Hemodynamic Effects of Intradialytic Food Ingestion and the Effects of Caffeine

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ABSTRACT

Although the hypotensive effects of food ingestion during hemodialysis have been documented, the hemodynamic mechanism is unclear. It could be decreased cardiac output due to splanchnic sequestration or decreased vascular resistance due to splanchnic vasorelaxation. Also, the effects of caffeine, which block postprandial hypotension in the elderly, have not been studied in a dialysis setting. Central hemodynamics were monitored by thoracic electric bioimpedance in 10 dialysis patients who ingested a test meal 1 h into dialysis. All ultrafiltration was done during the initial 2 h. Bicarbonate dialysate was used. Each patient was studied three times in a double-blind (with respect to placebo/caffeine) cross-over trial: placebo/no meal, placebo/meal, and caffeine/meal. Blood pressure decreased sooner and to a greater extent in the treatments in which food ingestion accompanied ultrafiltration (e.g., at 30 min after food ingestion, percent change in mean arterial pressure was $-12.4 \pm 1.8$ versus $-2.4 \pm 3.5$ mm Hg when food was not ingested; $P < 0.05$). The hemodynamic mechanism of food-associated hypotension was found to be a fall in systemic vascular resistance (SVRI). Caffeine pretreatment (200 mg), which resulted in intradialytic plasma caffeine levels of about $4 \mu g/mL$ at time of food ingestion, had no effect on food-associated reductions in blood pressure or SVRI. The results suggest that food ingestion during dialysis causes hypotension primarily because of decreased SVRI. The effects of food ingestion on mean arterial pressure and SVRI are not attenuated by the ingestion of 200 mg of caffeine 1 h before dialysis.

Key Words: Hemodialysis, eating physiology, blood pressure physiology, cardiac output-blood pressure-drug effects, renal failure-chronic

Sherman et al. recently demonstrated that food ingestion during hemodialysis is associated with a fall in blood pressure (1). These results were confirmed by Zoccali and colleagues (2). There is no information about the hemodynamic mechanism of the hypotension in such circumstances. Because food ingestion causes splanchnic vasodilation (3,4), hypotension due to food ingestion might be the result of one of two causes: (1) increased splanchnic sequestration of blood and decreased cardiac filling and cardiac output; or (2) decreased splanchnic resistance leading to decreased total peripheral resistance (systemic vascular resistance; SVRI) under circumstances where cardiac output cannot increase because it is limited by diminished venous return.

We undertook these studies to examine the hemodynamic changes associated with food ingested while fluid was being removed by dialysis. Because caffeine pretreatment has been shown to ameliorate postprandial hypotension in patients with autonomic insufficiency (5), we also studied whether or not the administration of 200 mg of caffeine predialysis would attenuate or eliminate food-associated hemodynamic changes during hemodialysis.

MATERIALS AND METHODS

Ten chronic hemodialysis patients were studied, of whom two were (adult-onset) diabetics. The mean age of the patients was 58 ± 4.5 yr. None of the patients had substantial residual renal function. None was exceptionally prone to dialysis-associated hypotension.

Each patient was studied three times, on the same day of the week. The study treatments were at least 1 wk apart, and the order of treatments was randomized by the use of a balanced block design to ensure that no one sequence of treatments predominated.
The treatments were as follows: (1) P0, placebo 1 h predialysis, no meal ingestion; (2) PM, placebo 1 h predialysis, meal ingestion; (3) CM, caffeine, 200 mg, 1 h predialysis, meal ingestion. The test meal, which consisted of two pieces of toast, two hard-boiled eggs, 5 mL of marmalade, two pats of butter, and 50 mL of fruit juice, was consumed after 1 h of dialysis (started at \( t = 65 \) min). Patients were instructed to abstain from coffee and caffeinated beverages for at least 12 h before the study. Otherwise, the patients gave a history of drinking coffee, tea, or other caffeinated beverages on an occasional or regular basis.

In each treatment, the normal practice of dividing the total desired ultrafiltration over the entire dialysis session was altered, and the total desired weight removal was achieved (with a constant ultrafiltration rate) over the first 2 h. The purpose of this maneuver was to maximize the hypovolemic stress during and after the period of food ingestion. After the initial 2 h of dialysis, the ultrafiltration rate was set to zero for the balance of the dialysis session.

