in coronary flow was significantly attenuated in normal and failing hearts.

3.4. Effects of tetraethylammonium (TEA)

Ten minutes infusion of TEA (1 mM) did not significantly modify basal coronary perfusion except for a transient but significant reduction in normal hearts (peak reduction = 27%; time to peak = 44 s; duration = 30–60 s). In the presence of 1 mM TEA, the vasodilator action of acetylcholine was significantly attenuated in failing hearts (Fig. 5B). However, in normal hearts, the acetylcholine-induced increase in coronary flow was not significantly affected by TEA.

4. Discussion

Basal coronary perfusion appears to be significantly impaired in the failing hamster heart. Experiments carried out in the presence of L-NAME elicited a similar reduction in coronary flow in normal and failing hearts, suggesting that basal coronary NO production is normal in the latter group. Failing hearts appear to be more sensitive to the dilator effects of acetylcholine which were not modified by L-NAME. Indomethacin elicited a slight increase in coronary flow and significantly attenuated acetylcholine-induced coronary dilation. Tetraethylammonium did not change the basal coronary perfusion but significantly reduced the vasodilator effect of acetylcholine in failing hearts. These results suggest that reactivity to endothelium-dependent and -independent vasoactive substances is maintained in coronary resistance vessels of the failing hamster heart despite the presence of significant coronary dysfunction.

The cardiomyopathic hamster is an accepted model of development of chronic heart failure, useful for the study of subcellular pathological processes and the evaluation of drug efficacy [24,25]. In the UM-X7.1 strain of cardiomyopathic hamster, myocardial lesions lead to cardiac hypertrophy, and heart failure begins at 190–200 days of age [26]. Genetic defects of membrane structure and function, intracellular calcium overload, increased adrenergic tone, microvascular spasms, excess free radical production and lipid peroxidation are considered contributing factors to the development of the disease [27–29].

Isolated heart preparations from this model of chronic heart failure have been used to determine, at different stages of the disease, myocardial contractile abnormalities as well as to evaluate the effects of drugs on cardiac performance [7]. Although alterations of the coronary vasculature might influence the progression of the disease, relatively few studies have focused on the coronary perfusion changes in this model of heart failure. Studies using cytochemistry or coronary perfusion with liquid silicone rubber techniques have disclosed numerous areas of microvascular constriction, diffuse vessel narrowing and luminal irregularities in the diseased heart [30]. Besides ours,
other studies have also reported a reduction of coronary flow in failing CMH hearts [7,8]. Although the origin of these coronary dysfunctions has been poorly explored, the reactivity of other vascular beds has been investigated. An increased vasoconstrictive responsiveness of cremaster muscle arterioles to norepinephrine and 5-hydroxytryptamine has been observed in cardiomyopathic hamsters during the active stage of necrosis [31]. Similarly, heightened vasoconstrictive responsiveness to arginine-vasopressin has been observed in the coronary vasculature of young cardiomyopathic hamsters [32]. Recently, an increased release of nitric oxide in response to norepinephrine and acetylcholine and an enhanced sensitivity to endothelin-1 have been observed in conduit arteries of 1-year-old cardiomyopathic hamsters [33]. Since the failing hamster heart resembles the failing human heart in its biochemical, mechanical and vascular dysfunctions, this model would seem suitable for the assessment of coronary reactivity to vasoactive substances.

Several lines of evidence suggest that regulation of coronary vasomotion is abnormal in heart failure. Some studies have reported that in patients with chronic heart failure, an altered coronary perfusion is present [2–4]. In experimental models of heart failure, a reduced myocardial endo/epi blood flow ratio suggests a compromised subendocardial coronary supply in this condition [5,6]. In isolated failing CMH hearts, basal coronary perfusion is significantly reduced [7,8]. Furthermore, coronary reactivity has been shown to be altered in this condition [6,9,10]. The contribution of an altered reactivity to vasoactive substances to these vascular dysfunctions remains to be determined.

In the present study, the NO-mediated control of coronary perfusion was estimated by the use of the specific NO-synthase inhibitor, L-NAME. Results indicate that L-NAME reduces coronary flow in normal and failing hearts, suggesting that NO significantly contributes to the coronary vascular tone in both conditions. The fact that the L-NAME-induced reduction in coronary perfusion was of the same magnitude in normal and failing hearts indicates that the coronary dysfunctions observed in the latter group does not originate from an altered activation of the NO-synthase pathway. Although some studies have reported a reduced basal NO production in the presence of heart failure [34,35], our results are consistent with other experimental data suggesting that basal production of NO is preserved or even increased in the presence of heart failure [36]. These discrepancies might be related to differences in experimental models, to differences in vessel sensitivity (conductance vs. resistance vessels) or to regional vascular differences in endothelial function.

In heart failure, the role played by cyclo-oxygenase by-products in the maintenance of vascular tone remains controversial [13,37]. The use of the specific cyclo-oxygenase inhibitor, indomethacin, allows us to determine the contribution of the cyclo-oxygenase pathway in the control of coronary resistance vessel tone. In the presence of indomethacin, we observed a slight increase in coronary flow that was similar in normal and failing hearts. Other studies reported a slight contribution of prostanoids to the control of coronary vascular tone. O'Murchu et al. [16], using isolated coronary rings from dogs with normal cardiac function and pacing-induced congestive heart failure, reported that indomethacin elicited only a slight change in resting tension (10%). In other studies, performed in isolated rat hearts, indomethacin had no significant effect on resting coronary perfusion pressure [20,21]. Although our data suggest the presence of some vasoconstrictor derivatives of the cyclo-oxygenase pathway that modulate to a certain extent basal coronary tone, the coronary dysfunction observed in the failing hamster heart does not appear to be mediated by alterations of this pathway.

