Research Article

Hemodynamic Response to Glucose-Insulin Infusion and Meals during Hemodialysis

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Keywords

Hemodialysis · Meal · Pulse wave velocity · Blood pressure · Augmentation index

Abstract

Introduction: Intradialytic nutrition may improve nutritional status and reduce mortality in patients on maintenance hemodialysis (HD) but has been associated with adverse events, mainly hemodynamic instability. Some dialysis centers therefore restrict intradialytic meals. In 2 clinical studies, we investigated the effects of intradialytic glucose-insulin infusion (GII) and meal intake on blood pressure (BP), pulse wave velocity (PWV), pulse wave analysis (PWA), and cardiac output (CO). PWA yielded augmentation index standardized with heart rate 75 (Alx@HR75). **Methods:** In the GII study, 12 nondiabetic HD patients had BP, PWV, PWA, and CO measured during 3 HD sessions: standard HD, HD with glucose infusion, and HD with GII. In the Meal study, 12 nondiabetic patients had BP and PWA measured on 3 study days: meal alone (non-HD), meal and HD, 2 meals and HD. Twelve matched healthy controls completed the non-HD day. **Findings:** In the GII study, glucose or GII had no additional effects on hemodynamic parameters compared with standard HD. HD resulted in a decrease in systolic BP of 13%, in diastolic BP of 9%, in Alx@HR75 of 17%, and CO of 18%. PWV was reduced by only 5%. In the Meal study, a meal alone did not change BP, whereas the combined influence of HD and meal intake reduced systolic BP with 22% and diastolic BP with 19%. Furthermore, Alx@HR75 decreased by 37% on HD days and by 36% in controls, but was unaffected on non-HD days. **Discussion:** In the GII study, HD significantly reduced BP, Alx@75, and CO, whereas PWV remained almost constant. No additional effects were observed by concomitant GII during HD. BP reductions seemed larger in the Meal study compared with the GII study. Taken together, HD per se appears as the main discriminant for intradialytic hypotension but in hemodynamically unstable patients the timing and route of nutrition provision should be considered carefully.

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Introduction

Meal ingestion during hemodialysis (HD) is subject to ongoing debate, as both beneficial and potential harmful effects may result. Protein energy wasting is one of the strongest risk factors for mortality in HD patients and may be mitigated by providing patients with intradialytic nutrition [1–3]. At the same time, however, intradialytic meal intake may cause postprandial reduction in blood pressure (BP) and thereby exacerbate the risk of symptomatic intradialytic hypotension (IDH) which in itself is associated with increased mortality [4–7]. For these reasons, some dialysis clinics routinely provide meals during HD, whereas other clinics prohibit in-center meals [3, 6, 7].

Noninvasive methods can assess central hemodynamic parameters such as arterial stiffness and central BP. Most important are pulse wave velocity (PWV) and augmentation index (AIx), derived from pulse wave analysis (PWA). These measurements are used for estimating arterial stiffness and are independent risk factors for cardiovascular events in the general population as well as in patients on maintenance HD [8–11].

BP, AIx, and PWV measurements can be affected by meal intake, insulin infusion, and HD. In healthy subjects, AIx and BP are reduced by insulin infusion [12] and by a meal [13, 14], whereas PWV response to a meal is less clear and may partly depend on meal composition [13, 15]. Insulin resistant subjects have impaired hemodynamic response to insulin, that is, AIx reduction is delayed and BP either unchanged [16] or the reduction has a shorter duration [17]. Patients on maintenance HD are characterized by insulin resistance and vascular calcification [18, 19], and HD is often complicated by IDH [2]. Most studies have reported that BP, AIx [20–26], and cardiac output (CO) [27, 28] decrease during HD, whereas observations on changes in PWV conflict more [22, 24, 25, 29, 30]. Importantly, the combined effect of HD with concomitant glucose-insulin infusion (GII) or meal intake on hemodynamic parameters has not yet been described although meal intake during HD is generally recommended but often withheld due to fear of causing symptomatic IDH [3].

