Prostaglandin modulation of venoconstriction to physiological stress in normals and heart failure patients

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Submitted 2 July 2001; accepted in final form 30 October 2002

Dzeka, T. Nancy, and J. Malcolm O. Arnold. Prostaglandin modulation of venoconstriction to physiological stress in normals and heart failure patients. Am J Physiol Heart Circ Physiol 284:H790–H797, 2003; 10.1152/ajpheart.00572.2001.—Prostaglandins released from blood vessels modulate vascular tone, and inhibition of their production during exogenous infusions of catecholamines causes increased venoconstriction. To determine the influence of prostaglandin production on venoconstriction during physiological stimuli known to cause sympathetic activation, and to assess its importance in chronic heart failure (CHF), we studied 11 normal subjects (62 ± 4 yr) and 14 patients with CHF (64 ± 2 yr, left ventricular ejection fraction 23 ± 1%, New York Heart Association classes II and III) (means ± SE). Dorsal hand vein distension was measured during mental arithmetic (MA), cold pressor test (CPT), and lower body negative pressure (LBNP; −10 and −40 mmHg), with saline infusion in one hand and local indomethacin (cyclooxygenase inhibitor) infusion (3 μg/min) in the other. Acetylcholine (0.01–1 nmol/min) dilated veins preconstricted with PGF2α, in normals but, consistent with endothelial dysfunction, barely did so in CHF patients (P = 0.001). Nonendothelial venodilation to sodium nitroprusside (0.3–10 nmol/min) was not different between normals and CHF patients. Resting venous norepinephrine levels were higher in CHF patients (2,812 ± 420 pmol/l) than normals (1,418 ± 145 pmol/l, P = 0.007). In normals, indomethacin caused increased venoconstriction to MA (from 4.9 ± 1.5 to 19.2 ± 4.5%, P = 0.022) and CPT (from 2.9 ± 3.8 to 17.6 ± 4.2%, P = 0.007). In CHF, indomethacin caused increased venoconstriction to MA (from 6.6 ± 3.9% to 19.0 ± 4.5%, P = 0.014), CPT (from 9.6 ± 2.1% to 20.1 ± 3.7%, P = 0.001), and −40 mmHg LBNP (from 10.7 ± 3.0% to 23.2 ± 3.8%, P = 0.041). Control responses for all tests were not different between normals and CHF patients. The effects of indomethacin on venoconstriction to MA and CPT were not different between normals and CHF patients, although a differential effect exists for LBNP.

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inhibiting cyclooxygenase with indomethacin on sympathetic venoconstriction after physiological stressors, mental arithmetic (MA), cold pressor test (CPT), and lower body negative pressure (LBNP), in normal subjects and patients with CHF. We hypothesized that if vasodilator prostaglandins play a role in modulating physiological venoconstriction to endogenous sympathetic activation, indomethacin would cause increased venoconstriction in normals, although its effects would be attenuated in patients with CHF, which is associated with endothelial dysfunction.

METHODS

Subjects

All subjects gave written informed consent to the study protocol as approved by the University of Western Ontario review board for health sciences research involving human subjects. Subjects with sensitivity to any of the pharmacological agents, Raynaud’s disease or any peripheral vascular disease, unstable heart failure (recent hospitalization or change in symptoms within 1 mo before studies), or acute myocardial infarction (within 3 mo) were excluded from the study. Documentation of systolic CHF was by New York Heart Association (NYHA) functional classification of symptoms, physical examination, and left ventricular ejection fraction (LVEF < 40%) as determined by echocardiography. Fourteen clinically stable outpatients with CHF (12 men and 2 women, mean age 64 ± 2 yr, NYHA classes II (n = 8) and III (n = 6), LVEF 28 ± 1%) participated in the study. Etiology of heart failure included ischemic heart disease (n = 11) and nonischemic cardiomyopathy (n = 3). None of the patients were taking calcium channel or adrenoceptor blockers. Patients who had been on long-acting angiotensin-converting enzyme inhibitors were switched to comparable doses of captopril, which is short acting, for at least 2 wk before the study. Digoxin and diuretics were withhold on the study morning to avoid acute hemodynamic changes and the urge to void during the study, whereas all other medications were withheld for 24 h before the study to minimize acute drug effects. Eleven age-similar normal subjects (8 men and 3 women, mean age 62 ± 4 yr) were normotensive, nondiabetic, nonsmokers, not taking any medications, had a normal electrocardiogram, and were in good general health by history and physical examination.

