

Haemodynamic effects of diuretics in heart failure

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The organic mercurials have been known to have a diuretic effect since the sixteenth century, but their use for treating dropsy first began in 1920 in Vienna, when it was realised that a mercury compound being used to treat syphilis greatly increased urine output. The direct descendant of that compound was mersalyl, which was to remain the drug of choice until 1951, when the carbonic anhydrase inhibitors were introduced.

One reason for the slow development of interest in the diuretics was the reluctance of the medical profession to accept that they were as good or even better than digitalis for the management of congestive heart failure (CHF). As late as 1959 it was still necessary for clinical trials to prove what is now generally accepted: that diuretics are more effective than digitalis glycosides and are the drugs of choice for this syndrome.¹

Experience has led to general acceptance that diuretics are very effective in relieving the dyspnoea and the oedema that are the hallmarks of heart failure, but it is still not clear how they achieve these results. Superficially, it seems obvious that if fluid retention results from heart failure, then anything that promotes fluid loss is bound to be beneficial. A diuretic is defined as any substance that promotes increased urine flow. In practice, however, the definition is usually confined to substances that promote the loss of sodium chloride and other small ions together with water from the extracellular fluid of the kidneys (solute diuretics). Hence the suggestion that diuretics should correct the fluid retention of heart failure, but although no one can deny that diuretics mobilise oedema and improve the quality of life, there is evidence to suggest that they may intensify the pathophysiological events that caused the oedema. The advent of peripheral vasodilators and the ACE inhibitors for the treatment of heart failure has added impetus to the examination of diuretics and their long-term effects in heart failure.

The haemodynamic effects of the diuretics

have been studied sporadically over the years, and a mass of contradictory findings has accumulated. It is possible, however, to make some generalisations that may give rise to speculations as to the future role of diuretics in the management of heart failure.

Normal people

There are few published findings on normal volunteers. Only frusemide and ethacrynic acid given intravenously have been studied (table 1). The results indicate a fall in pulmonary capillary wedge pressure and mean pulmonary artery pressure together with a fall in cardiac index and a sharp rise in systemic resistance.²⁻⁴ The mechanism of these effects has been extensively studied by Johnson and his coworkers.⁵ They gave varying doses of frusemide intravenously to a group of nine healthy volunteers, and found a considerable increase in venous capacitance five minutes after the dose which did not increase with higher doses. This was accompanied by a rise in systemic pressure that was correlated with a rise in plasma renin concentrations. They also showed that these effects could be blocked by captopril,⁶ suggesting that the response is mediated through activation of the renin-angiotensin system. This left the venodilatation to be explained, as angiotensin II is a weak vasoconstrictor. In another experiment,⁷ they found that the venodilatation could be blocked by indomethacin, and concluded that it was the result of local release of prostaglandins by angiotensin II. All of these peripheral vascular effects seemed to be divorced from the diuretic effects of the drug, which did not peak until 15 minutes after the dose.⁸ Curiously enough, a comparative study of frusemide and bumetanide concluded that bumetanide (which is also a loop diuretic) had no venodilatatory or renin-angiotensin stimulating properties when given intravenously.⁹ The authors considered that this finding might be dose related, as the early stimulation

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Table 1 Percentage change in haemodynamic effects of diuretics in normal volunteers

Author	No	HR	PCWP	mSAP	mPAP	CO	CI	PVR	Notes
Lal <i>et al</i> ²	8	NC	-	NC	NC	-	↓24	↑7	Frusemide (40 mg iv)
Ramirez and Abelman ³	5	-	-	↑9	-	-	↑12	↑23	Ethacrynic acid (50- 75 mg iv)
Samet and Bernstein ⁴	3	NC	↓16	↑8	↑17	-	↓26	↑48	Ethacrynic acid (100 mg iv)
Conclusion	16	NC	↓16	↑6	↓9	-	↓12	↑26	

HR, heart rate; PCWP, pulmonary capillary wedge pressure; mSAP, mean systemic arterial pressure; mPAP, mean pulmonary artery pressure; CO, cardiac output; CI, cardiac index; PVR, peripheral vascular resistance; NC, no change; iv, intravenous.