Postprandial hypotension is most likely caused by an inadequate compensatory increase in CO and heart rate (HR) to the increased splanchnic blood flow after a meal, but the pathophysiology is incompletely understood [31]. Therefore, 2 studies were conducted to describe the effects of GII and meal intake on hemodynamic parameters during an HD session, as HD, GII, and meal intake may separately influence peripheral and central hemodynamic parameters but only meal intake involves increased splanchnic blood flow [12–14, 22]. The aim of the GII study was to investigate the additional effects of intradialytic GII on BP, PWV, PWA, and CO compared with HD per se in a group of HD patients in the fed state. The Meal study aimed to investigate the effect of meal ingestion during HD on BP and PWA compared with changes observed after meal ingestion on a non-HD day and in a control group of healthy subjects.

Materials and Methods

Subjects

Baseline characteristics of the study participants are presented in Table 1. Experiments were performed at the Department of Nephrology, Aarhus University Hospital, between November 2010 and May 2012. Study inclusion criteria were age >18 years old, stable maintenance HD for >3 months, body mass index 18.5–30.0 kg/m², arteriovenous fistulas with recirculation <5%. Exclusion criteria were immunosuppressive treatment, malignant disease, malnutrition, pregnancy, and diabetes mellitus.

Table 1. Baseline characteristics of study participants

Study	GII study*	Meal study**		<i>p</i> value [†]
	HD patients (<i>n</i> = 11)	HD patients (<i>n</i> = 12)	controls (<i>n</i> = 12)	
<i>Clinical data</i>				
Age, years	58 (33–79)	61 (39–74)	58 (40–71)	0.89
Gender, males/females	8/3	8/4	8/4	1
BMI, kg/m ²	24.9±1.1	25.4±1.2	25.4±0.9	0.99
Dialysis vintage, months	35 (11–232)	44 (8–202)	–	–
Residual diuresis >200 mL/day	4	5	–	–
Kt/V	1.58±0.11	1.45±0.05	–	–
nPCR, g/kg/day	0.91±0.05	0.97±0.06	–	–
<i>Antihypertensive treatment</i>				
Antihypertensive treatment, <i>n</i>	6 (55)	9 (75)	–	–
>1 drug, <i>n</i>	3 (27)	4 (33)	–	–
ACE-inhibitors/ARBs	3 (27)	4 (33)	–	–
Beta-blockers	3 (27)	7 (58)	–	–
Calcium channel blockers	4 (36)	3 (25)	–	–
Loop diuretics	3 (27)	5 (42)	–	–
<i>Biomarkers</i>				
Hemoglobin, mmol/L	7.6±0.1	7.3±0.1	8.3±0.2	<0.001
B-glucose, mmol/L	5.2±0.1	5.3±0.1	5.4±0.2	0.47
S-insulin, pmol/L	33.9±3.3	55.9±6.6	35.1±8.2	0.03
HOMA-IR	1.14±0.12	1.96±0.25	1.23±0.29	0.05

Data are mean ± SEM, median (range), or n (%) as appropriate.

* GII study: fasting concentrations of biomarkers did not differ between study days and overall mean concentrations are listed.

** Meal study: fasting concentrations of biomarkers on HD days and at non-HD days did not differ between patient study days and overall mean concentrations are listed.

[†] p value for comparison of HD patients and controls in the meal study.

GII, glucose-insulin infusion; ACE, angiotensin-converting enzyme; ARBs, angiotensin-receptor blockers; HD, hemodialysis; nPCR, normalized protein catabolic rate; BMI, body mass index; HOMA-IR, homeostasis model assessment for insulin resistance.

The GII study included 12 nondiabetic HD patients. One patient withdrew after one visit and was excluded from statistical analysis. Another patient had brachial BP and CO measured, but PWA and PWV measurements were unavailable due to atrial fibrillation.

In the Meal Study, 12 nondiabetic HD patients had brachial BPs and HR measured at 3 visits. PWA measurements were not possible in 4 patients due to atrial fibrillation in 2 patients and former fistula in the other 2. Twelve healthy controls were matched by gender, age, height, and weight.

Informed, written consent was obtained from all participants in both studies. Protocol and consent formulas were approved by the Ethics Committee of the Central Danish Region, and the studies were performed in accordance with the Declaration of Helsinki and monitored by the Committee of Good Clinical Practice at Aarhus University Hospital. The GII study is registered NCT01209403 with the ClinicalTrials.gov registry and the Meal study NCT01446302.

