Peripheral haemodynamic effects of inhibition of prostaglandin synthesis in congestive heart failure and interactions with captopril

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Abstract

Objectives—To investigate the role of prostaglandins in maintaining circulatory homeostasis in chronic heart failure and the hypothesis that an increase in vasodilatory prostaglandin synthesis may contribute to the actions of angiotensin converting enzyme inhibitors in heart failure.

Design—Randomised, double blind, placebo controlled studies. Cardiac output and renal and limb blood flow were measured after oral indomethacin 50 mg or placebo followed by "open" intravenous infusion of prostaglandin E₂ (study A). In a second study the same measurements were made after oral indomethacin 50 mg or placebo was given 30 min before "open" captopril (study B).

Methods—Blood pressure was measured using a mercury sphygmomanometer. Cardiac output was determined by Doppler interrogation of blood flow in the ascending aorta and echocardiographic measurement of aortic root diameter. Renal blood flow was calculated from the effective renal plasma flow measured by *p*-aminohippurate clearance and the haematocrit, and glomerular filtration rate by endogenous creatinine clearance. Limb blood flow was measured by venous occlusion plethysmography using mercury in silastic strain gauges. The concentration of plasma prostaglandin E₂ was measured by radioimmunoassay.

Setting—University department of cardiovascular medicine.

Patients—12 patients with chronic stable heart failure before starting treatment with angiotensin converting enzyme inhibitors.

Results—Indomethacin resulted in adverse effects on cardiac output, systemic vascular resistance, renal blood flow, glomerular filtration, urinary sodium excretion, and calf vascular resistance. Changes were reversed with infusion of prostaglandin E₂. Pretreatment with indomethacin resulted in the attenuation of the acute increase in cardiac output and decrease in systemic vascular resistance that occurred with captopril. Similarly, an increase in renal blood flow with captopril was attenuated by indomethacin.

Conclusions—The acute adverse effects of indomethacin on central and peri-

pheral haemodynamic and renal function suggest that prostaglandins have a significant role in the regulation of peripheral blood flow and renal function in patients with stable chronic heart failure. The attenuation by indomethacin of captopril induced improvements in haemodynamic function and renal blood flow is consistent with the hypothesis that captopril may act in part via an increase in prostaglandin synthesis.

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Keywords: haemodynamic and renal effects of indomethacin; captopril; congestive heart failure; prostaglandins.

Prostaglandins are 21 carbon fatty acids synthesised from arachidonic acid by all body tissues including the kidney and vascular endothelium. Stimuli to prostaglandin production include ischaemia, catecholamines, angiotensin II, bradykinin, and vasopressin.^{1,2} Prostaglandins E₂ and I₂ are potent vasodilators and are thought to act locally to increase blood flow.² Many of the factors known to stimulate prostaglandin synthesis are present in heart failure and circulating concentrations of metabolites of prostaglandins E₂ and I₂ are increased in some patients with heart failure.³ It has been suggested that vasodilatory prostaglandins have an important role in maintaining circulatory homeostasis in heart failure when tissue perfusion is reduced.⁴ In parallel with the activation of nervous and humoral vasoconstrictor systems, increased prostaglandin synthesis may act as a "counter regulatory" mechanism to limit local vasoconstriction and maintain local blood flow. Uncontrolled studies have shown adverse renal and systemic haemodynamic effects after inhibition of prostaglandin synthesis in chronic heart failure.^{3,5}

Angiotensin converting enzyme and kininase II are structurally identical so that angiotensin converting enzyme inhibitors not only inhibit the renin angiotensin system but also inhibit the degradation of kinins. Bradykinin is a potent vasodilator and also a stimulus to the synthesis of prostaglandins.⁶ This pivotal position of the angiotensin converting enzyme means that angiotensin converting enzyme inhibitors not only inhibit the vasoconstrictor renin angiotensin system but may also facilitate the production of vasodilators such as bradykinin and prostaglandin.

