circulation is found as a disulfide — either as a mixed disulfide with protein, or as a low molecular species (homocystine and homocysteine–cysteine mixed disulfide). Therefore, efficacious treatment of hyperhomocysteinemia must result in the lowering of all disulfide forms of homocysteine. As Perna *et al.*[4] and others have shown, this is usually not possible in patients with ESRD when current therapeutic approaches are used. Patients with ESRD have much higher levels of tHcy than patients with coronary artery disease. A concerted effort is needed to identify homocysteinylated proteins in the ESRD patient population. Alternatively, experiments should be designed to isolate and identify homocysteinylated proteins from *in vivo* rather than *in vitro* settings. Protein homocysteinylation, whether it be *N*-linked or *S*-linked, may be the underlying mechanism in homocysteine causality.

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see original article on page 877

Adenosine and dialysis hypotension

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In this issue, Imai *et al.* report the results of a double-blind placebo-controlled study on the effect of an adenosine A1 receptor antagonist, FK352, on the incidence of dialysis hypotension in hypotension-prone patients. This Commentary discusses the use of selective adenosine A1 receptor antagonists for the prevention of dialysis hypotension from the perspective of the potential role of adenosine in its pathogenesis.

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Dialysis hypotension

Dialysis hypotension is one of the most frequent complications of hemodialysis and can lead to serious vascular events such as cerebral, cardiac, and mesenteric ischemia or infarction. Frequent dialysis hypotension contributes to overhydration because of an inability to reach dry weight and may lead to underdialysis because of interruptions or early termination of the dialysis session.

The cause of dialysis hypotension is multifactorial. The basic concept, however, is that frank hypotension occurs only when cardiovascular compensatory mechanisms do not adequately compensate for the inevitable blood volume reduction that results from the imbalance between the ultrafiltration rate and the plasma refilling rate.[1] Sudden hypotension can be triggered especially by activation of the sympatico-inhibitory cardiopressor reflex (Bezold-Jarisch reflex) in the context of a critical blood volume decline, impaired cardiovascular compensatory mechanisms, and cardiac underfilling.[2] Structural cardiovascular changes such as left ventricular hypertrophy and diastolic dysfunction also play an important role, as these conditions oppose ventricular filling and predispose to a fall in end-diastolic volume and stroke volume.

Standard measures to prevent or alleviate dialysis hypotension include careful assessment of dry weight, limitation of fluid and salt intake, reduction of the dialysate temperature, abstinence from food during hemodialysis, use of bicarbonate instead of acetate as buffer in the dialysate, avoidance of low-sodium and low-calcium dialysate, and adjustment of the dosage and/or time of administration of antihypertensive drugs. Notably, one of the most effective strategies to prevent dialysis hypotension is to increase the dialysis time and/or the dialysis frequency, for example by short daily hemodialysis or frequent nocturnal (home) hemodialysis. Finally, several classes of drugs have been reported to decrease the incidence of dialysis hypotension: for instance, the selective α_1 adrenergic agonist midodrine, the norepinephrine precursor L-*threo*-3,4-dihydroxyphenylserine (L-DOPS), and the selective serotonin reuptake inhibitor sertraline hydrochloride. Imai *et al.*[3] (this issue) now add a new class of drugs, the adenosine A1 receptor antagonists, to the therapeutic arsenal to combat dialysis hypotension. Drug treatment for dialysis hypotension, however, should be considered only when the measures listed above fail to prevent hypotension.

Adenosine

Adenosine is an endogenous purine nucleoside with vasodilating, cardiodepressant,

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and cardioprotective properties. Adenosine is released by endothelial cells and vascular myocytes, particularly during ischemia. Adenosine triphosphate and adenosine are also released by sympathetic fibers and by poorly myelinated or nonmyelinated fibers (discussed by Saadjian *et al.*[4]).