Protocols

Studies were performed in the morning after an overnight fast, and subjects refrained from alcohol- and caffeine-containing beverages for at least 12 h before the study. Subjects were allowed to rest for 30 min in a quiet temperature-controlled room (22–24°C), and the studies were carried out with the subjects in a semirecumbent position. Venous blood samples were collected 30 min after the insertion of needles into the hand veins, baseline measurements of vein distension were recorded at 3-min intervals by inflating the upper arm cuff for 2 min until two reproducible plateau distensions were attained (on average, this was achieved within 3 inflations). The saline syringe in one hand (randomly selected) was then replaced by indomethacin (Merck, Sharp & Dohme; Kirkland, Quebec, Canada) infusion (3 μg/min). After a 15-min equilibration period, the physiological stress tests were applied in a random order with ~15-min recovery intervals between tests to allow a return to baseline. Before each stress test, control vein distension was determined by inflation of the cuff for 2 min to achieve a stable plateau on the recorder, followed by application of the stress test for another 2 min before the cuff was deflated (Fig. 1B). Each subject acted as his or her own control, and venoconstriction was defined as the change in vein distension during application of the stimuli (control distension minus vein distension during the stress test was expressed as a percentage of the control distension). A comparison was made of responses in the hand with indomethacin to those in the hand without indomethacin during application of each test. A previous study (2) has demonstrated that α-adrenoceptor responsiveness is similar in both hands.

Arterial pressure and heart rate were monitored noninvasively throughout each study with a finger blood pressure monitor (Ohmeda 2300, Finapres; Louisville, CO) after verification in pilot studies that its operation would not interfere with linear variable differential transformer measurements. Skin temperature was monitored with a small temperature probe (YSI 409B, VWR Scientific, Mississauga, Ontario, Canada) on the dorsum of the hand.

Mental arithmetic. This consisted of rapid subtractions of a 1-digit odd number from 100 or a 2-digit odd number from 150 or multiplication of 2-digit numbers depending on the subject’s skill. The test was administered by a person not directly involved in the study. No attempt was made to directly frustrate or upset the subjects. Subjects were urged to proceed as quickly as possible, and if they made an error, they were informed and asked to quickly provide the correct answer or restart at the beginning.

Cold pressor test. An ice pack was placed on the forehead for 2 min.

Lower body negative pressure. A metal chamber was placed and sealed around the lower portion of the body below the iliac crest. LBNPs of −10 and −40 mmHg were applied consecutively for 2 min at each level by an adjustable vacuum pump.

To confirm that potential changes in forearm arterial inflow during application of the stimuli, especially LBNP (3, 17, 30), do not influence vein distension measurements, hand vein distension was measured in two normal subjects during...
reductions in arterial inflow produced by direct digital pressure on the brachial artery at the elbow just above its bifurcation into the radial and ulnar arteries. This allowed isolated blood flow reduction in the absence of generalized sympathetic activation, which would alter venomotor tone. Arterial flows were continuously monitored by color Doppler flow imaging of the radial artery to quantify the reduction in flow and ensure stable digital pressure (HDI 5000, ATL Ultrasound; Bothell, WA).