Samples from these studies have previously been used to describe changes in the insulin-like growth factor system and in postprandial mineral handling [32, 33].

Study Design

GII Study. The 11 subjects received in random order: (a) standard dialysis conditions (no infusion [NI] day), (b) dialysis with 10% glucose infusion 2.5 mL/kg/h (G day), and (c) dialysis with 10% glucose infusion 2.5 mL/kg/h with 30 IU insulin aspart/L added (GI day). Between interventions were 2 weeks wash-out intervals, during which subjects received their standard HD thrice weekly.

Meal Study. The 12 HD patients ingested in random order: (a) One meal on a non-HD day (NHDM1), (b) 1 meal on an HD day (HDM1), and (c) 2 meals on an HD day (HDM2). Controls went through an experiment identical to the non-HD day.

Experimental Study Day

GII Study. Each study day consisted of 3 phases: pre-HD (–120 to 0 min), HD (0–240 min), and post-HD (240–360 min). Pre-HD started between 7:30 and 9:00 a.m., when the patient after an overnight fast had a mixed meal with an average energy content of 650 kcal, after which only water was permitted. At G and GI days infusions were given in the pre-HD and HD phases, and blood glucose levels were kept at 8.0–10.0 mmol/L by additional glucose infusion. Insulin infusion on GI days ceased in the post-HD phase, and glucose infusion was gradually lowered to obtain a blood glucose level of 3.0–5.0 mmol/L. The design has been published in details [32].

CO measurement was performed at HD start (0 min), at 120 (mid dialysis), and at 240 min (end-dialysis). PWA and PWV measurements were performed at –60 min (60 min before start of HD), at 120 min, and at 300 min (60 min post-HD).

Meal Study. Participants fasted overnight and were admitted between 7:30 and 9:00 a.m. After 1 h of HD, a weight-adjusted standardized mixed meal with an average energy content of 633 kcal was consumed within 30 min. Afterward only water was permitted until the end of the study or until a similar second meal on HDM2 days. The design has been published in details [34]. Brachial BP and HR were measured at –60 min (HD start), at 0 min (meal), at 30 and 60 min, and then hourly until 540 min post-meal. PWA was measured at all these time points except from –60 min. At HD days, baseline values were obtained at –60 min (HD-start). At non-HD-days, baseline was obtained as 0 min (meal start).

Hemodialysis

Both studies used a standardized 4-h HD session with a high-flux polysulphone membrane (FX80, Fresenius Medical Care, Bad Homburg, Germany). Blood flow was between 300–350 mL/min and dialysate flow 500 mL/min. Linear scheduled ultrafiltration throughout the HD session aimed to obtain previously established estimated dry weight. Dose of low-molecular-weight heparin was unaltered across study visits. The standardized dialysate contained glucose 5.5 mmol/L, sodium 138 mmol/L, potassium 2.0 mmol/L, calcium 1.25 mmol/L, and bicarbonate 36 mmol/L.

Methods of Measurements

PWA and PWV were measured using SphygmoCor applanation tonometer (AtCor Medical, Sydney, Australia) according to manufacturer's instructions [35]. PWA was measured on the radial artery in the non-fistula arm.

BP was measured using validated automated oscillometric BP devices. CO, PWA, and PWV were measured twice at every time point. PWV measurements with a SD above 20% were discarded. At differences above 0.5 m/s between the 2 PWV measurements, a third measurement was conducted. As recommended, PWA measurements were not accepted if operator index was <80%, T1 was <80 or >150 ms, or AIx >50% [35].

Central BP, AIx, AIx standardized to HR of 75 (AIx@HR75), and subendocardial viability ratio (SEVR) were calculated from applanation tonometry using Sphygmocor software

