Dialysis hypotension: Do we see light at the end of the tunnel?

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Introduction

Symptomatic hypotension is a common problem in haemodialysis treatment. It seriously impairs the state of well-being of the patients and it may induce severe cardiac arrhythmias. Despite profound improvements of haemodialysis technique in recent years the frequency of recurrent intradialytic hypotensive episodes has remained nearly unchanged (occurring in approximately 20–30% of all HD sessions [1]). Because of the increasing age of today’s dialysis patients and because of the growing prevalence of diabetic end-stage kidney disease, this problem is likely to become even more important in the future.

From a clinical point of view one may consider two groups of subjects susceptible to dialysis hypotension:

(i) A larger group of basically normotensive or hypertensive patients who are prone to intradialytic decreases in systolic blood pressure of 30 mmHg or more, resulting in symptomatic hypotension. Patients in this group are often diabetics or have advanced left ventricular hypertrophy causing diastolic dysfunction.

(ii) A smaller group of patients with sustained hypotension that also persists throughout the interdialytic interval. This group usually includes anephric patients and those that have been on haemodialysis for many years. The systolic blood pressure of these patients will rarely exceed 100 mmHg. A modest reduction in blood pressure triggered by ultrafiltration will suffice to cause symptomatic hypotension.

This contribution is an attempt to develop diagnostic and therapeutic strategies for the prevention of dialysis hypotension on the basis of the—incompletely understood—pathophysiology of hypotension in dialysis patients.

Physiological response to ultrafiltration

Ultrafiltration (UF) removes fluid from the intravascular volume (IVV) compartment. In response to this process there is a fluid shift from the interstitial to the IVV compartment, the so called ‘refill’. The balance between UF and refill has major influence on the IVV. The more efficient the refill in proportion to UF, the more constant the IVV will be maintained. The main factors that influence the refill are listed in Table 1.

When refill lags behind ultrafiltration, other compensatory mechanisms are required to maintain blood pressure. In this context cardiac output, systemic vascular resistance (SVR) or both may increase to keep up perfusion pressure. There is a sequence of regulatory mechanisms that increases arterial and venous vascular tone in response to IVV diminution (extensively reviewed in [2]). These mechanisms are listed in Table 2. Sympathetic activation increases heart rate and contractility. However these effects are not very efficient in blood pressure defence, since their gain is limited by venous return. The latter is usually reduced in states of deficient vascular refill.

Based on these physiological considerations four pathophysiological conditions predisposing to intradialytic hypotension have been intensively investigated: (i) insufficient refill, (ii) autonomic dysfunction, (iii) left ventricular diastolic dysfunction, and (iv) imbalance of vasoactive agents.

Plasma refill

Plasma refill is important for cardiovascular stability during haemodialysis treatment. Its extent determines the gain of neurohumoral compensation. Typical pathophysiological conditions that impair the refill are listed in Table 3. It is paramount to realize that depletion of interstitial volume due to dry-weight error is

<table>
<thead>
<tr>
<th>Table 1. Factors that determine refill</th>
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<tr>
<td>Hydrostatic pressure gradient between the capillary and the interstitial space</td>
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<td>Oncotic pressure gradient between the capillary and the interstitial space</td>
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<tr>
<td>Osmotic gradient between the capillary and the interstitial space during treatment</td>
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<tr>
<td>Hydraulic conductivity of the capillary wall</td>
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<td>Capillary permeability coefficient to plasma proteins</td>
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Table 2. Pattern of physiological response to ultrafiltration

