Fig. 1. Effects of AT1 and AT2 receptor antagonists on Ang II-mediated modulation of noradrenaline release in (A) human atria and (B) renal cortex. An asterisk indicates significant effect of Ang II as compared with control. (Student’s unpaired t-test; *P<0.05). + indicates significant inhibition by antagonists (ANOVA, *P<0.05).

References


Diuretic therapy and diuretic resistance in cardiac failure

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Thiazides and loop diuretics have been the mainstay of treatment for symptomatic cardiac failure for the last 30–40 years. Diuretic therapy in congestive heart failure (CHF) is effective in relieving symptoms and improving cardiovascular haemodynamics [1–7]. The aim of the present report is briefly to review diuretic treatment in CHF, and to discuss underlying mechanisms of diuretic resistance (reviewed in more detail in [8]).

Diuretic therapy

Diuretic therapy in acute cardiac failure with loop diuretics i.v. reduces wedge pressure and increases...
venous capacitance within a few minutes before any measurable increase in urinary output can be seen [1,2]. This rapid haemodynamic improvement is thought to be due to the release of vasodilatory prostaglandins [3]. However, in a study in patients with severe oedema, i.v. piretanide did not cause a decrease in wedge pressure within 120 min (local oedema preventing venous dilation?) [4]. Acute haemodynamic improvements often are sustained during chronic treatment [2,5]. For example, an improvement of NYHA functional class (71 vs 10 NYHA III, 80 vs 112 NYHA II, 0 vs 29 NYHA I at baseline vs 4 weeks) was demonstrated in 151 patients with CHF on 5–10 mg of torasemide for 4 weeks [6,7]. Recent randomized trials have dealt with the treatment of CHF in 17825 patients as given in Table 1. In patients with advanced heart failure (NYHA III/IV), up to 100% are treated with a (loop) diuretic, whereas in patients with less advanced heart failure the percentage of patients on a diuretic is lower (Table 1). Despite the widespread use of diuretics in the treatment of heart failure, a survival benefit for patients on a diuretic has never been proven, though this appears to be very likely, at least in severe pulmonary oedema. Sharpe et al. randomized 60 patients with Q wave infarction and asymptomatic left ventricular dysfunction to treatment with either 40 mg of frusemide or 75 mg of captopril or placebo for 12 months [9]. Left ventricular volumes increased and ejection fraction decreased slightly in both the frusemide and placebo groups, whereas during captopril treatment end-systolic volume decreased and ejection fraction increased. Thus, in patients with asymptomatic left ventricular dysfunction, diuretic monotherapy may not be sufficient to preserve cardiac function.

Diuretic administration in heart failure

A thiazide may be used in less severe CHF; however, in most patients with advanced CHF, a loop diuretic will be necessary [6,7,10]. Hypokalaemia and hypomagnesaemia caused by a loop diuretic or a thiazide may be prevented by combination with a potassium-sparing diuretic (e.g. amiloride, triamterene or spironolactone) [10]. Most heart failure patients are on an angiotensin-converting enzyme (ACE) inhibitor, thereby necessitating careful dose titration and control of serum potassium levels, because of the considerable risk of hyperkalaemia with such a combination therapy [10,11].

Diuretic resistance

In patients started on a diuretic, there is an initial reduction in body weight and total body sodium. However, a new steady state with equal sodium intake and sodium excretion is soon reached. This physiological diuretic resistance has been termed the 'braking phenomenon', which has evolved to prevent excessive fluid and salt losses. Diuretic resistance in a patient with oedema is defined as a clinical state where the braking phenomenon occurs before the therapeutic goal is reached.

Causes and mechanisms of diuretic resistance

**Impaired kidney function.** Pre-renal azotaemia is very often present in patients with severe CHF either treated or untreated [12,13]. In renal failure, tubular delivery of loop diuretics is impaired due to diminished renal blood flow and to reduced activity of the proximal tubular carrier system caused by competition for the co-transporter from accumulated organic anions [14]. Loop diuretic doses have to be increased considerably to achieve sufficient drug concentrations within the tubular lumen.

**Hyponatraemia.** Hyponatraemia has been shown frequently to be associated with reduced diuretic efficacy. Hyponatraemia may be caused by thiazides, but is most often due to CHF with stimulation of thirst, and a non-osmotically stimulated vasopressin system that impairs excretion of free water [15]. This is particularly problematic when patients are not compliant with restrictions in free water intake.