Table 2 Percentage change in haemodynamic effects of diuretics after recent infarction

Author	No	HR	PCWP	mSAP	mPAP	CO	CI	PVR
Tattersfield and McNicolls ¹⁰	30	—	—	↑	↓	—	—	—
Valette <i>et al</i> ¹¹								
Frusemide	10	↑10	↓30	↑4	↓23	↓21	—	↑27
Piretanide	10	↑3	↓24	↓3	↓24	22	—	↑25
Larsen ¹²	15	NC	↓20	NC	↓33	—	4	—
Conclusion	45	↑6	↓24	NC	↓27	↓27	—	↑26

Abbreviations as for table 1.

of the renin-angiotensin system seen with loop diuretics only appeared with high dosage, but this is speculative. It is noteworthy that all the patients of Johnson *et al* were salt depleted—that is renin-angiotensin activated—whereas the normal people listed in table 1 were not salt depleted. No other diuretics seem to have been studied.

In summary, both in salt depleted and completely normal people, acute administration of frusemide induces haemodynamic changes that do not seem to be related to its diuretic effect. The fall in pulmonary capillary wedge pressure and the increase in venous capacitance would seem to be desirable properties for the management of heart failure. The decrease in cardiac index and increase in peripheral vascular resistance would seem to be undesirable properties, indicative of sustained activation of the renin-angiotensin system. Whether all diuretics have the same effects in normal subjects is not known.

Recent infarction without clinical heart failure

Patients in this category may be regarded as being in the earliest phase of left ventricular failure—that is, dyskinesia—but seem to have no fluid retention. There have been three publications reporting the effects of acute intravenous frusemide in this category,^{10–12} and the data have been incompletely documented (table 2). The general picture looks similar to that of the normal volunteer studies as the pulmonary capillary wedge pressure (or equivalent) was not unduly raised in these patients (mean < 15 mm Hg). This result was expected.

Acute left ventricular failure after infarction

Naturally, this situation has attracted many studies.^{13–19} All but one have used frusemide (usually intravenously), and there have been no published studies of thiazide diuretics. The

general conclusion is again similar to the findings in the normal population, with a sharp decrease in pulmonary capillary wedge pressure and right sided pressures, accompanied by a fall in cardiac index and a rise in peripheral vascular resistance (table 3). Venous capacitance is considerably increased and all of these changes are greater than seen in normal people, because the values were increased before the diuretic was given. Biagi and Bapat reported a case of acute pulmonary oedema that resolved dramatically with 20 mg of frusemide intravenously but without any diuresis.²⁰ They suggested that the haemodynamic effects of the drug were more important than the diuretic effects, and this concept was taken up by Dikshit *et al*.¹³ They made a series of careful measurements in a group of 20 patients with acute left ventricular failure induced by myocardial infarction, and found that the fall in venous capacitance and pulmonary capillary wedge pressure occurred within 15 minutes of infusion of frusemide, whereas the peak diuretic effect was not reached until 30 minutes. Kiely *et al* plotted stroke work index against pulmonary capillary wedge pressure and concluded that frusemide had no effect on left ventricular function,¹⁴ a conclusion supported by other workers.²¹ Biddle *et al* found that lung water does not start to clear for four hours after frusemide is given, and concluded that venodilatation was the most important effect of the drug.¹⁶ Nishimura and Kanbe, however, studied 30 patients with acute infarction but without pronounced pulmonary oedema and gave intravenous doses of frusemide of 40, 80, or 120 mg depending on the severity of symptoms.²² They found no change in pulmonary capillary wedge pressure until 15 minutes after injection, but a considerable increase in flow of urine at five minutes, reaching a maximum at 15 minutes. The initial pulmonary capillary wedge pressure in the three groups was 15, 22, and 25 mm Hg with an overall mean of 21 mm Hg—that is, comparable with the group of patients studied by Dikshit *et al*.¹³

