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Aspirin Inhibits the Acute Venodilator Response to Furosemide in Patients With Chronic Heart Failure

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OBJECTIVES We sought to determine the effect of aspirin on the venodilator effect of furosemide in patients with chronic heart failure (CHF)

BACKGROUND Furosemide has an acute venodilator effect preceding its diuretic action, which is blocked by nonsteroidal anti-inflammatory drugs. The ability of therapeutic doses of aspirin to block this effect of furosemide in patients with CHF has not been studied. For comparison, the venodilator response to nitroglycerin (NTG) was also studied.

METHODS Eleven patients with CHF were randomized to receive placebo, aspirin at 75 mg/day or aspirin at 300 mg/day for 14 days in a double-blind, crossover study. The effect of these pretreatments on the change in forearm venous capacitance (FVC) after 20 mg of intravenous furosemide was measured over 20 min by using venous occlusion plethysmography. In a second study, the effect of 400 μg of sublingual NTG on FVC was documented in 11 similar patients (nine participated in the first study).

RESULTS Mean arterial pressure, heart rate and forearm blood flow did not change in response to furosemide. After placebo pretreatment, furosemide caused an increase in FVC of 2.2% (95% confidence interval [CI] −0.9% to 5.2%; mean response over 20 min). By comparison, FVC fell by −1.1% (95% CI −4.2% to 1.9%) after pretreatment with aspirin at 75 mg/day, and by −3.7% (95% CI −6.8% to −0.7%) after aspirin at 300 mg/day ($p = 0.020$). In the second study, NTG increased FVC by 2.1% (95% CI −1.6% to 5.8%) ($p = 0.95$ vs. furosemide).

CONCLUSIONS In patients with CHF, venodilation occurs within minutes of the administration of intravenous dose of furosemide. Our observation that aspirin inhibits this effect further questions the use of aspirin in patients with CHF. (J Am Coll Cardiol 2001;37:1234–8) © 2001 by the American College of Cardiology

Intravenous furosemide is commonly administered to patients with acute heart failure to relieve pulmonary congestion through diuresis. However, it has been observed for some time that symptomatic relief occurs in these patients before the onset of diuresis (1–3). This effect is believed to result from an independent venodilator action, which precedes the diuretic effect of furosemide (4). This venodilator response to furosemide is inhibited by the cyclooxygenase inhibitor indomethacin (5,6). It is believed, therefore, that venodilation is brought about through the release of local prostaglandins (5,6).

Our hypothesis was that aspirin might also inhibit the acute venodilator response to furosemide in patients with chronic heart failure (CHF). The present study was designed to determine whether clinically relevant doses of aspirin (75 mg/day and 300 mg/day) affected this response to furosemide in patients who continued with all other prescribed heart failure medications, as normal. We also studied the immediate venodilator response to sublingual nitroglycerin (NTG) to compare its effect with that of furosemide.

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METHODS

Subjects. The study was performed with the approval of the Local Ethics Committee of the West Glasgow University Hospital NHS Trust. All patients gave written, informed consent. To study the effects of aspirin on the response to furosemide, 11 patients (10 men and 1 woman; mean [±SD] age 70 ± 7 years) with chronic heart failure (CHF) were studied. Patients had New York Heart Association class II or III CHF caused by left ventricular systolic dysfunction, confirmed by a left ventricular ejection fraction <40% on echocardiography. All patients were clinically stable and received a constant dose of an angiotensin-converting enzyme inhibitor. All medications, apart from aspirin, remained unchanged throughout the study period. To study the response to sublingual NTG, we studied 11 patients (10 men and 1 woman; mean [±SD] age 70 ± 7 years) similar to those who completed the furosemide protocols. Nine of these patients had participated in the furosemide arm of the study; the method of diagnosis and the severity of heart failure were the same as described previously.

Patients were not studied if they had a history of a recent myocardial infarction or cerebrovascular event, or a history of a clinically important hepatic, gastrointestinal, hematologic, endocrine, renal, pulmonary or neurologic disorder. Patients with uncontrolled or insulin-dependent diabetes mellitus or uncontrolled hypertension were also excluded.

