

MECHANISM OF DIALYSIS-INDUCED HYPOTENSION

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ABSTRACT

Dialysis-induced hypotension, the sharp decrease in blood pressure occurring during hemodialysis, remains one of the most difficult problems associated with hemodialysis even today. However, there is yet no established theory to explain the mechanism triggering dialysis-induced hypotension.

This review attempts to offer a consistent and cohesive source of information on the hemodynamics during dialysis-induced hypotension, and then analyzes etiologic factors in such hypotension reported by various investigators. Finally, three hypotheses concerning the mechanism of dialysis-induced hypotension including our own are introduced.

HEMODYNAMICS DURING DIALYSIS-INDUCED HYPOTENSION

The mean arterial blood pressure is the resultant product of cardiac output and total peripheral resistance. Therefore, dialysis-induced hypotension should be the result of lowered cardiac output and/or a decrease in total peripheral resistance.

Maeda et al.¹⁾ measured the hemodynamic parameters using the Swan-Ganz catheter immediately before and at the time of dialysis-induced hypotension, as well as after the blood pressure recovered under appropriate treatment. They found that as the blood pressure sharply fell, the cardiac output decreased but the total peripheral resistance failed to show any significant change. Azancot et al.²⁾ in the same type of research, reported that the cardiac output fell but the total peripheral resistance remained unchanged at the time hypotension developed.

The absence of any compensatory increase in the total peripheral resistance in relation to the decreased cardiac output, which is the common finding in either of the above investigations, may reflect the fact that hypotension involves some sympathetic failure. (Heart rate did not change at the time of dialysis-induced hypotension in either investigation.)

The decrease in cardiac output is the result of either lowered myocardial contractility or diminished venous return to the right atrium (or heart rate). Therefore, the decreased cardiac output at the time of dialysis-induced hypotension can be due to either the sudden reduction of myocardial contractility or diminished venous return. (As mentioned above, the heart rate does not change during hypotension.)

Numerous investigators have demonstrated that, in the hypovolemic condition, changes in myocardial contractility and heart rate do not exert much influence on the cardiac dynamics. In unanesthetized sheep, for example, blockade of beta-adrenergic responses with propranolol had little effect on the hemodynamic response to slow hemorrhage³⁾. In conscious dogs, cardiac denervation⁴⁾ or beta-adrenergic blockade⁵⁾ has a minimal effect on the hemodynamic response to hemorrhage. These findings suggest that the lowered cardiac output at the time of dialysis-

induced hypotension does not result from an abruptly reduced myocardial contractility but from a sharply diminished venous return to the right atrium, since the hypotension usually occurs during a hypovolemic condition. Moreover, the decreased mean right atrial pressure¹⁾ and mean pulmonary arterial pressure²⁾ which occur at the time of hypotension, indicate that at least one reason for the lowered cardiac output is the diminished venous return.

The reduced venous return to the right atrium must be due either to the rapid contraction of blood volume or to some kind of blood redistribution. If the rapid contraction of blood volume were the reason for the decrease in the venous return during dialysis-induced hypotension, it could only be because of the hemoconcentration due to a fluid shift from the plasma compartment to the interstitial compartment. However, Maeda *et al.*^{1,6)}, based on their studies of the continuous hematocrit monitoring during hemodialysis, discovered that there was no rapid hemoconcentration at the onset of hypotension. This finding suggests that the diminished venous return at the time of dialysis-induced hypotension results from redistribution of blood due to some dramatic and sudden increase in vascular capacity.

Splanchnic^{7,8)} and cutaneous⁹⁾ circulations are extremely important blood reservoirs, the volume of which can contract during hypovolemia. Therefore, the abrupt redistribution of blood at the time of hypotension would surely bring about extensive involvement of one or both of these vascular beds. Recently, Nakai *et al.*¹⁰⁾ suggested that cutaneous circulation did not increase at the time of dialysis-induced hypotension. Using an infrared ray monitoring system, they measured continuously the skin temperature during hemodialysis, only to find it did not rise but rather fell when hypotension occurred.

