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Invasive hemodynamic parameters in patients with hepatorenal syndrome

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ABSTRACT

Background: Hepatorenal syndrome (HRS), a form of kidney dysfunction frequent in cirrhotic patients, is characterized by low filling pressures and impaired kidney perfusion due to peripheral vasodilation and reduced effective circulatory volume. Cardiorenal syndrome (CRS), driven by renal venous hypertension and elevated filling pressures, is a separate cause of kidney dysfunction in cirrhotic patients. The two entities, however, have similar clinical phenotypes. To date, limited invasive hemodynamic data are available to help distinguish the primary forces behind worsened kidney function in cirrhotic patients.

Objective: Our aim was to analyze invasive hemodynamic profiles and kidney outcomes in patients with cirrhosis who met criteria for HRS.

Methods: We conducted a single center retrospective study among cirrhotic patients with worsening kidney function admitted for liver transplant evaluation between 2010 and 2020. All met accepted criteria for HRS and underwent concurrent right heart catheterization (RHC).

Results: 127 subjects were included. 79 had right atrial pressure >10 mmHg, 79 had wedge pressure >15 mmHg, and 68 had both. All patients with elevated wedge pressure were switched from volume loading to diuretics resulting in significant reductions between admission and post diuresis creatinine values (2.0 [IQR 1.5–2.8] vs 1.5 [IQR 1.2–2.2]; $p = 0.003$).

Conclusion: 62% of patients diagnosed with HRS by clinical criteria have elevated filling pressures. Improvement of renal function after diuresis suggests the presence of CRS physiology in these patients. Invasive hemodynamic data profiling can lead to meaningful change in management of cirrhotic patients with worsened kidney function, guiding appropriate therapies based on filling pressures.

1. Introduction

Hepatorenal syndrome (HRS) is a form of hemodynamically mediated kidney dysfunction seen with advanced cirrhosis in the absence of nephrotoxin exposure, shock, and intrinsic kidney disease, which is refractory to a trial of volume expansion [1]. It is characterized by arterial hypotension and marked activation of the renin-angiotensin-aldosterone and sympathetic nervous systems (SNS) which leads to intense renal and extra-splanchnic vasoconstriction [2]. Patients with cirrhosis who developed HRS have been reported to have lower right atrial and pulmonary capillary wedge pressures compared to those without HRS [2].

The maladaptive crosstalk between the heart, liver, and kidneys in patients with cirrhosis is being increasingly recognized [1]. In this context, worsening kidney function in the setting of elevated filling pressures, i.e., cardiorenal syndrome (CRS) physiology, may resemble the clinical phenotype of HRS. Emerging data substantiate that these organs are mechanistically linked, and elevated filling pressures (with/without cardiomyopathy) could possibly mediate progressive decline of

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renal dysfunction in cirrhosis, thus posing a challenge to accurate clinical diagnosis and treatment [2–4]. There are limited data on the clinical and invasive hemodynamic characteristics of patients with cirrhosis and HRS to guide accurate phenotyping and appropriate therapies. We conducted a study in patients with cirrhosis, diagnosed with HRS by accepted clinical diagnostic criteria, who had concurrent right heart catheterization as part of orthotopic liver transplant work-up. Our aim was to document hemodynamic profiles and kidney outcomes in this patient group.

2. Methods

This was a single center retrospective analysis involving patients admitted to Einstein Medical Center Philadelphia from 2010 to 2020 with a diagnosis of decompensated cirrhosis (based on ICD-codes) regardless of etiology. Included patients had to have decompensated cirrhosis and worsening kidney function defined as 0.3 mg/dL rise in serum creatinine from baseline within 48 h or increase in serum creatinine of $\geq$ 1.5 times baseline within 7 days [5]. Only patients with concomitant right heart catheterization (RHC) data were included in this study. Patients with worsening kidney function who did not have exposure to nephrotoxic agents, or evidence of intrinsic kidney disease (hematuria, proteinuria, or any evidence of urine sediment activity on microscopy) or structural kidney disease, and who did not show improvement in kidney function with a 2-day volume challenge were labeled as having HRS. This is in accordance with the currently used criteria for HRS diagnosis [6,7]. Patients with end stage kidney disease on hemodialysis, >mild valvular heart disease, kidney transplant recipients, or who did not undergo RHC were excluded. In our center's practice, right heart catheterization is frequently performed prior to listing for orthotopic liver transplantation (OLT) to exclude portopulmonary hypertension and/or assess volume status. Demographic and clinical variables as well as laboratory parameters were collected by review of the electronic health records. This study was approved by the Einstein Healthcare Network Institutional Review Board.

