Kidney International, Vol. 48 (1995), pp. 237–243

Effect of dialysate temperature on central hemodynamics and urea kinetics

ALEX W. YU, TODD S. ING, R.I. ZABANEH, and JOHN T. DAUGIRDAS

Departments of Medicine, Loyola University Stritch School of Medicine and VA Hines Medical Center, Maywood, Illinois, and University of Illinois College of Medicine at Chicago and VA Westside Medical Center, Chicago, Illinois, USA; and Chinese University of Hong Kong, Hong Kong

Effect of dialysate temperature on central hemodynamics and urea kinetics. Use of cool dialysate is associated with increased intradialytic blood pressure, but the hemodynamic mechanism is unknown. Whether changes in dialysate temperature affect muscle blood flow, which may the alter the degree of urea compartmentalization, also is unknown. We measured hemodynamics and blood and dialysate-side urea kinetic indices in nine hemodialysis patients during two cool (35.0°C) versus two warm (37.5°C) dialysate treatments. The % change in mean arterial pressure was different when using the cool (+6.5 ± 9.7 mm Hg) versus the warm (−13.4 ± 3.6) dialysate ($P < 0.01$), despite comparable amounts of fluid removal. Percent changes in cardiac output were similar with the two dialysates, and thus the blood pressure effect was due primarily to changes in total peripheral resistance (%ΔTPR, cool +26 ± 13.6, warm +8.6 ± 14.5; $P < 0.02$). During cool dialysate use tympanic membrane temperature changed by −0.51 ± 0.23°C, whereas body temperature increased by 0.52 ± 0.14°C during use of warm dialysate. Measured urea recovery normalized to the predialysis urea nitrogen concentration was similar with the two treatments: cool 31.3 ± 0.039 liter^{-1}; warm 29.7 ± 0.021; P = NS. In a second study, post-dialysis urea rebound values from 15 seconds to 30 minutes, expressed as the percent of the post-dialysis SUN, were similar after the two treatments: cool 11.79 ± 1.4; warm 12.21 ± 2.27, P = NS. The results suggest that increased blood pressure associated with use of cool dialysate is due to an increased TPR, and that this alteration in hemodynamics has no clinically important effects on either the amount of urea removal or the extent of post-dialysis urea rebound.

One maneuver designed to help prevent hypotension in dialysis patients is the use of a cool dialysis solution. A number of studies have shown that use of cool dialysate results in higher blood pressure and in fewer hypotensive episodes [1–8]. The hemodynamic mechanism whereby blood pressure is maintained with cool dialysate has not been completely defined. In a dog model, increased blood pressure associated with a cooled extracorporeal circuit is clearly due to increased total peripheral resistance [3]. Levy et al found increased cardiac contractility with cool dialysate, but cardiac output was not described [9]. Jost and colleagues found that calf muscle vascular resistance increased more with cool dialysate than with warm dialysate [8], and that use of cool dialysate also resulted in a larger increase in plasma norepinephrine levels on standing after dialysis. However, central hemodynamic changes during cool dialysate use have not been reported.

Received for publication August 19, 1994
and in revised form February 15, 1995
Accepted for publication February 16, 1995

It now is well established that a single-pool model is not adequate for describing urea kinetics during hemodialysis [10–12], particularly with high efficiency dialysis [13] and in pediatric dialysis [14]. What remains a point of controversy is the site of urea sequestration. One approach, derived from pharmacokinetics, holds that the principal site of urea sequestration is the intracellular space [10, 11]. Others have emphasized the role of tissue perfusion [15–17], and a formal regional blood flow model of urea kinetics based on physiologically derived organ water content and blood flow values has been described [18, 19]. One expected corollary of the regional blood flow model is that urea removal may be impaired when blood flow is reduced to organs such as muscle, where most of the urea is located [18, 19]. Reduced blood flow to muscle may occur after baroreceptor-mediated increases in vascular resistance, as in response to hypovolemic stress [20] or with increased vascular resistance associated with erythropoietin therapy [21, 22].

