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Post-Reperfusion Syndrome in Liver Transplantation: Does a Caval Blood Flush Vent Help?

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Background: Post-reperfusion syndrome (PRS) during liver transplantation can range from a benign event to a profound hemodynamic excursion from baseline with significant morbidity. Multiple variables can be responsible for the diverse presentations. Over time, our group noticed that a blood flush of the liver graft via a caval vent (in addition to a standard chilled flush via the portal vein) appeared to result in a milder reperfusion effect. Attenuation of PRS via caval vent seemed to minimize hemodynamic instability and reduce metabolic derangements associated with reperfusion.

Material/Methods: This was a prospective observational pilot study of standard practice with the addition of lab values and hemodynamic evaluations. We methodically observed normal clinical flow in 20 adult orthotopic liver transplant recipients. We analyzed blood and fluid samples at set time intervals during the peri-reperfusion phase.

Results: Sixteen out of 20 patients received a blood flush via caval venting. Mean arterial pressure (MAP) and heart rate were better preserved in the patient population that received a caval blood flush vent. Elevations in central venous pressure (CVP) were similar between the 2 groups. Lab values (blood gas, electrolyte, and hemoglobin) of the patients' blood were similar, with no notable differences. Analysis of the initial blood flushed through the liver graft proved to be hypothermic, acidotic, and hyperkalemic.

Conclusions: Pre-reperfusion caval venting in liver transplantation (in addition to a portal vent and a chilled LR/albumin portal flush solution) appears to have favorable hemodynamic effects. The literature on this technique is sparse and larger studies are needed.

MeSH Keywords: **Acidosis • Hemodynamics • Hyperkalemia • Liver Transplantation • Reperfusion • Vasoconstrictor Agents**

Abbreviations: **BPM** – beats per minute; **C°** – Celsius; **CO₂** – carbon dioxide; **CVP** – central venous pressure; **ESLD** – end-stage liver disease; **HCC** – hepatocellular carcinoma; **HR** – heart rate; **IRB** – Institutional Review Board; **IVC** – inferior vena cava; **L** – liters; **LR** – lactated Ringer's solution; **MAP** – mean arterial pressure; **Meq** – milliequivalents; **ml** – milliliters; **MMol** – millimoles; **NASH** – non-alcoholic steatohepatitis; **OLT** – orthotopic liver transplantation; **PaCO₂** – partial pressures of carbon dioxide in arterial blood; **pH** – potential hydration; **PaO₂** – partial pressure of oxygen in arterial blood; **PRS** – post-reperfusion syndrome; **SAS** – statistical analysis system; **TEE** – transesophageal echocardiography

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Background

A commonly accepted definition of post-reperfusion syndrome (PRS) in liver transplantation is a 30% decrease in mean arterial pressure (from baseline) lasting for at least 1 minute and occurring within 5 minutes of graft reperfusion. This physiologic sequence is reported to occur during orthotopic liver transplantation (OLT), with an incidence rate of 12.1% to 31.6% [1–3]. First described by Aggarwal et al. in 1987, PRS typically includes decreases in heart rate and systemic vascular resistance accompanied by increases in central venous pressure and pulmonary capillary wedge pressure [1,4]. The degree and duration of hemodynamic volatility is generally unpredictable and can be profound. Hilmi et al. further classified PRS into categories of mild versus significant based on the magnitude and duration of hemodynamic swings. The quantity and duration of necessary vasoactive drugs were considered in the designation of mild versus significant [5]. A recent review article on PRS in liver transplantation by Manning et al. summarizes the differing definitions of PRS, the risk factors involved, and the potential long-term implications [6].

In addition to hemodynamic perturbations, however, metabolic derangements also occur. Hyperkalemia is probably the most feared metabolic change and is typically observed immediately after graft reperfusion. Hyperkalemia occurs with variable severity, including arrhythmias and cardiac arrest [7–10]. The rapid influx of potassium is thought to come from the preservation fluid (University of Wisconsin solution [K^+ concentration 120 mEq/L]) remaining in the graft at the time of reperfusion [7,11–14].