<table>
<thead>
<tr>
<th>Physiological regulatory mechanism</th>
<th>Response</th>
</tr>
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<tr>
<td>Arterial system</td>
<td></td>
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<tr>
<td>Activation of cardiovascular reflex arcs involving:</td>
<td></td>
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<tr>
<td>cardiopulmonary receptors</td>
<td>Increased sympathetic activity</td>
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<tr>
<td>pressoreceptors</td>
<td>Increase of noradrenaline plasma levels</td>
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<tr>
<td>Activation of the renin–angiotensin system and vasopressin</td>
<td>Further increase of sympathetic activity</td>
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<td>Adrenal response</td>
<td>Blood redistribution from peripheral to central compartments (skin and splanchnic circulation)</td>
</tr>
<tr>
<td>Venous system</td>
<td>Increase of heart rate and contractility</td>
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<tr>
<td>Passive recoil of the venous bed due to decreased arteriolar flow, predominantly in skin and splanchnic circulation (De Krogh–Jaeger phenomenon)</td>
<td>Increase in renin, angiotensin II, aldosterone, and vasopressin plasma levels</td>
</tr>
<tr>
<td>Active venoconstriction?</td>
<td>Increase in adrenaline plasma levels</td>
</tr>
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Table 3. Impairment of refill by patient-related factors

<table>
<thead>
<tr>
<th>Pathophysiologial mechanism</th>
<th>Aetiological event</th>
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<tr>
<td>Depletion of interstitial volume</td>
<td>Error in estimation of dry weight</td>
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<tr>
<td>Low effective plasma osmolality</td>
<td>Low dialysate sodium concentration relative to plasma sodium concentration</td>
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<td>Decreased plasma oncotic pressure</td>
<td>Hypoalbuminaemia</td>
</tr>
<tr>
<td>Increased hydrostatic capillary pressure</td>
<td>Congestive heart failure</td>
</tr>
</tbody>
</table>

the most common cause of intradialytic hypotension. To assess this possibility one should resort to an objective method of measurement of the state of hydration (e.g. echocardiography and sonography of the inferior vena cava or measurement of tissue impedance). Several authors could clearly demonstrate that volume-depleted patients experience a significantly more pronounced decline in IVV in response to a given amount of UF than do normovolaemic or hypervolaemic patients [3,4]. In addition to dry weight the total amount and the rate of UF play important roles for intradialytic hypotension. For instance, both a high interdialytic weight gain and a short treatment time usually result in more aggressive UF, which in turn will be followed by an imbalance of the UF/refill ratio even in normovolaemic patients. Attempts to improve the refill in such circumstances have been made using UF profiling. Recommended protocols usually propose one of the following schedules: (i) removal of approximately two-thirds of the total fluid amount in the first half of the treatment, or (ii) a repetitive alternation of very high and very low UF rates, allowing better refill during low UF. However, the results obtained with such UF profiling have been equivocal. It is possible, however, that improved methods of profiling taking into account the actual IVV as well as individual factors may offer some benefit to patients at risk of hypotension in the future.

Furthermore, dialysate sodium concentration has been considered an important factor for plasma refill. A high dialysate sodium will increase the plasma sodium concentration. This results in an osmotic gradient from plasma to the interstitial compartment that improves refill. However, the increase in plasma sodium concentration may induce thirst and a more pronounced interdialytic weight gain. To solve this problem, several forms of sodium ramping were introduced (low→high or high→low dialysate sodium during treatment). The aim is a zero net sodium balance. Again, the results obtained with this method are conflicting. In a study by Sang et al. [5] of 23 patients only five had substantial benefit using this approach. Taken together it is conceivable that both UF profiling and sodium ramping may be beneficial in selected patients; however, at the present time any such patients have to be identified by trial and error.

Finally, it is interesting that isolated UF as well as techniques providing a high convective solute transport (haemofiltration, haemodiafiltration, acetate-free biofiltration) are associated with better cardiovascular stability than HD. This has been shown in numerous studies. This finding is, however, not completely understood. Haemofiltration seems to result both in a better weight and in an improved neurohumoral response to UF [7]. Such techniques may help to reduce hypovolaemic episodes in subjects prone to intradialytic blood pressure drop. A result of this kind was reported by Movilli et al. [8] in a population of elderly HD patients.