If the higher MAP seen with cool dialysate use is associated with reduced perfusion of muscle, then one might expect the degree of urea compartmentalization to be increased. In this case, use of cool dialysate should be associated with a greater degree of post-dialysis urea rebound and a reduced amount of urea removal. On the other hand, a higher MAP during cool dialysis might conceivably be associated with no change in muscle blood flow, because cold stress affects primarily blood flow to the skin. The total body water content, and hence urea content, of the skin is not nearly as great as that of muscle [19], and hence changes in skin blood flow alone should have little impact on urea compartmentalization. A third possibility is that use of cool dialysate may be associated with relatively increased flow to muscle due to better maintenance of systemic blood pressure and lack of baroreceptor-mediated vasoconstriction. If such were the case, the degree of urea compartmentalization might even be reduced with use of cool dialysate.

To evaluate the effects of dialysis solution temperature on central hemodynamics and urea compartmentalization, we measured blood pressure and cardiac output, and compared several indices of urea removal in patients as they were dialyzed with either a cool (35.0°C) or a warm (37.5°C) dialysis solution.

Methods

Nine patients were studied using a crossover design. The mean age was 63 ± 2.2 years. The mean post-dialysis weight was 75 ± 5.6 kg. Three patients were diabetic. Patients were not selected

based on hemodynamic instability. The patients underwent two separate studies, each involving two dialysis sessions (1 using cool and 1 using warm dialysate). One study focused on measurement of central hemodynamics (during which dialysate urea recovery also was measured) and the other focused on blood and dialysate measures of urea removal.

Hemodynamic study

Each patient was dialyzed twice, once using cool and once using warm dialysis solution. The two treatments were given on different days and the order of the treatments was randomized. The patients were blinded as to the nature of the treatment, although patients often were able to detect the coolness of the dialysate. All patients were dialyzed using Fresenius F-8 dialyzers and bicarbonate dialysate at a flow rate of 500 ml/min. The dialysis session length was always four hours. The average blood flow rate was 309 ± 3.3 SEM ml/min. Fresenius 2008 machines were used (which monitor the dialysate outflow), and the dialysate temperature was set at the desired level according to manufacturer's guidelines. Measurement of dialysate temperature by thermometer confirmed that dialysate of either 37.5 or 35.0°C was, in fact, being delivered.

Blood pressure and heart rate were measured every hour during dialysis. Cardiac output also was measured at hourly intervals using the NCCOM3-R7 thoracic electric bioimpedance device from Bomed, Inc. (Irvine, CA, USA). We previously have used this device to measure cardiac output during dialysis in an evaluation of different dialysate bases [23] and also to evaluate the hemodynamic effects of food ingestion during dialysis [24]. Heart rate was also measured. Mean arterial pressure (MAP) was computed as the diastolic blood pressure plus 1/3 of the pulse pressure. Total peripheral resistance (TPR) was estimated as the MAP divided by the cardiac index (cardiac output normalized to anthropometrically estimated body surface area). Tympanic membrane temperature was measured hourly during dialysis as well.

Serum urea nitrogen concentration was measured pre- and post-dialysis. Total spent dialysate was collected in a large tank containing sufficient acetic acid to neutralize all of the dialysate bicarbonate. The purpose of this maneuver was to keep the spent dialysate acidic, in order to limit the action of any urea-splitting organisms which may have been present in the dialysis machine drain tubing. At the conclusion of dialysis the entire tank was weighed, and three separate aliquots were taken after mixing to determine its urea concentration.

Urea kinetic study

In this study the patients underwent dialysis with cool and warm dialysis solution, but the only hemodynamic index measured was the blood pressure. Blood-sided urea removal measurements included sampling of serum urea nitrogen concentration predialysis, at 30, 30.25, 32, 60, and 90 minutes into dialysis, at the end of dialysis, and at 15 seconds and 2, 10, 20, and 30 minutes post-dialysis. At 30 minutes into dialysis, access recirculation and dialyzer clearance were quantified. At full blood flow the dialyzer inflow and outflow blood was sampled. Then the blood pump was reduced to 50 ml/min, and a third sample was drawn, with the draw beginning 15 seconds after having slowed the blood flow rate (this is based on a 10 ml volume between the inflow dialysis needle and sampling port). Dialysate-based indices of urea recovery again included total collection of spent dialysate as described above. Also, the Biostat-1000 device manufactured by Baxter Healthcare, Inc. (Deerfield, IL, USA) was used as a third measure of urea removal [25]. This device intermittently analyzes the urea concentration of the effluent dialysate. The Biostat creates a biexponential fit to the dialysate curve, and from this computes the intercompartmental urea clearance (Kc). Based on the initial blood urea level, which is estimated by equilibration with the blood at the outset of dialysis, the urea recovery, which is estimated from the intermittent measurements, and the Kc, the equilibrated postdialysis SUN is estimated and an effective Kt/V is calculated.

