Isothermic Dialysis for Hypotension-Prone Patients

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ABSTRACT

Standard hemodialysis (dialysate temperature ≥37°C) induces an increase in body temperature capable of eliciting circulatory adjustments dictated by the maintenance of thermal homeostasis. These adjustments oppose, and can overcome, those elicited by the hypovolemia caused by the ultrafiltration process, and thus predispose patients to develop hypotensive crises during the treatment. Hemodynamic studies in hypotension-prone patients treated with standard hemodialysis showed that during the hypotensive crisis the peripheral vascular resistances decrease, while the stroke volume decreases proportionally more than the blood volume, suggesting cardiac underfilling due to blood volume redistribution. On the other hand, removal of the body heat surplus by cool dialysis helped the same patients to sustain their peripheral vasoconstriction and cardiac filling. To prevent the increase in body temperature, dialysate temperature should be regulated in such a way as to remove through the dialyzer the heat surplus accumulated in the body as a result of the ultrafiltration process. The amount of heat removal should be tailored to each patient because there are wide interindividual and intraindividual variations in baseline body temperature and ultrafiltration requirements. This can be accomplished by the use of a device that can adjust the dialysate temperature automatically in order to keep the body temperature of the patient unchanged (isothermic hemodialysis). Isothermic hemodialysis reduced from 50% to 25% the incidence of treatments complicated by episodes of symptomatic hypotension in a large randomized clinical trial involving 95 high-risk patients. The thermoregulated treatment results in better patient tolerance because the cold stress inherent in this procedure is lower than that inflicted by the use of a fixed low temperature as was done in the past. Overall, the available evidence supports the Gotch hypothesis that the increase in body temperature during hemodialysis is due to the ultrafiltration process eliciting peripheral vasoconstriction and heat accumulation in the body. Heat accumulation brings into play the thermal homeostatic mechanisms endangering cardiovascular tolerance to ultrafiltration.

In the history of dialysis technology, the need for modulating the temperature setting of dialysis treatment emerged relatively late. Yet the first report documenting the influence of dialysate temperature on dialysis-induced hypotension dates back to as early as 20 years ago (1,2). Despite the repeated confirmations coming soon after the original report (3–8), nearly 10 years had to elapse before a revival of studies addressed the relationships among heat balance, body thermal homeostasis, and cardiovascular response to fluid removal during the hemodialysis treatment from a more rational pathophysiologic perspective. An excellent account of how the thermal setting of dialysis treatment affects body temperature appeared recently on this journal (9); my review focuses mainly on how the perturbations of body temperature affect the hemodynamic tolerance to body fluid removal.

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Body Hyperthermia and Dialysis-Induced Hypotension

It is an old notion that standard hemodialysis treatment (acetate or bicarbonate hemodialysis with cellulosic dialyzer) induces an increase in core body temperature averaging 0.67°C when dialysate temperature is set at 37°C (10,11). However trivial as this increase might appear, physiology teaches us that even quite modest deviations from the normal temperature provoke large changes in the circulation. Studies on healthy individuals have shown that environmentally induced increases in body temperature, of the order of magnitude seen in many patients during hemodialysis treatment (e.g., from 36.7°C to 37.7°C), cause substantial hemodynamic changes with an increase in cardiac output and a decrease in total peripheral resistance (12).

In addition to heat stress, however, hemodialysis treatment causes hypovolemic stress due to fluid removal through the ultrafiltration process. This stress causes a hemodynamic response on the peripheral circulation which is just the opposite of that caused by heat, namely, vasoconstriction instead of vasodilation.

How, then, will the human body react to these conflicting demands? An answer can be found in physiology. When healthy individuals were submitted simultaneously to a heat stress (an arm dipped in hot

water) and a hypovolemic stress (negative pressure, −40 mmHg, applied to the lower part of the body) the response to hypovolemic stress was offset by the response to heat stress, such that these individuals reacted with peripheral vasodilation instead of vasoconstriction, as assessed by digital plethysmography in the contralateral arm (13). These observations suggest that in the order of homeostatic priorities, the response to heat stress takes precedence over the response to hypovolemic stress.

Studies of dialysis patients are in line with these physiologic principles. When patients were exposed to three different levels of dialysate temperature (34°C, 37°C, 38°C) with a constant ultrafiltration rate, they showed variations in core (rectal) temperature spanning close to 1°C (11). The changes in core temperature significantly and inversely correlated with the percent variations in blood pressure, with steeper regression slopes in hypotension-prone patients than in hypotension-resistant patients. As expected, the increase in core temperature was associated with an increase in skin temperature suggestive of cutaneous vasodilation (11,14).