Table 2. Baseline hemodynamic parameters

Study	GII study*	Meal study**		<i>p</i> value [†]
	HD patients (<i>n</i> = 11)	HD patients (<i>n</i> = 12)	controls (<i>n</i> = 12)	
<i>Brachial measurements</i>				
Brachial systolic BP, mm Hg	140.5±3.1	130.4±3.7	133.2±3.6	0.69
Brachial diastolic BP, mm Hg	73.7±2.1	72.2±1.7	82.9±2.3	0.03
Brachial PP, mm Hg	66.8±2.6	55.1±2.9	50.25±2.8	0.47
HR, beats/min	73.2±1.9	74.6±2.0	59.0±4.0	<0.001
<i>PWA/PWV measurements, n</i>				
	10	8	11	
Aortic systolic BP, mm Hg	123.6 (117.4–130.1)	119.1 (112.6–126.0)	126.4 (118.8–134.5)	0.18
Aortic diastolic BP, mm Hg	74.0 (69.4–79.0)	76.7 (73.4–80.2)	85.0 (80.8–89.4)	0.005
Aortic PP, mm Hg	46.8 (40.9–53.6)	41.5 (36.6–47.1)	40.7 (35.0–47.4)	0.78
AIx, %	19.4 (14.2–26.4)	25.5 (20.8–31.4)	28.6 (23.0–35.5)	0.52
AIx@HR75, %	20.0 (15.9–25.2)	23.7 (19.6–28.7)	19.7 (13.2–29.5)	0.44
Aortic TR, ms	135.1 (131.3–139.0)	139.5 (132.5–146.9)	147.5 (140.0–155.5)	0.18
SEVR, %	122.8 (116.7–129.2)	151.7 (141.2–162.9)	165.9 (138.5–198.8)	0.48
Aortic PWV, mm Hg	9.3 (8.6–10.1)	–	–	–
CO, L/min	6.3 (5.9–6.7)	–	–	–

Data are mean ± SEM or geometric means (95% CI) as appropriate.

* GII study: at baseline, hemodynamic measurements did not differ between study days and overall mean values are listed.

** Meal study: on HD days, an additional brachial blood pressure was measured at –60 min and overall mean values are listed for measurements at baseline on HD days and at on non-HD days.

[†] *p* value for comparison of HD patients and controls in the meal study (unpaired *t* test or Wilcoxon-Mann-Whitney test).

GII, glucose-insulin infusion; HD, hemodialysis; AIx, augmentation index; BP, blood pressure; HR, heart rate; PP, pulse pressure; PWA, pulse-wave analysis; PWV, pulse-wave velocity; SEVR, subendocardial viability ratio; TR, time to reflectance; CO, cardiac output; AIx@HR75, AIx standardized to HR of 75.

version 8.2 that constructed the central pulse waveform from the radial waveform with a general transfer function. CO was measured using non-invasive ultrasound dilution technique infusing 30 mL isotonic NaCl Bolus (Transonic HDO2, Transonic Systems, Ithaca, NY, USA).

Statistics

Results are expressed as mean ± SEM or geometric mean (95% CI). Differences in baseline characteristics between HD patients and healthy controls were evaluated by unpaired *t* test or by Wilcoxon-Mann-Whitney test for continuous variables and by Fisher's exact test for categorical variables. Data were log transformed prior to statistical analysis to be well described by the models. Relative changes in hemodynamic parameters over time, between and within different study days were tested with linear mixed effect models with the order of study days, day of visit, and interaction between study days and time as fixed effects. Individual and the interaction between individual and day of visit were included as random effects. Percentage change from baseline was calculated from the geometric mean ratio between values at baseline and at the specific time point. Geometric mean ratio was obtained by taking antilog to the differences derived from linear mixed effect models (on a log-scale). Normality was checked by inspecting QQ-plots of the residuals. *p* values <0.05 were considered statistically significant. Data were analyzed using Stata version 14.2 (Lakeway Drive, TX, USA).

Fig. 1. GII study. Changes in brachial systolic BP (A), brachial diastolic BP (B), brachial PP (C), and HR (D) during NI (black circles), glucose infusion (G, open triangles), and GII (GI, black triangles). Data are means $\pm$ SEM derived from the linear mixed effect models. HD, hemodialysis; BP, blood pressure; NI, no infusion; PP, pulse pressure; HR, heart rate.

Results

GII Study

At baseline (–60 min), no significant differences were observed in the measured hemodynamic parameters between the 3 study days. Baseline values are shown in Table 2.

