CardioRenal Medicine

Cardiorenal Med 2015;5:229–236
DOI: 10.1159/000430505
Received: February 25, 2015
Accepted: April 14, 2015
Published online: June 6, 2015

1664–3828/15/0053–0229$39.50/0
www.karger.com/crm

Original Paper

Evidence of Mild Liver Dysfunction Identifies Stable Heart Failure Outpatients with Reversible Renal Dysfunction

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Key Words
Cardiorenal syndrome · Heart failure · Liver dysfunction

Abstract
Background: In decompensated heart failure (HF), reversible renal dysfunction (RD) is more frequently observed in patients with mild liver dysfunction likely due to the shared pathophysiologic factors involved. The objective of this study was to determine if these findings also apply to stable HF outpatients. ***Methods:*** Patients in the Beta-Blocker Evaluation of Survival Trial (BEST) were studied. Improvement in renal function (IRF) was defined as a 20% improvement in the estimated glomerular filtration rate from baseline to 3 months. ***Results:*** Elevated bilirubin (BIL), aspartate aminotransferase (AST), and alanine aminotransferase (ALT) were significantly associated with signs of congestion or poor perfusion. IRF occurred in 12.0% of all patients and was more common in those with elevated BIL (OR = 1.5, p = 0.003), ALT (OR = 1.4, p = 0.01), and AST (OR = 1.4, p = 0.01). In a model containing all 3 liver parameters and baseline characteristics, including markers of congestion/poor perfusion, BIL (OR = 1.6, p = 0.001) and ALT (OR = 1.7, p < 0.001) were independently associated with IRF. ***Conclusions:*** Biochemical evidence of mild liver dysfunction is significantly associated with IRF in stable HF outpatients. Given the widespread availability and low cost of these markers, additional research is necessary to determine the utility of these parameters in identifying patients with reversible RD who may benefit from cardiorenal interventions.

Drs. Brisco and Cheng contributed equally to this work and are co-first authors of this paper.

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Introduction

Renal dysfunction (RD) is highly prevalent in patients with heart failure (HF) [1, 2]. In addition to identifying patients at high risk for mortality, RD often presents an obstacle to the optimal use of neurohormonal antagonists and the maintenance of euvolemia [3]. As such, identifying patients with potentially reversible HF-induced RD is important. Unfortunately, methodology proven to differentiate reversible HF-induced RD from irreversible chronic kidney disease is not currently available.

Similar pathophysiologic factors such as venous congestion and reduced perfusion are thought to underlie both HF-induced liver dysfunction and RD [3–7]. Since these organs share a common venous system and are perfused by the same heart, factors such as venous congestion and the consequences of reduced cardiac output would be expected to affect both organs similarly and simultaneously. Unlike HF-induced RD, HF-induced liver dysfunction produces a relatively characteristic pattern of laboratory abnormalities [7]. To that end, we have recently demonstrated that in the setting of acute decompensated HF (ADHF), evidence of mild liver dysfunction is strongly associated with reversible RD. The purpose of this study was to determine if evidence of mild liver dysfunction may also identify stable HF outpatients with the potential for improvement in renal function (IRF).

Methods

The Beta-Blocker Evaluation of Survival Trial (BEST) was a National Heart, Lung and Blood Institute (NHLBI)-sponsored randomized, placebo-controlled trial investigating the impact of bucindolol on all-cause mortality in compensated chronic HF patients. The design and primary results have been previously published [8]. Briefly, 2,708 patients with New York Heart Association (NYHA) functional class III or IV HF, a left ventricular ejection fraction of ≤35%, and use of an angiotensin-converting enzyme inhibitor for ≥1 month (unless contraindicated) were randomized to bucindolol or placebo. Exclusion criteria were reversible HF, uncorrected primary valvular disease, decompensated HF, life expectancy of <3 years, a serum creatinine level of ≥3.0 mg/dl, active liver disease, or the use of a beta blocker within 30 days of baseline. This paper was prepared using BEST research materials obtained from the NHLBI Biologic Specimen and Data Repository Information Coordinating Center and does not necessarily reflect the opinions or views of the BEST study investigators or the NHLBI. Elevated levels of bilirubin (BIL; ≥1.0 mg/dl), alkaline phosphatase (AP; ≥113 U/l), aspartate aminotransferase (AST; ≥30 U/l), and alanine aminotransferase (ALT; ≥31 U/l) were defined as a value in the upper quartile for analyses of this dataset. Estimated glomerular filtration rate (eGFR) was calculated using the Modified Diet and Renal Disease equation [9]. IRF was defined as a ≥20% increase in eGFR, consistent with our prior work on the subject [10–14]. This study was determined to be exempt from institutional review board review by the Institutional Review Boards of Yale and Medical University of South Carolina.