Table 3 Percentage change in haemodynamic effects of diuretics in acute left ventricular failure after infarction

Author	No	HR	PCWP	mSAP	mPAP	CO	CI	PVR	Venous capacitance
Dikshit <i>et al</i> ¹³	20	NC	↓30	NC	—	—	↓41	↑20	↑58
Kiely <i>et al</i> ¹⁴	15	NC	↓35	slight	—	—	↓18	↓20	—
Davidson <i>et al</i> ¹⁵	10	NC	—	↓6	↓30	—	↓13	NC	—
Biddle and Yu ¹⁶	19	NC	↓29	↓5	↓20	—	NC	—	—
Nelson <i>et al</i> ¹⁷	20	NC	↓15	NC	—	NC	—	NC	—
Scheinman <i>et al</i> ¹⁸ (ethacrinic acid)	14	NC	↓37	NC	↓29	NC	NC	NC	—
Mond <i>et al</i> ¹⁹	17	NC	↓29	NC	↓30	↓4	—	↑7	—
Conclusion	115	NC	↓29	↓5	↓27	NC	↓19	↑18	↑58

Abbreviations as for table 1.

Table 4 Percentage change in haemodynamic effects of diuretics in CHF

Author	No	HR	PCWP	mSAP	mPAP	CO	CI	PVR	Notes
Radar <i>et al</i> ²³ (mersalyl)	14	↓7 ↓24	—	↓19 ↓14	↓20 ↓18	—	↑9 ↑21	↓25 ↓35	Mainly IHD on digoxin
Stampfer <i>et al</i> ²⁴	15	NC	↓46	↓12	↓21	↓5	—	↑21	Mainly RHD on digoxin
Ramirez and Abelman ²⁵	5	—	—	↓5	↓37	—	↑17	↓18	Mainly cardiomyopathy on digoxin
Wilson <i>et al</i> ²⁶ (frusemide thiazides + metolazone)	13	↓12	↓32	↓12	—	↑5	—	↓13	
Verma <i>et al</i> ²⁷ (bumetanide)	12	NC	↓16	↑4	—	—	↓7	↑12	0.25 mg/kg
Isbary <i>et al</i> ²⁹ (frusemide and torasemide)	12	NC	↓23	NC	↓16	—	NC	NC	24 hours off treatment
Langbehn <i>et al</i> ³⁰ (frusemide and torasemide)	9	NC	↓31	↑7	↓17	—	NC	↑4	
Podszus and Piesche ³¹ (oral torasemide (10 mg for 28 days))	12	NC	NC	—	NC	—	↑9	↓6.5	12 min during catheter studies Main corpulmonale
Anand <i>et al</i> ²⁸ (frusemide)	6	↓10	↓4	↓4	↓4	↓7	—	↑7	Sole treatment (40 mg once daily)
Conclusion	65	↓9	↓22	↓6	↓16	↓6	↑7	↓6	

IHD, ischaemic heart disease; RHD, rheumatic heart disease; other abbreviations as for table 1.

In summary, the weight of evidence suggests that the primary effect of the loop diuretics in acute pulmonary oedema is a reduction of preload produced by venodilatation. However, activation of the renin-angiotensin system undoubtedly increases afterload, and this effect is compounded by a significant fall in cardiac index. These effects do not seem to be related to the diuretic effects of the drug, although the findings of Nishimura and Kanbe raise some questions on this issue.²² If venodilatation is the prime mechanism for relief of pulmonary oedema, why not use an agent that produces this effect without activation of the renin-angiotensin system?

