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Cardio-Renal Syndrome Type 1: The Role of Central Venous Pressure and Left Ventricle Ejection Fraction

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Abstract

The aim of the study has been to explore the association between increased Central Venous Pressure (CVP), Ejection Fraction (EF) and renal dysfunction (manifested as reduced eGFR<60) in patients with Cardio-Renal Syndrome (CRS) type 1. The pathophysiology of impaired renal function in cardiovascular disease is complex and multifactorial. Recent investigations indicate that management of patients based on low-flow theory only does not lead to improved outcomes. Importance of Right-Sided Heart Failure (RSHF) and increased CVP in this process has not been well evaluated. Proper understanding of bi-directional mechanism by which heart and kidneys influence each other, would lead to correct clinical management and better outcome. The retrospective cross-sectional study has been performed on patients with Acute Decompensated Heart Failure (ADHF) and reduced eGFR (CRS type 1). With a total number of 11 participants, Pearson correlation analysis has shown moderate downhill (negative) relationship between CVP and eGFR (r = -0.48, Sig. 0.14), while correlation between LVEF and eGFR has been found to be weaker (r = 0.12, Sig. 0.72). In this study with a small number of participants, although not statistically significant, the effect size is considerable, suggesting that CVP, rather than LVEF could be directly associated with impaired renal function in patients with CRS type 1. Based on these results, further research with more participants (at least 32) can be performed to validate the correlation.

Keywords: Cardio-Renal Syndrome; Right-Sided Heart Failure; Central Venous Pressure; Left Ventricle Ejection Fraction; eGFR; Low-flow theory.

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1. Introduction

Prevalence of moderate to severe renal impairment (defined as a Glomerular Filtration Rate (GFR) < 60 mL/min per 1.73 m2) is approximately 30 to 60 percent in patients with Heart Failure (HF) [1-5]. Mortality is increased in patients with HF who have reduced GFR and patients with chronic kidney disease have an increased risk of both atherosclerotic cardiovascular disease and HF, and cardiovascular disease is responsible for up to 50 percent of deaths in patients with renal failure [6].

The term Cardio-Renal syndrome has been brought into systematic use by professor Claudio Ronco and his colleagues who have defined five subtypes of Cardio-Renal Syndrome, which are distinguishable from each other by the clinical course, pathophysiology, diagnostic approaches and management tactics [7]. CRS involves both - acute and chronic conditions which are characterized by heart's primary (CRS type 1 and type 2), and primary renal injury (CRS type 3 and type 4) [8]. When systemic illness like diabetes or sepsis leads to simultaneous heart and renal failure, the term - secondary CRS, or CRS type 5 is used.

In CRS type 1, worsening renal function complicates Acute Decompensated Heart Failure (ADHF) and Acute Coronary Syndrome (ACS). Depending on the population, 27%-40% of patients hospitalized for ADHF develop Acute Kidney Injury [9,10]. In CRS type 2 chronic abnormalities in myocardial function lead to Chronic Kidney Disease (CKD).

Pathophysiology of reduction in GFR in patients with HF is multifarious: abnormalities in systolic and diastolic myocardial performance can lead to a number of hemodynamic derangements, including reduced stroke volume and cardiac output, arterial underfilling, elevated atrial pressures and venous congestion [11]. These hemodynamic derangements trigger a variety of compensatory neurohormonal adaptations including activation of sympathetic nervous system, the Renin-Angiotensin-Aldosterone System and a range of adverse cellular processes (including oxidative injury and endothelial dysfunction) leading to apoptosis and renal fibrosis [12,13,1,5].

Recent investigations suggest that management of patients with primary cardiac and secondary renal dysfunction based only on the low-flow theory does not lead to improved outcomes [14]. Both animal and human studies have shown that Intra-Abdominal and Central Venous Pressure elevation, which also increases the renal venous pressure, lead to reduction of GFR [15]. There is a growing evidence to support the roles for elevated renal venous pressure and IAP in development of progressive renal dysfunction in patients with HF. The study by Kevin Damman and his colleagues has shown that CVP is associated with impaired renal function and independently related to all-cause mortality in a broad spectrum of patients with cardiovascular disease [16]. The study by Heiko Uthofft and his colleagues further supported the concept that CVP is an important hemodynamic factor for impaired renal function, especially in combination with decreased cardiac output [17].