Many studies have investigated the effect of flushing and venting the graft with several permutations of fluids (e.g., blood, albumin, and LR) and via different routes (e.g., portal, caval, and arterial). These studies found inconsistent results in terms of metabolic changes (serum potassium) as well as short- and long-term clinical outcomes [7,8,15–18]. During clinical observation, some members of our multidisciplinary transplant team felt that that an LR/albumin portal vein flush combined with caval venting allowed for improved hemodynamic stability and a decreased requirement for vasopressors and inotropes. It was thought that the additional step of caval venting prevented the most acidic, hyperkalemic, and hypothermic blood (the initial reperfusion blood bolus) from entering the systemic circulation and initiating the spiral of PRS. Subsequently, the present pilot study was conducted to examine and estimate differences in hemodynamic and laboratory values between patients who received a portal blood flush with caval venting compared to those who received a portal flush only.

Material and Methods

Approval for this study was granted from the Medical University of South Carolina's Institutional Review Board (IRB Pro0004952). In addition, prior to patient enrollment, this clinical trial was registered with clinicaltrials.gov on June 29th, 2015 with NCT03563404 as the identifier. Informed and written consent was obtained from all patients enrolled in this prospective observational study of standard practice with the addition of lab values and hemodynamic evaluations. Induction of anesthesia, monitoring, and invasive line placement was carried out in standard fashion. Dissection and surgical technique for transplantation were not altered or influenced in this study. All liver grafts were procured after declaration of brain death and were preserved in a University of Wisconsin solution. All recipient donor livers received a flush via the portal vein with 1 liter of an ice-bath chilled lactated Ringer's solution and 12.5% albumin solution while the cava was being anastomosed. The decision to add caval venting of blood prior to reperfusion was a joint decision between the anesthesiologists and surgeons, based on hemodynamic stability (or instability) of the recipient, duration of "warm ischemic time", potential hydration (pH), and electrolyte status. A caval vent (in addition to the LR flush via the portal vein) was typically requested for a recipient deemed to be unstable prior to reperfusion. Labs were drawn hourly from incision to the anhepatic phase, every 30 minutes while anhepatic, and then hourly from reperfusion until cessation of case management. Five minutes prior to reperfusion, an arterial blood gas and lactate were drawn as a baseline. If a caval vent was performed, a sample of the caval vent fluid was obtained immediately prior to reperfusion (as it was vented into the peritoneal cavity). The sample was then analyzed for temperature and the following lab values: potassium, pH, and lactate. Follow-up arterial blood gases and lactates were drawn at 1 minute and 5 minutes after reperfusion to assess changes from baseline. Vital signs were recorded at 5 minutes prior to reperfusion and at 1, 5, and 20 minutes after reperfusion. The type and amount of vasopressors/inotropes were recorded and tallied.

Analysis

Descriptive statistics for participant and procedural characteristics were calculated across all study participants and within the 2 treatment groups. Mean hemodynamic characteristics by treatment group over time were estimated using linear contrasts from a series of linear mixed models evaluating hemodynamic characteristics over time. The dependent variables considered in the mixed models included mean arterial pressure (MAP), heart rate (HR), and central venous pressure (CVP), and the independent fixed-effects included treatment group, time (5 minutes prior to transplant and 1, 5, and 20 minutes after reperfusion), and a group-by-time interaction. All models also included a random subject effect to account for correlation

between measures collected on the same subject over time. Because this was a pilot study, no formal hypothesis tests were conducted, but the linear mixed models were used to estimate the mean hemodynamic characteristics over time while accounting for the correlation within subjects. We also examined serum sample characteristics over time using a mixed-modeling approach. Serum characteristics evaluated over time included potential hydration (pH), partial pressure of oxygen in arterial blood (PaO_2), partial pressures of carbon dioxide (PaCO_2), bicarbonate, base excess/deficit, total carbon dioxide (CO_2), sodium, potassium, calcium, glucose, hemoglobin, hematocrit, and lactate. Model assumptions for all analyses were evaluated graphically, and transformations were considered when needed. All analyses were conducted using the Statistical Analysis System (SAS) version 9.4 (SAS Institute, Cary, NC).