Brachial and Aortic Systolic and Diastolic BP, Pulse Pressure, and HR

Changes in brachial systolic BP, diastolic BP, and pulse pressure (PP) did not differ between the 3 study days (all $p > 0.12$; Fig. 1). In an overall analysis including the 3 days, systolic BP decreased by maximum 13% ([10–16%], mean [95% CI], $p < 0.001$) at 240 min,

Fig. 2. GII study. Relative changes in PWV (**A**), AIx@HR75 (**B**), SEVR (**C**), and CO (**D**) during NI (black circles), glucose infusion (G, open triangles), and GII (GI, black triangles). Data are geometric mean ratios $\pm$ SEM derived from the linear mixed effect models. PWV, pulse wave velocity; HD, hemodialysis; AIx75, augmentation index 75; SEVR, subendocardial viability ratio; NI, no infusion; CO, cardiac output.

diastolic BP decreased by maximum 9% ([5–13%], $p < 0.001$) at 120 min, and PP decreased by maximum 18% ([13–23%], $p < 0.001$) at 240 min. Likewise, changes in central aortic systolic BP, diastolic BP, and PP did not differ significantly between study days (all $p > 0.9$) and changes followed the same patterns as the brachial measurements (online suppl. Fig. S1; for all online suppl. material, see www.karger.com/doi/10.1159/000506012). Changes in HR were similar across study days ($p = 0.49$) and HR increased by maximum 7% ([3–10%], $p < 0.001$) at 240 min.

PWV, AIx@HR75, SEVR, and CO

Changes in PWV, AIx@HR75, SEVR, and CO did not differ between study days (all $p > 0.57$; Fig. 2). In an overall analysis including all 3 days, PWV decreased from baseline by only 5% ([0–9%], $p = 0.03$) at 120 min, AIx@HR75 decreased by maximum 17% ([7–27%], $p = 0.002$)

Table 3. Dialysis data

Dialysis data	Weight preHD, kg	Weight postHD, kg	Weight loss, kg	Ultrafiltration, mL	Glucose infusion, mL
<i>GII study</i>					
NI	74.7±4.7	73.1±4.5	1.55±0.31	2,398±318	0
Glucose infusion	74.8±4.6	73.9±4.5 ^α	0.92±0.18	3,039±236 ^α	1,334±66
GII	74.8±4.5	74.2±4.6 ^α	0.65±0.22 ^α	3,378±194 ^α	1,764±100 ^β
<i>Meal study</i>					
HDM1	77.8±5.8	76.0±5.6	1.8±0.33	2,258±371	–
HDM2	77.3±5.7 ^χ	75.6±5.5 ^χ	1.7±0.36	2,173±359	–

Values are expressed as the mean ± SEM.

In the GII study (GII study): ^α $p < 0.02$ compared with NI days; ^β $p < 0.001$ for glucose infusion versus GII days (ANOVA). In the meal study: ^χ $p < 0.05$ for HDM1 versus HDM2 (paired t test).

HD, hemodialysis; HDM1, HD days with one meal; HDM2, HD days with two meals; GII, glucose-insulin infusion; NI, no infusion.

at 120 min, SEVR increased by maximum 23% ([18–29%], $p < 0.001$) at 120 min, and CO decreased by maximum 18% ([13–22%], $p < 0.001$) at 240 min.

Hemodialysis

Dialysis data are shown in Table 3. On G and GI study days, 10% glucose without and with insulin added, respectively, was infused (2.5 mL/kg/h) during pre-HD and HD period, and additional 10% glucose was infused to maintain blood glucose concentrations between 8.0 and 10.0 mmol/L. The infused volume on GI days was greater than on G days ($p < 0.001$). Ultrafiltration rates were higher on G and GI days compared with NI days ($p < 0.01$), and intradialytic weight loss was greater on NI days compared with GI days ($p = 0.013$). There were no statistical differences in ultrafiltration rates or weight loss between G and GI days ($p > 0.3$). Hourly hematocrit measurements from beginning to end of the study yielded no significant differences in the changes between study days ($p = 0.94$).

Meal Study. At baseline, only brachial and aortic diastolic BP and HR differed between patients and healthy controls (Table 2).

