Increased extravascular forces limit endothelium-dependent and -independent coronary vasodilation in congestive heart failure

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Abstract

Objective: The increase in coronary blood flow (CBF) in response to endothelium-dependent vasodilators is reduced in congestive heart failure (CHF) suggesting endothelial dysfunction. However, increases in extravascular compressive forces secondary to elevated left ventricular diastolic pressure (LVEDP) in CHF might contribute to this abnormality. Methods: We measured CBF responses to intracoronary doses of the endothelium-dependent vasodilators acetylcholine (ACH) and bradykinin (BK) and the endothelium-independent vasodilator sodium nitroprusside (SNP) in the same eight dogs before (control) and after CHF was produced by 23±3 days of rapid ventricular pacing. In five of the dogs with CHF the zero-flow pressure (P₀), which reflects extravascular compressive forces in the maximally vasodilated coronary circulation (adenosine) was measured and found to strongly correlate with LVEDP (r=0.91). Coronary vascular resistance (CVR) at each concentration of vasodilator before and after the development of CHF was corrected for estimated coronary back pressure: CVR=(P_m−LVEDP)/CBF, where P_m is mean aortic pressure. Results: CHF resulted in a significant decrease in CBF and increase in heart rate and LVEDP compared to control (P<0.05). The CBF responses to ACH, BK and SNP were all significantly reduced in the failing hearts (P<0.01). However, after correction for the elevated LVEDP in CHF, the response of CVR to the endothelium-dependent vasodilators was not different from normal. Conclusion: These findings suggest that endothelium mediated vasodilation is preserved in CHF, but that increased extravascular compressive forces act to limit the increase in CBF. © 2001 Elsevier Science B.V. All rights reserved.

Keywords: Coronary circulation; Endothelial function; Heart failure; Nitric oxide; Vasoconstriction/dilation

1. Introduction

Previous studies in patients and animals with congestive heart failure (CHF) have demonstrated abnormally increased vasomotor tone in the coronary circulation during basal conditions and a blunted increase in coronary blood flow in response to cardiac pacing [1,2], exercise [3] and infusion of vasodilators [4]. This abnormality has been ascribed to a variety of alterations that occur in CHF including heightened sympathetic tone [5], increased production of vasoconstrictors such as endothelin-1 [6] and impaired endothelial production of nitric oxide (NO) and other endogenous vasodilators [4]. In addition, CHF is accompanied by hemodynamic changes that might adversely affect myocardial perfusion and which could blunt the increase in coronary blood flow in response to vasodilator stimuli. Thus, the decrease in aortic pressure and increase in left-ventricular diastolic pressure (LVEDP) with progressive heart failure causes a decrease in the net perfusion pressure across the coronary circulation. The increase in left ventricular filling pressure may be especially important, since in the normal heart this variable is...
strongly correlated with the effective intramyocardial compressive forces that act to impede coronary blood flow [7,8].

To account for the effects of extravascular forces, we determined zero-flow pressure (P_{z0}) in the maximally vasodilated failing heart as an index of the effective back pressure opposing coronary perfusion [8]. This variable was found to be strongly correlated with LVEDP. When calculations of coronary vascular resistance (CVR) in response to the intracoronary vasodilators were corrected by subtracting LVEDP from aortic pressure, we observed that although the coronary flow responses to the vasodilators were reduced in CHF, vascular reactivity as assessed by the reductions in CVR were similar in normal and failing hearts. These findings demonstrate that the endothelium remains responsive to endothelium-dependent vasodilators in CHF, but that increased extravascular compressive forces act to limit the increase in coronary blood flow.

2. Methods

Studies were carried out in eight adult mongrel dogs weighing 25–30 kg. All studies were performed in accordance with the Position of the American Heart Association on Research Animal Use and were approved by the Animal Care Committee of the University of Minnesota.