Statistical Methods

The primary analyses in this study focused on the associations between laboratory markers of liver dysfunction and subsequent IRF. Values reported are the mean ± standard deviation, median (quartile 1 to quartile 4), and percentile. Independent Student's t test or the Mann-Whitney U test was used to compare continuous parameters. Pearson's χ^2 was used to evaluate categorical variables. The independent association between AST, ALT, AP, and BIL and IRF was determined using logistic regression. Candidate covariates were obtained by screening clinical characteristics for a univariate association with IRF at $p < 0.2$. Covariates that had a $p > 0.2$ but a theoretical basis for potential confounding were retained in the final model. Covariates were removed using backward elimination (likelihood ratio test), and variables with a $p < 0.2$ were retained [15]. Significance was defined as two-tailed $p < 0.05$ for all analyses. Statistical analysis was performed with PASW Statistics version 19 (SPSS Inc., Chicago, Ill., USA).

Table 1. Baseline characteristics stratified by IRF

Characteristics	Overall cohort (n = 2,490)	IRF		p value
		yes (n = 299, 12%)	no (n = 2,191, 88%)	
Demographics				
Age, years	60.3±12.2	59.8±12.3	60.4±12.2	0.501
White race	1,759 (70.6)	195 (65.2)	1,564 (71.4)	0.028*
Male	1,955 (78.5)	222 (74.2)	1,733 (79.1)	0.056
Past medical history				
Hypertension	1,469 (59)	178 (59.5)	1,291 (58.9)	0.841
Diabetes	902 (36.2)	102 (34.1)	800 (36.5)	0.418
Coronary artery disease	1,203 (48.3)	134 (44.8)	1,069 (48.8)	0.197
Alcoholic cardiomyopathy	163 (6.5)	23 (7.7)	140 (6.4)	0.393
Physical examination				
BMI	28.0±5.93	27.8±6.12	28.1±5.90	0.565
Heart rate, bpm	82.0±13.4	83.6±13.4	81.8±13.3	0.032*
Systolic blood pressure, mm Hg	118.5±19.4	115.8±18.3	119.3±19.5	0.004*
Hypotension[1]	633 (25.4)	85 (28.4)	548 (25.0)	0.205
Proportional pulse pressure <25%	149 (6.0)	22 (7.4)	127 (5.8)	0.281
Jugular venous distention	495 (19.9)	64 (21.4)	431 (19.7)	0.500
Peripheral edema	532 (21.4)	69 (23.1)	463 (21.1)	0.444
Rales	356 (14.3)	40 (13.4)	316 (14.4)	0.626
S3 gallop	1,086 (43.7)	136 (45.5)	950 (43.4)	0.499
Hepatomegaly	300 (12.1)	38 (12.7)	262 (12.0)	0.723
Medications (baseline)				
Digoxin	2,297 (92.2)	276 (92.3)	2,021 (92.2)	0.968
Vasodilators	1,086 (43.6)	130 (43.5)	956 (43.6)	0.96
ACE inhibitor	2,288 (91.9)	276 (92.3)	2,012 (91.8)	0.777
Bucindolol	1,231 (49.4)	125 (41.8)	1,106 (50.5)	0.005*
Antiarrhythmic drug use	67 (2.7)	10 (3.3)	57 (2.6)	0.456
Laboratory values				
Hemoglobin, g/dl	14.0±1.7	14.1±1.7	14.0±1.6	0.235
Serum sodium, mmol/l	138.9±3.4	138.3±3.5	139.1±3.3	<0.001*
Uric acid, mg/dl	8.1±2.4	8.5±2.6	8.0±2.4	<0.001*
Glucose, mg/dl	135.5±75.3	145.3±85.1	134.1±73.8	0.031*
Serum creatinine, mg/dl	1.2±0.4	1.4±0.4	1.2±0.4	<0.001*
eGFR, ml/min/1.73 m^2	65.6±23.1	55.2±16.8	67.0±23.5	<0.001*
Blood urea nitrogen, mg/dl	24±15	28±16	24.1±15	<0.001*
AP, U/l	98±48	98±44	98±48	0.931
AST, U/l	27±15	29±18	26±14	0.008*
ALT, U/l	27±19	30±26	26±18	0.002*
Total BIL, mg/dl	0.8±0.5	0.9±0.5	0.8±0.5	0.013*
Functional status/ejection fraction				
Left ventricular ejection fraction, %	23±7	23±8	23±7	0.149
Right ventricular ejection fraction, %	35±14	34±14	35±13	0.202