The effects of adenosine are mediated by specific cell-surface receptors.[5] Adenosine-induced artery relaxation is mediated by adenosine A2 receptors. The activation of A1 receptors mediates cardiac depression through negative chronotropic and inotropic effects and diminishes blood vessel tone via the prejunctional inhibition of neurotransmitter release on the perivascular sympathetic and capsaicin-sensitive sensory afferents.[4] Importantly, stimulation of adenosine A1 receptors by adenosine triggers and mediates ischemic preconditioning of cardiac muscle, which delays ischemia-induced cell death and decreases infarct size.[6]

Adenosine has a very short half-time (seconds), because there is rapid scavenging by many types of cells, including erythrocytes, and because it is rapidly degraded. Rapid changes in plasma adenosine concentrations are, therefore, difficult to detect. Metabolites of adenosine such as inosine and hypoxanthine are more stable, and plasma levels are thought to reflect adenosine release.

What is the evidence that adenosine plays a role in dialysis hypotension?

Patients on maintenance hemodialysis were found to have increased predialysis plasma levels of adenosine and inosine in comparison with healthy controls and patients on peritoneal dialysis.[7] During hemodialysis, plasma levels of adenosine and inosine rose even further compared with predialysis levels.[7] A previous study reported higher intradialytic plasma concentrations of adenosine metabolites in patients who were dialyzed with an acetate-based dialysate in comparison with patients on a bicarbonate-based dialysate.[8] This finding can be explained by the conversion of acetate to lactate in the liver, a process that involves dephosphorylation of adenosine triphosphate to adenosine monophosphate, which is converted to adenosine in a concentration-dependent manner.

To date, there are two studies from one group that have addressed the relationship between dialysis hypotension and plasma levels of adenosine metabolites.[9,10] Shinzato *et al.* showed that sudden, but not gradual, intradialytic hypotension was associated with increases in plasma levels of adenosine metabolites in comparison with predialysis and prehypotension levels.[9,10] In light of their findings, Shinzato *et al.* postulated an interesting hypothesis on the pathogenic role of adenosine in dialysis hypotension (Figure 1). However, elevated levels of adenosine metabolites do not prove that adenosine plays a pathogenic role, as adenosine release may have simply resulted from tissue ischemia that accompanied the sudden hypotension. Notably, in the first study of Shinzato *et al.*, the blood pressure nadir was much lower in patients with sudden hypotension than in those with gradual hypotension.[9] In their second study, blood pressure data were not reported.[10] Until now, the relationship between sudden dialysis hypotension and increased plasma levels of adenosine metabolites has not been confirmed by other groups.

Indirect evidence for a role of adenosine was sought by adenosine receptor blockade by the nonselective (A1 and A2) adenosine receptor antagonist caffeine. In a placebo-controlled crossover study, caffeine was indeed found to prevent sudden, and not gradual, intradialytic hypotension.[10] However, caffeine has other cardiovascular effects besides adenosine receptor antagonism that may have led to its beneficial effect.

The nucleoside transport inhibitor dipyridamole inhibits cellular uptake of adenosine and increases its half-time. If adenosine indeed plays an important role in the pathogenesis of dialysis hypotension, one would expect the use of dipyridamole to be associated with an increased incidence of dialysis hypotension. However, to my knowledge, no studies have linked chronic dipyridamole use to an increased incidence of dialysis hypotension. The lack of such reports, however, does not rule out such a relationship.