2.1. Surgical preparation

Animals were premedicated with acepromazine (10 mg, i.m.), anesthetized with sodium pentobarbital (30–35 mg/kg, i.v.), intubated and ventilated with room air supplemented with oxygen. A left thoracotomy was performed in the fifth intercostal space. A heparin-filled polyvinyl catheter, 3.0 mm O.D. was introduced into the internal thoracic artery and advanced until the tip was positioned in the ascending aorta. The pericardium was opened and the heart suspended in a pericardial cradle. A left ventricular catheter and high-fidelity Konigsberg micromanometer were introduced through the apical dimple and secured in place. The proximal left-anterior descending coronary artery (LAD) was dissected free and a hydraulic occluder and Doppler velocity probe (Craig Hartley, Houston, TX, USA) were placed around the vessel. A heparin-filled silicone rubber catheter (0.3 mm I.D.) was placed into the artery immediately distal to the Doppler probe [9]. In three of the animals a hydraulic occluder was not implanted because of insufficient length of the LAD artery. A unipolar epicardial pacing electrode was screwed into the right ventricle. The pericardium was loosely closed and the catheters and electrical leads were tunneled subcutaneously to exit at the base of the neck. The thoracotomy was closed in layers and evacuated of air. A programmable pacing generator (Medtronic no. 5385, Minneapolis, MN, USA) was placed in a subcutaneous pocket in the lateral chest wall and connected to the pacing lead. Postoperative pain relief was achieved using buprenorphine (6.6 μg/kg/i.m. q. 4 h) for the first 24 h postoperatively and then p.r.n. as needed for relief of discomfort. Catheters were flushed daily to maintain patency.

2.2. Coronary blood flow responses in the normal heart

One week after surgery the animals were returned to the laboratory and placed in a sling for control measurements of coronary flow responses to the endothelium-dependent agonists acetylcholine chloride (ACH, Sigma, St. Louis, MO, USA) and bradykinin acetate (BK, Sigma) and the endothelium-independent agonist sodium nitroprusside (SNP). Aortic and left ventricular pressures were measured with fluid-filled pressure transducers (Spectramed model TNF-R) at midchest level. The LV solid state micromanometer was calibrated to the fluid-filled LV catheter and pressure was recorded at normal and high gain for measurement of LVEDP. Data were recorded on an eight-channel direct writing recorder. After a 30-min period of acclimatization to the sling, baseline hemodynamics and coronary blood flow were recorded. ACH dissolved in normal saline was infused through the LAD coronary catheter at rates of 1.5, 3.75, 7.5, 15, 37.5 and 75 μg/min (infusion rates between 0.6 and 3.0 ml/min). Coronary blood flow was recorded continuously and individual measurements at each dose of ACH were taken after blood flow had achieved a steady state (generally within 10–15 s of beginning the infusion). Infusion rates were increased at approximately 1-min intervals. Normal saline was infused at the same rate to determine the effects of vehicle on coronary blood flow. Fifteen minutes later BK dissolved in normal saline was infused through the coronary catheter in a similar manner at rates of 0.3, 0.6, 1.5, 3.0 and 6.0 μg/min. Following completion of the BK infusions, the endothelium-independent agonist SNP was infused at rates of 7.5, 15, 37.5 and 75 μg/min.

2.3. Coronary blood flow responses in the failing heart

The day after completion of the baseline studies the programmable pacemaker was activated at 220 beats/min and was continued at that rate or increased to 250 beats/min if evidence of CHF did not occur after 3 weeks of pacing. Hemodynamics were assessed weekly during sinus rhythm with the dogs standing quietly in a sling 1 h after the pacemaker had been deactivated. CHF was deemed to have developed when the resting LVEDP was greater than 20 mmHg or when the visual estimation of ejection fraction by echocardiography was <25%. The duration of pacing ranged from 14 to 39 (mean = 23±3) days.

On the day of study the pacemaker was deactivated and
the dogs were placed in a sling. The catheters and flow probe were reconnected and resting measurements of hemodynamics and blood flow were obtained 1 h after pacemaker deactivation. The coronary flow responses to ACH, BK and SNP were then repeated as previously described.

2.4. Measurement of zero-flow pressure ($P_{zf}$)

On a separate day measurement of zero-flow pressure to estimate the effective back pressure to coronary perfusion as a surrogate of extravascular compressive forces was performed in the five dogs with CHF in which an arterial occluder had been implanted. The animals were placed in a sling and aortic, LV and coronary pressures were measured as described above. Adenosine (50 $\mu$g/kg/min) dissolved in warm saline was infused into the coronary catheter at a rate of 0.3 ml/min throughout the study. This dose was sufficient to produce maximal vasodilation as evidenced by the absence of reactive hyperemia following a 15-s coronary occlusion. While the adenosine infusion continued, the LAD hydraulic occluder was inflated with saline using a micrometer-driven syringe to create a complete coronary occlusion. Absence of coronary flow was confirmed by the flowmeter signal. The zero flow pressure was recorded by briefly switching the stopcock on the infusion line to the pressure transducer. Interruption of the adenosine infusion never exceeded 15 s. In three of the dogs the occluder was partially inflated to produce 10–15 separate measurements over a range of coronary pressure and flow to construct a full pressure-flow plot. At each measurement the occluder was inflated for approximately 10 s to permit equilibration of pressure and flow and then completely deflated to restore normal arterial inflow. Individual measurements were made every 30 s.