Values are mean ± SD or n (%). ACE = Angiotensin-converting enzyme; ARB = angiotensin receptor blocker.
* Significant p value. [1] Hypotension defined as a systolic blood pressure in the bottom quartile (<104 mm Hg).

Results

In total, 2,490 patients in the BEST study had data available on RF both at baseline and at 3 months after randomization. The baseline characteristics of these patients are presented in table 1. Similar to previous reports, elevated BIL, AST, ALT, and AP were associated with multiple markers of congestion and/or poor perfusion (table 2). BIL was

Table 2. Association between liver dysfunction laboratory values and physical examination findings in HF outpatients

	BIL		AP		AST		ALT	
	OR	p	OR	p	OR	p	OR	p
Jugular venous distension	2.8	<0.001*	2.3	<0.001*	1.7	<0.001*	1.2	0.185
Hepatomegaly	2.8	<0.001*	2.4	<0.001*	1.6	0.001*	1.1	0.446
Edema	2.2	<0.001*	1.7	<0.001*	1.1	0.695	1.0	0.771
Rales	1.3	0.017*	1.3	0.05	1.1	0.707	0.8	0.220
S3 gallop	1.6	<0.001*	1.4	<0.001*	1.3	0.004*	1.1	0.404
Hypotension	1.9	<0.001*	1.4	0.001*	1.4	<0.001*	1.0	0.751
Proportional pulse pressure <25%	2.9	<0.001*	1.9	<0.001*	1.9	<0.001*	1.9	0.001*

BIL, AP, AST, and ALT were dichotomized using the 75th percentile such that the levels of BIL (≥1.0 mg/dl), AP (≥113 U/l), AST (≥30 U/l), and ALT (≥31 U/l) were considered elevated. * Significant p value.

strongly associated with all metrics of congestion, in addition to having the strongest association with hypotension and a low proportional pulse pressure. AP generally demonstrated stronger associations with measures of congestion than did AST or ALT but was similarly associated with markers of poor perfusion. AST, but not ALT, was associated with several markers of congestion. ALT was only associated with a low proportional pulse pressure. RV ejection fraction (available in n = 1,999) was lower in patients with higher BIL (30.2 ± 12.7 vs. 36.6 ± 13.4%, p < 0.001), AP (31.36 ± 12.7 vs. 36.0 ± 13.6%, p < 0.001), AST (32.2 ± 13.5 vs. 35.7 ± 13.5%, p < 0.001), and ALT (33.5 ± 14.0 vs. 35.3 ± 13.3%, p = 0.014) levels.

