Preventing haemodynamic instability in patients at risk for intra-dialytic hypotension

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Introduction

In haemodialysis patients, structural abnormalities at all levels of the cardiovascular system are common [1-4]. This has enormous clinical implications, which is reflected by the fact that the majority of haemodialysis patients die from cardiovascular disease [5].

Also, the presence of cardiovascular abnormalities is a risk factor for the development of intra-dialytic hypotension [6,7]. This explains also the clinical observation that the incidence of symptomatic hypotension is high in elderly haemodialysis patients, who often have a history of long-standing hypertension and atherosclerosis. As the age of patients on haemodialysis increases steadily, it is a challenge to provide a comfortable treatment in these patients by reducing the incidence of symptomatic hypotensive periods. As will be discussed, this can often be accomplished by the use of relatively simple manoeuvres.

Which patients are at risk for intra-dialytic hypotension?

As will be discussed later, two major factors play a role in the pathogenesis of intra-dialytic hypotension: the decrease in plasma volume and an impairment in cardiovascular regulatory mechanisms. Still, in many haemodialysis patients, fluid removal is not a problem and even a decline in plasma volume of 20% is well tolerated [8]. However, there is a substantial group of especially elderly dialysis patients and patients with primary cardiovascular disease in whom even minor fluid removal results in severe intra-dialytic hypotension. In these patients, the incidence of left ventricular systolic dysfunction is high [9] and is undoubtedly a major risk factor for the symptomatic hypotensive periods during haemodialysis treatment.

However, recent research suggests that also other cardiovascular abnormalities, such as left ventricular hypertrophy and a reduced compliance of the venous system, are of major importance in the pathogenesis of intra-dialytic hypotension [6,7]. Left ventricular hypertrophy is a common finding in haemodialysis patients [10]. Although the pathogenesis of left ventricular hypertrophy in dialysis patients is multifactorial [11], the presence of long-standing hypertension is an especially important risk factor [12].

Left ventricular hypertrophy predominantly affects diastolic function of the left ventricle [13]. In patients with diastolic dysfunction, the compliance (volume/pressure ratio) of the left ventricle is reduced. These patients are very sensitive to changes in plasma volume, as small changes in preload induce large changes in cardiac filling pressure. Therefore, patients with diastolic dysfunction are at risk for both intra-dialytic hypotension and pulmonary oedema [1].

In a study by Ritz et al. [6], patients with recurrent hypotensive periods had a significantly reduced left ventricular compliance compared to a control group of dialysis patients.

Abnormalities of the venous system are also common in haemodialysis patients. In hypertensive haemodialysis patients, venous compliance is reduced, probably due to structural abnormalities of the venous wall [3]. In a morphological study of specimens of the iliac and inferior caval veins of patients with end-stage renal failure and controls, we observed an increase in thickness in the media of the venous wall in hypertensive patients with end-stage renal failure [14].

The haemodynamic consequences of a reduction in venous compliance are 2-fold. Firstly, because of a disturbance in the capillary Starling equilibrium, refill of plasma volume from the interstitium is impaired. We observed a steeper decrease in plasma volume during ultrafiltration in patients with a reduced venous compliance [7]. Secondly, because of the altered volume/pressure relationship of the venous system, patients with a reduced venous compliance are highly sensitive to changes in plasma volume. An inverse relationship was observed between venous compliance and the fall in central venous pressure in dialysis patients during isolated ultrafiltration, which was independent of the effect on plasma volume [7].

Thus, the presence of a reduced venous and left...
ventricular compliance, in combination with a decline in plasma volume and impaired vascular reactivity, poses the patient at risk for severe intra-dialytic hypotensive periods. However, several manoeuvres may reduce the incidence of hypotensive episodes in patients who are hypotensive prone, as discussed below.

**Improving plasma volume preservation**

In patients prone to intra-dialytic hypotension, great care should be applied to avoid large changes in plasma volume. The reduction in plasma volume during haemodialysis depends on the amount of fluid removed and on the refill of plasma volume from the interstitium.