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Patient details

Patient no	Age (years)	Sex	Diagnosis	Ejection fraction (%)	NYHA class	Fruzemide (mg/day)
1	48	F	CAD	17	III	80
2	62	F	CAD	13	IV	80
3	64	M	CAD	17	III	160
4	69	M	CAD	27	III	80
5	54	M	DCM	32	III	80
6	68	M	CAD	31	III	80
7	42	M	DCM	30	III	80
8	66	F	CAD	19	IV	120
9	67	M	CAD	20	IV	80
10	61	M	CAD	22	III	80
11	58	M	CAD	27	III	40
12	60	M	CAD	18	IV	160
mean (SD)	60 (8)			23 (6)		93 (35)

CAD, coronary artery disease; DCM, dilated cardiomyopathy; NYHA, New York Heart Association.

Despite reducing many stimuli to prostaglandin production treatment with captopril seems to increase rather than reduce the circulating concentration of vasodilatory prostaglandins in patients with heart failure.⁷ There is evidence that in patients with essential hypertension the hypotensive effects of captopril may be mediated in part by an increase in prostaglandin production^{8,9} and it is possible that some of the effects of captopril in heart failure may also be mediated by prostaglandins.

Prostaglandin synthesis can be inhibited by inhibitors of cyclo-oxygenase such as indomethacin. Because prostaglandins are not stored but are synthesised de novo their actions are inhibited by such agents. We have administered indomethacin to patients with heart failure in an attempt to determine the role of prostaglandins in the maintenance of renal and skeletal muscle blood flow in heart failure. Second, we have investigated the role of prostaglandins in mediating the acute haemodynamic effects of captopril in heart failure by comparing the effects of captopril with and without pretreatment with indomethacin.

Patients and methods

PATIENTS

Twelve patients (nine men) with chronic stable heart failure in New York Heart Association symptomatic class III or IV who had never received treatment with angiotensin converting enzyme inhibitors were studied. The mean (SD) age was 60 (8) years and the mean (SD) ejection fraction determined by radionuclide ventriculography was 23 (6)%. All patients were receiving chronic diuretic medication, the dosage of which was maintained without change for at least 2 weeks before the studies. No patient was taking concurrent vasodilator medication. The table gives the causes of heart failure and other individual patient details. Each patient gave written consent and the study was approved by the ethics committee of the South Birmingham Health Authority.

RENAL BLOOD FLOW

Renal blood flow was determined by measurement of effective renal plasma flow using *p*-

aminohippurate clearance.¹⁰ Renal blood flow was calculated as effective renal plasma flow $\times$ 1/haematocrit. Renal vascular resistance was calculated as the ratio of mean blood pressure to renal blood flow and the results expressed in $\text{dyne.s.cm}^{-5} \times 10^3$. The concentration of *p*-aminohippurate in plasma and urine was assayed in duplicate using a colorimetric assay.

GLOMERULAR FILTRATION RATE

Glomerular filtration rate was measured by endogenous creatinine clearance.

LIMB PLETHYSMOGRAPHY

Forearm and calf blood flow were measured by venous occlusion plethysmography using mercury in silastic strain gauges connected to a plethysmograph (Hokanson EC-4; DE Hokanson, WA, USA) the output of which was connected to a pen chart recorder (Oxford Instrument Company, UK). The venous cuff was connected to a rapid cuff inflator device (Hokanson E-20 rapid cuff inflator) filled from a compressor (Hokanson AG-101 cuff inflator source) allowing inflation of the cuff to a preset pressure (50 mm Hg) in less than 0.3 s. Arterial occlusion to the hand or foot was provided by a cuff connected via a three way tap to a reservoir containing air at a pressure of 200 mm Hg. The limb bearing the apparatus was positioned above heart height before readings were taken. Limb blood flow was derived from the rate of increase in limb circumference during venous occlusion using an electronic calibration signal and expressed in ml/ 100 ml/min. Limb vascular resistance was calculated from the ratios of mean blood pressure and forearm and calf blood flows. The results are expressed in units of $\text{dyne.s.cm}^{-5} \times 10^3$.