Endothelial and nonendothelial venous responses. On a second day, 3–10 days from the first study day and under the same controlled conditions, two 27-gauge butterfly needles were placed in a suitable dorsal hand vein with the tip of the proximal one ~10 mm upstream from the measurement transducer. Saline infusions were started in each needle at a rate of 0.2 ml/min. Vein distension was measured by the same technique as on the first day. When a stable baseline distension (2 consistent peaks) at 45 mmHg was attained, the vein was preconstricted to ~50% (control) with PGF$_{2\alpha}$ (Upjohn; Don Mills, Ontario, Canada) infusion (256–1,024 ng/min depending on individual responses) through the most distal needle, and this infusion was maintained throughout the study. To test endothelial function, five graded doses (0.01, 0.03, 0.1, 0.3, and 1 nmol/min) of acetylcholine (Ciba-Geigy, Mississauga, Ontario, Canada) were infused through the more proximal needle for 5 min at each dose level with vein distension measurements being made in the last 2 min. This was followed by a washout period with saline through the needle that was used for acetylcholine until control preconstriction with PGF$_{2\alpha}$ was reattained. To test nonendothelium-dependent vasodilation, six doses (0.3, 0.625, 1.25, 2.5, 5, and 10 nmol/min; 5 min at each dose level) of sodium nitroprusside (Hoffman-La Roche; Mississauga, Ontario, Canada) were given through the proximal needle, and measurements were made in the same manner as those described for acetylcholine. Maximum changes in vein distension at each dose level were expressed as a percentage of the control value with PGF$_{2\alpha}$ (%venodilation).

One normal subject was hypersensitive to PGF$_{2\alpha}$, and the vein remained completely constricted for such an extended period of time that the study could not be completed. One normal subject and five patients with CHF were unable to return for the additional study day to complete this part of the study.

Data Analysis

The study was designed to be conducted at the 95% confidence level (α = 0.05) with 90% power to show a 20% difference in venoconstriction between the two groups. Data are presented as means ± SE. Statistical calculations were performed using the computer-based SPSS program (SPSS;
Within-subject comparisons of responses to the stress tests were made using the paired Student’s t-test. For the response to CPT in normals under control conditions (saline), the nonparametric sign test was used. Between-group comparisons of means were made using the unpaired Student’s t-test. All graphs were plotted using a computer software program, Graphpad Inplot 4.0 (H. J. Motulsky; San Diego, CA). Comparisons of responses to acetylcholine and sodium nitroprusside between groups were made using one-way ANOVA. Two-tailed P values <0.05 were considered statistically significant.

RESULTS

Subject Characteristics

Baseline characteristics of the subjects before application of the stress tests are shown in Table 1. Indomethacin infusion did not affect baseline vein distension in either group. Skin temperatures did not vary significantly throughout the studies, averaging 31.5 ± 0.1°C in normals and 31.8 ± 0.1°C in patients with CHF. Baseline characteristics for the day on which endothelial and nonendothelial venous responses were studied are shown in Table 2. Skin temperature on the day on which endothelial responses were assessed did not vary significantly during the studies, averaging 31.4 ± 0.2°C in normals and 31.5 ± 0.2°C in patients with CHF. Skin temperature did not differ significantly between the two groups and did not vary between study days.

Endothelial and Nonendothelial Venous Responses

The average responses to acetylcholine (0.01–1 nmol/min), an endothelium-dependent venodilator, are shown in Fig. 2A. In normals, ACh dilated PGF$_{2\alpha}$-constricted veins. In CHF patients, venous responses to acetylcholine were variable, with responses ranging from constriction to no response or venodilation. Venodilator responses to acetylcholine were significantly reduced in CHF patients (Fig. 2A) compared with normals (P = 0.001).

<table>
<thead>
<tr>
<th>Normal Subjects</th>
<th>Patients With CHF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma norepinephrine, pmol/l</td>
<td>1,418 ± 145</td>
</tr>
<tr>
<td>Total cholesterol, mmol/l</td>
<td>4.80 ± 0.24</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>61 ± 1</td>
</tr>
<tr>
<td>Mean arterial pressure, mmHg</td>
<td>85 ± 1</td>
</tr>
<tr>
<td>Baseline hand vein distension, mm</td>
<td>1.08 ± 0.17</td>
</tr>
<tr>
<td>Saline infusion</td>
<td>1.10 ± 0.17</td>
</tr>
</tbody>
</table>

Values are means ± SE; *P < 0.01 compared with normal subjects.