The first step in improving plasma volume preservation in haemodialysis patients is the assessment of optimal dry weight. In patients who are ultrafiltrated to less than their optimal dry weight, refill of plasma volume is impaired because the interstitium is relatively dry [15], which may lead to a quick decline in plasma volume when ultrafiltration is continued. For this goal, today objective methods are available, such as echography of the inferior caval vein or bioimpedance measurements [16].

The second step is the use of a moderate ultrafiltration rate. In a recent study by our group in patients with a compromised cardiovascular system, haemodialysis with a relatively high ultrafiltration rate (1000 ml/h) resulted in a steep decline in plasma volume and a significant reduction in blood pressure compared with a moderate (500 ml/h) ultrafiltration rate [17]. This is explained by the quick removal of plasma volume with insufficient time for refill from the interstitium.

The degree to which plasma volume declines during a constant ultrafiltration rate differs between patients, depending among other factors on the compliance of the vascular system and pre-dialysis hydration state [7,15].

The use of continuous plasma volume measurements [18] may help in optimizing plasma volume preservation because ultrafiltration can be tapered or stopped when a critical reduction in plasma volume has occurred. This critical threshold has to be determined empirically for each individual patient.

Whether plasma volume preservation differs between the various intermittent renal replacement techniques is still a matter of debate. In earlier investigations, pronounced differences in plasma volume preservation were observed between isolated ultrafiltration and ultrafiltration combined with haemodialysis [19,20]. However, in these studies acetate was used as dialysate buffer, which has a predominant effect on the capillary Starling equilibrium, mainly because of precapillary dilatation [21]. In a more recent study, in which bicarbonate dialysis was compared with isolated ultrafiltration, no difference in plasma volume preservation was observed [22].

Another important factor is the sodium concentra-

tion of the dialysate. The use of a physiological or high sodium concentration dialysate prevents a major reduction in plasma osmolality and is clearly associated with an improved plasma volume preservation compared with low-sodium dialysis [23,24], during which the decline in plasma osmolality is much more pronounced. The combination of acetate with a low-sodium concentration dialysate is particularly deleterious for the preservation of plasma volume [25].

Some studies suggest that the use of sodium modelling may reduce the incidence of intra-dialytic hypotension [26,27]. In our opinion, more research concerning the plasma volume changes during haemodialysis in different patient groups is needed before recommending this approach as routine treatment. However, the idea of combining sodium modelling with continuous plasma volume monitoring is appealing. Supraphysiological sodium concentration dialysate should be used with caution because it may lead to thirst and increased inter-dialytic weight gain [28].

Few studies have been performed in which plasma volume preservation is compared between haemodialysis and haemo(dia)filtration. In a study by de Vries et al., a small difference in plasma volume preservation was observed between haemofiltration and bicarbonate dialysis, which was explained by a smaller reduction in plasma osmolality during haemofiltration because of the lower urea clearance [29]. However, the pronounced difference in cardiovascular stability between haemofiltration and haemodialysis is most probably due to differences in vascular reactivity, as will be discussed in the following section.

**Cardiovascular reactivity**

The second important factor in the pathogenesis of hypotensive periods is a disturbance in cardiovascular reactivity during haemodialysis treatment. During a decline in plasma volume, haemodynamic stability can be maintained by an increase in peripheral vascular tone. Constriction of the resistance vessels mainly serves to maintain blood pressure at the pre-capillary level, whereas by venous constriction cardiac filling pressures are maintained by the centralization of blood volume. Also heart rate and myocardial contractility will increase during a decline in plasma volume, although the latter factor is restricted by the reserve in cardiac function of the patient.

It is evident that especially patients with a compromised cardiovascular system depend upon intact regulatory mechanisms to maintain haemodynamic stability during a decline in plasma volume. In many haemodialysis patients signs of autonomic neuropathy can be found, resulting in disturbances in the baroreceptor reflex arc [30]. However, in non-diabetic haemodialysis patients, vascular reactivity during a sympathetic stimulus is remarkably intact [3,31].