Brachial and Aortic Systolic and Diastolic BP, PP, and HR

Changes in brachial systolic and diastolic BP did not differ between HD days with either one (HDM1) or 2 meals (HDM2; $p > 0.51$; Fig. 3). Likewise, changes on non-HD days and in controls were similar ($p > 0.08$). Changes on HD days differed significantly from changes on non-HD days and in controls (all $p < 0.01$). On HD days, systolic BP decreased from baseline by maximum 22% ([18–27%], $p < 0.001$) at 120 min on HDM1 and by maximum 25% ([21–29%], $p < 0.001$) at 180 min on HDM2 days. On non-HD days, brachial systolic BP increased at 300 min and to the end of study by maximum 12% ([6–19%], $p < 0.001$), whereas changes in controls did not reach statistical significance ($p > 0.05$). Changes in diastolic BP behaved similarly; on HD days diastolic BP decreased from baseline by maximum 19% ([14–24%], $p < 0.001$) at 120 min on HDM1 and by maximum 22% [17–27%] ($p < 0.001$) at 180 min on HDM2 days. On non-HD days, brachial diastolic BP increased at 480 min and to the end of study by maximum 10% ([3–16%], $p = 0.003$), whereas controls demonstrated no significant changes ($p > 0.07$). Changes in brachial PP did not differ significantly between study days ($p = 0.23$).

Fig. 3. Meal study. Changes in brachial systolic BP (**A**), brachial diastolic BP (**B**), brachial PP (**C**), and HR (**D**) on NHDM1 (black triangles), HDM1 (open circles), HDM2 (black circles), and in controls (open triangles). $^{\alpha} p < 0.05$ for HDM1 and HDM2 versus NHDM1 and controls; $^{\beta} p < 0.04$ for HDM1 and HDM2 versus NHDM1; $^{\delta} p < 0.006$ for HDM1 versus NHDM1; $^{\epsilon} p < 0.05$ for controls versus HDM1 and HDM2; $^{\chi} p < 0.04$ for controls versus NHDM1, HDM1 and HDM2. Data are means derived from the linear mixed effect models (error bars not shown for clarity). BP, blood pressure; HD, hemodialysis; HDM2, two meals on an HD day; NHDM1, One meal on a non-HD day; HDM1, one meal on an HD day; PP, pulse pressure; HR, heart rate.

Changes in central aortic systolic BP, diastolic BP, and PP followed the same patterns as for brachial measurements (online suppl. Fig S2).

Changes in HR differed between HD patients and healthy controls. HR did not change significantly from baseline on any patient study day, whereas HR in controls increased from 30 to 120 min by maximum 13% ([6–20%], $p < 0.001$).

AIx@HR75 and SEVR

AIx@HR75 and SEVR demonstrated similar changes on HDM1 and HDM2 days ($p = 0.71$ and $p = 0.36$, respectively), so HD days were pooled for a common analysis (Fig. 4). On HD

Fig. 4. Meal study. Relative changes in Alx@HR75 (**A**) and SEVR (**B**) on NHDM1 (black triangles), HDM1 + HDM2 (open circles with black edge), and in controls (open triangles). α $p < 0.05$ for HDM1 + HDM2 versus NHDM1 and controls; β $p < 0.03$ for NHDM1 versus HDM1 + HDM2 and controls; χ $p < 0.005$ for controls versus NHDM1 and HDM1 + HDM2; δ $p < 0.02$ for controls versus NHDM1. Data are geometric mean ratios derived from the linear mixed effect models (error bars not shown for clarity). Alx, augmentation index 75; HD, hemodialysis; SEVR, subendocardial viability ratio; NHDM1, 1 meal on a non-HD day; HDM1, 1 meal on an HD day; HDM2, 2 meals on an HD day.

Fig. 5. Comparison between the GII study and the Meal study. Relative changes in brachial systolic BP on NI days in the GII study (black circles) and on HDM1 + HDM2 in the Meal study (open circles with black edge). α $p < 0.001$ for NI versus HDM1 + HDM2. Data are geometric mean ratios $\pm$ SEM derived from the linear mixed effect models. BP, blood pressure; NI, no infusion; HDM1, 1 meal on an HD day; HDM2, 2 meal on an HD day; HD, hemodialysis.