Abbreviations and Acronyms

CHF = chronic heart failure
CI = confidence interval
FVC = forearm venous capacitance
NTG = nitroglycerin

Warfarin therapy or known intolerance to nonsteroidal anti-inflammatory drugs, acetaminophen (paracetamol) or nitrates was used as the final exclusion criteria.

Study design. Each patient was studied on three separate occasions in a randomized, double-blind, crossover protocol. Prescribed aspirin therapy was suspended for all patients, who were randomly assigned to 14 days of 75 mg aspirin, 300 mg aspirin or 120 mg acetaminophen (as a nonvasoactive placebo), taken once daily. Acetaminophen was chosen as the placebo for this study to help ensure that the study was done in blinded manner. The preparation of this dose of acetaminophen was soluble, as were the two doses of aspirin used. Acetaminophen at doses 25 times the dose used in the present study does not alter the excretion of the metabolites of prostaglandins, suggesting that it does not inhibit prostaglandin production (7). At the end of each treatment period, patients were studied using forearm venous occlusion plethysmography. During each 14-day period, patients abstained from all other aspirin, aspirin-containing or aspirin-like medications. On the day of the plethysmographic study, patients attended the vascular laboratory at least 5 h after their last light meal, having abstained from alcohol, tobacco and caffeine for 24 h. Patients were instructed to withhold their diuretic therapy on the day of the study, but to take all other medication as normal, including the therapy to which they were randomized at that time (i.e., aspirin 75 mg, aspirin 300 mg or placebo [acetaminophen]).

The response to NTG was measured in patients whether or not they were taking aspirin, as prescribed by their physician. Patients were asked to attend one venous occlusion plethysmographic study, having taken all medications for that day, except for nitrate therapy, as normal. When the patients' therapy included nitrates, they were asked to withhold the last dose that was scheduled before attending the study.

Venous occlusion plethysmography protocol. Studies were performed in a quiet laboratory, as previously described, with the temperature controlled at 25°C (8–10). Patients lay supine on a bed, and a 20-gauge intravenous cannula (Biovalve, Vygon U.K. Ltd., Cirencester, United Kingdom) was inserted into a vein in the left or right forearm and then flushed with 5 ml of physiologic saline solution (0.9% wt/wt NaCl, Steripak Ltd., Runcorn, United Kingdom). In each patient, the forearm that was used to place the cannula on the first study day was used on subsequent study days.

Forearm blood flow and forearm venous capacitance (FVC) were measured by venous occlusion plethysmography using mercury-in-Silastic strain gauges (D.E. Hokanson Inc., Bellevue, Washington) placed around the forearm at the point of greatest circumference (11). Blood flow was measured from the rate of change in forearm circumference after exclusion of the hand's circulation by wrist cuffs inflated to 220 mm Hg and inflation of upper-arm cuffs to 45 mm Hg for 12 s of every 16 s for 2 min, 30 s (8–10). Venous capacitance was determined by the equilibration technique at a venous occlusion pressure of 45 mm Hg for 2 min, 30 s. The cuffs were inflated using rapid cuff inflators (Model E-20, D.E. Hokanson Inc.) (8–10).

Baseline recordings of forearm blood flow and forearm venous capacitance (FVC) in both arms were made every 5 min for 20 min. At the end of 20 min, a 20-mg bolus of furosemide (Antigen Pharmaceuticals, Roscrea, Ireland) was administered over the course of 30 s through the intravenous cannula placed in the forearm. The cannula was then flushed with another 5 ml of physiologic saline solution. Further measurements of forearm blood flow and FVC were made at 5-min intervals for 20 min after the administration of furosemide.

Measurement of the effects of NTG was conducted in identical circumstances, except that instead of intravenous furosemide, one dose of 400 μg NTG (Lipha Pharmaceuticals Ltd., West Drayton, United Kingdom) was administered sublingually.

Blood pressure and heart rate were measured at the same intervals as venous capacitance using an automatic blood pressure monitor (Dinamap Plus 8700; Johnson & Johnson, Newport, United Kingdom), with a lower limb cuff wrapped around the leg.