2.5. Data analysis

Heart rate, pressures and coronary velocity were measured directly from strip chart recordings. Coronary blood flow was calculated from the Doppler frequency shift (kHz) using the equation $q = 2.5 \times d^2 \times f$, where $q$ is coronary blood flow in ml/min, $d$ is the internal diameter of the LAD in mm and $f$ is the Doppler frequency shift measured in kHz [10]. Based on our previous observations the internal diameter of the artery was taken as 80% of the flow probe diameter. Coronary vascular resistance (CVR) in the LAD artery distribution was calculated in normal hearts and after development of CHF at baseline and during each infusion, subtracting LVEDP (as a surrogate for $P_{zf}$) from aortic pressure to correct for the effective back pressure to coronary perfusion. Thus, CVR = ($P_{Ao}$ – LVEDP) / CBF, where $P_{Ao}$ is the mean arterial pressure. The concentration of agonists to which the vessels were exposed depended not only upon the rate of infusion, but also the coronary flow-rate into which the agonist was diluted. Consequently, the agonist infused ($\mu$g/min) was normalized to the coronary flow-rate in each animal before and after the development of CHF and expressed as an absolute blood concentration (Figs. 1–3).

Data were compared within and between Control and CHF groups by ANOVA for repeated measures; a value of $P<0.05$ was considered significant. When a significant result was found, individual comparisons were performed with the Wilcoxon signed-rank test. Data are expressed as mean±S.E.M.

Fig. 1. Changes in coronary blood flow (A) and coronary vascular resistance (B) in response to increasing intracoronary doses of the endothelium-dependent vasodilator acetylcholine in the same animals before and after the development of CHF. (A) Increases in coronary blood flow are significantly reduced in CHF compared to control ($P<0.01$). (B) Changes in coronary vascular resistance in CHF are similar to normal after normalizing CVR for differences in the back pressure to coronary perfusion ($P_{zf}$).
3. Results

3.1. Hemodynamics and coronary blood flow

The development of CHF following rapid ventricular pacing was associated with a decrease of mean aortic pressure from $115\pm3$ to $88\pm4$ mmHg; an increase of resting heart rate from $119\pm5$ to $141\pm11$ beats/min and an increase of LVEDP from $8\pm1$ to $25\pm2$ mmHg (all $P<0.05$) (Table 1). Resting coronary blood flow decreased from $58\pm5$ to $33\pm3$ ml/min ($P<0.05$).

3.2. Coronary blood flow responses to vasodilators

During control experiments, intracoronary ACH progressively increased CBF from $58\pm8$ ml/min at baseline to $130\pm11$ ml/min at the highest dose ($75 \mu g/min$) ($P<0.01$), with no significant change in systemic hemodynamics (Table 1 and Fig. 1). After the development of CHF, the same dose of ACH increased CBF only to $74\pm8$ ml/min ($P<0.05$ vs. Control). In a similar manner, BK progressively increased CBF from $60\pm5$ ml/min at baseline during control conditions to $129\pm9$ ml/min at the highest dose ($6 \mu g/min$) ($P<0.01$). Following the development of CHF, the same dose of BK increased CBF only to $84\pm11$ ml/min ($P<0.05$ vs. Control) (Table 1 and Fig. 2). In the normal hearts infusion of the endothelium-independent vasodilator SNP progressively increased CBF from $61\pm5$ to $110\pm6$ ml/min at a dose of $75 \mu g/min$ ($P<0.01$). The same dose of SNP also resulted in a...
smaller increase in CBF to a maximum of 64±5 ml/min in the failing hearts (P<0.05 vs. Control) (Table 1 and Fig. 3).