CARDIAC OUTPUT

Cardiac output was measured by Doppler interrogation of ascending aortic blood flow using a 2.0 MHz continuous wave transducer positioned in the suprasternal notch. The spectral Doppler display was recorded on to light sensitive silver paper at 100 mm/s by use of a Biosound ND-256-8 echo Doppler machine. The flow velocity integral was determined for at least three cardiac cycles on a digitising tablet (Terminal Display Systems,

Figure 1 Changes in haemodynamic and renal function at 1 and 2 h after oral indomethacin 50 mg or placebo and during subsequent intravenous infusion of prostaglandin E₂ (PGE). Values are mean changes (SEM), * $P < 0.05$; ** $P < 0.01$.

Blackburn) connected to a personal computer (Archimedes 420/1; Acorn Computers, UK). Stroke volume was calculated using the aortic diameter measured by M mode echocardiography and cardiac output as the product of stroke volume and heart rate.

The studies were performed with the patients resting semisupine in bed in a quiet clinical research room where the temperature was maintained between 20 and 24°C. Patients were asked to take a light breakfast at least 2 h before the study period and to refrain from taking any medication on the day of the studies. A 5% dextrose solution was infused continuously at a rate of 200 ml/h to encourage adequate urine volumes for clearance studies. Oral fluid intake in the form of water or non-caffeinated beverages was allowed *ad libitum*.

A loading dose of *p*-aminohippurate (10 mg/kg) was given at the beginning of the studies followed by continuous intravenous infusion at 10 mg/min. Patients were asked to void all urine after a 40 min equilibration period and a timed 2 h baseline urine collection was started. During this time pulse rate and blood pressure were measured and baseline cardiac output and forearm and calf blood flow determined. Blood samples were taken from a forearm venous cannula for

subsequent measurement of the concentration of plasma prostaglandin E₂ and haematocrit. Urine was voided at the end of the baseline period and the volume measured by weighing. Samples of urine and blood were collected for measurement of creatinine and *p*-aminohippurate clearances.

Two studies were conducted. Patients in study A were randomised to receive oral indomethacin 50 mg or placebo at the end of the baseline period. All measurements were then repeated at 60 and 120 min. Further measurements were taken after a 60 min infusion of prostaglandin E₂. Patients in study B were once again assigned randomly to receive indomethacin 50 mg or placebo 30 min before an oral dose of captopril 25 mg. Measurements were repeated at 60 and 120 min after captopril administration. For each study indomethacin (non-proprietary) was placed in a gelatin capsule and packed around with dextrose powder. Identical capsules containing only dextrose were used as placebo. Randomisation was in blocks of four.

Blood samples for assay of prostaglandin E₂ were collected in to chilled heparinised tubes containing 0.5 ml of 1% indomethacin in solution and centrifuged immediately. Concentrations of plasma prostaglandin E₂ were measured by radioimmunoassay using

Figure 2 Changes in the concentration of plasma prostaglandin E_2 (PGE) after oral indomethacin 50 mg or placebo and during subsequent infusion of PGE with time. There was no significant difference between indomethacin and placebo treatment groups. Values are mean (SEM). BL, baseline.

materials from Amersham International (UK) (assay system RPA 530). The plasma was acidified using acetic acid and after centrifugation was extracted on C18 columns. Prostaglandin E_2 was converted to the methyl oximate derivative using methoxyamine hydrochloride after drying and reconstitution with phosphate buffered gelatin saline solution. The concentration of prostaglandin E_2 methyl oximate was assayed by radioimmunoassay using prostaglandin E_2 labelled with iodine-125 as a competitive agonist for a specific antibody. The claimed antiserum cross reactivity for this assay is 5% with prostaglandin E_1 . The coefficient of variation for the assay calculated using paired duplicates was 6.4%.