Dialyzers used were the Fresenius F-60 hollow-fiber (Fresenius USA, Inc.) parallel plate (CGH Medical Inc., Lakewood, CO) kidneys. The blood flow ranged from 250 to 350 mL/min and was the same for each of the three treatments studied. Bicarbonate-containing dialysis solution (35 mEq/L) containing 135 mEq/L of sodium was used for all treatments.

Blood pressure was measured at 15-min intervals by an automatic blood pressure cuff method (SpaceLabs, Inc., Park Ridge, IL). Cardiac output was measured by thoracic electric bioimpedance with the NCCOM3-R7 CDDP System manufactured by BoMed Inc. (Irvine, CA). This method is based on resistance to a small alternating current applied to the thorax. An excellent recent review on the theory and applications of thoracic electric bioimpedance can be found in an article by Buell (6). Thoracic electric bioimpedance has been used by us to study hemodynamic changes with \( L \)-lactate and other dialysis solution bases (7) and easily detects well-known hemodynamic differences between acetate and bicarbonate dialysis (7). Hemocrit was estimated from centrifugation in microcapillary tubes of duplicate specimens collected from the dialyzer blood inlet. Plasma caffeine levels were measured by the use of a fluorescence polarization immunoassay (8) (TDX: Abbott Laboratories, Deerfield, IL).

SVRI was estimated as the mean arterial pressure divided by the cardiac output. Hemodynamic data were analyzed by two-factor, repeated-measures analysis of variance, with time and treatment being the factors tested. The SPSS Statistical Package for the Social Sciences (SPSS, Inc., Chicago, IL) PC computer software package was used for the analysis. Initial analysis was performed on percent change values with the mean of the values obtained at 50 and 60 min (just before food ingestion) as a denominator. The times between 40 and 120 min were then used in the analysis to detect an overall time effect, an overall treatment effect, and a time \( \times \) treatment interaction. In those areas where significant interactions were found, differences between treatments were further explored by analysis of contrasts, separate two-factor ANOVA of each pair of studies (placebo/no meal–placebo/meal [PO-PM], PO-caffeine meal [CM], and PM-CM), and time \( \times \) treatment interactions.

**RESULTS**

All dialysis treatments were tolerated without symptomatic hypotension. The test meal was ingested without incident and without postprandial nausea or vomiting. The baseline hemodynamic measurements at 60 min into dialytic ultrafiltration are listed in Table 1. There were no significant differences in any of these 60-min baseline values among the three treatments (nor among the true baseline values [data not shown] obtained before the start of the hemodialysis session).

**ANOVA Results**

Significant time effects were present for each of the hemodynamic variables measured, including mean arterial pressure (MAP), cardiac index (CI), SVRI, and heart rate (HR). A treatment effect was present for MAP (\( P = 0.034 \)), for SVRI (\( P = 0.009 \)), and for HR (\( P = 0.023 \)). There was no treatment effect nor time \( \times \) treatment interaction present for CI (\( P = 0.148 \)).

**TABLE 1. Baseline (60 min) values (mean \( \pm \) SE)**

<table>
<thead>
<tr>
<th></th>
<th>P0</th>
<th>PM</th>
<th>CM</th>
<th>( P )</th>
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<tbody>
<tr>
<td></td>
<td>P0-PM</td>
<td>P0-CM</td>
<td>PM-CM</td>
<td></td>
</tr>
<tr>
<td>Mean Blood Pressure (mm Hg)</td>
<td>101.7 ( \pm ) 3.8</td>
<td>98.7 ( \pm ) 4.5</td>
<td>104.6 ( \pm ) 4.5</td>
<td>NS</td>
</tr>
<tr>
<td>CI (L/min-m(^2))</td>
<td>2.54 ( \pm ) 0.15</td>
<td>2.62 ( \pm ) 0.17</td>
<td>2.52 ( \pm ) 0.22</td>
<td>NS</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>80.2 ( \pm ) 4.1</td>
<td>76.9 ( \pm ) 4.8</td>
<td>75.4 ( \pm ) 4.4</td>
<td>NS</td>
</tr>
<tr>
<td>SVRI (mmHg + (L/min-m(^2))</td>
<td>41.75 ( \pm ) 3.15</td>
<td>40.01 ( \pm ) 3.07</td>
<td>46.15 ( \pm ) 6.88</td>
<td>NS</td>
</tr>
</tbody>
</table>
In the ANOVA analysis of the P0-PM, P0-CM, and PM-CM pairs, a time effect persisted in each of the analyses for MAP, CI, SVRI, and HR. A time x treatment interaction for MAP was found in the P0-PM, P0-CM, and PM-CM comparisons. A time x treatment interaction for SVRI was also present in the P0-PM and P0-CM comparisons. This and the analysis of contrasts suggested that the MAP and SVRI overall treatment effects were the result of P0 versus PM + CM and that PM was not different from CM.