Overall, the incidence of IRF at 3 months was 12.0%, and the average improvement in eGFR amongst those experiencing IRF was 37.2 ± 18.8%. Table 1 describes the characteristics of patients with and without IRF. Similar to our findings in the setting of ADHF, baseline values of BIL, AST, and ALT were higher in patients who experienced IRF, while AP levels were similar between groups. Patients with laboratory values in the top quartile of BIL, ALT, and AST were significantly more likely to experience IRF than patients not in the top quartile (table 3). There was no difference with respect to elevated AP levels (table 3). Notably, changes in liver laboratory values between baseline and 3 months were also associated with IRF such that those patients with the greatest improvements in AST and ALT demonstrated a significantly increased incidence of IRF at 3 months (table 3). In a multivariable model including all 4 elevated liver dysfunction-related parameters (BIL, AP, ALT, and AST), only BIL in the top quartile (OR = 1.6, p = 0.001) and ALT in the top quartile (OR = 1.4, p = 0.019) were independently associated with IRF. Interestingly, the individual metrics of congestion and poor perfusion that were associated with markers of mild liver dysfunction were not directly associated with IRF (table 1). Both an elevated BIL (OR = 1.6, p = 0.001) and an elevated ALT (OR = 1.4, p = 0.018) remained significantly associated with IRF after adjusting for metrics of congestion and poor perfusion (edema, rales, S3 gallop, hepatomegaly, jugular venous distention, hypotension, and low proportional pulse pressure). Following the addition of baseline characteristics (eGFR, blood urea nitrogen, race, sex, coronary disease, blood pressure, heart rate, randomization to bucindolol, serum sodium, uric acid, glucose, and left ventricular ejection fraction) to the above model, both BIL (OR = 1.6, p = 0.001) and ALT (OR = 1.7, p < 0.001) remained independently associated with IRF. The odds for IRF were particularly high when comparing patients with elevated BIL and ALT versus normal parameters (adjusted OR = 2.9, p < 0.001)

Table 3. Association between liver dysfunction laboratory values and IRF

Laboratory value	IRF	
	OR (95% CI)	p
BIL	1.5 (1.1–1.9)	0.003*
AP	0.9 (0.7–1.2)	0.330
AST	1.4 (1.1–1.8)	0.012*
ALT	1.4 (1.1–1.9)	0.011*
Delta BIL	1.2 (0.9–1.6)	0.167
Delta AP	1.2 (0.9–1.5)	0.265
Delta AST	1.4 (1.1–1.8)	0.023*
Delta ALT	1.4 (1.1–1.8)	0.010*

BIL, AP, AST, and ALT were dichotomized using the 75th percentile such that levels of BIL (≥1.0 mg/dl), AP (≥113 U/l), AST (≥30 U/l), and ALT (≥31 U/l) were considered elevated. The delta values were dichotomized using the 75th percentile of the percent change in the laboratory values from baseline to 3 months such that a percent improvement in BIL (≥23.5%), AP (≥14.9%), AST (≥16.2%), and ALT (≥21.6%) was compared to the rest of the cohort. * Significant p value.

Discussion

The principal finding of this analysis is that the significant and independent association between laboratory evidence of mild liver dysfunction and subsequent IRF is detectable in stable HF outpatients. Similar to our previously reported findings in ADHF, elevated levels of BIL, ALT, and AST were significantly more common in patients who subsequently experienced IRF. Additionally, improvements in laboratory evidence of liver dysfunction, particularly AST and ALT, were associated with improvements in RF over the course of 3 months, further supporting the potential use of observed HF-induced dysfunction in one organ to infer HF-induced dysfunction in another.

The relationship between liver dysfunction and RD in patients with HF rests on the fact that these two organs share a common venous system and are perfused by the same heart. As such, the sequelae of HF should affect these organs similarly and simultaneously. Potential mechanisms reportedly involved in both HF-induced RD and hepatic dysfunction may thereby explain these relationships and include increased neurohormonal activation, decreased perfusion, and venous congestion [3–7]. As a result, the strong association between elevated BIL (a marker of hepatic congestion) and elevated transaminases (a marker of decreased perfusion and ischemic hepatitis) with IRF may implicate the aforementioned mechanistic pathways [16]. Interestingly, these parameters of mild liver dysfunction appeared to provide unique information above and beyond traditional markers of congestion and poor perfusion. This was evidenced by the inability of signs of congestion/poor perfusion to directly predict IRF and the unchanged association between liver dysfunction and IRF after adjusting for these parameters. These data taken collectively provide further evidence that reversible RD may be a discernible entity in patients with HF.