Laboratory measurements

Samples for urea were centrifuged, and the serum was separated and stored at −80°C until analysis. Urea was quantified by converting to ammonia with urease and then assaying product concentrations of the Berthelot reaction (Sigma Inc., St. Louis, MO, USA) [26]. All samples were assayed in triplicate, and separate standards were used for dialysate. The possible confounding effects of acetic acid added to the dialysate on the Berthelot assay were tested for using appropriate *in vitro* standard curves and were found to be absent. The coefficient of variation for the method was 3 to 4%.

Post-dialysis urea rebound between 15 seconds and 30 minutes was computed by two methods. In one method, rebound was expressed as percent increase above the 15 second post-concentration. In another method, rebound was computed as a fraction of the decrease in SUN during dialysis [100 × (rebound value − 15 seconds post-value]/(pre-value − 15 seconds post-value). Rebound at 30 minutes was corrected for urea generation in these calculations. Total grams of urea removed in the dialysate were obtained from the Biostat-1000 output, and also were calculated from the average urea concentration of the samples taken from the tank containing the total volume of spent dialysate. To correct for variations in predialysis SUN between the two treatments, the number of grams of urea removed per treatment was normalized by dividing by the predialysis SUN level.

Results

Hemodynamic study

Initial hemodynamic conditions were similar prior to the two treatments: MAP cool: 110 ± 4.0 mm Hg, warm: 105 ± 4.0, P = NS; Cardiac index cool: 3.14 ± 1.3 liter/min/M^2, warm 3.42 ± 2.5, P = NS, heart rate cool: 79 ± 2.0 beats/min, warm: 81 ± 3.2, P = NS. Initial tympanic membrane temperatures also were similar: cool 35.7 ± 0.22°C, warm 35.6 ± 0.17°C, P = NS.

All patients tolerated both treatments well, without hypotension of a degree sufficient to warrant intervention. The ultrafiltration volume (liters) was similar for the two treatments: cool 2.76 ± 0.37; warm 2.87 ± 0.55, P = NS. However, during the cool dialysate treatments, mean arterial pressure was significantly higher than during the warm treatments (%ΔMAP cool +6.5 ± 9.7 mm Hg, warm: −13.4 ± 3.6, $P < 0.01$). The percent changes in cardiac output were similar with the two dialysates (cool −14.0 ± 3.1%, warm −13.6 ± 6.9, P = NS). The blood pressure effect was thus due primarily to changes in total peripheral resistance (%ΔTPR, cool +26 ± 13.6, warm +8.6 ± 14.5, $P < 0.02$). Based on a two factor repeated measures ANOVA design assessing time and treatment effect, a time × treatment interaction was present