Results

Study structure and participants

The study included 20 total participants, with 16 receiving blood flush via caval venting at the time of reperfusion while 4 did not receive blood flush via caval venting at reperfusion. A majority were males (70%) and white (85%). The mean age was 59.4 ± 10.4 years; however, patients that received the blood flush via caval venting tended to be older (48.8 ± 18.8 years in those with no caval vent versus 62.1 ± 4.2 years in those who had a flush via caval vent). The most common cause of end-stage liver disease (ESLD) in transplant recipients was alcoholic cirrhosis (30%), followed by hepatitis C (25%), non-alcoholic steatohepatitis (NASH) (15%), and hepatocellular carcinoma (HCC) (15%). The most common comorbidities observed were portal hypertension (40%) and esophageal varices (35%). Comorbidities were distributed evenly between the 2 groups, but the primary cause of ESLD varied, with NASH patients more typically not receiving blood flush via caval venting while hepatitis C and alcoholic cirrhosis patients more often received blood flush via caval venting. For surgical technique, the majority of patients underwent caval anastomosis via piggy-back technique (74%) followed by the bi-caval method (21%). Additionally, the majority of patients' hepatic allografts were reperfused by primary portal vein reperfusion (74%) followed by simultaneous portal vein and hepatic artery reperfusion (26%). There were no major differences in surgical technique and reperfusion technique between the 2 groups. Participant and procedural characteristics across all participants and by group are presented in Table 1.

Hemodynamic characteristics

Figure 1 compares values for the mean MAP, HR, and CVP at 5 minutes prior to reperfusion and at 1, 5, and 20 minutes after reperfusion.

Patients who received a blood flush via caval venting maintained their baseline mean arterial pressure (MAP) (mean=70–75 mmHg) taken 5 minutes before reperfusion through the initial 20 minutes after reperfusion. However, patients who did not receive a blood flush via caval venting experienced a notable decrease in MAP at 5 minutes after reperfusion (mean=55 mmHg) from baseline 5 minutes before reperfusion (mean=75–80 mmHg) with partial recovery by 20 minutes after reperfusion (mean=60–65 mmHg).

Patients who received a blood flush via caval venting also maintained their average heart rate at 5 minutes after reperfusion (mean=90 BPM) and 20 minutes after reperfusion (mean=93 BPM) compared to the baseline heart rate taken 5 minutes before reperfusion (mean=95 BPM). Patients who did not receive a blood flush via caval venting experienced a similar maintenance of baseline heart rate (mean=77 BPM) from 5 minutes before reperfusion (mean=80 BPM). However, heart rate at 20 minutes after reperfusion was elevated from baseline (mean=90 BPM).

Patients receiving a blood flush via caval venting appeared to show increasing mean central venous pressure (CVP) at 5 minutes after reperfusion (mean=9 mmHg) compared to baseline CVP taken 5 minutes before reperfusion (mean=7 mmHg). Patients not receiving blood flush via caval venting experienced a similar increase in CVP at 5 minutes after reperfusion (mean=12 mmHg) compared to baseline taken at 5 minutes before reperfusion (mean=8 mmHg).

Serum characteristics

Arterial pH, PaO_2 , PaCO_2 , and base excess/deficit, and serum levels of bicarbonate, total CO_2 , sodium, potassium, ionized calcium, glucose, hemoglobin, hematocrit, and lactate taken at 5 minutes before reperfusion and at 1 and 5 minutes after reperfusion are shown in Table 2. There were no notable differences in serum levels over time between the 2 groups.

Characteristics of blood flushed through the liver graft

Potassium, pH, lactate, and temperature of the flushed blood collected from the caval vent after passage through the allograft liver were assessed immediately prior to reperfusion. The samples collected were highly acidotic (7.09), hyperkalemic (21.8), and hypothermic (23.8°C), and contained a high lactate load (12.5). Average values with standard deviations are shown in Table 3.

Table 1. Participant and procedural characteristics across all participants and by treatment group. Categorical variables are reported as n (%) and continuous variables as mean (SD) or * median (IQR).