However, large differences in cardiovascular reactivity are observed between the various forms of renal replacement therapy. During acetate dialysis, signific-
containing phosphate binders. Dialytic hypotension with low-calcium dialysate in patients with acute renal failure, vascular reactivity improve during 'cold dialysis', with a dialysate temperature of approximately 35°C [36,37]. However, this factor probably does not account for all of the difference [36]. Rapid changes in acid–base and sodium status do not seem to contribute to the reduction in vascular reactivity during haemodialysis (van Kuijk et al., unpublished results). Perhaps activation of vasoactive substances by contact of unsterile dialysate with dialysis membranes plays a role, as suggested by the 'interleukin hypothesis' [38,39].

Vascular reactivity is also more physiological during haemofiltration and is comparable with isolated ultrafiltration. The reason for the haemodynamic differences between haemodialysis and haemofiltration also remain speculative, and a discussion of the possible pathogenetic factors is beyond the scope of this review.

Surprisingly few haemodynamic studies have been performed during haemodiafiltration. In a study in patients with acute renal failure, vascular reactivity was reduced compared with haemofiltration but increased compared with haemodialysis [40].

Haemodialysis treatment itself does not seem to have a negative impact on cardiac contractility, except for the use of acetate in patients with severely impaired cardiac function [34]. Cardiac output may even increase because of a decrease in afterload by peripheral vasodilation during haemodialysis treatment [41]. Therefore, the difference in haemodynamic stability between haemodialysis on the one hand and isolated ultrafiltration and haemofiltration on the other hand is probably explained by differences in vascular reactivity, rather than by differences in cardiac function.

However, several manoeuvres during haemodialysis can influence cardiac function. Even in cardiac-stable patients, haemodynamic stability is better maintained during high-calcium (1.75 mmol/l) compared to low-calcium (1.25 mmol/l) dialysis [42], which is probably explained by differences in cardiac function rather than by an effect on vascular reactivity [42,43]. This should be kept in mind when treating a patient prone to intra-dialytic hypotension with low-calcium dialysate in order to prevent hypercalcaemia by the use of calcium-containing phosphate binders.

Cardiac contractility is increased during cold dialysis [44], probably by sympathetic activation [37]. The improved cardiac function together with the improvement in vascular reactivity explains the reduced number of hypotensive episodes during this form of treatment [45].

Summary and conclusion

Although as yet no major breakthroughs have occurred to improve long-term survival of haemodialysis patients with impaired cardiovascular function, it is possible to reduce morbidity by intra-dialytic hypotension in these patients by the use of relatively simple manoeuvres. In our experience, this can be achieved using the following approach (Table 1).

First, the decline in plasma volume can be reduced by adequate estimation of the optimal dry weight by objective methods, such as echography of the inferior caval vein or bioimpedance measurements. Furthermore, the ultrafiltration rate during haemodialysis should be moderate and should be limited to a maximum value, which has to be defined empirically for each individual patient. Especially in patients with excess inter-dialytic weight gain, isolated ultrafiltration should be used when the required amount of fluid cannot be removed during haemodialysis.

The use of low-sodium dialysate should be avoided. Probably it is best to use a physiological sodium concentration of the dialysate because a greater sodium concentration may result in increased thirst and intra-dialytic weight gain. Sodium profiling should be based on further studies concerning plasma volume changes during haemodialysis in different patient groups.

Because of the deleterious impact of acetate on vascular reactivity, it should never be used in patients prone to hypotensive periods. Vascular reactivity can also be impaired by the use of vasoactive medication prior to haemodialysis treatment. Therefore, in patients prone to hypotensive periods, vasoactive medication should be withheld the morning before haemodialysis, if possible. Also, one should be very cautious with the...
use of low-calcium dialysate in patients with frequent hypotensive periods, and ideally it should be avoided. If the use of these manoeuvres fails to control intradialytic hypotension, one should consider the use of cold dialysate. Switching to haemofiltration or to continuous treatment modes such as CAPD are other options. Future studies should address hemodynamics during other treatment modes, such as haemodiafiltration or acetate-free biofiltration.

References
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