Acetylcholine, through muscarinic receptor stimulation, induces endothelium-dependent vasodilation. This vascular response appears to be mediated by several mechanisms including the release of nitric oxide, the production of vasodilator prostaglandins or the release of a hyperpolarizing factor [38,39]. Conflicting results have been published regarding the acetylcholine-induced coronary response in the presence of heart failure. Wang et al. [13] reported reduced coronary dilation to acetylcholine in dogs with pacing-induced heart failure. In patients with dilated cardiomyopathy and depressed cardiac function, a reduced coronary dilator response to acetylcholine has also been reported [10,12]. Conversely, in isolated coronary artery rings from dogs with pacing-induced congestive heart failure, Main et al. [14] reported a maintained vasodilator response to acetylcholine. In a recent study, the threshold for relaxation with acetylcholine occurs at significantly lower concentrations in the presence of heart failure [16]. In the present study, the acetylcholine-induced increase in coronary flow was maintained in failing hearts. Indeed, at concentrations exceeding its EC50 ($>100$ nM), the acetylcholine response was more important in the failing hearts. This upregulation of acetylcholine-induced coronary flow increase may therefore compensate for the coronary vasoconstriction present in this model of chronic heart failure.

According to the present study, NO-synthase activity does not appear to be a major contributor to the acetylcholine-induced coronary response since pre-treatment with L-NAME did not alter its response. On the contrary, cyclo-oxygenase by-products appear to modulate the coronary flow increase elicited by acetylcholine as demonstrated by the significant inhibitory effect of indomethacin. In addition, EDHF seems to be somewhat implicated in this response since tetraethylammonium significantly inhibited acetylcholine-induced increase in coronary flow in the failing group. Apart form these mechanisms it appears that, in the hamster heart, acetylcholine-induced coronary dilation is mediated by several factors that are influenced by the presence of the disease. Although the observed upregulated acetylcholine vascular effects must be related
to a preserved endothelium-dependent response, our data
could not specifically point to any unaltered receptor-
stimulated NO production and/or release in the failing
hamster heart.

Nitroprusside is known to induce smooth muscle relaxation
through activation of soluble guanylate cyclase with
subsequent cGMP-dependent protein phosphorylation. The
sodium nitroprusside dose–response curve resulted in a
similar EC50 and maximal dilation in normal and failing
hearts, suggesting that cGMP activation of coronary smooth
muscle is not altered in this model of chronic heart failure.

Previous studies have also suggested that endothelium-in-
dependent dilation of large conductance coronary arteries
was not altered in heart failure [14]. The coronary vasodila-
tor action of sodium nitroprusside was surprisingly potenti-
ated in the presence of L-NAME. Since this effect was of
similar amplitude in normal and failing hearts, we must rule
out the contribution of the underlying pathology (heart
failure). The increased response to sodium nitroprusside
may be a nonspecific consequence of a reduced coronary perfusion in the presence of L-NAME. However, the sodium nitroprusside-induced increase in coronary flow was similar in the presence of the vasoconstrictor PGF2α (data not shown). One possibility is that L-NAME, by reducing NO-synthase activity, limits the activation of smooth muscle cGMP by endogenous NO but renders it more sensitive to exogenous NO derived from sodium nitroprusside. Indeed, increased sensitivity to nitrovas-
odilators after treatment with NO-synthase inhibitors has been previously reported in isolated vascular tissues [40,41]. Similar potentiation has also been reported in vivo. Weldon et al. [42] reported that L-NAME potentiates the vascular effects of sodium nitroprusside in conscious Cynomolgus primates.

Since the reduction in basal coronary flow observed in failing hamster hearts could modulate the increased response observed with acetylcholine, we undertook a series of experiments where normal hearts were exposed to the vasoconstrictor, PGF2α. Pre-exposure to infusion of PGF2α (100 nM) resulted in a significant reduction in coronary flow (5.3 ± 0.4 vs. 7.2 ± 0.6 ml/min under control condi-
tions). Under these conditions that mimic the basal reduc-
tion of coronary flow documented in failing hamster hearts, the acetylcholine-induced increase in coronary flow was not modified significantly (28 ± 6% in the presence of PGF2α vs. 54 ± 6% under control conditions). Therefore, it seems that the increase in basal vascular tone observed in failing hearts does not contribute to the increased vasodilator response in the presence of acetylcholine.

The results obtained in isolated hamster hearts let us to conclude that: (1) significant coronary dysfunctions are present in this model of chronic heart failure; (2) neither the NO-synthase nor the cyclooxygenase pathway contributes to these coronary dysfunctions; (3) an adequate vasodilator response whether endothelium-dependent or not is present in the failing hamster heart.

Acknowledgements

This study was supported by a grant from la Fondation Québécoise des Maladies du Coeur (FQMC). We thank Mrs. Elizabeth Pérès for art illustration and Mr. Florine Sasaran for technical assistance.

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