**Pharmacokinetics.** The pharmacokinetics of loop diuretics are altered in CHF (reduced peak concentration, prolonged time to peak concentration, but with no significant reduction of the total amount of frusemide absorbed). These differences are not marked and are overcome by a moderate increase in dose [16]. Furthermore, proximal tubular secretion of the diuretic may be impaired by organic anions that use the same transport pathway (probenecid, penicillins, endogenous organic acids in uraemia) [14].

**Sodium and fluid retention.** In severe CHF, proximal and distal tubular reabsorption of sodium is stimulated, due to direct (proximal) tubular effects of angiotensin II and catecholamines, to facilitation of passive sodium reabsorption in the proximal tubule and to aldosterone-mediated sodium reabsorption in the collecting duct [8,13,17]. Furthermore, resistance to the natriuretic action of atrial natriuretic peptide contributes to sodium retention in CHF [18,19]. Even in asymptomatic heart failure, a defective adaptation of sodium reabsorption in the proximal nephron in response to salt intake is present [20]. One main cause for the activation of sodium retention in CHF is a reduction in ‘effective’ arterial blood volume (reduced cardiac output and/or reduced peripheral vascular resistance) [21]. When patients with severe CHF with increased proximal tubular sodium reabsorption are treated with a loop diuretic, the ensuing natriuresis is reduced further by stimulation of sodium reabsorption at more distal sites of the nephron. In animals treated chronically with a loop diuretic, a marked hypertrophy of the distal tubule was observed [22]. The above mechanisms all contribute to the well-known rightward shift of frusemide dose–response curves in patients with CHF [23].
Table 1. Management of diuretic resistance in cardiac failure

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Fig. 1. Overview of diuretic treatment in cardiac failure according to recent large, randomized trials

Concomitant ACE inhibition. ACE inhibition has been proven successful for the treatment of refractory oedema in patients with diuretic resistance [12]. These beneficial effects may be due to improvement of cardiac performance and suppression of angiotensin II-mediated effects (stimulation of thirst, vasopressin release, tubular sodium reabsorption). However, administration of an ACE inhibitor without a loop diuretic was not effective [26]. It is suggested to institute ACE inhibition in patients with severe CHF on a loop diuretic with small starting doses [10]. However, standard ('standard' as defined in clinical survival trials) doses of ACE inhibitors should be given to all patients with CHF during long-term therapy [10].

**Therapeutic measures**

Control of sodium and fluid intake. A major cause of apparent diuretic resistance in clinical practice is non-compliance with prescribed sodium/fluid intake. A marked increase in sodium absorption 6–24 h after administration of frusemide to healthy subjects on a high sodium diet, thereby abolishing any natriuretic effect of a single daily dose of frusemide, has been shown [24]. In contrast, during a low sodium diet, such a compensatory increase in sodium reabsorption did not occur, because sodium reabsorption had been near maximal already at baseline, thus causing a negative sodium balance during a low-sodium diet, only [2]. Brater et al. have shown also in patients with CHF that depending on the mode of administration (bolus vs infusion) of the loop diuretic bumetanide, retention of an i.v. sodium load occurs [25]. Fluid intake should therefore be limited to 1.0–1.5 l/day and salt intake should be restricted in patients with CHF [10].
sufficiently suppressed (‘aldosterone escape’). In the RALES study, small doses of spironolactone effectively blocked aldosterone action when given in addition to a loop diuretic and an ACE inhibitor [11]. In the pivotal RALES study, a survival benefit of 27% in 1660 patients randomized to spironolactone (mean dose 27 mg/day) vs placebo in addition to ACE inhibition/loop diuretic was shown (B. Pitt; Annual Meeting American Heart Association, November 1998).

Mode of diuretic administration. The route of diuretic administration may need to be varied to overcome diuretic resistance; i.e. administration of a loop diuretic avoids uncertainties regarding intestinal resorption of the diuretic, while a continuous diuretic infusion, multiple bolus or a long-acting diuretic all prevent a rebound in post-diuretic sodium reabsorption [29–31]. Furthermore, the use of prostaglandin synthase inhibitors may contribute to diuretic resistance by impairing renal function [32]. Finally, the management of diuretic resistance is summarized in Table 1.

Future treatment approaches in the patient with heart failure and diuretic resistance may include blockade of the neutral endopeptidase or blockade of the V2 vasopressin receptor [33,34].

References
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