days, Alx@HR75 decreased by maximum 37% ([20–50%], $p < 0.001$) at 120 min and a similar decrease by maximum 36% ([17–50%], $p = 0.001$) at 120 min were observed in controls. In contrast, on non-HD days no statistical significant changes were observed in Alx@HR75 ($p = 0.61$). Changes in Alx@HR75 between study days did not reach statistical difference ($p = 0.052$), which may be due to lack of power. Changes in SEVR differed significantly between HD days, non-HD patient days, and controls ($p < 0.001$). On HD days, SEVR increased above baseline at 120–180 min by maximum 9% ([4–15%], $p = 0.001$). On non-HD patient days, SEVR decreased below baseline at 30–120 min by maximum 10% ([4–16%], $p = 0.002$) and at 300–360 min by maximum 8% ([2–13%], $p = 0.01$). In the healthy controls, SEVR decreased below baseline at 30–60 min by maximum 11% ([6–15%], $p < 0.001$), then increased above baseline at 180 min and to the end of the study by maximum 16% ([10–22%], $p < 0.001$).

Hemodialysis

Dialysis data are shown in Table 3. No differences were observed in weight loss, ultrafiltration rates, or changes in hematocrit between HDM1 and HDM2 days ($p = 0.69$, $p = 0.35$, and $p = 0.97$, respectively).

Comparison of Changes in Systolic BP between the GII Study and the Meal Study

On NI days in the GII study and on HDM1 and HDM2 days in the meal study, the lowest average systolic BP was reached at the end of HD. The relative decrease from baseline was, however, significantly greater ($p < 0.001$) on HDM1 and HDM2 days (average 23% [19–27%]) compared with NI days (10% [5–15%]; Fig. 5). The meals served on NI days in the GII study and on HDM1 and HDM2 days in the meal study had the same average energy content (661 vs. 629 kcal, $p = 0.66$), but protein content was lower on NI days in the GII study than on HDM1 and HDM2 days in the Meal study (20 vs. 33 g, $p < 0.001$). Weight loss and ultrafiltration rates during HD were similar on NI days compared with average for HDM1 and HDM2 days ($p = 0.58$ and $p = 0.73$, respectively).

Discussion

The GII study showed that HD markedly reduced BP, AIx@HR75 , and CO, whereas PWV was only slightly reduced. Neither glucose nor GII had any additional effects on the hemodynamic response to HD. In the Meal study, the combination of HD and meal intake reduced BP and AIx@HR75 , whereas on non-HD days BP increased and AIx@HR75 remained unchanged postprandially. In comparison, healthy controls demonstrated no postprandial changes in BP and AIx@HR75 decreased.

In healthy subjects, a hyperinsulinemic-euglycemic clamp rapidly reduces AIx through dilatation of the large arteries [12]. In the GII study, we aimed to determine if superimposing glucose or GII on top of HD had further hemodynamic implications than HD alone. Although insulin concentrations differed significantly between the 3 study days ($p < 0.001$ for each pairwise comparison) [32] no differences in BP, AIx@HR75 , PWV, or CO were observed between study days. A reduced effect of insulin on central BP and AIx has been demonstrated in type 2 diabetics and obese individuals [12, 16, 36]. HD patients are characterized by insulin resistance which may have contributed to the lacking effect of hyperinsulinemia on investigated hemodynamic parameters by reducing insulin-mediated arterial relaxation. Another explanation is that HD induces a large hemodynamic response veiling a relatively smaller vasodilatory effect of insulin.

In contrast to the rather large HD-induced reductions in BP, AIx@HR75 , and CO, only a minor decrease was observed in PWV of 5%. The observed reductions in brachial BP, AIx , and CO during HD are in agreement with the current literature [20–24, 26–28], whereas study results are more conflicting regarding whether HD render PWV unchanged [22–24, 30, 37] or reduce PWV significantly [25, 29]. The studies with significant PWV reductions had slightly higher dialytic weight loss than studies with unchanged PWV (1st dialysis session by Georgianos et al. [22] being an exception). Overall, literature brings the impression of PWV being more stable than AIx@HR75 , though still influenced by a sufficiently large ultrafiltration, a conclusion consistent with the result of the GII study.

According to previous studies [27, 28], the reduction in CO found in the GII study could be induced by decreased blood volume resulting from ultrafiltration. In healthy subjects, a positive correlation between insulin levels and CO has been reported [38], but in the GII study, changes in CO were similar across study days although S-insulin levels were very different. As with AIx@HR75 , either insulin resistance, interference between HD and insulin pathways or the large impact of HD per se on CO may explain the lacking effect of insulin infusion on CO.