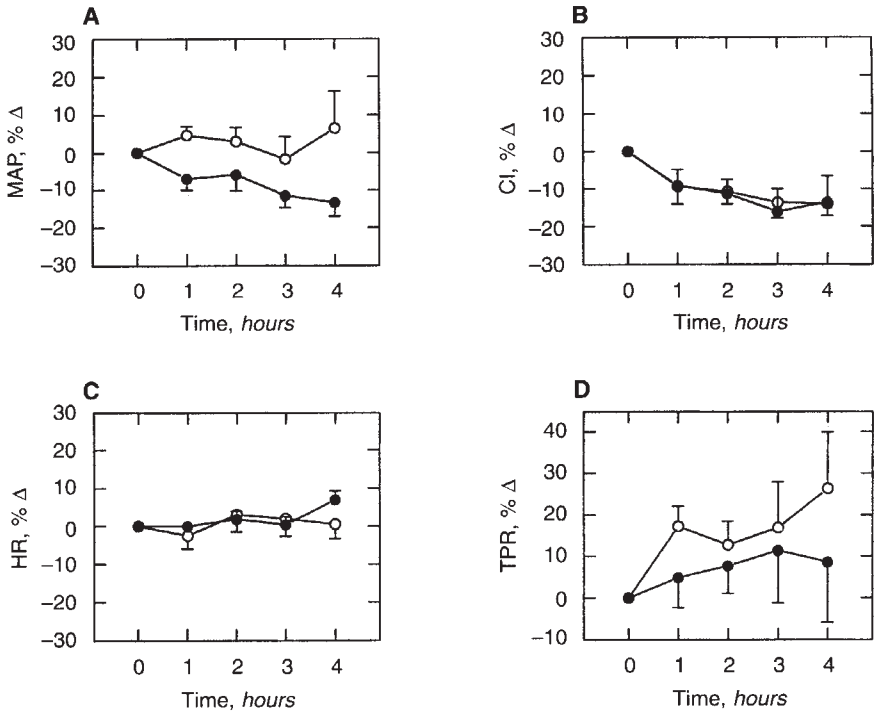

Fig. 1. *Hemodynamic study: Hemodynamic indices including MAP, cardiac index (CI), TPR, and heart rate (HR) during cool (○) and warm (●) dialysis.* Only changes in MAP and TPR were statistically significant.

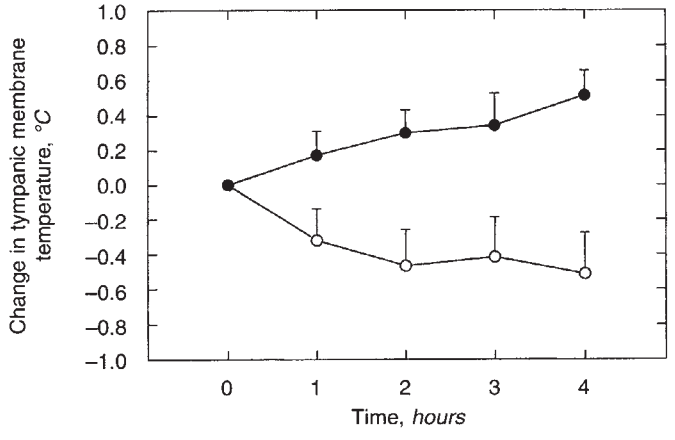

Fig. 2. *Hemodynamic study: Results of hourly measurements of tympanic membrane temperature during cool (○) versus warm (●) dialysis.* The differences in body temperatures assessed in this manner were highly significant.

for diastolic and mean blood pressure (P = 0.035 and 0.022, respectively). There was no time × treatment interaction for cardiac output (P = 0.805), and a borderline significant (P = 0.08) time × treatment interaction for TPR. These hemodynamic indices, including changes in heart rate, are summarized in Figure 1. The change in tympanic membrane temperature as a result of cool dialysate use −0.51 ± 0.23°C was significantly different from that during warm dialysate +0.52 ± 0.14°C, $P < 0.001$. Hourly changes in tympanic membrane temperature are shown in Figure 2.

Single pool urea Kt/V, derived from the 15 second post-dialysis SUN, was similar with the cool and warm treatments: 1.25 ± 0.14 and 1.38 ± 0.10 Kt/V units, respectively; P = NS. Total urea recovered in the spent dialysate normalized to the predialysis SUN concentration also was comparable (cool 31.3 ± 3.9 liter^{-1}, warm 29.7 ± 2.1; P = NS), suggesting that cool dialysate use had neither an adverse or beneficial effect on urea removal.

Detailed urea kinetic study

Blood pressure results. The blood pressure differences between the cool and warm dialysis treatments in this study are shown in Figures 3 and 4, this time in terms of systolic and diastolic blood pressures. The magnitude of the blood pressure difference was quite similar to that found in the hemodynamic study. Treatment effects or a time × treatment interaction were present by two factor repeated measures ANOVA for both systolic (P = 0.008) and diastolic (P = 0.023) blood pressures. Again, there was no significant difference in the amount of fluid removed between the two treatments.

Dialyzer urea clearance measurements. During cool dialysis, mean urea clearance, based on measurements taken 30 minutes into dialysis, was 225 ± 4.0 ml/min. During warm dialysis, dialyzer clearance averaged 230 ± 2.9 ml/min. These values were not significantly different.