**Left ventricular diastolic dysfunction (LVDD)**

Approximately 70% of the dialysis population shows left ventricular hypertrophy [9]. The latter is typically associated with marked diastolic dysfunction. The genesis of left ventricular hypertrophy is multifactorial, and factors other than preceding hypertension also play a role, for example anaemia, hyperparathyroidism, and impaired aortic compliance. Such patients usually have concentric left ventricular hypertrophy and elevated left ventricular enddiastolic pressure (LVEDP) with reduced ventricular compliance. In contrast to this, systolic left ventricular function is usually preserved. The diastolic dysfunction does not cause hypotension per se, rather it is a factor that decreases tolerance to ultrafiltration. A patient with LVDD subjected to inadequate refill in response to UF will probably experience a significant reduction in
cardiac output. This will occur more readily than in a patient without LVDD, because in the former case stroke volume depends more strongly on the elevated LVEDP than it does in the latter. In other words, even a mild reduction in venous return, tolerable to a patient with normal diastolic function, results in a marked decrease in cardiac output and blood pressure in a patient with LVDD. The blood pressure drop in patients with LVDD often will be sudden and pronounced. Furthermore, in this situation an increase in heart rate may not compensate for the drop in cardiac filling, because the associated shortening of diastolic filling time will diminish stroke volume. These events may eventually lead to a dramatic decrease of venous return, resulting in cardiac emptying. This chain of events may lead to paradoxical bradycardia via the Bezold–Jarisch reflex.

In a study by Ruffmann et al. [10], diastolic function in patients prone to intradialytic hypotension was significantly more ‘dysfunctional’ than in a group of stable HD patients.

The cardiac emptying may explain the brisk response of such patients to rapid volume supplementation. The latter will readily improve venous return and thereby re-establish an adequate left ventricular filling. On the other hand, patients with LVDD are also very susceptible to volume overload. This can result in a rapid rise of blood pressure and in cardiac ‘backward failure’, causing pulmonary oedema.

Taken together, correct assessment of dry weight is essential to the management of patients with LVDD. Only modest interdialytic weight gain should be adhered to by the patient. Long-term treatment with an ACE inhibitor may be tried for reduction of left ventricular hypertrophy even in the absence of overt hypertension. In addition the nephrologist should guide the UF judiciously and individually during the dialysis procedure.

**Autonomic dysfunction**

Increasing sympathetic activity is an integral part of the neurohumoral response to UF. This reaction is initiated by the cardiopulmonary and pressoreceptor reflex arc. It results in blood redistribution from skin and splanchnic circulations to central compartments.

Uraemia is associated with autonomic dysfunction, demonstrable even in early states of renal insufficiency [11]. Numerous studies have been performed to clarify the role of impaired autonomic function in dialysis hypotension.

Using different autonomic function tests, most authors reported parasympathetic dysfunction. In persistently hypotensive HD patients this was accompanied by sympathetic impairment [12,13]. These patients are not able to increase heart rate and/or systemic vascular resistance adequately in response to UF [14]. Continuous registration of sympathetic nerve activity in hypotension prone HD patients during UF showed a paradoxical withdrawal of sympathetic drive in their studies. The result was vasodepressor syncope with bradycardic hypotension. However, this mechanism cannot account for all hypotensive episodes, since most intradialytic hypotensive episodes will be accompanied by tachycardia [15]. Bradycardic hypotension seems to be more a product of severe cardiac underfilling than of sympathetic impairment. The dialysis procedure itself appears to have no appreciable effect on autonomic function [16].

As first shown by Elias et al. [17], chronic uraemia is associated with elevated plasma catecholamine levels. This change is attributable to early impairment of the afferent parasympathetic baroreflex arc and to decreased renal clearance of catecholamines. In response to both increased levels of catecholamines and an elevated basal sympathetic tone [14], there is downregulation of adrenoceptors in the cardiovascular system causing impaired responsiveness to sympathetic stimuli [18]. This phenomenon is typically present in persistently hypotensive patients with low tolerance to ultrafiltration [13].