	Missing	All (n=20)	No caval vent No (n=4)	Caval vent Yes (n=16)
Sex (Male)	0	14 (70.0)	4 (100)	10 (62.5)
Age	0	59.4 (10.2)	48.8 (18.8)	62.1 (4.72)
BMI	0	28.3 (5.14)	28.6 (8.55)	28.2 (4.33)
Race (White)	0	17 (85.0)	4 (100.0)	13 (81.3)
MELD	3	22.5 (4.95)	22.3 (3.77)	22.6 (5.39)
ASA (IV)	0	12 (60.0)	1 (25.0)	11 (68.8)
Reason for transplant	0			
Alcohol cirrhosis		6 (30.0)	1 (25.0)	5 (31.3)
Hep C cirrhosis		5 (25.0)	0 (0.00)	5 (31.3)
Hepatic carcinoma		3 (15.0)	0 (0.00)	3 (18.8)
NASH		3 (15.0)	2 (50.0)	1 (6.25)
Polycystic liver Dx		1 (5.00)	0 (0.00)	1 (6.25)
Other		7 (35.0)	1 (25.0)	6 (37.5)
Comorbidities	0			
Pulmonary HTN		0 (0.00)	0 (0.00)	0 (0.00)
Alcohol/substance abuse		4 (20.0)	1 (25.0)	3 (18.8)
Portal HTN		8 (40.0)	1 (25.0)	7 (43.8)
Coagulopathy		5 (25.0)	2 (50.0)	3 (18.8)
Esophageal Varices		7 (35.0)	2 (50.0)	5 (31.4)
Other		2 (10.0)	1 (25.0)	1 (6.26)
Number comorbidities	0			
0		7 (35.0)	1 (25.0)	6 (37.5)
1		4 (20.0)	0 (0.00)	4 (25.0)
2		9 (45.0)	3 (75.0)	6 (37.5)
Venovenous bypass (yes)	6	2 (14.3)	0 (0.00)	2 (15.4)
Method vascular anastomosis	1			
Bicaval		4 (21.1)	1 (33.3)	3 (18.8)
Piggyback		14 (73.7)	2 (66.7)	12 (75.0)
Other		1 (5.26)	0 (0.00)	1 (6.25)
Extubated (yes)	2	4 (22.2)	1 (25.0)	3 (21.4)
EBL (mL)*	7	1850 (1000)	2000 (1200)	1775 (1300)
CIT (min)	4	308.8 (69.4)	295.7 (70.2)	311.8 (71.7)
WIT (min)	2	46.8 (9.56)	44.8 (6.99)	47.4 (10.3)

Table 1 continued. Participant and procedural characteristics across all participants and by treatment group. Categorical variables are reported as n (%) and continuous variables as mean (SD) or * median (IQR).

	Missing	All (n=20)	No caval vent No (n=4)	Caval vent Yes (n=16)
Method of reperfusion	1			
Primary portal		14 (73.7)	4 (100.0)	10 (66.7)
Simultaneous portal/hepatic artery		5 (26.3)	0 (0.00)	5 (33.3)
Reperfusion drugs				
Phenylephrine		10 (50.0)	2 (50.0)	8 (50.0)
If yes, amount phenylephrine		370 (640)	620 (920)	370 (645)
Epinephrine		12 (60.0)	2 (50.0)	10 (62.5)
If yes, amount epinephrine		35 (55.25)	52 (24)	25 (57)
Vasopressin		3 (15.0)	0 (0.00)	3 (18.0)
If yes, amount vasopressin		2.0 (1.2)	–	2.0 (1.2)
Sodium bicarb		12 (60.0)	3 (75.0)	9 (56.3)
If Yes, amount Na ₂ CO ₃		50 (50)	50 (50)	50 (50)
Calcium chloride		18 (90.0)	4 (100.0)	14 (87.5)
If yes, amount CaCl ₂		1000 (0)	1000 (375)	1000 (250)
Lidocaine		12 (60.0)	3 (75.0)	9 (56.3)
If yes, amount lidocaine		100 (0)	100 (0)	100 (0)
Mannitol		0 (0.00)	0 (0.00)	0 (0.00)
Other		4 (20.0)	0 (0.00)	4 (25.0)
Caval flush volume (mL)		210 (200)	–	210 (200)
LR flush volume (mL)		1600 (700)	1650 (500)	1600 (900)
Pre-flush blood products*				
RBC	2	4 (6)	0.5 (3.5)	4 (4)
FFP	2	3 (5)	3 (0, 5)	4 (5)
Platelets	2	0 (0)	0 (0)	0 (0)
Cryoprecipitate	2	0 (0)	0.5 (1.5)	0 (0)
Post-flush blood products*				
RBC	3	2 (4)	1.5 (4.5)	2 (4)
FFP	3	2 (3)	3 (5)	2 (3)
Platelets	4	0 (0.5)	0 (0)	0 (1)
Cryoprecipitate	4	1 (1)	1 (1)	1 (1)