Intradialytic and postdialysis SUN results. The mean levels of SUN for the two treatments are presented in Figure 5. For ease of comparison, all values are normalized to the predialysis SUN (cool 56.2 ± 3.2 mg/dl, warm 50.0 ± 12.6; P = NS). As evident from the Figure, there was no difference in intradialytic urea profile between the warm and cool dialysate treatments. The postdialysis SUN rebound values between 15 seconds and 30 minutes were not significantly different between the two dialysates, whether rebound was computed as a % of the post-SUN value, or as a % of the fall in SUN. These results are shown in Figure 6.

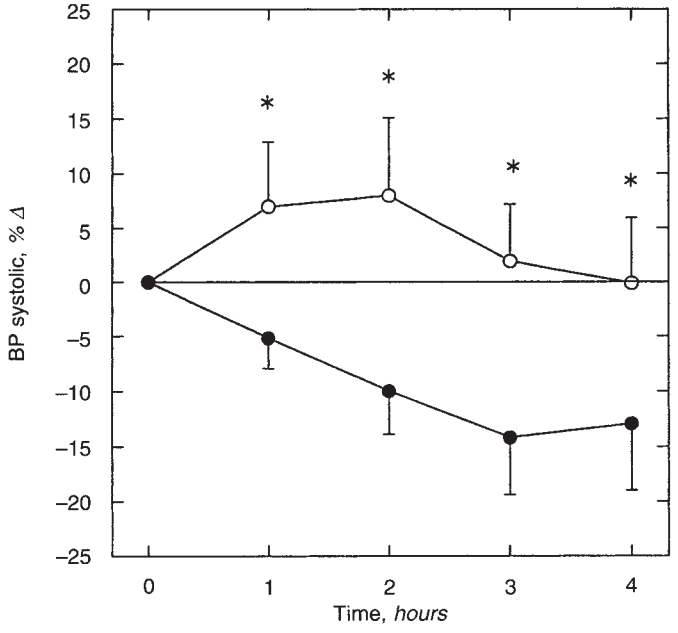

Fig. 3. *Urea kinetic study: Systolic blood pressure during dialysis with cool (○) and warm (●) dialysate.* By repeated measures ANOVA, the blood pressures are significantly different between the two treatments ($P < 0.01$). Asterisks identify significance levels at each individual time point by paired *t*-testing.

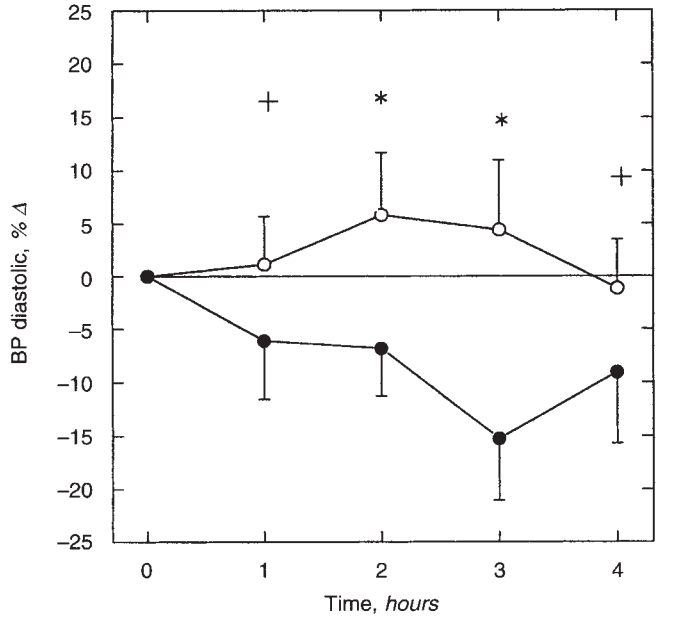

Fig. 4. *Urea kinetic study: Diastolic blood pressure during dialysis with cool (○) and warm (●) dialysate.* By repeated measures ANOVA, the blood pressures are significantly different between the two treatments ($P < 0.02$). Asterisks identify significance levels at each individual time point by paired *t*-testing. Points marked by (+) signs are significant using a one-tailed test only.