In normals, sodium nitroprusside, a non-endothelium-dependent venodilator, strongly dilated PGF$_{2\alpha}$-constricted veins (Fig. 2B). In CHF patients, sodium nitroprusside also similarly dilated PGF$_{2\alpha}$-constricted veins (Fig. 2B). Responses to sodium nitroprusside were not different between the two groups.

There was no difference in the dose of PGF$_{2\alpha}$ required to preconstrict the veins before pharmacological tests in normals (341 ± 85 ng/min) and CHF patients (484 ± 108 ng/min).

Table 1. Subject characteristics before application of the stress tests

Table 2. Baseline characteristics of subjects on day of endothelial studies
**Hemodynamic Responses to Physiological Stress**

Heart rate and mean arterial pressure responses are shown in Table 3. In normals, MA increased heart rate and mean arterial pressure, CPT increased mean arterial pressure only, and −40 mmHg LBNP increased heart rate but reduced arterial pressure. In CHF patients, similar effects of the stress tests on hemodynamics were observed. However, increases in heart rate (percent change from control) were significantly less in CHF patients during MA (+12.5 ± 1.2% vs. +18.8 ± 1.6% in normals, P = 0.006) and −40 mmHg LBNP (+12.7 ± 2.7% vs. +22.9 ± 3.6% in normals, P = 0.035). Percent changes in mean arterial pressure were not different between the two groups for any of the tests.

**Venous Responses to Physiological Stress**

Reductions of arterial blood flow of 20% and 39% in each of two normal subjects caused no effect (0%) or minimal reduction of vein distension (1.5%), respectively. The return of arterial flow to normal on release of the digital pressure did not alter plateau vein distension in either case.

Application of the physiological stress tests under control (saline) conditions in normals caused vеноconstriction and a significant reduction in hand vein distension during each of the stress tests (1.03 ± 0.17 vs. 0.98 ± 0.16 mm for MA, P = 0.011; 1.05 ± 0.16 vs. 1.00 ± 0.16 mm for CPT, P < 0.05; 1.03 ± 0.15 vs. 0.95 ± 0.15 mm for −10 mmHg LBNP, P = 0.019; and 1.02 ± 0.15 vs. 0.93 ± 0.15 mm for −40 mmHg LBNP, P = 0.031). In CHF patients, application of the physiological stress tests under control conditions also caused a significant reduction in hand vein distension during each of the stress tests (0.91 ± 0.09 vs. 0.82 ± 0.08 mm for MA, P = 0.045; 0.96 ± 0.10 vs. 0.87 ± 0.09 mm for CPT, P = 0.002; 0.95 ± 0.10 vs. 0.87 ± 0.10 mm for −10 mmHg LBNP, P = 0.024; and 0.95 ± 0.10 vs. 0.84 ± 0.09 mm for −40 mmHg LBNP, P = 0.005). Control responses to all stress tests were not significantly different between normals and CHF patients. In normals (Fig. 3), indomethacin caused increased vеноconstriction to MA (from 4.9 ± 1.5% to 19.2 ± 4.5%, P = 0.022) and CPT (from 2.9 ± 3.8% to 17.6 ± 4.2%, P = 0.007). In contrast, indomethacin did not significantly alter vеноconstriction to −10 mmHg LBNP (from 9.1 ± 3.0% to 3.4 ± 1.7%, P = not significant [NS]) or −40 mmHg LBNP (from 14.1 ± 5.3% to 7.3 ± 3.9%, P = NS). In CHF patients (Fig. 4), indomethacin caused increased vеноconstriction to MA (from 6.6 ± 3.9% to 19.0 ± 4.5%, P = 0.014), CPT (from 9.6 ± 2.1% to 20.1 ± 3.7%, P = 0.001), and −40 mmHg LBNP (from 10.7 ± 3.0% to 23.2 ± 3.8%, P = 0.041). However, indomethacin did not significantly alter vеноconstriction to lower-level (−10 mmHg) LBNP (from 8.0 ± 2.6% to 13.5 ± 3.3%, P = NS). Changes in vеноconstriction (Fig. 5) caused by indomethacin (expressed as %vеноconstriction with indomethacin minus %vеноconstriction with saline) were not different between normals and CHF patients for MA (14.3 ± 5.3% vs. 12.4 ± 4.4%, respectively, P = NS) and CPT (14.9 ± 4.4% vs. 10.5 ± 2.6%, respectively, P = NS) but tended to be greater in CHF patients compared with normals for −10 mmHg LBNP (5.5 ± 4.2% vs. −5.7 ± 3.7%, P = 0.057) and were greater in CHF patients at −40 mmHg LBNP (12.5 ± 5.4% vs. −6.8 ± 6.6%, P = 0.036).