Hemodynamic studies have outlined how the dialysate temperature setting affects the cardiovascular adjustment to fluid removal during the treatment. One study involving 10 hypotension-prone patients (15,16) compared the effects of dialysate temperature set at 37.5°C and at 35.5°C by serially measuring plasma volume and aortic velocity time integral (a surrogate index of systolic stroke volume), determined by Evans blue and Doppler echocardiography, respectively. During the 37.5°C dialysis the patients showed an increase of 0.6°C in core temperature, in spite of a slightly negative thermal balance in the extracorporeal circulation. The onset of symptomatic hypotension was associated with a decrease in the stroke volume/blood volume ratio of nearly 25%, while the peripheral vascular resistance, after a modest increase early in dialysis, fell by an average of 20%. The greater decrease in stroke volume than in total plasma volume strongly suggests a redistribution of blood volume away from the central circulation, as has been pointed out by others (17–19).

The hemodynamic derangements seen during treatment with a dialysate temperature set at 37.5°C can be largely prevented with a dialysate temperature of 35.5°C, despite an unchanged ultrafiltration rate (15,16). Use of the cooler dialysate prevented heat accumulation in the body, as suggested by a nearly unchanged estimated body temperature throughout the treatment. In spite of the tendency of blood volume to decrease at a faster rate with cooler dialysate, stroke volume fell less than during the standard treatment, while peripheral vascular resistance increased above its predialysis level. Thus preventing dialysis-induced hyperthermia by altering the conventional thermal setting of dialysis treatment improves hemodynamic tolerance to treatment.

Not all patients benefit from the use of "cool dialysis," however. Considering the multifactorial origin of dialysis-induced hypotension, this is not unexpected. Recent studies have shed more light on the complex relationships between thermal regulation and hemodynamic response during dialysis treatment. Fine and Penner (20) showed that dialysis patients with subnormal body temperature (below 36°C) dialyzed against a 37°C dialysate had the highest incidence of symptomatic hypotensive episodes. These patients were those who most benefited from the use of dialysate of 35°C, with the incidence of symptomatic hypotension decreasing from 15.9% to 3.4% of treatments. In contrast, the incidence of symptomatic hypotension in euthermic patients remained nearly unchanged with the use of cool dialysate (7.0% versus 7.6%). The important point emerging from this study is that the dialysate temperature should be tailored to the predialysis body temperature of the patients.

Another important notion emerged from the study of Rosales et al. (21). They showed that with increasing ultrafiltration, more heat needs to be removed through the extracorporeal circuit to keep the body temperature unchanged (isothermic dialysis). They calculated that about 6% of estimated energy expenditure needs to be removed from the body for each percent unity of body water change in order to maintain body temperature. It is well known that patients requiring large body weight reductions are at greater risk of developing episodes of acute hypotension. Because ultrafiltration is associated with increased heat accumulation, which in turn promotes cardiovascular instability, their findings suggest that dialytic removal of the body heat surplus (isothermic dialysis) should improve hemodynamic tolerance to ultrafiltration. Once more, this study points out that the thermal regulation of dialysis treatment should be tailored to the individual patient.

These two studies should prompt a change in our approach to the management of cardiovascular instability by dialysate temperature manipulation (9). Rather than using a fixed low temperature for all patients at risk of hypotension [a maneuver that in the past was not well tolerated by the patients (22)], one should remove only the surplus heat accumulated in the body as a result of the dialytic process. The adjustment should also take into account the variable body temperature between and within patients at the start of the hemodialysis.

These thermal goals can be pursued by using the Fresenius blood temperature monitor (BTM). This device noninvasively measures the blood temperature on either the arterial or venous side of extracorporeal circulation with an accuracy to less than 0.1°C (23). The arteriovenous temperature gradient multiplied by blood flow and blood heat capacity provides a measure of thermal energy flow trough the extracorporeal circulation. The arterial temperature corrected for access recirculation, which can also be measured by this device, provides a good estimate of inner body temperature. Through a feedback loop connecting the arterial and venous temperature sensor with the dialysate thermostat in the dialysis monitor, the device can automatically adjust the dialysate temperature to regulate the extracorporeal heat flux according to a prefixed target.

A multicenter crossover clinical trial (24) tested the effects of modulating dialysate temperature, keeping body temperature unchanged (isothermic dialysis) compared with keeping heat balance in the extracorporeal circulation close to neutral (thermoneutral dialysis), in 95 hypotension-prone patients. Compared with thermo-

neutral dialysis, isothermic dialysis halved the incidence of treatments complicated by symptomatic hypotension (from 50% to 25% of the treatments). This clinical effect is comparable to that reported in previous studies with fixed low dialysate temperatures (14,25). However, the cold stress inflicted on patients (average 219 kJ removed) with isothermic hemodialysis was considerably less than in previous studies which employed a fixed dialysate temperature, probably accounting for the observation that the procedure was well tolerated by all patients. The good tolerance may also have been due to the gradual reduction in dialysate temperature, which reached the nadir value of 35.7°C only toward the end of treatment, when hypotensive episodes are most likely to occur.

Since cool dialysis causes an increase in peripheral vascular resistance of about 20%, assessed either indirectly from the ratio of cardiac output and mean arterial pressure (14–16) or directly by calf plethysmography (26), some investigators have expressed concern that this hemodynamic effect could cause urea compartmentalization in vasoconstricted bed, and thus a decrease in the depurative efficiency of treatment (28). However, urea kinetics studies have shown that this is not the case, most likely because the peripheral vasoconstriction associated with "cool" hemodialysis involves chiefly the skin, which contains only 10–15% of the total body water (and hence urea). Urea sequestration may well occur in the skin during cool dialysis, but it should have little impact on total urea extraction (28).