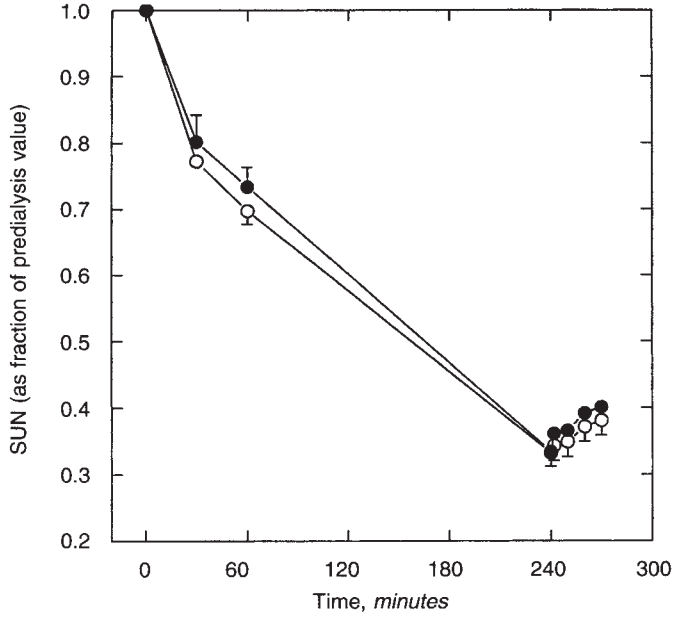

Fig. 5. *Urea kinetic study: Serum urea nitrogen (SUN) values for cool and warm dialysis, with the data expressed as a fraction of the predialysis SUN level.* There was no significant treatment difference for either the intradialytic or postdialytic SUN profile by two-factor repeated measures ANOVA.

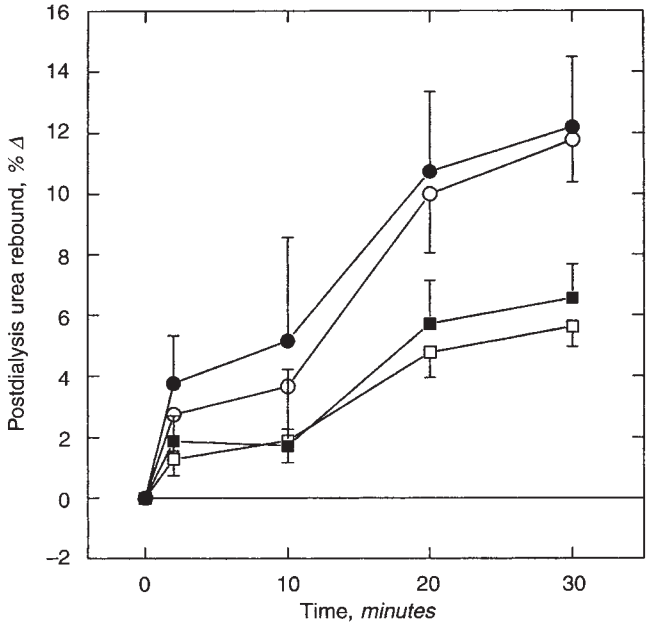

Fig. 6. *Urea kinetic study: Postdialysis urea rebound, using the 15 second post-dialysis value, expressed by two different methods.* In one method (circles), rebound was expressed as percent increase above the 15-sec post concentration. In another method (squares), rebound was computed as a fraction of the decrease in SUN during dialysis: 100 × (rebound value − 15 second post-value)/(pre-value − 15 second post-value). Rebound was corrected for urea generation. There was no significant treatment effect of either rebound profile by two factor repeated measures ANOVA.

Access recirculation

The mean ratio of the 30 minutes and post-dialysis urea concentrations to the values in specimens drawn 15 seconds later after slowing the pump to 50 ml/min was 1.0, and the ratio was always greater than 0.92, strongly suggesting that, in these studies, given the coefficient of variation for urea measurements, significant access recirculation was not present (when the outlet to inlet

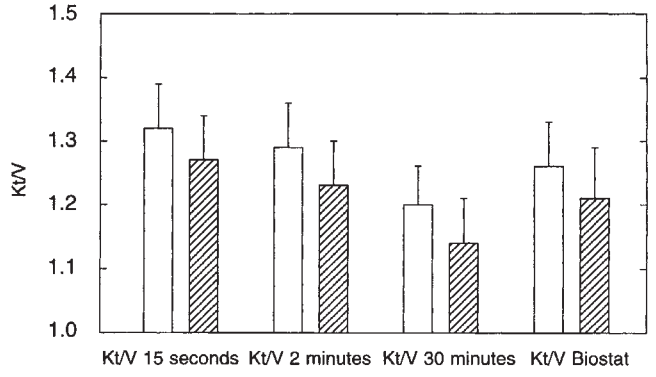

Fig. 7. *Urea kinetic study: Three blood-side derived Kt/V measures and one dialysate-side Kt/V measure are shown for both cool (hollow bars) and warm (hatched bars) dialysate.* The blood-sided Kt/V values were computed based on post-dialysis SUN values taken at 15 seconds, 2 minutes, and 30 minutes post-dialysis, corrected for g. In none of the comparisons was there a significant difference between cool and warm dialysate; in fact, the trend was for a slightly higher Kt/V with use of cool dialysate.