STATISTICAL METHODS

Patients were randomised in blocks of four so that equal numbers were allocated to treatment and placebo. Because of the wide inter-patient variation in the baseline values of all parameters we have not examined absolute values but have compared the changes after administration of indomethacin with those after placebo between groups using an unpaired *t* test. Values are means (SEM) unless otherwise specified.

Results

EFFECTS OF INDOMETHACIN

Figure 1 shows the changes in central and peripheral haemodynamics and renal function after administration of indomethacin and during the subsequent prostaglandin E_2 infusion. Indomethacin had no significant effect on mean blood pressure but there was a reduction in cardiac output at 2 h after administration of indomethacin of -0.42 (0.2) l/min which differed significantly from the mean increase after placebo of 0.33 (0.2) l/min ($P < 0.05$). The change in systemic vascular resistance at 2 h after indomethacin was an increase of 6.1 (2.5) Wood units compared with a mean decrease of -2.7 (1.6) Wood units after administration of placebo ($P < 0.05$). Renal blood flow at 2 h after indomethacin decreased (-79 (31) ml/min), while there was an increase in the placebo group (52 (23) ml/min) ($P < 0.01$). Renal

vascular resistance increased with indomethacin (8.1 (3.2) units) in contrast to placebo (-3.6 (1.4) units) ($P < 0.02$). The changes in glomerular filtration rate at 1 and 2 h after indomethacin were -15 (4) ml/min and -9 (7) ml/min compared with 2 (4) ml/min and 1 (5) ml/min respectively in the placebo group ($P < 0.02$ at 1 h and 0.19 at 2 h). Filtration fraction was not significantly affected by indomethacin; the mean change in filtration fraction in the indomethacin group was 4 (6)% at 2 h compared with -5 (3)% in the placebo group ($P = 0.2$). There was a small decrease in urinary sodium excretion in the indomethacin group (-9 (4) μ mol/min and -10 (7) μ mol/min at 1 and 2 h) in contrast to the small increases in the placebo group (8 (5) μ mol/min and 9 (12) μ mol/min) ($P < 0.05$ at 1 h and 0.2 at 2 h).

The changes in forearm blood flow and vascular resistance after indomethacin were not significantly different from those of placebo. At 2 h after indomethacin, however, the mean change in calf blood flow was -0.2 (0.05) ml/min/100 ml compared with 0.07 (0.04) ml/min/100 ml after placebo ($P < 0.01$). The change in calf vascular resistance after indomethacin was also significantly different from placebo; the mean change in vascular resistance at 2 h after indomethacin was 13 (5) units compared with -4 (3) units after placebo ($P < 0.01$).

Infusion of prostaglandin E_2 increased cardiac output in the indomethacin group to near baseline values with a mean change of only 0.03 (0.3) l/min; in contrast, there was a significant increase over baseline values in the placebo group of 0.9 (0.3) l/min ($P < 0.05$). Renal vascular resistance in the placebo group was significantly reduced in comparison with baseline values by infusion of prostaglandin E_2 but returned to near baseline values after administration of indomethacin. Improvements in limb vascular resistance with prostaglandin E_2 were evident but not significantly different between the two groups.

Concentration of plasma prostaglandin E_2

The mean baseline concentration of prostaglandin E_2 in the patients was 4.9 (0.50) pg/ml, a value not significantly different from that of ten normal control subjects (not age matched) who had a mean concentration of 4.40 (1.70) pg/ml. Figure 2 shows the changes in mean concentration of plasma prostaglandin E_2 after administration of indomethacin or placebo. There was no significant change in the concentration of plasma prostaglandin E_2 compared with that of placebo but, in comparison with the baseline value a significant decrease occurred in the indomethacin group. There was no increase in the concentration of venous prostaglandin E_2 during exogenous infusion of the agent.