Voltage output from the plethysmographs (Model EC-4, D.E. Hokanson Inc.) was transferred through MacLab/8E (ADInstruments, Hastings, United Kingdom) to a Macintosh personal computer (PowerMac, Apple Computers Inc., Cupertino, California) for analysis using Chart (version 3.2.8, ADInstruments) and Excel (version 4 for Macintosh, Microsoft Corp., Seattle, Washington).

Data analysis. All hemodynamic data were analyzed without knowledge of the treatment allocation. The baseline for each period was taken as the last point before furosemide administration. The study design has repeated measurements over time (percent change over baseline FVC at 5, 10, 15 and 20 min) at each of three periods. The data were analyzed using a covariance pattern, mixed model, as previously described (12,13), with treatments, time, period and treatment crossed with time as the fixed effects, assuming a compound symmetry covariance pattern for the measurements over time. For the parallel groups' comparison of NTG versus furosemide with placebo, a covariance pattern, mixed model, assuming compound symmetry over the four post-dose time points, was fitted (14). For both the crossover and parallel groups' models, when no treatment by time interaction was found, the main effects model was used. The p values and 95% confidence intervals (CIs) for the three

Table 1. Baseline Values

	Study Day			
	Placebo	**Aspirin, 75 mg**	**Aspirin, 300 mg**	**Nitroglycerin**
Mean arterial pressure (mm Hg)	75.18 ± 16.82	80.18 ± 16.82	77.36 ± 11.99	79.73 ± 12.75
Heart rate (beats/min)	60.82 ± 6.55	61.91 ± 8.73	63.09 ± 5.87	57.64 ± 8.76
Forearm blood flow (ml/min per 100 ml forearm volume)	1.23 ± 0.30	1.16 ± 0.36	1.12 ± 0.44	1.34 ± 0.38
Venous capacitance (ml/100 ml forearm volume)	1.47 ± 0.34	1.54 ± 0.40	1.43 ± 0.37	1.61 ± 0.32

Data are presented as the mean value ± SD.

adjusted pairwise comparisons of treatment mean values (low vs. high dose aspirin and low and high dose aspirin vs. placebo) were Bonferroni-corrected for multiple comparisons. The results are expressed as the mean values with 95% CIs in the text, and as the mean values ± SD in the table, and as the mean values ± SE in figures.

RESULTS

Mean arterial pressure and heart rate. Baseline mean arterial pressure did not differ between treatments (Table 1). Similarly, heart rate did not differ between treatments (Table 1). Mean arterial pressure and heart rate did not alter significantly after administration of furosemide with any of the three treatments or after the administration of NTG.

Forearm blood flow. Baseline forearm blood flow was similar for all treatments (Table 1). Forearm blood flow was not changed by the administration of furosemide or NTG on any study day.

FVC. Baseline FVC did not differ between treatments (Table 1). In the compound symmetry mixed model, the effects of period ($p = 0.53$) and time ($p = 0.84$) and the interaction of time with period ($p = 0.34$) were nonsignificant. In the placebo period, the mean (95% CI) response to furosemide over 20 min was a 2.2% (−0.9% to 5.2%) increase in FVC. After pretreatment with 300 mg of aspirin, there was a 3.7% (−6.8% to −0.7%) fall in FVC when furosemide was administered. After 75 mg aspirin, there was a 1.1% (−4.2% to 1.9%) fall in FVC (Fig. 1). The difference in response to furosemide between placebo, 75 mg aspirin and 300 mg aspirin was statistically significant ($p = 0.020$ by the overall F test, placebo vs. 75 mg aspirin vs. 300 mg aspirin). The response to furosemide after pretreatment with placebo was not significantly different from the response after pretreatment with 75 mg aspirin ($p = 0.29$ after Bonferroni correction, placebo vs. 75 mg aspirin), and was statistically different for 300 mg aspirin ($p = 0.017$ after Bonferroni correction, placebo vs. 300 mg aspirin).

Sublingual NTG caused a 2.1% (95% CI −1.6% to 5.8%) increase in FVC (Fig. 2). This was not statistically different from the increase observed with furosemide administration after placebo pretreatment ($p = 0.95$, NTG vs. furosemide and placebo), with little evidence of a trend over time ($p = 0.65$) or an interaction between treatment and time ($p = 0.25$).