3. Statistical analyses

Demographic and clinical variables were presented using descriptive statistics, frequencies, and percentages. The mean and standard deviation was generally used except for skewed variables where median and IQR was used. Hemodynamic parameters were compared between patients who were diuresed compared to those who were not. Independent T tests were used to compare the differences in these parameters while non-parametric Mann Whitney *U* test was used to compare skewed variables. Wilcoxon signed rank paired test was utilized in determining differences in serum creatinine before and after diuresis, between diuresed and non-diuresed groups. A p-value of < 0.05 was considered statistically significant. All analyses were done using IBM SPSS Statistics for Windows, version 23.0. Armonk, NY.

4. Results

Of 135 patients with decompensated cirrhosis admitted between 2010 and 2020, the final sample included 127 patients. The mean age of the study sample was 60.09 ± 9.77 years. Thirty-nine percent of patients were female, 40 % were Caucasian and 29 % were Black (Table 1). Sixty-three percent of patients had a prior history of hypertension, 46 % had diabetes while 24 % had coronary artery disease. The mean EF (ejection fraction) was 57.0 ± 13.8. The most common etiologies for cirrhosis were alcoholic (40 %), hepatitis C virus (21 %) and non-alcoholic fatty liver disease or steatohepatitis (16 %). The majority of these patients (73 %) had ascites while 40 % had esophageal varices. The median time to occurrence of worsening kidney function was 3 days from admission (IQR: 2–6). The median time to RHC was 3 days (IQR: 1–5). Forty patients (44 %) received at least 2 or more components of the "triple therapy" (midodrine [or norepinephrine], octreotide and albumin) that is standard treatment for HRS.

Table 1
Demographic and clinical parameters of HRS patients.

Variables	Total n = 126 mean ± SD/ n (%)
Mean age	60.09 ± 9.77
Mean BMI	31.37 ± 9.16
Females	50(39)
Race	
African American	37(29)
Caucasian	51(40)
Hispanic	12(10)
Others	27(21)
Diabetes	58(46)
Hypertension	80(63)
Atrial fibrillation	22(17)
Chronic Obstructive Pulmonary Disease	25(20)
Coronary Artery Disease	30(24)
Ascites	93(73)
Esophageal varices	51(40)
Spontaneous bacterial peritonitis	25(20)
History of TIPS	7(6)
Given albumin	71(56)
Norepinephrine	15(12)
Octreotide	41(32)
Midodrine	52(41)
Diuresed	79(62)
Serum creatinine on admission median (IQR)	1.9(1.4–2.6)
Serum creatinine on admission median (IQR) (among those diuresed)	2.0 [1.5–2.8]
Serum creatinine 3 days after diuretics (among those diuresed)	1.5(1.2–2.2)
Serum creatinine on discharge (among those diuresed)	1.2(1–2.1)
EF Mean ± SD	57.0 ± 13.8
RV dysfunction on echocardiography	
None	92(75)
Mild	18(15)
Moderate	7(6)
Severe	5(4)

Abbreviations: BMI (body mass index), EF (ejection fraction), IQR (interquartile range), SD (standard deviation), TIPS (transjugular intrahepatic portosystemic shunt).

Hemodynamic parameters from RHC showed that 79 (62 %) patients clinically diagnosed as HRS had right atrial pressure (RAP) > 10 mmHg, 79 (62 %) had pulmonary capillary wedge pressure (PCWP) > 15 mmHg, and 68 (53 %) had both RAP > 10 mmHg and PCWP > 15 mmHg (see Figs. 1 and 2; and Tables 1 and 2). All 79 patients with high PCWP, 68 of whom also had high RAP, were switched to diuretic therapy. In this particular group, there was a significant difference between admission serum creatinine and post diuresis (3 days of diuresis) serum creatinine values (2.0 [IQR 1.5–2.8] vs 1.5 [IQR 1.2–2.2]; p = 0.003; see Table 1).

Patients with elevated cardiac filling pressure (diuresed group) had significantly elevated serum creatinine values on admission compared to those with normal filling pressures (non-diuresed group) (2.0 [1.5–2.8] vs 1.6 [1.3–2.2]; p = 0.016); however, there was no significant differences on serum creatinine on discharge (1.2 [1.0–2.2] vs 1.0 [1–1.3]; p = 0.20). Among the non-diuresed group who received triple therapy, the admission creatinine also trended down on discharge, but did not reach statistical significance (1.6 [1.3–2.2] vs 1[1–1.3]; p = 0.07).

5. Discussion

To our knowledge, this analysis is the first to report the following notable findings from the invasive hemodynamic profiles in patients with advanced cirrhosis and kidney dysfunction. First, patients with a clinical diagnosis of HRS often have elevated right and left filling pressures. Second, improvement of renal function after diuresis in patients with elevated filling pressures suggests that these patients actually had CRS which was misdiagnosed as HRS given similar clinical phenotypes.