ratio is 0.3, an access recirculation of 14% translated into a ratio of 0.90). Also, the ratio of the SUN values in these specimens to those taken two minutes later after slowing the blood pump to 50 ml/min averaged 0.95, the expected values for the A/V SUN ratio under these dialysis conditions and was never less than 0.91, again, militating against the presence of vascular access recirculation in any of the studies. Computed in the standard fashion [100 × (S-I)/(S-O)] 30 minutes after dialysis, access recirculation for cool dialysate averaged −1.8 ± 3.5%, maximum 9.7%, and for warm dialysate averaged −4.5 ± 6.2%, maximum 8.7%.

Blood-sided urea modeling results

Kt/V based on 15 seconds post- or two minutes post-dialysis SUN measurements was calculated using a two-point variable-volume single pool urea kinetic model [27], and also using the Daugirdas 2nd generation estimation [28]. "Equilibrated" Kt/V also was computed based on the 30-minute post-dialysis SUN reduced appropriately for urea generation during the 30-minute post-dialysis rebound period. As evident from Figure 7, there was no difference in either standard single-pool Kt/V or in the "equilibrated" Kt/V between the two treatments. As expected, the "equilibrated" Kt/V (30 min) was lower than the single-pool Kt/V (15 seconds), by 9.43% ± 1.06 in the cool dialysate treatments, and by 10.3% ± 1.8% in the warm studies, P = NS between the two treatments. Based on two-minute post-dialysis samples and single-pool urea kinetics (including multiplication of K_d by the ratio of the 0 to 2 minute post-dialysis sample to correct K_d of A/V gradient), the modeled V was 37.3 ± 2.1 for the cool dialysate treatments, and 40.1 ± 2.6 liter for the warm studies, P = NS between the two. K/V values for the cool and warm studies were 5.38 ± 0.31 ml/min/liter and 5.12 ± 0.29 ml/min/liter, respectively.

Dialysate modeling results

Based on total dialysate recovery, the total urea removed normalized to predialysis SUN was again similar in the cool (31.1 ± 2.5 liter^{-1}) and warm (28.6 ± 1.4 liter^{-1}) treatments, P = NS. The same values calculated based on Biostat-1000 derived total urea removal were quite similar, although about 10% higher (cool 35.1 ± 2.7 liter^{-1}, warm 33.0 ± 1.8; P = NS). The slight shortfall in dialysate urea recovery with the total collection method may have been due to incomplete mixing of the spent dialysate in the large collection tank, or else to differences in assay procedures for urea used with the two methods. Total urea recovered by dialysate collection correlated highly with that estimated by the Biostat-1000 device (cool r = 0.96, warm r = 0.85). The Biostat-1000 also can derive a dialysate-based Kt/V value that is an "equilibrated" Kt/V and generally similar to that obtained using a 30-minute post-dialysis rebound sample [25]. This dialysate-side "equilibrated" Kt/V was 1.26 ± 0.07 for those studies in which cool dialysate was used, and 1.21 ± 0.08 for the warm studies. Again, there was no difference between cool and warm dialysate use.

Discussion

In our study, moderate cooling of the dialysate to 35°C was associated with an increased mean arterial pressure as reported previously by many other authors [1–8]. We extended previous observations by measuring bioimpedance-derived cardiac output, which suggested that the blood pressure difference between cool and warm dialysate use could be accounted for entirely by differences in total peripheral vascular resistance (TPR), confirming our previous finding in dogs [3]. Our observation is consistent with data by Jost and colleagues in humans, that cool dialysate results in increased vascular resistance in the lower leg as measured by plethysmography [8]. The magnitude of the difference in TPR was not large, on the order of 20%, suggesting that it might be accounted for largely or entirely by changes in skin blood flow.