DISCUSSION

Furosemide caused an increase in FVC in our patients with CHF. Previously, venodilation has only been described in patients with acute heart failure secondary to myocardial infarction (4) and in salt-depleted healthy volunteers (5,15–19). Our data support the hypothesis that furosemide has a potentially beneficial hemodynamic effect before diuresis has time to occur, leading to an indirect hemodynamic change. Furthermore, we have demonstrated that the degree of venodilation evoked by furosemide is of a similar magnitude to that evoked by the venodilator NTG.

Effect of aspirin and role of prostaglandins in furosemide-mediated venodilation. A daily dose of 75 mg and 300 mg of the cyclooxygenase inhibitor aspirin inhibited the venous effect of furosemide in our study. This observation provides further evidence that prostaglandins are involved in the mechanism of this vascular action of furosemide (5,20). What is not clear, however, is precisely how inhibition of prostaglandin synthesis inhibits venodilation. The most obvious explanation is that aspirin inhibits the local production of prostaglandins, which provide the dilatory stimulus to veins. Whether these are released

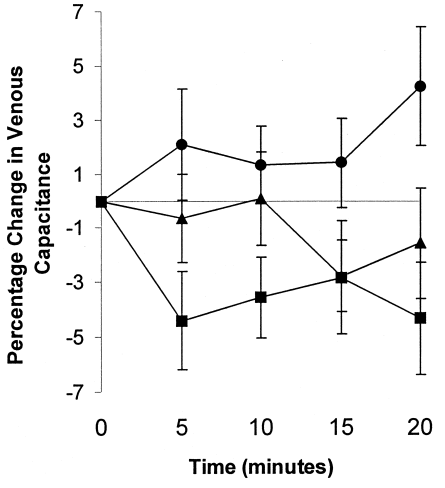

Figure 1. Mean (±SEM) percent change in venous capacitance in response to furosemide according to treatment group. **Line with circles** = placebo group; **line with triangles** = 75-mg aspirin group; **line with squares** = 300-mg aspirin group.

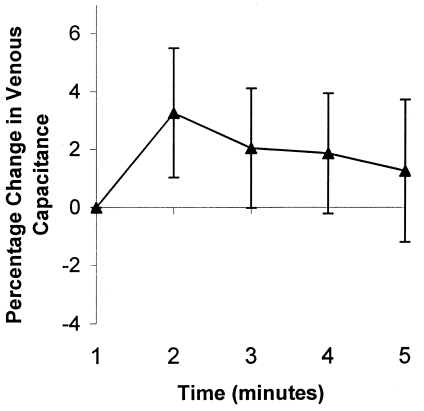

Figure 2. Mean (±SEM) percent change in venous capacitance in response to nitroglycerin **(line with triangles)**.

directly in response to the action of furosemide on the veins (6), or indirectly in response to the action of angiotensin II on the venous endothelium, is unknown (17,21). If the latter is the mechanism, aspirin could block it at two sites. Aspirin may block furosemide-induced renal renin release, which is prostaglandin-dependent (20,22,23), and hence, subsequent generation of angiotensin II. Alternatively, aspirin could block the direct effect of angiotensin II on veins, presumably mediated by cyclooxygenase.

Possible direct effect of aspirin on furosemide action in veins. A direct effect of furosemide in veins may be more likely and has previously been described by Pickkers et al. (6). In their study, furosemide was found to have a direct dilatory effect on the veins on the dorsum of the hands of healthy volunteers. The effect was independent of nitric oxide, and the concentration of furosemide in the veins was far less than the supratherapeutic concentrations that are needed to inhibit $Na^+/K^+/2Cl-$ ion channels (24). Instead, the authors found that the effect of furosemide was blocked by cyclooxygenase inhibition (with indomethacin), and was therefore deemed to be prostaglandin-dependent. However, this direct action of furosemide has not been reported by all investigators (25). Differences in the venous constrictor used and the percentage of preconstriction of the veins before furosemide was administered, however, could account for this discrepancy

Further support for the hypothesis that furosemide stimulates prostaglandin release through action on the venous endothelium comes from a recent in vitro study by Liguori et al. (26). These authors studied the effects of therapeutic concentrations of furosemide on cultures of human umbilical vein endothelium. They reported that secretion of prostacyclin, measured indirectly by 6-ketoPGF$5_{1\alpha}$ production, increased within 5 min of exposure of the culture to furosemide. Secretion was maximal at ~15 min and was maintained for 20 to 30 min. This time scale for the release of prostacyclin fits well with our finding, as well as that of others (4,15,16), that the venous dilator effect of furosemide occurs within 15 to 20 min of drug administration in vivo.