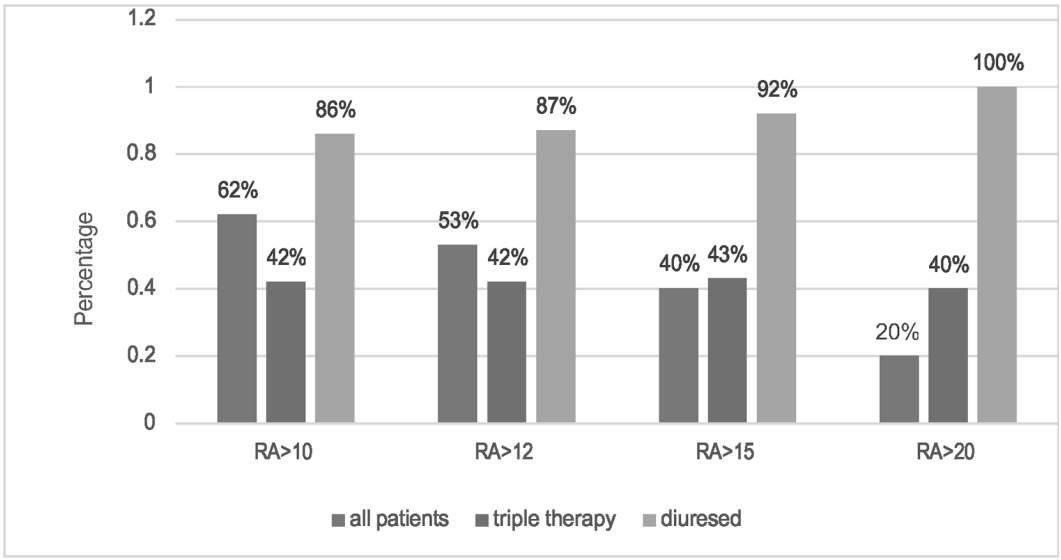

Fig. 1. Percentages of patients with clinical HRS, those received triple therapy and those started on diuresis stratified by RAP cutoff.

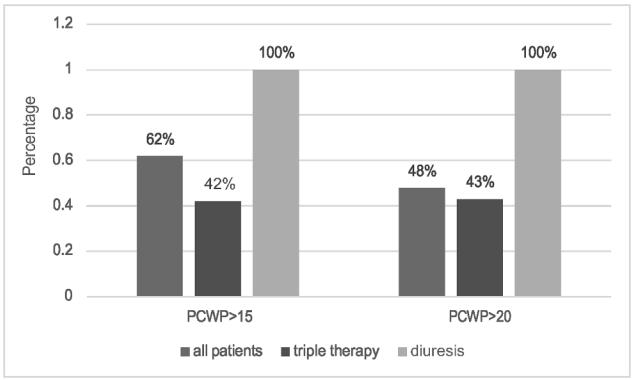

Fig. 2. Percentages of patients with clinical RHS, those who received triple therapy and those started on diuresis stratified by PCWP cutoff.

Table 2
Hemodynamic parameters of HRS patients.

Hemodynamics (mean ± SD)	Diuresed (n = 79)	Not diuresed (n = 48)	p value
RA pressure (mmHg)	16.9 ± 6.9	6.9 ± 4.9	<0.001
RV systolic (mmHg)	49.0 ± 14.9	36.2 ± 15.0	<0.001
RV diastolic (mmHg)	13.6 ± 7.6	4.8 ± 4.1	<0.001
PA systolic (mmHg)	49.0 ± 12.9	34.1 ± 17.0	<0.001
PA diastolic (mmHg)	24.6 ± 7.2	13.6 ± 6.7	<0.001
Mean PA (mmHg)	33.5 ± 8.5	21.2 ± 9.3	<0.001
PCWP (mmHg)	23.9 ± 6.2	10.2 ± 3.2	<0.001
PVR (Wood units; median IQR)	1.9(0.8–3.18)	1.1(0.7–1.7)	0.060
SVR (median IQR) dynes/seconds/cm-5	568(348–880)	480(442–880)	0.740
Cardiac Index (median IQR)	4(2.7–5.3)	3.9(3.2–4.8)	0.990

Abbreviations: IQR (interquartile range), PA (pulmonary artery), PCWP (pulmonary capillary wedge pressure), PVR (pulmonary vascular resistance), RA (right atrium), RHC (right heart catheterization), RV (right ventricle), SD (standard deviation), SVR (systemic vascular resistance).

Third, hemodynamic data obtained via RHC frequently led to change in management of patients that met the clinical definition of HRS.