Circulation in other organs may well increase at the time of dialysis-induced hypotension. However, the compliance of the vascular beds of these organs is far lower than that of a splanchnic vascular bed. Hence, although no study to date has clearly demonstrated that the splanchnic vascular bed is most extensively involved in redistribution of blood occurring at the time of dialysis-induced hypotension, there is little reason to believe that the increased vascular capacity in other organs is the main cause of redistribution of blood at the time of hypotension.

There are two mechanisms whereby the regional vascular capacity can be increased. One is a reduction of venous wall tension. The actual decrease in venous wall tension¹¹⁾ and the elevation¹²⁾ of plasma levels of calcitonin-gene-related peptide, which is a vasodilatory substance, might suggest that the reduction of venous wall tension plays some role in the increased regional vascular capacity occurring at the time of dialysis-induced hypotension. The other mechanism for the increased regional vascular capacity is the elevation in venous bed distending pressure due to the decrease in resistance vessel tone (De Jager-Krogh phenomenon)^{13,14,15)}. This elevation of distending pressure can cause prominent sequestration of blood in the venous bed and consequent diminution of venous return¹⁶⁾.

ETIOLOGIC FACTORS IN DIALYSIS-INDUCED HYPOTENSION

In attempting to explain the cause of the hemodynamic changes at the time of hypotension discussed above, the analysis of the various etiologic factors in dialysis-induced hypotension is extremely important. Here, we will discuss the main etiologic factors proposed to date.

1. Hypovolemia

Clinical experience has made it a matter beyond doubt that one most important factor in dialysis-induced hypotension is hypovolemia. However, Maeda *et al.*⁶⁾ have demonstrated that such hypotension is not the direct result of hypovolemia. In their study, they measured the hematocrit

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value continuously during hemodialysis using the system they had developed, and found that there was no contraction of blood volume at the time of dialysis-induced hypotension and that the hypotension occurred when the blood volume was more than 10% higher than the minimum level in the course of hemodialysis.

The mechanism by which hypovolemia contributes to dialysis-induced hypotension remains unknown. Hypovolemia may play a role in the dialysis-induced hypotension via one or another secondary step; or dialysis-induced hypotension may result from the combining of hypovolemia with some sudden failure of a compensatory mechanism for entirely different reasons.

Hypovolemia can result when the ultrafiltration rate exceeds the plasma refilling rate (rate of fluid shift from the interstitial compartment to the plasma compartment)^{17,18}. Thus, not only the large and rapid ultrafiltration but the factors diminishing the plasma refilling rate are what exacerbate the hypovolemia.

The two most important determinants of the plasma refilling rate, as reflected in Starling's principle, are the static pressure gradient and the oncotic pressure gradient between the plasma and the interstitial compartments through the capillary wall. Thus, the plasma refilling rate would be lower in patients with a lower predialysis plasma protein concentration. The plasma refilling rate is also affected by interstitial fluid volume. The contracted interstitial fluid volume would translate into lower interstitial static pressure and higher interstitial oncotic pressure. Hence, when the patient is close to "dry weight," the plasma refilling rate is less¹⁹.

A low dialysate sodium level serves to lower the plasma refilling rate through the greater ensuing diminution of interstitial volume because of the fluid shift from the extracellular to the intracellular compartment^{17,18}. Daugirdas et al.²⁰, for example, showed in their dog experiments that the plasma volume decreases more quickly when the dialysate sodium level is lower than the plasma sodium level. Kimura et al.¹⁸ demonstrated in human that the plasma volume decrease became marked and swift whenever a low sodium dialysate was used during the hemodialysis. Van Stone et al.²¹ also showed that when the dialysate sodium concentration is below the plasma sodium concentration, there is a fluid shift from the extracellular to the intracellular compartment.

2. Dialysate temperature

Employment of a warm dialysate results in unstable hemodynamics, while use of a cool dialysate leads to stabilization^{22,23}. The core body-temperature rise resulting from the employment of a warm dialysate leads to a resultant decrease in cutaneous resistance vessel tone and increased cutaneous circulation; on the other hand, the core body-temperature fall resulting from the use of a cool dialysate leads to an increase in cutaneous resistance vessel tone and a decrease in cutaneous circulation. (The reader is referred to several excellent reviews on thermoregulatory control of human cutaneous circulation²⁴⁻²⁶.)