Possible venoconstrictor effect of furosemide in presence of aspirin. It is possible that aspirin did not just block the venodilator action of furosemide, it may have even changed the response to a venoconstrictor one. This might argue for at least some indirect vascular effects of furosemide. In other words, it would seem that the most likely explanation for this reversal of the action of furosemide is that when angiotensin II-stimulated vasodilator prostanoid production is inhibited by aspirin, the unopposed vasoconstrictor effect of angiotensin II is revealed (whereas, normally, it is completely negated by the prostanoids).

Study limitations. The present study was potentially limited by the crossover design used (i.e., because of the risk of a carryover effect). Given the short-lived effect of low dose aspirin on the blood vessel wall, a carryover effect seems most unlikely at the time of the vascular studies, which were carried out at the end of 14 days of randomized treatment. A small sample size and the measurement of the response in only one venous system also may limit this study.

It is not known, from these data, whether all venous beds in the body respond similarly to furosemide. Nevertheless, we have been able to show that furosemide has an effect of similar magnitude to that of the recognized generalized venodilator NTG. Although 9 of 11 patients were taking aspirin at the time of NTG administration, cyclooxgenase inhibitors are known to not inhibit nitrate-induced venodilation (27). The degree of venodilation obtained in our study was also in keeping with that seen previously in older patients on NTG (28).

Conclusions. We have demonstrated that venodilation occurs in patients with CHF in the minutes after the administration of a 20-mg intravenous dose of furosemide. The degree of venodilation is comparable to that which occurs after sublingual NTG administration. This is obviously potentially advantageous, even more so in the clinical scenario of acute heart failure. Our observation that venodilation could be inhibited by both high and low dose aspirin further questions the use of aspirin in patients with CHF (29–31).

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REFERENCES

1. Weinstein FR, Solis-Gil V. The treatment of acute pulmonary edema with furosemide. Curr Ther Res 1966;8:435–40.
2. Biagi RW, Bapat BN. Frusemide in acute pulmonary oedema. Lancet 1967;1:849.
3. Bhatia ML, Singh I, Manchanda SC, Khanna PK, Roy SB. Effect of frusemide on pulmonary blood volume. BMJ 1969;2:551–2.
4. Dikshit K, Vyden JK, Forrester JS, Chaterjee K, Prakash P, Swan HJC. Renal and extrarenal haemodynamic effects of furosemide in congestive heart failure after acute myocardial infarction. N Engl J Med 1973;288:1087–90.
5. Johnston GD, Hiatt WR, Nies AS, Payne A, Murphy RC, Gerber JG.