3.3. Coronary vascular resistance in response to vasodilators

Because of the increase in LVEDP in the failing hearts and its direct correlation with \( P_{st} \), coronary vascular resistance curves were constructed for each vasodilator incorporating LVEDP into the calculation to approximate the effective back pressure to coronary perfusion. In the same dogs baseline CVR was 1.99±0.29 mmHg/ml/min during control conditions and was 2.04±0.28 mmHg/ml/min after the development of CHF (Table 1). During infusion of ACH, CVR was decreased in both groups to similar values at the highest dose of 75 \( \mu \)g/min i.e. (0.83±0.09 vs. 0.76±0.06 mmHg/ml/min; \( P<0.01 \) vs. baseline, Fig. 1). Similarly, BK decreased CVR to a similar level at the highest dose (6 \( \mu \)g/min) to 0.85±0.09 during control conditions and to 0.87±0.09 mmHg/ml/min after the development of CHF (\( P<0.01 \) vs. baseline, Fig. 2). SNP decreased CVR in a dose-dependent manner in both normal (control) and CHF hearts. However, the fall in CVR to increasing doses of SNP was less in CHF than in normal hearts (\( P<0.05 \); Fig. 3).

3.4. Measurement of the zero-flow pressure during adenosine infusion

In the five dogs with a hydraulic coronary artery occluder, \( P_{zf} \) was measured during infusion of adenosine (50 \( \mu \)g/kg/min, i.c.) after the development of CHF. Before beginning the adenosine infusion mean aortic pressure was 93±4 mmHg, LVEDP was 28±4 mmHg, heart rate was 138±12 mmHg and CBF was 33±3 ml/min (Table 2). During intracoronary infusion of adenosine CBF increased to 96±12 ml/min (\( P<0.05 \)) but there was no significant change in the other hemodynamic variables. Fig. 4 shows the coronary pressure–flow relationship observed in one animal during control conditions and after the development of CHF. In this animal \( P_{st} \) increased from 12 mmHg during control conditions to 27 mmHg after development of CHF, while LVEDP increased from 13 to

### Table 1

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Acetylcholine (ACH) Low dose (1.5 ( \mu )g/min)</th>
<th>Acetylcholine (ACH) High dose (75 ( \mu )g/min)</th>
<th>Bradykinin (BK) Low dose (0.3 ( \mu )g/min)</th>
<th>Bradykinin (BK) High dose (6 ( \mu )g/min)</th>
<th>Sodium nitroprusside (SNP) Low dose (7.5 ( \mu )g/min)</th>
<th>Sodium nitroprusside (SNP) High dose (75 ( \mu )g/min)</th>
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</thead>
<tbody>
<tr>
<td>CBF (58±5 mHg)</td>
<td>CON</td>
<td>82±10</td>
<td>130±11</td>
<td>84±3</td>
<td>129±9</td>
<td>72±4</td>
<td>110±6</td>
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<tr>
<td>HR (119±5 beats/min)</td>
<td>CHF</td>
<td>48±11</td>
<td>74±38</td>
<td>41±31</td>
<td>84±11</td>
<td>39±41</td>
<td>64±51</td>
</tr>
<tr>
<td>( P_{ao} ) (115±3)</td>
<td>CON</td>
<td>119±5</td>
<td>127±13</td>
<td>127±8</td>
<td>90±6</td>
<td>115±6</td>
<td>104±3</td>
</tr>
<tr>
<td>LVEDP (8±1)</td>
<td>CON</td>
<td>8±1</td>
<td>112±4</td>
<td>112±4</td>
<td>112±4</td>
<td>8±1</td>
<td>9±2</td>
</tr>
<tr>
<td>CVR (1.99)</td>
<td>CHF</td>
<td>25±21</td>
<td>8±1</td>
<td>25±21</td>
<td>25±21</td>
<td>25±21</td>
<td>25±31</td>
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</table>

Abbreviations: CBF, coronary blood flow; HR, heart rate; \( P_{ao} \), mean aortic pressure; LVEDP, left ventricular end-diastolic pressure; CVR, coronary vascular resistance.