The experiments performed by Maggiore et al.²⁷ suggested that at least some of the hemodynamic differences between hemofiltration and hemodialysis²⁸⁻³⁰ are due to a thermal factor. They indicated that standard hemofiltration using warmed replacement fluid was not always thermally equivalent to conventional hemodialysis using a warmed dialysate. Thus, they compared hemodialysis with thermally equivalent hemofiltration in terms of vascular stability and found that there were no significant differences in blood pressure between the two treatment modes.

3. Autonomic insufficiency

It is well recognized that there is baroreflex arc dysfunction in hemodialysis patients³¹⁻³⁸. To date, however, it remains a matter of controversy whether or not this autonomic insufficiency

plays a role in triggering dialysis-induced hypotension. Kersh *et al.*³¹⁾ showed that on the basis of the Valsalva maneuver and the amyl nitrate test, six of eight patients who suffered severe hypotension during hemodialysis had autonomic insufficiency. On the other hand, Nies *et al.*³²⁾ reported no difference in the response to the Valsalva maneuver between hypotension-prone and hypotension-resistant patients. Lilley *et al.*³⁴⁾ and Nakashima *et al.*³⁹⁾ found no difference between hypotension-prone and hypotension-resistant patients in terms of blood pressure response to tilting. Thus, the autonomic insufficiency experienced by a substantial proportion of hemodialysis patients may not be the cause of dialysis-induced hypotension.

Maeda *et al.*⁴⁰⁾ made an interesting discovery based upon plasma catecholamine levels estimated from ultrafiltrate catecholamine levels: although the estimated plasma catecholamine levels rose significantly immediately before the onset of hypotension as compared with the time at which hemodialysis was begun, they decreased to the predialysis level when the hypotension occurred; and when the appropriate hypotension treatment was given and the crisis passed, they again rose to the pre-hypotension level. Based upon these results, the investigators considered acute sympathetic failure to play a role in the dialysis-induced hypotension, and they hypothesized that this failure was separate from the autonomic insufficiency that hemodialysis patients already have outside of hemodialysis. The fact that at the time of dialysis-induced hypotension there was no compensatory elevation in the heart rate^{1,2)} may well suggest a connection between hypotension and acute sympathetic failure.

4. *Decreasing plasma osmolality*

Kobayashi *et al.*⁴¹⁾ first reported that isolated ultrafiltration did not produce symptomatic hypotension. The result was later confirmed by Ing *et al.*⁴²⁾. Moreover, Bergström *et al.*⁴³⁾ and Keshaviah *et al.*⁴⁴⁾ demonstrated that isolated ultrafiltration was well tolerated but not when combined with diffusion. This series of observations demonstrates that diffusive solute transport plays a key role in dialysis-induced hypotension. However, which aspect of diffusive solute transport is responsible for dialysis-induced hypotension is as yet unclear.

A fluid shift from the extracellular to the intracellular compartment due to decreased plasma osmolality may be one of the reasons for the unstable hemodynamics accompanying highly diffusive solute transport. In fact, Falls *et al.*⁴⁵⁾ and Oh *et al.*⁴⁶⁾ indicated in early studies that hemodialysis provokes a fluid shift on the order of 1 to 1.5 liters from the extracellular to the intracellular compartment.

Sodium is the most important solute determining plasma osmolality. Thus, as discussed earlier, when the dialysate sodium concentration is lower than the plasma sodium concentration, a fluid shift from the extracellular to the intracellular compartment results^{17,18,20,21)}. Urea is another solute which substantially determines plasma osmolality. Even so, it has been believed that decreased plasma urea concentration during hemodialysis does not affect the rate of plasma volume contraction, since it rapidly traverses various body water compartments^{47,48)}. However, there has been a recent report of a substantial rebound of plasma urea concentration immediately after completion of hemodialysis⁴⁹⁾. This finding would tend to indicate a substantial fluid shift from the extracellular to the intracellular compartment due to the urea concentration gradient during very high-efficiency hemodialysis treatment.

In a mechanism involved in other than a fluid shift to the intracellular compartment, the decreased plasma osmolality could also exert some effect upon the hemodynamic stability. Schultze *et al.*⁵⁰⁾ found that low sodium dialysis elevated the concentration of prostaglandin E₂, which is known to have venodilatory properties. Moreover, Kunze *et al.*⁵¹⁾ reported that acute changes in plasma sodium concentration impair baroreceptor function in experimental animals.