A substantial portion of our patients (62 %) clinically ascertained to have HRS actually had elevated filling pressures based on RHC data. It is increasingly recognized that there is an existing hemodynamic heterogeneity in patients catalogued as having HRS which suggests the need for individually tailored therapeutic intervention [1]. In fact, one prospective study found that 21 % of patients with HRS were volume-expanded on POCUS (point-of-care-ultrasound) examination with inferior vena cava (IVC) diameter of $>$ 2.0 cm and IVC collapsibility index of $<$ 40 % [8]. This prompted initiation of intravenous furosemide with 30 % of these patients showing reduction of serum creatinine by more than 20 % within 48–72 h of therapeutic intervention. This is in consonance with the findings of our analysis showing more than half of patients with HRS had high filling pressures on RHC and showed improvement in kidney function after switching the management from volume expansion to diuretic therapy. In general, hypervolemia in patients with advanced liver disease may be driven by several pathophysiological pathways including sodium retention due to relative arterial underfilling, co-existent cirrhotic cardiomyopathy, pulmonary hypertension, tense ascites resulting in abdominal hypertension, and excessive IV fluid expansion in oliguric AKI resulting in venous congestion [8].

Our observations would support CRS physiology as one possible driving mechanism for worsening kidney function in cirrhosis patients diagnosed with and managed as HRS. High cardiac filling pressures are directly correlated with poor renal function as evidenced by significantly elevated serum creatinine values seen among HRS patients with elevated filling pressures compared to those with normal filling pressures [9,10]. Although this difference did not reach statistical significance on discharge, this suggests the beneficial effects of decongestive therapy directed towards addressing the elevated filling pressures found during evaluation of these patients originally diagnosed to have HRS. Pathophysiologically, elevated filling pressures may drive kidney dysfunction by virtue of high backward pressure from renal venous congestion. Despite the absence of an established diagnosis of cirrhotic cardiomyopathy in our patients, CRS physiology remains a plausible hypothesis to explain the correlation between reducing cardiac filling pressures and improving renal function. This is supported by a recent study utilizing a combined grading of IVC, hepatic vein waveform, and portal vein pulsatility (VEXUS: venous excess ultrasound score) to determine venous congestion among patients with a provisional diagnosis of CRS; the resultant score correlated well with kidney function [11]. Improvement in kidney function in two-thirds of these patients was associated with a downward trend in VEXUS score. Finally, the burden of concomitant cirrhotic cardiomyopathy is underestimated [12], and future studies in this area may help shed light on the role of heart-kidney-liver interactions in patients with cirrhosis that may guide therapeutics.

Additionally, serum creatinine values of HRS patients that were not diuresed based on their normal filling pressures trended down with triple therapy, albeit without statistical significance, which strongly indicates true HRS physiology [13–15]. In patients with advanced liver cirrhosis, portal hypertension results in various vascular alterations including high cardiac output and low total peripheral resistance as seen in the RHC data of our patients [16].

With the utilization of RHC, more than half of the patients meeting the clinical definition of HRS were actually switched to diuretics, in consonance with high measured filling pressures. These findings are clinically meaningful given the challenge clinicians face in clinical assessment of volume status of patients with complex medical conditions including heart failure, cirrhosis and kidney dysfunction [17]. The discrepancy between clinical assessment and RHC findings, as shown in this study, may potentially lead to incorrect treatment for worsening kidney function in a subset of patients with advanced cirrhosis. The standard management for HRS is directed towards volume expansion with albumin and increasing renal blood flow by administering splanchnic vasoconstrictors (i.e., telipressin, norepinephrine, octreotide + midodrine) as well as reversal of precipitant factors, including diuretic withdrawal in many [18–22]. This is clinically important as further volume expansion in this particular subset of HRS patients may worsen kidney function, impacting overall renal function trajectory, including, potentially, the need for simultaneous liver-kidney transplantation.

6. Limitations

This study is limited by virtue of its retrospective nature and being a single center analysis. Some of our patients may also have had underlying cardiomyopathy from other etiologies such as coronary artery disease as patients with these comorbidities were not excluded in this study. While the temporal association between the hemodynamic parameters and development of worsening kidney function cannot be fully established in a retrospective study, most of these events occurred early, within a median 3 days from admission. The diagnosis of worsening kidney function was based on a rise in serum creatinine levels from baseline, and urine output/24-hour interval was not considered as this was not universally documented.

7. Conclusion

A substantial portion of patients with clinical diagnosed HRS actually have elevated cardiac filling pressures. Improvement of renal function after diuresis suggests that this subgroup actually had CRS. From this data it appears that clinical HRS criteria may be inadequate to distinguish low from high filling pressures. Invasive hemodynamic data potentially leads to a meaningful change in the management of kidney dysfunction in these patients with advanced cirrhosis.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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