MAP

As shown in Figure 1, the blood pressure fell more rapidly in the PM and CM treatments during the 60- to 120-min time period than in the P0 group.

CI

Results are shown in Figure 2. It can be seen that in the P0 treatment, CI was well maintained during the 2-h ultrafiltration period. In both the PM and the CM treatments, CI appeared to increase after meal ingestion, despite continued fluid removal. Although no significant treatment effect was found here, the data certainly suggest that the accelerated fall in MAP observed in the PM and CM groups was not due to a fall in CI.

SVRI

Results are shown in Figure 3. It is clear that the mechanism of the decrease in MAP after food inges-

Figure 1. Changes in MAP during dialysis. P0, placebo, PM, placebo plus meal; CM, caffeine plus meal. The caffeine or placebo was given 1 h before dialysis. The meal was consumed at $t = +65$ to 80 min in the PM and CM groups only. All ultrafiltration was performed during the initial 120 min, after which diffusion dialysis was performed. Two-factor, repeated measures ANOVA (Table 2) showed that a treatment effect for MAP was due to P0 versus PM + CM.

Figure 2. Changes in CI during dialysis. Treatments are as described in the legend to Figure 1. There was a trend for CI to increase in the two treatments in which the meal was given (PM and CM). However, there was no treatment effect or time x treatment interaction on two-factor, repeated measures ANOVA (Table 2).

Figure 3. Changes in SVRI in the three treatments. The treatment groups are as identified in the legend to Figure 1. SVRI decreased more in the two treatments in which the meal was given (PM and CM) than in the P0 treatment. There was a significant treatment effect by two-factor, repeated measures ANOVA (Table 2). Analysis of subgroups and contrasts showed that the treatment effect was the result of P0 versus PM + CM. Caffeine pretreatment (200 mg) failed to prevent the food-induced fall in SVRI.

Results are shown in Figure 4. Increases in HR occurred concurrent with food ingestion in both the PM and CM treatments. HR did not change with ultrafiltration in the P0 treatments.
Figure 4. HR in the three treatments. The treatments are as identified in the legend to Figure 1. There was a treatment effect (Table 2), and the data suggest that increases in HR occurred to a greater extend in the PM or CM groups.

Hematocrit and Ultrafiltration

Baseline hematocrit values were similar before the three study treatments: P0, 28.7 ± 1.8%; PM, 28.5 ± 1.7%; CM, 29.3 ± 1.0%; P = not significant (NS). The changes in hematocrit were similar among the three sessions, suggesting that comparable levels of plasma volume contraction occurred in the three treatment arms. At the end of ultrafiltration, for example, the hematocrit values were again comparable: P0, 35.2 ± 2.0%; PM, 35.3 ± 2.1%; CM, 35.2 ± 1.1%; P = NS. The volume of fluid removed (in a linear fashion during the first 120 min with a volumetric ultrafiltration controller) did not differ significantly during the three treatments: P0, 2.09 ± 0.25 L; PM, 2.27 ± 0.26 L; CM, 2.12 ± 0.27 L; P = NS.

Plasma Caffeine Values

These data are shown in Figure 5. It can be seen that plasma caffeine values were about 5 μg/mL at the start of dialysis in the caffeine-treated sessions and that levels had declined to about 3.0 μg/mL at 2 h into dialysis. It can be inferred that, at the time of meal ingestion, plasma caffeine values were approximately 4 μg/mL.

DISCUSSION

Our results confirm and extend previous findings by Sherman et al. (1) and by Zoccali and colleagues (2) that MAP decreases more rapidly during dialysis when a meal is ingested. Our data disclose that the mechanism of the food-associated fall in MAP during dialysis is a decreased SVRI. These hemodynamic results in dialysis patients are not surprising, given the information we have about the mechanism of postprandial hypotension in nondialysis settings. In normal individuals, food ingestion increases both total splanchnic (3,4) and hepatic (9) blood flow. As a result, in normal individuals, the SVRI does fall after food ingestion, and the main mechanism whereby blood pressure is maintained is by a compensatory increase in cardiac output (10). In patients with autonomic nervous system dysfunction (4,5,11,12) and in the elderly (12-15), the MAP is not maintained after food ingestion. The exact hemodynamic mechanism for this has not been very well studied. One reason might be that cardiac output in such patients cannot increase to compensate for the decreased SVRI. Another reason might be diminished compensatory contraction of nonsplanchnic vascular beds and an accentuated fall in SVRI.