Chronic congestive heart failure

The published studies of the effects of diuretics in chronic CHF are on a variety of agents, protocols, therapeutic regimes, and aetiologies (table 4). The best that can be said is that all measured haemodynamic indices were depressed or unchanged by acute intravenous or oral diuretics in patients undergoing chronic treatment with digoxin and diuretics.²³⁻³¹ It is not really justified to attempt a generalisation from such a disparate group, but most studies indicate less venodilatation and peripheral vasoconstriction than in patients with acute left ventricular failure. Anand and his coworkers performed a study on six untreated patients in whom frusemide was the sole medication.³¹ They documented modest falls in right sided pressures and cardiac output with a rise in peripheral vascular resistance. Verma and co-workers obtained similar results with bumetanide²⁷ but perhaps the clearest results were those of Ikram and colleagues who gave larger doses of frusemide to 11 patients on a salt controlled diet and digoxin only.³² They found a rapid fall in right heart pressures without a significant change in cardiac output, urine output, concentrations of aldosterone, or renin activity at five minutes, which was maintained over four hours. With oral treatment over a period of 8-10 days the cardiac output fell and plasma aldosterone and renin activity rose, suggesting late activation of the renin-angiotensin system.

Similar haemodynamic results were found by Fiehring and Achhammer who compared intravenous frusemide and toresamide.³³ These authors also documented comparable reductions in cardiac work during standardised exercise tests.

Rader and colleagues published a detailed study of the organic mercurial compound mersalyl given to 14 patients with congestive heart failure to the resolution of physical signs.²³ The findings were a fall in right sided pressures with an increase in cardiac index and a fall in peripheral vascular resistance. Interestingly, all of these effects were considerably improved by the addition of oral digoxin. This suggests that mersalyl may not induce further activation of the renin-angiotensin system, and might merit further investigation. The only studies involving thiazides produced results similar to those found with the loop diuretics.^{24, 26}

In summary, the diuretics used to treat chronic congestive heart failure seem to produce further activation of the renin-angiotensin system, with a concomitant increase in arteriolar resistance. The organic mercurials seem to be the only exception. Whether this effect is good or bad remains controversial.

Diuretics or vasodilators?

If the effects of the diuretics in producing further activation of the already activated renin-angiotensin system might be disadvantageous to the patient with CHF—and there is no firm evidence that this is the case—then it seems logical to consider vasodilator drugs as a possible alternative. Drugs that produce venodilatation could reproduce the immediate haemodynamic effects of the diuretics, and if they also produce arteriolar dilatation, they might reduce afterload on the failing left ventricle and raise the cardiac output. This hypothesis was tested by Nelson and colleagues in a group of 20 patients with acute left ventricular failure after myocardial infarction.³⁴ Intravenous nitrate was compared with intravenous hydralazine, with and without the addition of intravenous frusemide. Both reduced systemic blood pressure and periph-

eral vascular resistance and the nitrate also reduced pulmonary artery pressure. Cardiac output was increased by hydralazine but not nitrate. The addition of frusemide to nitrates reduced pulmonary capillary wedge pressure by 1 mm Hg, whereas the addition to hydralazine reduced pulmonary capillary wedge pressure by 5 mm Hg, but peripheral vascular resistance was increased. They concluded, with some reservations, that venodilatation with nitrates was preferable to arteriolar dilatation. Franciosa *et al* arrived at similar conclusions for nitroprusside and frusemide.³⁵ It seems that the combination of nitrates and hydralazine has yet to be studied; the results would be of great interest, particularly in chronic CHF.

Conclusion

There can be no doubting the efficacy of the diuretics in mobilisation of oedemic fluid and the relief of dyspnoea. There is, however, a well founded suspicion that these results are related more to their haemodynamic effects than their diuretic effects, and the increased activation of the renin-angiotensin system they produce must be regarded with suspicion. It would seem that the haemodynamic effects are much the same whether the oral or intravenous route is used, but it is not clear that all diuretics induce the same haemodynamic and neurohumoral effects. It is thought that the only reliable measure of drug efficacy in heart failure is increased longevity,³⁶ but there are no studies of the effects of diuretics on prognosis or indeed on quality of life. Until these studies are done, it would seem rash to replace the diuretics with other, more physiological drugs.

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