There are interesting similarities between sudden dialysis hypotension and disorders characterized by sudden hemodynamic instability due to autonomic neuropathy, such as neurocardiogenic syncope. Both are characterized by relative or absolute bradycardia, sudden hypotension, and arterial vasodilatation. A paradoxical withdrawal of central sympathetic outflow is thought to play a role in these disorders. Exogenous adenosine or adenosine triphosphate is an effective agent for the provocation of neurally mediated syncope in susceptible patients.[4] Patients with unexplained syncope who had a positive tilt test were found to have elevated baseline adenosine plasma levels. Adenosine plasma levels rose significantly during tilt testing-induced syncope in these patients.[4]

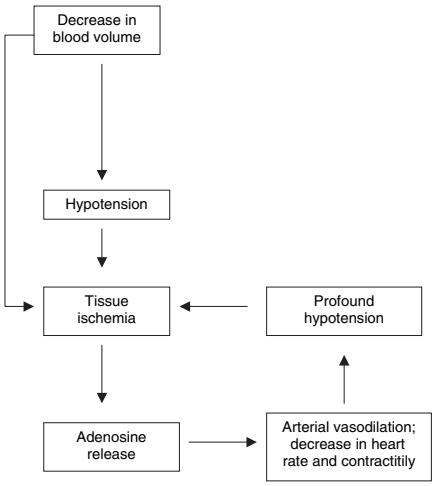

Figure 1 | Hypothesis on the role of adenosine in dialysis hypotension. A decrease in circulating blood volume may lead to tissue ischemia, either as a result of vasoconstriction in certain vascular beds (for example, the splanchnic circulation) or as a result of hypovolemia-induced systemic arterial hypotension. The ischemia results in increased local adenosine release, which causes inhibition of norepinephrine release, vasodilation, and a decrease in heart rate and contractitily. These adenosine-mediated cardiovascular effects result in deepening hypotension.[9,10]

FK352 for the prevention of dialysis hypotension?

In the well-designed study of Imai *et al.*, FK352 had a significant but modest effect on the incidence of dialysis hypotension.[3] Overall, FK352 reduced the occurrence of intradialytic hypotension by 12.8% in comparison with that seen during the observation period. The incidence of dialysis hypotension during the active treatment period did not differ significantly

between FK352 (56.1%) and placebo (62.5%). During the observation period, the incidence of dialysis hypotension was slightly higher in the FK352 (68.4%) than in the placebo group (54.2%). Imai *et al.* do not provide data on the cardiovascular comorbidity of the study group. Notably, patients randomized to FK352 were on dialysis significantly longer than those randomized to placebo. Therefore, it is possible that the FK352 group comprised more patients with serious cardiovascular comorbidity, contributing to the higher incidence of dialysis hypotension during the observation period.

The postdialysis weight was kept constant throughout the study. Weight is not the best marker of an adequate hydration status, as a change in lean body mass may occur unnoticed because of an opposite change in extracellular volume. However, unless FK352 influenced appetite, it is unlikely that a change in real dry weight influenced the results, because of the randomized and double-blind design of the study.

Imai *et al.*[3] did not report plasma levels of adenosine (metabolites) to show that dialysis hypotension was indeed associated with increased adenosine release. They did not perform detailed studies on the effects of FK352 with respect to the cardiovascular and autonomic nervous system.

Concluding remarks

The study of Imai *et al.*[3] adds weight to the attractive hypothesis that adenosine plays a role in the pathogenesis of dialysis hypotension. It is plausible that adenosine plays a role as a mediator in the deepening of hypotension. However, in my opinion, this concept is still not proven. The availability of specific adenosine receptor antagonists, however, will undoubtedly facilitate future research to delineate the exact role of adenosine in dialysis hypotension. Such studies should preferably include detailed assessment of the effects of these drugs on vascular tone, heart function, and the autonomic nervous system.

At present, FK352 cannot be recommended as a drug for prevention of dialysis hypotension. First, as Imai *et al.*[3] also point out, the optimal dose and time of administration must be determined. Next, efficacy should be confirmed in another clinical trial with hypotension-prone dialysis patients. Finally, the safety of this class of drugs should be established especially with regard to possible cardiovascular side effects. Special attention should be given to the possible occurrence of (silent) cardiac ischemia, as adenosine mediates thoracic chest pain in cardiac ischemia and adenosine A1 receptor antagonism may impair the occurrence of cardioprotective ischemic preconditioning.

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