Factors modifying the early nondiuretic vascular effects of furosemide in man. Circ Res 1983;53:630–5.
6. Pickkers P, Dormans TPJ, Russel FGM, et al. Direct vascular effects of furosemide in humans. Circulation 1997;96:1847–52.
7. Bippi H, Frolich JC. Effects of acetylsalicylic acid and paracetamol alone and in combination on prostanoid synthesis in man. Br J Clin Pharmacol 1990;3:305–10.
8. Love MP, Haynes WG, Gray GA, Webb DJ, McMurray JJV. Vasodilator effects of endothelin-converting enzyme inhibition and endothelin ET(A) receptor blockade in chronic heart failure patients treated with ACE inhibitors. Circulation 1996;94:2131–7.
9. Davie AP, Dargie HJ, McMurray JJV. Role of bradykinin in the vasodilator effects of losartan and enalapril in patients with heart failure. Circulation 1999;100:268–73.
10. Davie AP, McMurray JJ. Effect of angiotensin-(1-7) and bradykinin in patients with heart failure treated with an ACE inhibitor. Hypertension 1999;34:457–60.
11. Whitney RJ. The measurement of volume changes in human limbs. J Physiol (Lond) 1953;121:1–27.
12. Jones B, Kenward R. The analysis of repeated measures in serial measurements. In: Jones B, ed. Design and Analysis of Cross-Over Trials. London: Chapman and Hall, 1989:242–9.
13. Brown H, Prescott R. Other applications of mixed models. In: Brown H, ed. Applied Mixed Models in Medicine. Chichester: Wiley, 1999:295–305.
14. Brown H, Prescott R. Repeated measures data. In: Brown H, ed. Applied Mixed Models in Medicine. Chichester: Wiley, 1999:199–226.
15. Johnston GD, Nicholls DP, Leahey WJ. The dose-response characteristics of the acute non-diuretic peripheral vascular effects of frusemide in normal subjects. Br J Clin Pharmacol 1984;18:75–81.
16. Johnston GD, Nicholls DP, Kondowe GB, Finch MB. Comparison of the acute vascular effects of frusemide and bumetanide. Br J Clin Pharmacol 1986;21:359–64.
17. Johnston GD, Nicholls DP, Leahey WJ, Finch MB. The effects of captopril on the acute vascular responses to frusemide in man. Clin Sci 1983;65:359–63.
18. Johnston GD, O'Conner PC, Nicholls DP, Leahey WJ, Finch MB. The effects of propranolol and digoxin on the acute vascular responses to frusemide in normal man. Br J Clin Pharmacol 1985;19:417–21.
19. Passmore AP, Whitehead EM, Johnston GD. Comparison of the acute renal and peripheral vascular responses to frusemide and bumetanide at low and high doses. Br J Clin Pharmacol 1989;27:305–12.
20. MacKay IG, Muir AL, Watson ML. Contribution of prostaglandins to the systemic and renal vascular response to frusemide in normal man. Br J Clin Pharmacol 1984;17:513–9.
21. Gimbrone MA, Alexander RW. Angiotensin II stimulation of prostaglandin production in cultured human vascular endothelium. Science 1975;189:219–20.
22. Goldiner WH, Valente WA, Hamilton BP, Mersey JH. The effect of prostaglandin inhibition on renin release. J Lab Clin Med 1981;98:929–37.
23. Tan SY, Mulrow PJ. Inhibition of the renin-aldosterone response to furosemide by indomethacin. J Clin Endocrinol Metab 1977;45:174–6.
24. Ellory JC, Stewart CW. The human erythrocyte Cl-dependent Na-K cotransport system as a possible model for studying the action of loop diuretics. Br J Pharmacol 1982;75:183–8.
25. Harada K, Ohmori M, Fujimura A, Ohashi K. No evidence of a direct venodilatory effect of furosemide in healthy human subjects. J Clin Pharmacol 1996;36:271–3.
26. Liguori A, Casini A, Di Loreto M, Andreini I, Napoli C. Loop diuretics enhance secretion of prostacyclin in vitro, in healthy persons, and in patients with chronic heart failure. Eur J Clin Pharmacol 1999;55:117–24.
27. Munzel T, Stewart DJ, Holtz J, Bassenge E. Preferential venoconstriction by cyclooxygenase inhibition in vivo without attenuation of nitroglycerin venodilation. Circulation 1988;78:407–15.
28. Gascho JA, Fanelli C, Zelia R. Aging reduces venous distensibility and the venodilatory response to nitroglycerin in normal subjects. Am J Cardiol 1989;63:1267–70.
29. Cleland JG, Bulpitt CJ, Falk RH, et al. Is aspirin safe for patients with heart failure? Br Heart J 1995:74:215–9.
30. Guazzi M, Pontone G, Agostoni P. Aspirin worsens exercise performance and pulmonary gas exchange in patients with heart failure who are taking angiotensin-converting enzyme inhibitors. Am Heart J 1999;138:254–60.
31. Jones CG, Cleland JGF. Meeting report: the LIDO, HOPE, MOXCON and WASH studies. Eur J Heart Failure 1999;1:425–31.