Taken together, some degree of autonomic dysfunction as well as of diminished responsiveness to sympathetic stimuli seems to play a role both in patients with frequent hypotensive episodes and in persistently hypotensive subjects. At the present time a reliable therapy for autonomic impairment is lacking. However, there are two helpful manoeuvres to augment blood redistribution to central compartments. They are: (i) cool dialysis using a dialysate temperature of about 35°C (reviewed in [19]), and (ii) avoidance of food intake during the HD session. Not all patients may tolerate cool HD, however. The negative effect of food intake on haemodynamics during HD seems to be more pronounced in the presence of advanced autonomic neuropathy [20].

Midodrine, a sympathicomimetic drug has been used by practising nephrologists against dialysis hypotension for a long time. Recently midodrine was shown to be effective in improving cardiovascular stability during HD in 10 hypotension-prone patients [21].

**Role of endogenous vasoactive systems**

Numerous studies have looked into the possibility of an imbalance between vasoconstricting and vasodilating endogenous agents as a cause of dialysis hypotension. Investigating this issue is complicated. Most endogenous vasoactive compounds are part of a complex network of regulating factors. In defining the role of an individual agonist, one has to consider not only its plasma concentration, but also the level of any possible endogenous antagonist, the receptor density and the biological response to this setting of agonist/antagonist that is present.

Moore et al. [22] demonstrated higher plasma levels of renin (PRA), angiotensin II (AII), and aldosterone in persistently hypotensive HD patients than in normotensive HD patients. There was a blunted response to
pressor dose infusions of AII in hypotensives. This was attributed to decreased AII-receptor density. Similar results were reported by Esforzado Armengol et al. [13]. In their study PRA and AII levels were highest in the hypertensive HD patients. Corresponding results have also been reported for plasma catecholamines (see above in the section on autonomic dysfunction).

In contrast, anephric patients show significantly lower PRA and AII plasma levels than do those with kidneys present. The fact that PRA and AII is low but not completely absent in anephric patients is usually attributed to extrarenal generation of these compounds. The levels of PRA and AII do not increase in response to volume depletion [23]. This may explain, why some anephric patients are persistently hypotensive and/or have a poor tolerance to UF.

In summary, there seems to be a reduced vascular response to catecholamines and to AII in persistently hypertensive HD patients. This lack of vascular responsiveness may contribute to their sustained low blood pressure and reduced tolerance to ultrafiltration. Whether this is true also for other vasopressors like endothelin-1, arginine vasopressin, or thromboxane A2 is not known at present.

Recently several studies focused on the role of nitric oxide (NO). This agent is a potent vasodilator. It is conceivable in principle that NO could contribute to dialysis hypotension. Based on the interleukin hypothesis, Beasley and Brenner [24] proposed that dialysis causes induction of NO-synthase (iNOS, NOS II). This would result in sustained NO ‘overproduction’ and possibly hypotension. There is evidence indeed to show an association of end stage renal failure with elevated plasma levels of NO-related compounds [25,26]. However, patients on peritoneal dialysis showed similar levels [25]. Measurement of native NO in biological fluids is technically difficult if not impossible at present. It is therefore unclear whether those NO related compounds actually represent the haemodynamically active NO pool [27]. Moreover there is evidence of uraemia-associated endogenous NOS inhibitors (ADMA, [28]). They may be of major importance in terms of NO effectiveness and blood-pressure regulation. We showed recently that infusion of L-NMMA (a blocker of NOS) into the brachial artery of normotensive HD patients and controls results in a similar reduction of forearm blood flow in both groups [29]. This result suggests that NO participates in the regulation of vascular tone in normotensive HD patients and healthy controls alike.

A related question may have to do with sterile dialysate. It is possible that sterile dialysate would improve cardiovascular stability by reducing cytokine release. Van Kuijk et al. [30] treated 10 HD patients with either sterile or unsterile dialysate in a cross-over study. They found no significant differences in blood pressure, heart rate, forearm vascular resistance, and venous tone. These results may suggest that the use of sterile dialysate has little if any influence on vascular reactivity during HD.