Use of cool dialysate had no effect on the compartmentalization of urea during dialysis. There was no effect on the magnitude of post-dialysis urea rebound, and no effect on the amount of urea recovered from spent dialysate. How can one explain the negative results of this study and still support a regional blood flow model [18, 19] of urea kinetics? The key question is not what happens to total cardiac output, or to total peripheral vascular resistance, but what happens to the regional distribution of blood flow. Certainly regional blood flow can be markedly altered with little change in cardiac output or TPR [29]. Of the three organs (muscle, skin, and bone) that contain most of the total body water and hence urea, muscle is by far the most important. For example, muscle alone should contain about 55% of the total body urea [19]. During the mild cold stress imposed by use of cool dialysate, calf vascular resistance has been shown to increase [8]. It is possible that the increase in vascular resistance found during use of cool dialysate may be focused primarily on the cutaneous circulation. Perhaps actual blood flow to muscle decreases only slightly, if at all. Based on pathologic data, the skin contains only 10 to 15% of the total body water (and hence urea). Thus, increased sequestration of urea in the skin during dialysis should, of itself have little impact on total urea compartmentalization or extraction. To the contrary, use of cool dialysate may actually help maintain blood flow by maintaining blood pressure. Normally there is tonic inhibition of sympathetic outflow. A fall in MAP during dialysis can activate baroreceptors and disinhibit sympathetic outflow. Sympathetic outflow increases vascular resistance primarily to cutaneous, renal, and muscle circulations [20]. Thus, one scenario regarding muscle blood flow with warm versus cool dialysate might play as follows:

Warm. Volume depletion → fall in MAP → baroreceptor activation → fall in muscle blood flow → increased urea compartmentalization

Cool. Volume depletion + cutaneous vasoconstriction → no fall in MAP → little baroreceptor activation → little change in muscle blood flow → no change in urea compartmentalization

Conceivably, cool dialysate use might augment venous tone during hemodialysis. Augmented venous tone may limit sequestration of blood in veins and thus help preserve cardiac filling [20]. However, in our hemodynamic study there was no difference in cardiac output during cool versus warm dialysis.

How can our results be reconciled with those of Depner et al, who measured end-dialysis urea concentration and post-dialysis urea rebound in access blood and opposite arm cutaneous vein blood [30]? Depner and colleagues found that, at the end of dialysis when cool dialysate was used, there was a marked difference between arterial blood (as represented by access blood drawn while the access segment between the two dialysis needles was occluded) and opposite arm cutaneous blood (the latter being higher). The difference increased as dialysis progressed. When dialysis was performed using a 'hot' dialysate (39°C), the arterial/cutaneous vein difference in urea concentration all but disappeared. The results were interpreted to suggest that dialysate temperature affected the degree of urea compartmentalization. However, in Depner et al's study, cool versus 'hot' and not cool versus warm dialysates were being compared. The heat stress associated with use of the hot dialysate probably caused a marked increase in cutaneous blood flow with opening of cutaneous arteriovenous shunts [31, 32]. Thus, in Depner et al's study with 'hot' dialysate, there may have been some arterialization of blood in the opposite arm cutaneous venous sample, which may have partially obliterated the expected difference between venous and arterial blood that should have been present due to dialysis [33]. In Depner et al's study, the total post-dialysis urea rebound was significantly lower after 'hot' dialysis compared to after use of 'cool' dialysate. The apparent reduction in the degree of urea compartmentalization associated with use of 'hot' dialysate may have been due to increased cardiac output and perhaps increased muscle flow due to the associated heat stress [31, 32].

In summary, our findings suggest that the increased blood pressure associated with cool dialysis is due largely, if not completely, to an increased TPR. The hemodynamic changes associated with use of cool dialysate are not associated with increased urea compartmentalization and do not impair urea removal, probably because blood flow alterations are largely confined to the skin, and possibly because a higher level of mean arterial pressure may actually help maintain muscle blood flow. Lowering the dialysate temperature to 35°C can be done without fear of reducing overall dialysis efficiency.

Acknowledgment

This study was supported by a grant from the Baxter Extramural Grant Program.

Reprint requests to John T. Daugirdas, M.D., (151) VA Westside Hospital, 820 South Damen Ave., Chicago, Illinois 60612, USA.

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