Discussions

The most notable observation from this study was the decline in MAP for the 20 minutes following reperfusion in the group that did not have caval venting. This decrease in MAP of roughly 30% for at least 1 minute within the first 5 minutes after reperfusion meets the criteria for post-reperfusion syndrome (PRS) [1]. Fifty percent of patients in the non-caval

vent group met the definition of PRS, while only 19% of patients receiving caval vent did. In addition to maintaining their MAP, it should be kept in mind that the caval vent group inherently lost approximately 200–300 milliliters (ml) of blood due the venting technique. Both groups had similar vasopressor requirements in the reperfusion phase. Our analysis did not have the ability to identify patients who may have met the criteria of PRS if the pharmacologic interventions (e.g., vasopressor

Figure 1. Values for the mean MAP, HR and CVP at 5 minutes prior to reperfusion and at 1, 5, and 20 minutes post-reperfusion.

Table 2. Patient serum characteristics over time by treatment group.

Characteristics	Time	No caval vent (n=4)		Caval vent (n=16)	
pH	–5	7.36	(0.030)	7.33	(0.016)
	1	7.32	(0.032)	7.29	(0.015)
	5	7.34	(0.030)	7.30	(0.015)
PaO ₂	–5	241.5	(59.3)	251.7	(31.9)
	1	315.5	(65.6)	333.8	(31.1)
	5	268.0	(59.3)	310.8	(29.7)
PaCO ₂	–5	40.2	(2.81)	38.3	(1.38)
	1	41.3	(2.81)	42.1	(1.35)
	5	43.0	(2.61)	41.6	(1.30)
Na ₂ CO ₃	–5	21.8	(1.70)	19.4	(0.94)
	1	23.6	(1.88)	21.1	(0.89)
	5	23.5	(1.78)	20.6	(0.85)
Base Ex/Def	–5	–3.25	(1.62)	–5.68	(0.85)
	1	–1.97	(1.70)	–5.40	(0.83)
	5	–2.50	(1.62)	–5.56	(0.81)
Total CO ₂	–5	23.3	(1.45)	21.2	(0.79)
	1	25.0	(1.53)	22.4	(0.74)
	5	25.0	(1.45)	22.0	(0.73)
Na	–5	137.3	(2.24)	138.5	(1.13)
	1	136.8	(2.27)	138.5	(1.13)
	5	138.0	(2.24)	138.9	(1.12)
K	–5	4.18	(0.32)	4.13	(0.17)
	1	4.43	(0.35)	4.51	(0.17)
	5	4.10	(0.32)	3.94	(0.16)
Ca	–5	0.99	(0.11)	1.09	(0.06)
	1	1.27	(0.13)	1.19	(0.06)
	5	1.25	(0.11)	1.20	(0.06)

Table 2 continued. Patient serum characteristics over time by treatment group.

Characteristics	Time	No caval vent (n=4)		Caval vent (n=16)	
Glucose	–5	123.3	(22.6)	136.3	(12.6)
	1	140.4	(24.4)	163.6	(11.7)
	5	129.9	(22.6)	176.0	(11.7)
Hgb	–5	9.53	(0.76)	10.5	(0.42)
	1	9.02	(0.84)	9.95	(0.40)
	5	9.00	(0.76)	8.80	(0.39)
Hematocrit	–5	28.0	(3.03)	28.7	(1.60)
	1	26.2	(3.19)	27.4	(1.55)
	5	26.5	(3.03)	25.9	(1.53)
Lactate	–5	3.20	(0.80)	3.98	(0.41)
	1	4.25	(0.81)	5.09	(0.41)
	5	4.05	(0.80)	4.94	(0.40)

Table 3. Characteristics of the caval blood flush in patients that received a caval vent flush. Values are reported as mean (SD) or * median (IQR).