SEVR is a ratio between myocardial perfusion and left ventricular workload calculated from BPs to PWA and is used to determine myocardial stunning and ischemia [39]. Low SEVR is associated to higher cardiac mortality [39]. Myocardial perfusion is increased by raising DBP and diastolic duration time. In the GII study, SEVR increased although myocardial perfusion was compromised during HD as a result of increasing HR and decreasing DBP. Accordingly, the observed increase in SEVR resulted from an even more pronounced decrease in left ventricular workload due to a marked decrease in SBP which most likely resulted from ultrafiltration overriding the capacity of the left ventricle to maintain BP. Consequently, the observed increase in SEVR during HD cannot necessarily be interpreted as improved myocardial perfusion or reduced ischemia. Furthermore, previous studies have shown that HD causes subclinical ischemia and myocardial stunning [40]. SEVR can determine overall cardiac risk under standardized conditions but is less useful when BP changes rapidly, for example, during HD.

In the Meal study, the healthy controls showed no significant changes in BP after meal ingestion but demonstrated a significant rise in HR, probably reflecting an adequate response to increased splanchnic blood pooling [31]. In contrast, HR did not change significantly from baseline on any patient study day in the meal study which may reflect autonomic dysfunction [31].

In the meal study, $AIx@HR75$ decreased in controls and in patients during HD, whereas patients on NHDM1 days had unchanged $AIx@HR75$. The decrease in $AIx@HR75$ among healthy subjects matches other findings [13, 15]. The unchanged $AIx@HR75$ on NHDM1 days is best explained by poor autoregulation due to insulin resistance [14, 16, 17], as the HD patients had significantly higher HOMA-IR than controls.

The relative reduction in systolic BP was 2 times greater on HDM1 and HDM2 days in the Meal study compared with NI days in the GII study (average decrease of 23 vs. 10%). The most notable difference between the HD days in the 2 studies was that the meal was ingested 1 h before start of HD in the GII study, whereas the meal was ingested after the first hour of HD in the Meal study. The different impacts on BP suggest that meal ingestion prior to the HD session may diminish the risk of symptomatic IDH. Furthermore, since intradialytic GII had no additional effects on hemodynamic parameters compared with HD per se in the GII study, caloric intake during HD may successfully be obtained in this way in hemodynamically unstable patients.

Our studies have their strengths as well as limitations. Cross-over designs eliminating confounding factors and real time collection of data add positive to the studies, whereas the limited number of subjects reduced the studies' power, as some trends did not reach statistic significance. In the Meal study, a protocol with HD but no meal would have been a powerful control. Additionally, as the studies were run individually without the purpose of interstudy comparison, meal protein content was different between the studies, making comparison biased.

In conclusion, HD induced marked reductions in BP, $AIx@75$, and CO, whereas only minor changes were observed in PWV. HD per se seemed by far the most important determinant for the acute hemodynamic changes observed, whereas GII had no additional effects. Furthermore, IDH appeared more pronounced when meals were ingested during HD in the meal study compared with meal ingestion an hour prior to HD start in the GII study even when intradialytic GII was administered. In hemodynamically unstable patients, the timing and route of nutrition provision should therefore be considered in order to alleviate meal-related IDH but at the same time supply calories to counteract the catabolic effects of HD.

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Statement of Ethics

Informed, written consent was obtained from all participants in both studies. Protocol and consent formulas were approved by the Ethics Committee of the Central Danish Region, and the studies were performed in accordance with the Declaration of Helsinki and monitored by the Committee of Good Clinical Practice at Aarhus University Hospital. The GII study is registered NCT01209403 with the ClinicalTrials.gov registry, and the Meal study NCT01446302.

Disclosure Statement

The authors declare no conflicts of interests.

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Author Contributions

C.S.-J. has written this article and built the database from the paper sources. M.R. has performed the studies from which the data are derived as part of his PhD. Furthermore, he has made the statistics and discussed findings and article with C.S.-J. P.I. has supervised the study, discussed findings, and article with C.S.-J.

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