The evidence summarized in the foregoing strongly supports the theoretical model proposed by Gotch et al. (29) and suggests the following scenario: the ultrafiltration process, with the attendant reduction in circulating blood volume, evokes peripheral vasoconstriction, which tends to impair heat dissipation through the skin. Peripheral vasoconstriction, together with the concurring increase in metabolic heat production (30), causes heat accumulation manifested by an increase in body temperature. As a consequence, skin blood flow increases to dissipate the heat surplus, manifested by an increase in skin temperature. Diversion of blood flow toward the skin, while blood volume is decreasing (due to ultrafiltration) and peripheral vascular resistance is decreasing (due to heat accumulation), leads to cardiac underfilling and a decrease in stroke volume. A sudden withdrawal of the preceding sympathetic activation may follow (19,31,32), with further impairment of the peripheral vascular response to hypovolemia. If severe enough, cardiac underfilling may even elicit bradycardia (Benzold–Jarisch reflex), as happens in vasodepressor syncope (32).

While supporting Gotch's volume hypothesis, the available evidence is hardly consistent with the pyrogen hypothesis (33), which had an important impact on dialysis practice. According to this hypothesis (34), dialysis "fever" is caused by the release of interleukin (IL)-1 and other cytokines resulting from the activation of macrophages induced by substances present in the dialysate (endotoxin fragments and possibly other substances). Release of IL-1 would account for both fever and dialysis hypotension because of its known property of activating the cyclooxygenase cascade with formation of prostaglandins acting on the hypothalamus to alter the set-point of body temperature regulation, and on the peripheral circulation to produce peripheral vasodilation and hypotension.

In support of the hypothesis that the devil lays chiefly in the dialysate, it was argued that depurative procedures based on convective transport only, such as isolated ultrafiltration or hemofiltration, produced fewer perturbations of body temperature and afforded better protection of vascular stability than procedures based on the combined diffusive-convective transport, such as standard hemodialysis (35). This theory gained wide popularity among nephrologists, having an important impact on dialysis practice as witnessed by the increasing use of hemofiltration and related techniques (chiefly in Europe) in the early 1980s. That the hemodialysis-induced increase in body temperature is unlikely due to a clinically subtle pyrogenic reaction was suggested early on. Studies showed that body temperature perturbations cannot be prevented by continuous infusion of salicylic acid in antipyretic doses (10), nor by the use of sterile dialysate (10).

The allegedly better hemodynamic tolerance to convective compared to diffusive depurative procedures can no longer be taken as a valid argument against the use of diffusive transport. Both isolated ultrafiltration and hemofiltration entail a heat loss across the extracorporeal circulation, which might well account for the better cardiovascular stability claimed for these procedures (1,2,36). On the other hand, the membrane type (cellulosic or noncellulosic; low flux or high flux) has no bearing on the hemodynamic response to fluid removal, as shown by a recent randomized clinical trial (37). Finally, as pointed out by Schneditz (9) in his review, the newer procedures, such as highly efficient short hemodialysis or hemodiafiltration, cause a substantial heat loss across the extracorporeal circulation due to the high blood flows required for implementing these techniques, hence possibly accounting for their alleged hemodynamic benefit. Hemodiafiltration implies an even more negative heat balance when nonwarmed infusate is administered as replacement fluid. These predictions are borne out by experimental data (38,39). Thus the alternative procedures offer no hemodynamic benefit that cannot be achieved with the cheaper traditional procedures, provided that heat balance is appropriately controlled and the dialysate is not unduly contaminated.

Even though the pyrogen hypothesis is unsupported by experimental verification with respect to dialysate and membrane composition, clinical experience suggests that the role of pyrogen should not be dismissed as far as patient-related predisposing factors are concerned. First, patients with febrile intercurrent illness often show more of an increase in body temperature during dialysis days than off-dialysis days, which tends to favor the development of symptomatic hypotension. Second, there is preliminary evidence showing that patients with chronic inflammatory states, as evidenced by persistently raised serum levels of C-reactive protein (CRP), tend to show a higher incidence of symptomatic hypotension than patients with normal levels of this acute-phase reactant (40,41). It is known that the raised levels in CRP are associated with increased release of various cytokines;

whether this induces greater perturbations of body temperature during hemodialysis, remains to be assessed.

Conclusion

A large body of evidence supports an important role for the thermal setting of hemodialysis in modulating the hemodynamic response to ultrafiltration, and indicates the advantage of tailoring the treatment's thermoregulation in the individual patient.

Thermoregulated hemodialysis is no panacea, however, because it can bring benefit to not much more than about 50% of hypotension-prone patients. In the others, one should attempt other maneuvers (42), never forgetting that there are patient-related hypotensive factors that are not amenable to correction by changes in treatment modality or treatment parameters.

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