Characteristic	Value
Caval flush volume*	210 (75, 500)
Flush pH	7.09 (0.14)
Flush K	21.8 (7.11)
Flush lactate	12.5 (3.34)
Flush temperature (°C)	23.8 (3.08)

administration) had not been performed. Judicious use of a vasopressor (or a combination of 2) with targeted fluid boluses and adjustments in anesthetic levels can all have profound effects on the MAP. A proposed mechanism for this drop in MAP is myocardial stunning and transient loss of contractility due to an abrupt increase in serum potassium, decreased pH, and decreased temperature in the reperfusion blood (which is not vented via the cava) that subsequently enters the systemic circulation. In addition to myocardial stunning, reperfusion is known to include release of vasodilatory mediators that can further reduce MAP [17–19].

Remarkably, the blood flushed through the allograft from the portal vein and vented from the infrahepatic caval anastomosis had the following average values: potassium [21.8 milliequivalents/Liter (Meq/L)], pH 7.09, lactate [12.5 millimoles/liter (MMol/L)], and temperature of 23.8°C. We suspect that these extreme serum abnormalities are due to the University of Wisconsin solution retained in the allograft and cellular metabolism occurring during cold and warm ischemic time. Any of

these abnormalities delivered (almost directly) to the right atrium via the inferior vena cava (IVC) could certainly contribute to the known phenomenon of myocardial stunning associated with PRS. This hypothesis is supported by the similar vasopressor requirements between the 2 groups despite *dis-similar* MAP values between the 2 groups. Clinical correlation via transesophageal echocardiography would be useful in determining acute functional cardiac changes observed in the peri-reperfusion stage, but this was inconsistently available for this study due to preoperative patient comorbidities. There was a slight increase in heart rate in the non-caval vent group, which could have been a compensatory mechanism secondary to the drop in SVR related to reperfusion with higher concentrations of the vasodilatory mediators mentioned above. Use of epinephrine peri-reperfusion was similar between the 2 groups, and the amount used was typically small boluses of 8–16 micrograms. Both groups had a rise in CVP despite a measurable loss of circulating blood volume associated with caval venting (210 mL). The validity of CVP measurements is known to be affected by several factors present at the time of reperfusion (e.g., pressor use and right-heart function); therefore, we cannot make reliable statements related to changes of CVP and caval venting. Interestingly, serum lab values from 5 minutes before reperfusion to 20 minutes after reperfusion showed no major differences between the 2 groups. This observation supports the hypothesis that the abnormalities measured in the flushed blood normalize rapidly in the serum, but not before potentially causing myocardial stunning after their initial release.

The most significant limitation of this study is the inability to randomize caval venting. Given the existing literature, we found no way to ethically withhold caval venting from patients

who may have met our existing clinical indicators for the technique (e.g., elevated serum potassium, long warm ischemic time, new arrhythmias, and overall hemodynamic instability). By performing an observational study, our groups were too unbalanced in size for comparison. In addition, this was a pilot study. Carrying out an adequately-powered randomized double-blinded study posed significant timing and practical problems. Since some favorable trends were identified, we encourage additional high-volume transplant centers to perform further studies with larger sample sizes, or the results of smaller studies could be compiled and critically reviewed. Finally, another limitation of this study, and perhaps a limitation of clinical delivery of orthotopic liver transplantation in general, was the inconsistent use of transesophageal echocardiography (TEE) to measure changes in cardiac output and/or myocardial function during critical portions of the procedure.

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Conclusions

Post-reperfusion syndrome has been shown to be a reasonable predictor of 3-month mortality and an independent risk factor for primary graft non-function [6,20]. This pilot study describes a caval venting blood flush technique that can mitigate the degree of PRS during liver transplantation. Further research is needed to evaluate the effects of caval venting on graft function, morbidity, and mortality, and we encourage including real-time transesophageal echocardiography to better explain the proposed mechanism of hemodynamic changes.

Conflicts of Interests

None.