Central Hemodynamic Effects of Diuretic Therapy in Chronic Heart Failure

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Summary. In chronic heart failure diuretic drugs improve central hemodynamic variables and cardiac pumping secondary to altered plasma and extracellular volumes; humoral markers of these changes include increased plasma renin and aldosterone levels. The latter increases are maximal over the first week but decline with chronic therapy. The plasma alpha-ANP levels show a reciprocal effect; these data are compatible with a rapid contraction of the plasma volume which is sustained during chronic therapy.

The acute hemodynamic actions of diuretic agents reflect both immediate and direct vascular actions and also effects secondary to diuresis (volume redistribution). At rest substantial reductions in pulmonary "wedge" pressure (−29%), with a consequent fall in cardiac output (−10%), are described. Total systemic vascular resistance initially increases but "reverse autoregulation" over subsequent weeks returns this elevation gradually towards control values. Tolerance to these initial hemodynamic effects does not occur with maintained therapy; moreover, echocardiographic markers of contractility and exercise capacity may increase. The early venodilator effects of diuretic drugs can be attributed to prostaglandin release and the initial pressor actions to activation of the renin angiotensin system; these vascular actions may have limited relevance to long-term beneficial effects on hemodynamics. Direct pulmonary vasodilation and improved pulmonary compliance remain an interesting finding. Although most patients are both symptomatically and hemodynamically improved at rest, the actions during exercise are more varied. Some individuals with severely impaired left ventricular function show little hemodynamic improvement, whereas those with milder dysfunction usually benefit; in the main this is probably related to the latter being on a steeper cardiac function curve. The impact of diuretic therapy on the underlying disease process is unclear; however, there is little convincing evidence of remodelling or improvement in intrinsic performance (as distinct from that induced by altered loading conditions).

Volume and Humoral Consequences of Diuretic Treatment in Heart Failure

Freis [1] postulated the following cascade of hemodynamic events on initiation of diuretic therapy; these are largely based on the concept of "reverse autoregulation" as expounded by Tobian [2]. Acutely thiazide drugs reduced extracellular fluid volume (ECF) with a resultant fall in central venous pressure and cardiac output; systemic vascular resistance increased. Autoregulation over the subsequent weeks led to a gradual decline in total peripheral resistance, with cardiac output returning towards normal, albeit remaining slightly depressed. Whether the plasma and ECF remained chronically depressed with sustained diuretic therapy was the subject of some controversy; Conway and Lauwers [3] reported that it essentially returned to normal, while Wilson and Freis [4] reported that it remained depressed after 6 months. The latter findings were subsequently confirmed by Tarazi et al. [5].

The humoral correlates of these volume changes observed during chronic diuretic therapy were increased plasma renin and aldosterone levels [6,7]. The degree of plasma renin activity (PRA) stimulation and
the time course have varied between studies; however, recent data indicated that PRA level increased to a maximum over the first week but thereafter fell over several weeks. Nonetheless, long term the PRA remained elevated compared with control pretreatment values. The plasma alpha-ANP (atrial natriuretic peptide) showed an inverse relationship, falling to a minimum by 1 week with a subsequent rise; it remained subnormal during chronic therapy [7].

These results are compatible with a rapid initial fall in plasma volume over the first week's therapy and a small, longer term maintained volume contraction.

There are additional well-known direct (nondiuretic) vascular actions of diuretics; the acute improvement in peripheral and pulmonary vascular compliance may be largely attributed to release of vasodilator prostacyclins from the kidney [8,9]. There are also mild pressor effects noted; the acute elevation of the systemic arterial pressure is due to the effects of the induced angiotensin release on the peripheral vasculature [10,11]. Although it has been suggested that there may be some difference between different agents in terms of their ability to elicit these responses [12,13], such findings have not proven universal [10]. Although such vasodilator actions may contribute to the short-term relief of pulmonary congestion, the main hemodynamic impact of diuretic therapy is not due to these, but rather to the reduction in central circulatory volumes.

**Acute Hemodynamic Actions of Diuretics**

The acute effects of intravenous frusemide (= furosemide) in patients with valvular heart disease [14] or acute myocardial infarction [8,15-19] have been well documented. Frusemide (0.5–1.0 mg/kg IV (40 mg IV fixed dose 14–17) reduced pulmonary artery wedge pressure (PWP), usually with a reduction in cardiac output. On average the PWP fell from 20.7 to 15.7 mmHg (−24%) with an associated fall in cardiac output from 2.77 to 2.46 l/min/m² (−11%). The time course of the effects of frusemide on the cardiac function curve is illustrated in Figure 1. In 20 patients with acute left ventricular failure following myocardial infarction [9], intravenous frusemide resulted in progressive reductions in PWP (and presumably volume) and cardiac index (−13.8%) over 90 minutes. These observations were extended by Franciosa et al. [20]. In 13 patients with acute exacerbation of chronic heart failure, a 200-mg rapid frusemide infusion was compared with the actions of nitroprusside in a crossover study. These diuretic resistant patients showed a relatively small fall in PWP (−3.5 mmHg; 8%) from a very high initial value (43.8 mmHg) and the cardiac index was not altered. However, one would not expect a reduction of 3 mmHg on a starting level of 44 mmHg to contribute much towards an optimization of cardiac pumping; the lack of change in cardiac index and systemic vascular resistance in this study is not at variance with the hemodynamic data obtained in the earlier acute heart failure studies. It is also notable that the maximum reduction in PWP appeared delayed to 60 minutes [20]; the observations of Dikshit et al. [8] and others would anticipate more rapid actions. However, if the hemodynamic actions of diuretics are largely dependent on the induction of diuresis [16,21], and the subsequent contraction of plasma and ECF volume with a redistribution of blood volume away from the central circulation [22,23], then patients with resistant heart failure might be predicted to have an attenuated hemodynamic response together with the prolonged delay to diuresis.

The acute hemodynamic effect of piretanide (12 mg IV) was determined in 11 patients with congestive heart failure due to either congestive cardiomyopathy or mixed mitral valvular disease [24]. There were significant falls in PWP (5.7 to 3.9 mmHg) without a change in cardiac index. The total blood volume in all cases fell more rapidly than the right-sided filling pressures; the initial fall in PWP was evident by 15 minutes and increased over the subsequent 30 minutes.

A comparison of the acute hemodynamic actions of frusemide and piretanide was undertaken in patients recovering from an uncomplicated myocardial infarction who had normal PWP pressures [25]. The vascular activities of both agents were quite similar in