### Table 2

<table>
<thead>
<tr>
<th></th>
<th>( P_{ao} ) (mmHg)</th>
<th>HR (beats/min)</th>
<th>LV (mmHg)</th>
<th>LVEDP (mmHg)</th>
<th>CBF (ml/min)</th>
<th>( P_{zf} ) (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>93±4</td>
<td>138±12</td>
<td>112±7</td>
<td>28±4</td>
<td>33±3</td>
<td>–</td>
</tr>
<tr>
<td>Adenosine (50 ( \mu )g/kg/min)</td>
<td>91±7</td>
<td>132±9</td>
<td>110±9</td>
<td>28±4</td>
<td>96±12*</td>
<td>26±4</td>
</tr>
</tbody>
</table>

Abbreviations: CBF, coronary blood flow; HR, heart rate; \( P_{ao} \), mean aortic pressure; LVEDP, left ventricular end-diastolic pressure; \( P_{zf} \), zero flow pressure.

\* \( P<0.05 \) vs. Baseline.
investigators have observed that the increase of coronary resistance is determined not only by the responsiveness of the coronary vasodilator but also by the extravascular forces that accounted for when coronary resistance is calculated. However, the drugs were administered intravenously, producing substantial decreases of arterial pressure and increases of heart rate that might have influenced the results. In that studies [4] the oxidative products of NO (NOx) from isolated epicardial arteries and coronary microvessels were reduced in dogs with CHF during both basal and acetylcholine-stimulated conditions. In subsequent studies [14] these investigators found that the coronary arteriovenous production of NOx decreased during the development of CHF produced by rapid ventricular pacing, although the production of NOx to endothelium-dependent agonists was not measured.

4.2. Effect of extravascular compressive forces

Previous reports of coronary resistance in the failing heart have calculated vascular resistance as the ratio of arterial pressure (Ps) to CBF (Q), thus assuming that the coronary outflow pressure is negligible. This assumption neglects the contribution of the elevated LV diastolic intracavitary pressure to the extravascular compressive forces that act to impede blood flow in the myocardium. Permut and Reilly [15] demonstrated that true vascular resistance should be defined as (Ps − Pd)/Q, where Pd is the effective back pressure that results as extravascular compressive forces interact with the intravascular distending pressure in a collapsible segment of the vasculature to form vascular waterfalls. This phenomenon has been demonstrated to occur in the coronary circulation during both systole and diastole [7,8,16] so that coronary back pressure exceeds venous pressure measured in the coronary sinus or right atrium [17]. The effective back pressure to coronary perfusion can be experimentally estimated in the maximally vasodilated coronary circulation as the zero-flow pressure (Psf). In the normal heart, Ellis and Klocke [7] demonstrated that an increase in LVEDP from 6 to 16 mmHg caused an increase of the Psf from 12 to 19 mmHg, while Duncker et al. [18] observed that as the LVEDP increased from 20 mmHg at rest to 37.5 mmHg during exercise in dogs with left ventricular hypertrophy, the Psf increased from 26 to 41 mmHg. Our measurements are the first report of Psf in the failing heart and also demonstrate a good correlation between LVEDP and Psf (Fig. 5). Our findings indicate that the effective back pressure to coronary perfusion is elevated in the failing heart and must be accounted for when coronary resistance is calculated.

4.3. Coronary responses to vasodilators

This study reports the first measurements of the responses of coronary flow and vascular resistance to the response to intracoronary substance P was preserved in patients with dilated cardiomyopathy, suggesting intact endothelium-mediated vasodilation but impaired muscarinic receptor activity. Wang et al. [4] reported that the coronary flow responses to acetylcholine and nitroglycerine were reduced in dogs with pacing-induced CHF. However, the drugs were administered intravenously, producing substantial decreases of arterial pressure and increases of heart rate that might have influenced the results. In that studies [4] the oxidative products of NO (NOx) from isolated epicardial arteries and coronary microvessels were reduced in dogs with CHF during both basal and acetylcholine-stimulated conditions. In subsequent studies [14] these investigators found that the coronary arteriovenous production of NOx decreased during the development of CHF produced by rapid ventricular pacing, although the production of NOx to endothelium-dependent agonists was not measured.

4. Discussion

This study presents several new findings regarding the effects of increased extravascular compressive forces on agonist mediated coronary vasodilation in the failing heart, including the first description of changes in coronary blood flow in response to intracoronary endothelium-dependent and independent agonists in the same animals before and after the development of CHF. The data demonstrate that the increased LV diastolic pressure in the failing heart is associated with an increased Psf that contributes to the decreased response to the vasodilators.