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5. *Ingestion of food*

The association of food ingestion with dialysis-induced hypotension now has been well documented^{52,53}, and it is considered that feeding causes an obligatory increase in splanchnic blood flow⁵⁴ and a consequent decrease in venous return.

6. *Anemia*

Sherman et al.⁵⁵ reported that patients with a low hematocrit appeared to be inordinately susceptible to dialysis-induced hypotension, and the problem could be ameliorated by blood transfusion. The mechanism of the hematocrit effect has not been clarified.

Patients with low hematocrit have a high plasma volume in relation to their blood volume, so the concentration rate of their plasma protein along with ultrafiltration is thought to become slower. It is this delayed plasma protein concentration (slow rise of plasma oncotic pressure) together with the lower plasma refilling rate which probably undermines hemodynamic stability in patients with low hematocrit.

The blood viscosity increases exponentially with increasing hematocrit, and blood viscosity is an important component of total peripheral resistance⁵⁶. For this reason, patients with severe anemia may appear to be inordinately susceptible to dialysis-induced hypotension.

Furthermore, it may be that anemia plays a role in triggering hypotension during hemodialysis, since it modulates tissue ischemia in hypovolemia. (See the adenosine hypothesis proposed later.)

7. *Acetate hemodialysis*

It is known that acetate increases splanchnic blood flow through an adenosine-mediated action⁵⁷. Moreover, some reports suggested that acetate causes vasorelaxation⁵⁸ through a cyclic AMP-related action⁵⁹. Thus, during acetate dialysis, increased venous capacity and reduced total peripheral resistance may well be produced by a direct effect on the veins and by a vasorelaxant effect on splanchnic and cutaneous resistance vessels, which can contribute to hypotension during hemodialysis.

HYPOTHESES CONCERNING THE MECHANISM OF DIALYSIS-INDUCED HYPOTENSION

Some investigators have combined some of the above-mentioned etiologic factors in order to create a viable hypothesis concerning the mechanism of dialysis-induced hypotension. Two of the previously proposed hypotheses and our own new one are herewith presented.

1. *Interleukin-1 hypothesis*

Exposure of whole blood to the cuprophane membrane causes the release of the anaphylatoxins C3a⁶⁰ and C5a⁶¹. The thus-released C5a serves to stimulate monocyte production of interleukin-1^{62,63}. And if interleukin-1 is present in sufficient quantity in the circulating blood, it could produce fever and shock.

Henderson et al.⁶⁴ hypothesized that such monocyte release of interleukin-1 is the key factor in terms of dialysis-induced hypotension, which may be modulated by hypovolemia, vasodilation by acetate, autonomic insufficiency and so on. The same investigators have maintained that their hypothesis is supported by the fact that the 3- to 4-hour time lag⁶⁵ from when the monocyte is activated until the release of interleukin-1 has peaked, coincides with the peak incidence of dialysis-induced hypotension. They also explained that the difference in the incidence of

hypotension between hemofiltration and hemodialysis is due to the reduced interleukin-1 production during hemofiltration. They speculated that, during hemofiltration, there would be much less production of interleukin-1 because of use of a noncellulosic membrane which has little capacity to activate complement^{60,61}, and minimal rise in body temperature. (It has been shown that an increase in body temperature enhances monocyte production of interleukin-1 after monocyte stimulation^{65,66}.)

However, research results which contradict this hypothesis have recently been reported⁶⁷.

2. *Thermal amplification hypothesis*

Gotch *et al.*⁶⁸ have advanced the hypothesis that dialysis-induced hypotension results from abrupt expansion of the cutaneous vascular bed as a means to disperse the heat build-up within the body during the latter part of the hemodialysis session. This process is held to take place as follows: If hypovolemia results because of ultrafiltration in the course of hemodialysis, the sympathetic tone increases correspondingly and the cutaneous circulation decreases. As a result, the metabolic heat produced during hemodialysis no longer can be dispersed from the skin surface, thereby causing a gradual elevation in the core body-temperature. Once the core body-temperature reaches threshold during the latter part of a hemodialysis session, the cutaneous vessels suddenly open, leading to patient shock.