The roles of calcitonin-gene-related peptide (CGRP), adrenomedullin, atrial natriuretic peptide, prostaglandins, and other vasodilators in the blood pressure regulation of HD patients have not received a great deal of attention and could not be conclusively clarified. Odar-Cederlof et al. [31] reported a continuous rise of CGRP plasma levels during isovolaemic HD. However, the relevance of this finding for dialysis hypotension is presently unknown.

Prediction of hypovolaemic episodes

An interesting approach to the prediction of hypotensive episodes is the continuous monitoring of the IVV. Such methods may be important because they show the balance between UF and refill.

Several approaches for measuring the IVV have been developed in the past. One method uses the continuous registration of haematocrit or haemoglobin concentration in the extracorporeal circuit. This method requires that the red-cell mass remains unchanged during treatment.

Kim et al. [32] were the first to investigate the relationship between reduction of IVV (as measured by a dilution technique) and hypotension during dialysis. In their study, approximately 80% of hypotensive episodes were predicted by a reduction of IVV below a threshold of 50 ml/kg body mass. Similar results were obtained by Steuer et al. [33]. By continuously monitoring the haematocrit they clearly demonstrated an association between intradialytic morbidity (hypotension, cramping, nausea) and hypovolaemia. In particular there was an individually defined threshold value for the haematocrit at which hypotension became predictable. By manipulating the UF rate in such a way that the haematocrit threshold value was avoided (increasing UF when haematocrit was low; decreasing UF when haematocrit was approaching the threshold), they were successful at reducing hypovolaemic symptoms by 50%. This was accomplished without prolongation of treatment time. Moreover these and other authors [3] found, that hypotension was predicted by an accelerated IVV reduction in the 10 min immediately prior to the event. However, other authors could not reproduce this particular observation [34].

The concept of a threshold haematocrit is an attractive one because of its conceptual relation to an individual blood volume at which neurohumoral mechanisms will fail to maintain an adequate blood pressure. To deal with such an individual threshold, however, a computerized, IVV-controlled regulation of the UF would appear to be promising. Using an automated system that guides the intradialytic IVV along a predefined trajectory, Mancini et al. [35] recently demonstrated a considerable reduction of intradialytic hypotensive episodes compared to standard HD in five hypotension-prone HD patients. None the less there are still several unresolved issues. Bleeding, erythropoietin therapy, recirculation in the fistula, or changes
in neurohumoral responsiveness (due to infection for example) may alter the patient’s ‘usual’ relationship between haematocrit and hypotension. The individual threshold haematocrit will then have to be redefined. This raises questions as to the practicability of this concept in routine dialysis. Nevertheless, most of the patients with frequent intradialytic hypotension benefit from IVV controlled UF according to our own experience. Newer and commercially available automatic devices have been recently introduced. Such devices will also control dialysate conductivity. They may eventually allow an improved handling of the refill along with better prevention of hypotension.

**Summary: approach to the susceptible patient**

Dialysis hypotension is a multifactorial phenomenon. With respect to the individual patient, one or more of the factors discussed may predominate over others and they may occur in an unpredictable fashion. Despite clinical differences between hypotension-prone and persistently hypertensive patients, recommendations are basically the same for both conditions. Generally, therapy should improve (i) the refill and (ii) the neurohumoral response to UF.

Accordingly we propose the following guidelines for diagnosis and treatment:

1. Identify the susceptible patient by case history (long-term diabetes mellitus, anephric patient, valvular heart disease, diastolic/systolic cardiac dysfunction, poor nutritional state, anaemia etc.).
2. Assess and maintain dry weight by an objective method; avoid high interdialytic weight gain.
4. Allow for adequate treatment time; avoid aggressive UF.
5. Lower the dialysate temperature; avoid food intake patients.
6. Try sodium ramping and/or UF profiling; monitor IVV continuously, perhaps following the haematocrit threshold concept.
7. Switch to HF, HDF, or AFB.
8. Try sympathicomimetic drugs (midodrine) before treatment.
9. Consider peritoneal dialysis.

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