**DISCUSSION**

The results from this in vivo study using direct continuous measurement of vein distension have shown that inhibition of cyclooxygenase with indomethacin modulates hand vein constriction to endogenous sympathetic activation in normal subjects and patients with CHF. The three stressors that were employed, MA, CPT, and LBNP, are well-established physiological stress tests that increase sympathetic activity (3, 17, 29, 31, 35, 39, 40) and may increase vascular tone, although this has been assessed using mainly indirect indexes such as changes in blood pressure, blood flow, or venous volume. In our laboratory, we (12) have also recently demonstrated increased venoconstriction and venous norepinephrine levels during application of the forehead CPT in normal subjects.

Blockade of prostaglandin synthesis by indomethacin significantly increased venoconstriction during MA.

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**Table 3. Heart rate and mean arterial pressure responses to different physiological stress tests for normal subjects and patients with CHF**

<table>
<thead>
<tr>
<th>Stress Test</th>
<th>Normal Subjects</th>
<th>Patients with CHF</th>
<th>Normal Subjects</th>
<th>Patients with CHF</th>
</tr>
</thead>
<tbody>
<tr>
<td>MA Control</td>
<td>62 ± 2</td>
<td>74 ± 4</td>
<td>85 ± 3</td>
<td>79 ± 2</td>
</tr>
<tr>
<td>During MA</td>
<td>74 ± 2*</td>
<td>83 ± 4*</td>
<td>97 ± 3*</td>
<td>91 ± 3*</td>
</tr>
<tr>
<td>CPT Control</td>
<td>61 ± 2</td>
<td>74 ± 4</td>
<td>85 ± 2</td>
<td>79 ± 2</td>
</tr>
<tr>
<td>During CPT</td>
<td>63 ± 2</td>
<td>75 ± 4</td>
<td>101 ± 3*</td>
<td>94 ± 4*</td>
</tr>
<tr>
<td>LBNP Control</td>
<td>60 ± 3</td>
<td>71 ± 4</td>
<td>86 ± 2</td>
<td>78 ± 2</td>
</tr>
<tr>
<td>−10 mmHg</td>
<td>64 ± 3</td>
<td>72 ± 4</td>
<td>84 ± 3</td>
<td>78 ± 3</td>
</tr>
<tr>
<td>−40 mmHg</td>
<td>73 ± 3*</td>
<td>79 ± 4*</td>
<td>76 ± 3*</td>
<td>69 ± 3*</td>
</tr>
</tbody>
</table>

Values are means ± SE; n = 11 normal subjects and 14 patients with CHF except for lower body negative pressure (LBNP) data, where n = 13 patients with CHF. MA, mental arithmetic; CPT, cold pressor test. *P < 0.01 compared with control.