EFFECTS OF PRETREATMENT WITH INDOMETHACIN ON THE ACUTE RESPONSES TO CAPTOPRIL

Figure 3 shows the effects of pretreatment with indomethacin on the acute responses to

Figure 3 Changes in haemodynamic and renal function at 1 and 2 h after oral captopril 25 mg with oral indomethacin 50 mg or placebo pretreatment. Values are mean changes (SEM). * $P < 0.05$; ** $P < 0.01$.

captopril. The increase in cardiac output with captopril was significantly attenuated by indomethacin pretreatment. The change in cardiac output with indomethacin pretreatment was 0.02 (0.2) l/min at 1 h and -0.15 (0.15) l/min at 2 h compared with 0.60 (0.17) l/min and 0.70 (0.2) l/min with placebo pretreatment ($P < 0.05$ at 1 h and < 0.01 at 2 h). There was no significant difference between the indomethacin and placebo groups when changes in blood pressure after captopril were examined. The reductions in calculated sys-

temic vascular resistance were significantly attenuated by indomethacin pretreatment. At 1 h the mean fall in systemic vascular resistance with placebo pretreatment was -8.9 (1.5) Wood units compared with only -2.7 (1.1) Wood units with indomethacin pretreatment ($P < 0.01$). At 2 h the difference was still apparent with a mean decrease in systemic vascular resistance in the placebo group of -9.6 (2.0) Wood units and -3.1 (1.5) Wood units in the indomethacin group ($P < 0.05$).

The increase in renal blood flow after captopril was significantly reduced by indomethacin pretreatment. At 2 h the change in renal blood flow after captopril was -74 (41) ml/min with indomethacin pretreatment compared with 73 (52) ml/min in the placebo pretreatment group ($P < 0.05$). The change in renal vascular resistance in the indomethacin group at 2 h was 2 (2) units compared with -10 (5) units in the placebo group ($P < 0.05$). Changes in urinary sodium excretion and glomerular filtration rate were not significantly different in the two groups, although the mean change in urinary sodium excretion at 2 h after captopril in the indomethacin pretreatment group was -25 (14) μmol/min compared with 3 (8) μmol/min in the placebo pretreatment group ($P = 0.09$).

Figure 4 Changes in the concentration of plasma prostaglandin E_2 (PGE₂) after oral captopril 25 mg with oral indomethacin 50 mg (○) or placebo (●) pretreatment with time. There was no significant difference between indomethacin and placebo pretreatment groups. Values are mean (SEM). BL, baseline.

Changes in forearm and calf blood flow and vascular resistance after captopril were not significantly affected by indomethacin pretreatment.

Concentration of plasma prostaglandin E₂

No significant differences in the concentration of plasma prostaglandin E₂ between the indomethacin and placebo pretreatment groups were detected (fig 4). In comparison with the baseline value, however, there was a small increase in the concentration of prostaglandin E₂ after captopril in the placebo pretreatment group ($P < 0.05$, paired t test).

Discussion

In this controlled randomised study indomethacin caused adverse effects on cardiac output and systemic vascular resistance in patients with chronic heart failure. In addition, there was an increase in renal vascular resistance, a reduction in glomerular filtration rate and urinary sodium excretion, and an increase in calf vascular resistance. Infusion of prostaglandin E₂ resulted in restoration to near baseline values of cardiac output, renal blood flow, and urinary sodium excretion. Limb muscle haemodynamics were improved to values greater than the baseline by prostaglandin E₂ in indomethacin and placebo groups.

In an uncontrolled study similar adverse effects on cardiac output and systemic vascular resistance were reported in a group of patients with severe heart failure and associated pre-renal failure.³ Much smaller increases in systemic vascular resistance have also been reported in normal individuals during intravenous infusion of indomethacin.¹¹ Taken with the results of this controlled study, such evidence suggests that products of the cyclooxygenase system (the synthesis of which is inhibited by indomethacin) exert a vasodilating effect which may be of importance in states characterised by vasoconstriction such as heart failure. The reversal of the effects of indomethacin on cardiac output and renal haemodynamics by exogenous prostaglandin E₂ supports the contention that the actions of indomethacin were caused by inhibition of vasodilatory prostaglandin synthesis.