If this hypothesis were valid, at least until sweating developed the skin temperature should rise together with the sudden increase in cutaneous circulation. However, Nakai *et al.*¹⁰ recently employed an infrared ray monitoring system to monitor skin temperature continuously in the course of hemodialysis. They found that even when dialysis-induced hypotension occurred there was no corresponding elevation in skin temperature.

3. *Adenosine hypothesis*

We found it interesting that several important etiologic factors in dialysis-induced hypotension could result in tissue ischemia. For example, the hypovolemia due to large-volume ultrafiltration and use of low sodium dialysate obviously leads to tissue ischemia. Also, an increase in cutaneous circulation associated with the employment of a warm dialysate inevitably redistributes blood to the skin from other organs, resulting in ischemia of organs other than skin.

Once highly metabolic organs become ischemic through such mechanisms, adenosine, which is a powerful vasorelaxant substance, is released⁶⁹. Here, we posited the hypothesis explained in what follows, namely, that the adenosine released from hypoxic cells plays a key role in the development of dialysis-induced hypotension. When highly metabolic organs become ischemic, regional ATP synthesis is inhibited; and with hydrolysis of ATP, adenosine is released in those organs. Since adenosine inhibits Ca^{2+} flux into vascular smooth muscle⁷⁰ and at the same time inhibits norepinephrine release from the nerve endings at the junction with vascular smooth muscle^{71,72}, resistance vessel tone falls in ischemic organs. This fall of resistance vessel tone leads to elevation of vascular bed distending pressure and expansion of regional vascular capacity (De Jager-Krogh phenomenon)¹³⁻¹⁵, especially in the splanchnic vascular bed¹⁴. Accordingly, venous return to the right atrium diminishes markedly¹⁶. These pathophysiological changes induced by adenosine conjoin with the underlying hemodynamic alteration induced by hypovolemia. Thus, the more tissue ischemia is aggravated, the more adenosine is released, and dialysis-induced hypotension finally results. It may be important that some acutely ill patients evidence more adenosine release during hypotensive events compared with others, suggesting more cellular hypoxia⁷³⁻⁷⁵. For the same reason that individual differences exist in purine metabolism among non-uremic patients during hypotensive events, the incidence of dialysis-induced hypotension might differ with the individual.

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Skin is a low metabolic organ. Therefore, even though the cutaneous circulation is reduced dramatically, a drop in resistance vessel tone due to adenosine mechanism would not be induced. In fact, as long as the core body-temperature is not remarkably high, the skin resistance vessel tone increases because of normal baroreflex in the hypovolemic condition^{76,77}.

Thus, the rise in resistance vessel tone in the skin and the decrease in the resistance vessel tone in other organs may mutually cancel each other out, leaving little change in the total peripheral resistance at the time dialysis-induced hypotension occurs.

This hypothesis is corroborated by our recent results, which indicate that, at the time of dialysis-induced hypotension, there was a pronounced elevation in the plasma level of inosine and hypoxanthine, both of which are adenosine metabolites⁷⁸. Also, the fact that patients with low hematocrit are susceptible to dialysis-induced hypotension⁵⁵ may be because the decreased red blood cell mass results in further reduction of the O₂ delivery to various organs in hypovolemic condition. Again, one may explain the association of food ingestion with dialysis-induced hypotension^{52,53} in terms of an adenosine-mediated increase of splanchnic circulation accompanying such food intake⁷⁹. Moreover, at least part of the reason for the high incidence of hypotension during acetate dialysis may be increased splanchnic circulation through adenosine-mediated action⁵⁷. It is known that the blood pressure rises dramatically with rapid administration of only 100 to 200 ml of biological fluid. The reason for the remarkable effect of such a small volume of biological fluid administration on dialysis-induced hypotension may be the rise in the resistance vessel tone and recovery from the inhibition of sympathetic neurotransmission in ischemic organs (e.g., intestines and liver) due to the decreased adenosine release. Fluid administered is thought to distribute mainly to the relatively dilated vascular bed.

It is the authors' hope that their adenosine hypothesis will be given careful consideration from many different viewpoints in the days to come.

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