*AJP-Heart Circ Physiol • VOL 284 • MARCH 2003 • www.ajpheart.org*
and CPT, suggesting a role for vasodilator prostaglandins in modulating venoconstriction to endogenous sympathetic activation in both normal subjects and patients with CHF. Indomethacin did not affect baseline vein distension and, while this is consistent with veins being in a state of near to maximal dilation at room temperature, with little intrinsic tone (1, 4), it may also be an indication that prostaglandins do not play a significant role in maintenance of basal tone, their effects becoming obvious only upon further stimulation. Contrary to our hypothesis, the changes in venoconstriction with indomethacin were not different between normals and patients with CHF for MA and CPT, suggesting a comparable role of vasodilator prostaglandins in attenuating the resultant venoconstriction. This was despite the demonstration of endothelial dysfunction by impaired vasodilator responses to acetylcholine in CHF patients. Prostaglandins have generally been regarded as being endothelium derived (22, 37), based largely on in vitro studies reporting a progressive decrease in the intrinsic ability to synthesize prostaglandins from the intima to the adventitia (27). Our in vivo findings are consistent with observations in the isolated rat aorta: that contractile agonist-induced prostaglandin production is independent of the presence of endothelium (18), suggesting that smooth muscle may be a source of prostaglandins. An alternative suggestion might be that endothelial dysfunction (9), a complex phenomenon that is not yet fully characterized, may result in a specific deficit in nitric oxide responses rather than a generalized impairment of vasodilator responses such that prostaglandin responses are not altered. However, this would be unlikely if the mechanism involved in reduced nitric oxide synthesis with endothelial dysfunction is a defect in the phosphoinositol calcium signaling pathway (8), the same one involved in phospholipase A2 activation leading to arachidonic acid release and subsequent prostaglandin synthesis (6, 38). Another study demonstrated that removal of endothelium increased vasoconstrictor responses to norepinephrine applied on the intimal but not adventitial surface of isolated arteries (33). This raises the possibility that prostaglandins stimulated by extraluminal neurally released norepinephrine are not reduced by endothelial dysfunction, most likely because they are derived mainly from vascular smooth muscle. Responsiveness to sodium nitroprusside, an endothelium-independent vasodilator, was similar in the two groups, suggesting that smooth muscle function was not altered in CHF.

In contrast to MA and CPT, indomethacin did not significantly increase venoconstriction to both levels of LBNP in normal subjects but did so in CHF patients at −40 mmHg LBNP. In fact, venoconstriction with indomethacin trended in opposite directions in normal subjects compared with CHF patients. It appears therefore that vasodilator prostaglandins do not modulate venoconstriction to LBNP in normal subjects but do so in CHF patients. Afferent neural pathways for LBNP-mediated sympathetic activation are triggered by baroreceptor deactivation (3, 17) and have a greater...

Fig. 3. Effects of indomethacin on venoconstriction to mental arithmetic (MA), CPT, and lower body negative pressure (LBNP; −10 and −40 mmHg) in normal subjects (n = 11). NS, not significant.

Fig. 4. Effects of indomethacin on venoconstriction to MA, CPT, and LBNP (−10 and −40 mmHg) in patients with CHF (n = 14 for MA and CPT and 13 for LBNP).

Fig. 5. Changes in %venoconstriction (indomethacin − saline) for MA, CPT, and LBNP in normal subjects (n = 11) and patients with CHF (n = 14 except for LBNP, where n = 13).
potential for concomitant activation of the renin-angiotensin-aldosterone system (26, 29) than MA (cortical foci (25)) and CPT [pain and thermal receptors (31)], which are independent of baroreflexes. Low-intensity LBNP (−10 mmHg) selectively unloads low-pressure cardiopulmonary baroreceptors causing reflex vasoconstriction and increased peripheral resistance (3, 17), whereas higher-intensity LBNP (−40 mmHg) unloads high pressure arterial baroreceptors with further increases in peripheral resistance (17). Qualitative and quantitative differences in mechanisms mediating vasoconstriction, which were outside the scope of the present study, may form the basis for the differential role of prostaglandins in modulating vasoconstriction to LBNP compared with the other stress tests.