The individual vascular beds in which prostaglandins have a role in maintaining blood flow in heart failure have not been subject to detailed investigation. This study helps to confirm a small body of uncontrolled evidence suggesting that the inhibition of prostaglandin synthesis has adverse effects on renal blood flow in heart failure.⁵ Similar evidence exists for other pathological states in which renal blood flow is reduced such as liver disease.¹² There are also experimental data showing that indomethacin reduces renal blood flow during acute reduction in cardiac output in dogs.¹³ In contrast, inhibition of prostaglandin synthesis in healthy sodium replete individuals has little or no effect on renal perfusion or function suggesting that

normal renal prostaglandin synthesis does not contribute to maintaining renal blood flow.^{14 15}

The effects of indomethacin on limb muscle blood flow in heart failure have been little studied. While no significant change in forearm blood flow or vascular resistance occurred after indomethacin, a small but significant decrease in calf blood flow and increase in vascular resistance was evident. Infusion of exogenous prostaglandin E₂ resulted in large increases in limb blood flow and reductions in vascular resistance. In healthy human individuals indomethacin seems to have no effect on resting skeletal muscle blood flow.¹⁶ In experimental animals, however, angiotensin induced vasoconstriction in skeletal muscle is potentiated by indomethacin.¹⁷ Thus the role of prostaglandins may be to maintain muscle blood flow during conditions of prior vasoconstriction. The reason for the lack of effect of indomethacin on forearm blood flow in heart failure when such an effect was demonstrable in the calf is unclear but may be related to the smaller muscle mass or occasional practical difficulties in obtaining good quality plethysmographic results from the forearm which patients find more difficulty in holding stationary than the calf. There may also be differences in the control mechanisms in the two vascular beds. Differences between the forearm and calf vascular responses to changes in posture, contralateral arm exercise, and mental stress have been described.^{18 19} These are thought to be the result of differences in innervation but it is possible that there may also be differences in local control mechanisms.

The results of study B indicate that some of the beneficial haemodynamic effects of captopril in heart failure may be mediated by an increase in vasodilatory prostaglandin synthesis. Pretreatment with indomethacin significantly attenuated the increase in cardiac output and the reduction in systemic vascular resistance after captopril. A similar study examining the effect of aspirin on the haemodynamic changes after enalapril in heart failure demonstrated that aspirin significantly attenuated the decrease in pulmonary and systemic vascular resistance and left ventricular filling pressure seen when enalapril was given with inactive placebo.²⁰

Indomethacin severely attenuated the renal haemodynamic response to captopril. The increase in renal blood flow as a result of a reduction in renal vascular resistance in the placebo pretreatment group was in contrast to the mean reduction in renal blood flow with a slight increase in vascular resistance seen after indomethacin pretreatment. These results suggest that prostaglandins may be important in mediating the acute increase in renal blood flow caused by angiotensin converting enzyme inhibitors in chronic heart failure. An increase in renal blood flow is believed to be an important part of the action of these agents in heart failure.^{21 22} The increase in renal blood flow is larger than the increase in cardiac output; almost half of the increase in cardiac output may be distributed to the kidney.²¹ This "selective" renal vasodilatation is a feature of

angiotensin converting enzyme inhibitors not seen with most other vasodilators and may be related to an increase in renal vascular prostaglandin synthesis. In some respects, however, the finding is paradoxical as angiotensin II stimulates prostaglandin synthesis.²³

No significant effect of indomethacin pretreatment on captopril mediated changes in forearm and calf blood flow or vascular resistance was demonstrated in this study. This is in contrast to the work of Nishimura *et al*²⁴ who examined the effect of captopril on plasma prostaglandin levels and forearm haemodynamic function in 14 patients with severe heart failure. Captopril caused a significant acute increase in forearm blood flow which was associated with increases in plasma prostaglandin E₂ and prostaglandin I₂ metabolites. Pretreatment with indomethacin eliminated the increase in plasma prostaglandins (leaving the effects on the renin angiotensin system unchanged) and significantly blunted the increase in forearm blood flow. The study was not blinded or controlled and no measurements were made of cardiac output so that it cannot be certain whether the effects of indomethacin were "central" or peripheral. The results of the work presented here lend no support to the suggestion that vasodilatory prostaglandins have a role in increasing muscle blood flow after angiotensin converting enzyme inhibitor treatment in heart failure.