4.1. Endothelial function in the failing heart

There is controversy concerning the effect of CHF on coronary endothelial function. Several investigators have reported that the epicardial artery dilator response to acetylcholine is impaired in CHF [4,11], while others have found no difference in the maximum relaxation produced by acetylcholine between epicardial coronary arteries from CHF and normal animals [12]. Unlike epicardial arteries, however, the response of coronary blood flow to vasodilators is determined not only by the responsiveness of the resistance vessels but also by the extravascular forces that surround the intramural coronary microvessels [7]. Several investigators have observed that the increase of coronary blood flow produced by intra-arterial acetylcholine is reduced in patients with CHF suggesting endothelial dysfunction [11]. However, Holdright et al. [13] found that

![Fig. 5. Relationship between Psf measured during total coronary occlusion and LVEDP. Measurements were obtained after development of CHF in five dogs in which a coronary occluder had been implanted; in two of these animals Psf was also determined during control conditions prior to the onset of pacing.](https://academic.oup.com/cardiovascres/article-abstract/52/3/454/348550)
intracoronary administration of endothelium-dependent and -independent vasodilators in the same animals before and after the development of CHF. Our findings that coronary flow responses are impaired after the development of CHF are in agreement with other studies [2–4]. However, the degree of impairment of the coronary flow response to the endothelium-independent vasodilator sodium nitroprusside was similar to the impairment of the responses to the endothelium-dependent vasodilators, suggesting that endothelial changes were not the primary cause of this abnormality. Furthermore, the impairment of the coronary flow responses could be explained by an abnormally increased extravascular component of coronary resistance with no impairment of the response of the vascular component of resistance. Thus, the novel finding of our study is that the response of coronary vascular resistance to endothelium-dependent vasodilators was unchanged in the failing hearts when the responses were corrected for the elevated LV diastolic pressure. In contrast to the endothelium-dependent vasodilators, the fall in CVR in the failing hearts in response to the endothelium-independent vasodilator SNP was shifted rightward compared to normal. This contrasts to previous findings in the peripheral circulation where the response to SNP was unchanged in patients with CHF [19] and in isolated epicardial coronary artery segments where the response to nitroglycerine was unchanged [20]. These findings may suggest that smooth muscle sensitivity or bioavailability of NO donors differs between conduit vessels and the microcirculation or, alternatively, that alternate vasodilator pathways (such as EDHF) assume greater importance in the failing heart.

Our findings are not incompatible with previous studies suggesting that CHF results in an impaired basal or stimulated NO release by the coronary endothelium, since the endothelium produces other vasodilator substances in addition to NO in response to ACH and BK [21,22]. For example, ACH and BK can activate phospholipase A2 through increases in intracellular Ca2+ to cause release of arachidonic acid from cell membranes with production of vasodilator prostaglandins such as PGL2. Arachidonic acid can also be metabolized by a cytochrome P-450 epoxyenase to form epoxyeicosatrienoic acids (EET) that can hyperpolarize vascular smooth muscle via KCa channel activation. These compounds, which likely represent the endothelium derived hyperpolarizing factor (EDHF) [23], appear to exert more potent vasodilator effects on resistance vessels [24] than NO, which acts preferentially on conductance vessels. Furthermore, there is evidence to suggest a reciprocal regulation between NO and EDHF, since NO has been demonstrated to inhibit the production of EDHF [25], possibly through a direct effect on the P-450 enzyme system. In the eNOS knockout mouse, Huang et al. [26] demonstrated that endothelium-dependent vasodilation is preserved, but that the vasodilation produced by ACH is mediated primarily through metabolites of cytochrome P-450 epoxyenase, since inhibition of this enzyme resulted in 80–90% inhibition of the vasodilator response. In the wild type mouse, vasodilation to ACH was mediated principally through NO, as EDHF contributed to arteriolar vasodilation to a significant degree only after blockade of NOS with LNNA. Although blockade of EET synthesis has not been accomplished in the intact animal, our results demonstrating that endothelium-dependent vasodilator activity is not markedly impaired in the coronary circulation of the failing heart might be explained by increased importance of these alternate vasodilator mechanisms.

5. Conclusions

Coronary flow responses to endothelium-dependent and -independent vasodilators were reduced after the development of CHF. However, the reductions in coronary vascular resistance evoked by these compounds were similar to normal when the effective back pressure to coronary perfusion was taken into account. These findings demonstrate that the coronary circulation of the failing heart retains significant vasodilating capability in response to endothelium-dependent agonists, although coronary flow responses are reduced as a result of increased extravascular compressive forces.

Acknowledgements

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