In one patient with postprandial hypotension, Hoeldtke found that hypotension was accompanied by no change in cardiac output and by a fall in SVRI (16). Lipsitz et al., studying postprandial hypotension in the elderly (14), found that hypotension was accompanied by a lack of increase in the HR and also by a minimal rise in plasma norepinephrine levels. Hakusui et al. (17) performed microneurographic re-

TABLE 2. Summary of two-factor, Repeated Measures ANOVA

<table>
<thead>
<tr>
<th></th>
<th>Time Effect</th>
<th>Treatment Effect</th>
<th>Time x Treatment Interaction</th>
</tr>
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<tbody>
<tr>
<td>MAP (%Δ)</td>
<td>0.001</td>
<td>0.034</td>
<td>0.125</td>
</tr>
<tr>
<td>Cardiac Output (%Δ)</td>
<td>0.046</td>
<td>0.124</td>
<td>0.548</td>
</tr>
<tr>
<td>SVRI (%Δ)</td>
<td>0.001</td>
<td>0.009</td>
<td>0.307</td>
</tr>
<tr>
<td>Pulse Rate (%Δ)</td>
<td>0.001</td>
<td>0.023</td>
<td>0.055</td>
</tr>
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</table>
cordings of sympathetic nerve traffic in patients with postprandial hypotension and healthy controls. They found that oral intake of glucose was associated with hypotension and blunted increase of muscle sympathetic nerve activity in the affected patients. Thus, the inability of cardiac output to increase in affected patients after eating may be the primary hemodynamic cause of their hypotension.

During dialysis and the associated hypovolemic stress, cardiac output may not be able to increase at a time when it is limited by diminished venous return. For this reason, presumably, intradialytic eating might result in hypotension in dialysis patients, even in the absence of autonomic nervous system impairment. In our patient sample, the added fall in MAP associated with food ingestion was rather minor and was not associated with a necessity of reducing the ultrafiltration rate or giving iv saline, despite the use of a reasonably rapid ultrafiltration rate.

Onrot et al. first reported the beneficial effects of caffeine in patients with autonomic nervous system defects and postprandial hypotension (5). In these patients, the preadministration of caffeine before the ingestion of a test meal almost completely abolished postprandial hypotension. The results were confirmed in a different patient population (the elderly) by Heseltine et al. (18). Caffeine might be acting by one of two mechanisms. Acute caffeine administration increases blood pressure, and in the study by Heseltine et al., caffeine administration was found to result in higher plasma levels of noradrenaline after food ingestion. Thus, one effect of caffeine might be a nonspecific, pressor action, mediated either by an increased SVRI or by an increase in cardiac output. A second mechanism of caffeine action might be related to its adenosine receptor–blocking activities. In dogs, postprandial jejunal hyperemia has been shown to be an adenosine-mediated phenomenon (19). Caffeine, like other theophylline derivatives, is known to block the effects of adenosine (20,21). Thus, caffeine administration before eating might conceivably be preventing some of the associated splanchnic vasodilation and increased splanchnic blood flow.

Given the above positive findings relative to caffeine administration, our results with caffeine preadministration were disappointing. Caffeine pretreatment failed to block the accelerated fall in MAP seen after food ingestion (Figure 1) and also did not block the observed decrease in SVRI after food ingestion (Figure 3). It may be that the dose of caffeine used, 200 mg (equivalent to two cups of coffee), and the associated loss of caffeine due to dialytic removal during the first 2 h resulted in plasma levels that were insufficiently high for caffeine to exert its beneficial effect.

In summary, our results confirm and extend previous reports by Sherman and colleagues and by Zoccaelli et al. (1,2) that food ingestion during dialysis causes an accelerated fall in blood pressure. The mechanism of the accelerated fall in MAP was found to be a decrease in SVRI. There was no evidence for splanchnic sequestration of blood with reduction of cardiac filling and reduced cardiac output as a mechanism of postprandial hypotension. It might be argued, however, that food-induced splanchnic sequestration of blood was occurring and was limiting the extent of the compensatory increase in cardiac output in these patients.

ACKNOWLEDGMENTS

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REFERENCES