Some methodological problems may have influenced the results obtained in this study. We have measured several variables in a relatively small number of patients raising concern about the possible detection of false positive results and about the power of the study to detect biologically meaningful differences. In a study of this size the two sample unpaired *t* test assuming equal variances has a power of approximately 90% to detect a difference in group means of a magnitude of one standard deviation of the variable and approximately 60% to detect a difference of half a standard deviation. Most of the effects of interest in this study were nearer to the former situation. Although false positive results cannot be excluded the effects appear to be consistent and to occur in the directions that their biological correlation would suggest.

The use of indomethacin as a pharmacological probe to evaluate the effects of inhibition of prostaglandin synthesis assumes that prostaglandins are the only vasoactive system affected by this drug and that indomethacin has no direct vascular actions. Apart from inhibition of cyclo-oxygenase, other effects of indomethacin include inhibition of superoxide generation, interference with leukocyte migration, and *in vitro* inhibition of the enzyme phosphodiesterase,²⁵ although the blood concentrations of indomethacin reached in man are not known to affect other enzyme systems. An investigation of the effects of other structurally dissimilar non-steroidal agents would be helpful. Perhaps surprisingly, no reduction in the concentration of circulating prostaglandin E₂ after administration of indomethacin compared with that after placebo

was demonstrated in this study. Several factors may have influenced the measurement of plasma prostaglandin E₂ concentrations. Although blood was taken via indwelling canulae and collected into tubes containing indomethacin, release of prostaglandins by the vessel wall and cellular components of blood during sample collection may have increased the concentration of the plasma sample tending to obscure decreases due to indomethacin. In addition, all of the available radioimmunoassays, including the one employed in this work, operate close to their lower limits of detection when measuring concentrations of about 5 pg/ml. Perhaps most importantly, it must be remembered that prostaglandins are locally acting substances and thus it is the local tissue concentrations which cause the physiological effects; such concentrations may bear little relation to circulating concentrations. Similarly, the failure of plasma prostaglandin E₂ concentrations to increase with intravenous infusion may be a function of the rapid degradation of these compounds during their passage through the various vascular beds.

Clearance techniques to determine renal blood flow and glomerular filtration rate allowed serial measurements but they are critically dependent on accurate urine volumes, we could not justify the use of urinary catheters and therefore had to assume that voiding was complete. In addition, the use of endogenous creatinine clearance to measure glomerular filtration rates is inaccurate at low levels of glomerular filtration²⁶; inulin or radio-labelled chelate clearance techniques are more accurate. When determining consecutive changes in the same patient, however, the error in creatinine clearance should be consistent and the method avoids repeated exposure to ionising radiation and the generally acknowledged difficulties of inulin assay.

Despite these problems this study provides controlled evidence that prostaglandin synthesis has a role in the regulation of renal and probably also limb muscle blood flow in heart failure. In addition, interactions of captopril with the kinin prostaglandin system may account for some of the well known beneficial effects of this agent in heart failure. This study also confirms the adverse haemodynamic effects of non-steroidal anti-inflammatory agents in heart failure and provides further evidence that the benefits of angiotensin converting enzyme inhibitors in heart failure may be attenuated by such agents. The implications of this interaction in the clinical setting are obvious but may not be generally recognised. In the SOLVD (Studies on Left Ventricular Dysfunction) prevention study, enalapril had a significantly lesser effect on mortality in patients receiving antiplatelet agents than on those not receiving such treatment.²⁷ There is increasing evidence to suggest that not only should non-steroidal agents be avoided in heart failure but that aspirin should be discontinued in patients starting angiotensin converting enzyme inhibitor treatment for heart failure.

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