Control responses to all tests were not different between normal subjects and patients with CHF, despite evidence for endothelial dysfunction and resting sympathetic activation in CHF as reflected by the increased plasma catecholamines and heart rate at rest in patients with CHF in our study. While measurement of plasma catecholamine levels as an index of sympathetic activity may be limited by the altered catecholamine pharmacokinetics occurring in CHF, it is usually consistent with other indexes of sympathetic activation (15). The neurohormonal response to these physiological stress tests has been previously documented (3, 12, 17, 20, 21, 29, 41). However, understanding of the mechanisms behind our responses in normals and patients with CHF is limited as we did not measure neurohormonal responses during the interventions because the experimental setup with venous occlusion arm cuffs and legs in the LBNP chamber did not allow blood sampling other than at baseline before the start of each study. Further studies in which receptor responsiveness is evaluated and neurohormonal sympathetic responses are quantified may be helpful. Our results are consistent with a previous report (25) demonstrating that sympathetic nerve activity responses to mental stress are not augmented in CHF despite elevated resting levels of sympathetic activity. A comparison of our results, based on direct in vivo hand vein measurements, with previous studies of vascular responses to physiological stress is difficult because all were based on different techniques, with most measuring generalized forearm vascular responses by plethysmography (17, 25, 35, 39). Some have reported a blunting of arterial constrictor responses to LBNP in patients with varying degrees of CHF, suggested to be due to impaired baroreflex mechanisms (10, 30), but our results indicate that hand vein responses to all stressors are not altered, at least in patients with mild-to-moderate CHF. The increases in mean arterial pressure (MA and CPT) and heart rate (MA and −40 mmHg LBNP) are consistent with a number of previous studies (15, 17, 25) except for one study (10), which reported no change in heart rate for −40 mmHg LBNP, but this study was in patients with more severe symptomatic CHF, NYHA classes III and IV. The forehead CPT is unique in that its effects are predominantly α-adrenoceptor mediated, and it causes sympathetic activation with no significant effects on heart rate (36, 39).

During application of the physiological stress tests, redistribution of cardiac output may occur, potentially leading to differences in arterial inflow compared with baseline, and this may be particularly important during application of LBNP (3, 17, 30), which involves a shift in blood distribution to the lower extremities. Changes in flow also have the potential to affect small venule function (23). We demonstrated that isolated reductions in forearm arterial inflow, comparable with those reported in the literature during LBNP (up to 40%), do not influence our large hand vein distension measurements. Therefore, the observed venoconstriction in our study reflects the change in venomotor tone.

The choice of indomethacin as an inhibitor of prostaglandin synthesis was based on its greater potency compared with other nonsteroidal anti-inflammatory drugs (19) as well as its availability as an intravenous dosage form suitable for use in humans. Although there have been reports of nonspecific effects of indomethacin (5, 14, 19), these were reported at concentrations much higher than those used in this study. It is unlikely that indomethacin had nonspecific effects, and this is supported not only by lack of effects of indomethacin on basal vein distension, but also previous studies showing that indomethacin does not alter vasoconstriction to PGF2α in human hand veins (7).

In summary, indomethacin significantly increased hand vein constriction to sympathetic activation with MA and CPT but not LBNP in normal subjects. Therefore, vasodilator prostaglandins may significantly modulate vasoconstriction to MA and CPT but do not seem to play a role in modulating vasoconstriction to LBNP in normal subjects. In CHF patients, indomethacin similarly increased vasoconstriction to MA and CPT, indicating that prostaglandin modulation of MA- and CPT-induced vasoconstriction is maintained in CHF. Indomethacin also increased vasoconstriction to −40 mmHg LBNP in CHF patients. Our findings suggest that vasodilator prostaglandins modulate vasoconstriction to physiological sympathetic activation, but differences exist between stimuli and in the presence of CHF.

We gratefully acknowledge the assistance of Ian Callow, Dr. Gordon Marchiori, Ruth Miles, Pat Squires, and Marie Krupa during the studies.

This study was supported by the Heart and Stroke Foundation of Ontario and the Medical Research Council of Canada. T. N. Dzeka was supported by the Canadian Commonwealth Scholarship Program.

REFERENCES

3. Baily RG, Prophet SA, Shenberger JS, Zelis R, and Sino-way LI. Direct neurohumoral evidence for isolated sympathetic nervous system activation to skeletal muscle in response to...