The pathophysiology underlying 'cardiorenal syndrome' is complex and incompletely understood. Our limited understanding has been highlighted by the recent high-profile failure of several 'cardiorenal' interventions. Despite strong preclinical data, approaches such as the natriuretic peptides, adenosine antagonists, low-dose dopamine, loop diuretic infusions, and ultrafiltration have failed to provide meaningful benefit [17–21]. Although it is possible that the problem lies in that all of these agents are ineffective, an equally likely possibility is that

patient selection is driving the lack of observed effectiveness. Importantly, RD in the setting of HF is not a single disease but rather a prognostically and mechanistically diverse group of overlapping disorders [10, 22–24]. Much in the way that we would not expect vitamin B_{12} supplementation to show efficacy in a trial of unselected anemic patients with diverse etiologies for the anemia, better patient selection in cardiorenal clinical trials is likely also important. Additional research will be necessary to determine if markers such as BIL and ALT will provide sufficient discrimination of patients with RD that will be useful in future clinical trials.

Qualitatively, the observations in this study were very similar to those previously reported in the setting of ADHF [25]. Notably, BIL and ALT demonstrated the strongest associations with IRF, and AP was unrelated to IRF. However, there were quantitative differences. Notably, the incidence of IRF in this population of stable outpatients (12% in the current study) was substantially lower than the rate of IRF occurring in patients with ADHF (30–50%) [13, 26]. Similarly, the strength of the association between markers of liver dysfunction and subsequent IRF was also lower than that observed in ADHF. However, this is not surprising since, by definition, there is a clear treatment target present at the time of ADHF presentation. As such, it follows that in a population with decompensated HF, IRF will often accompany the return to compensation. However, in stable HF outpatients, overt opportunities for improving patients' overall HF status are less common, and targeted therapies to improve RF are currently not available. Although this may represent a limitation of the current study design, the fact that the signals were detectable in spite of this limitation is very encouraging, showing that with the application of new cardiorenal treatments (i.e., renal sympathetic denervation), the rate of IRF in these subgroups may substantially increase.

Limitations

Given the post hoc and observational nature of this study, the limitations inherent to retrospective analyses apply, and uncontrolled confounding cannot be excluded. Although large and multicenter, the BEST study population may have dissimilarities to more contemporary HF populations given that enrollment ended in 1998, prior to the widespread use of aldosterone antagonists. Additionally, the exclusion of patients with active liver disease from the BEST study, potentially excluding patients with overt HF-induced liver dysfunction, is a limitation. The occurrence of liver dysfunction unrelated to HF was not accounted for in this analysis likely decreasing the effect size of the associations. Furthermore, alcohol use in those included in the trial was not further assessed, preventing adjustment for the degree of alcohol consumption. Given that clinicians were not blinded to the laboratory results, treatment may have been modified in response. However, the current lack of consensus regarding the methods to improve RF in HF patients limits the impact of this possibility. Since IRF is assumed to occur as a result of improvement in volume overload and/or hemodynamics, appropriate treatment or spontaneous improvement in HF must occur. As a result, patients with HF-induced RD with no change in therapy or no improvement in HF would not be detected by IRF.

Conclusion

In the setting of chronic stable HF, patients with laboratory evidence of mild liver dysfunction have a significantly higher prevalence of reversible RD. Although in need of further replication, these findings indicate that biochemical evidence of mild liver dysfunction may provide a widely accessible, inexpensive method by which patients with potentially reversible HF-induced RD can be identified. Additional research will be necessary to determine if these findings can be applied toward improved patient selection for cardiorenal interventions.

Acknowledgement

The study was funded by NIH grant 1K23HL114868.

Disclosure Statement

The authors declare that there are no conflicts of interest to disclose.

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