Right ventricular dysfunction could be a potent prognostic factor in developing Cardio-Renal Syndromes [18], but assessing RV function remains a challenge. At this time, there is no single commonly accepted and generally applicable index of RV function[19]. The CVP, an estimate of right atrial pressure, could assist in the diagnosis

of right-sided heart failure, but it should always be considered in conjunction with other cardiovascular parameters, e.g. LVEF, as the right heart sided pressures should indirectly reflect left sided pressures, and the left sided filling pressure may be an indicator of left ventricular function [20].

Proper understanding of mechanisms by which heart and kidneys interact in CRS type 1 is critical, as in a clinical practice it may lead to precise management of the patients with CRS type 1, leading to improved course and subsequently, influencing the long-term outcome.

2. Materials and methods

The research has been based on a hypothesis that CVP rather than LVEF correlates directly with the level of renal impairment manifested as reduced eGFR in patients with CRS type 1.

This study has been a part of a bigger project, where patients with CRS type 2 made another group (non-CVP group) and the role of LVEF and HF functional class had been evaluated. The project registration number at clinicaltrials.org is NCT02792387. The study involved patients with ADHF and reduced eGFR, who had undergone treatment at in-patient units of six different hospitals of Georgia between September 2015 and May 2016. In a cross-sectional manner, the participants were selected according to the predetermined selection criteria, and necessary data had been extracted from the medical charts retrospectively. Estimated Glomerular Filtration Rate had been assessed with the Modification of Diet in Renal Disease formula, and CVP measurements had been performed with an electronic pressure transducer in spontaneously breathing non-ventilated patients. Central vein access was established trough the subclavian or internal jugular veins. Mean CVP was recorded for each patient, measured in mmHg.

2.1. Participants – study population

The study included patients with clinically manifested ADHF and reduced GFR (CRS type 1). List of criteria that would exclude a subject from the study included the following:

1. Independent risk factors for renal impairment (e.g. diabetes, sepsis).
2. Primary nephropathy or secondary nephropathy due to diseases other than HF.

eGFR (MDRD formula) had been defined as an outcome variable, while LVEF %, CVP and Arterial hypertension (According to JNC VIII classification) comprised the predictor variables. LVEF had been treated as a potential confounding factor.

2.2. Sample size and statistical Plan

In a studied period of time only 11 patients met both the inclusion criteria and had had the CVP measurement performed according to the study requirements. As there was no sample size calculation performed in advance (due to the lack of preliminary figures), the statistical tests were run on the available data of 11 patients, to provide an expected correlation coefficient for a sample size determination of the subsequent study. IBM SPSS

Statistics version 19 had been used to obtain the standard descriptive statistics, summary statistics and statistical tests for outcome variable.

2.3. Ethical considerations

The study is of observational-analytical (non-experimental) type and has been based on a retrospective chart review. Confidentiality of patients' personal information had been the main ethical issue to address. In order to limit the access to patients' personal identifiers, data extraction had been performed by the treating physicians only and an anonymized datasets used for data analysis (unique code had been given to each patient, which was kept secure under the control of hospital staff).

3. Results

With a total number of 11 participants, mean age was 65 (SD 12.5), and 63.6% were men. Mean eGFR was 43 ml/min/1.73m2 (SD 10), Mean LVEF - 46 (SD 6) and Mean CVP – 10.4 mm Hg (SD 1.1). Pearson correlation analysis was used to characterize the association between CVP and eGFR, which was found to be -0.48 (Sig. 0.14), and correlation between LVEF and eGFR, 0.12 (Sig. 0.72).

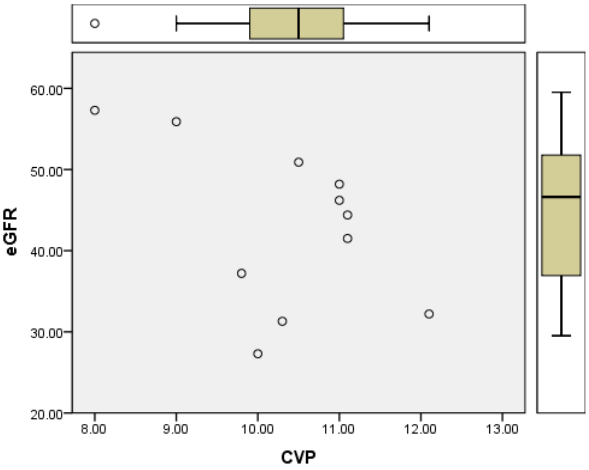

Figure 1: Correlation scatter plot of CVP and eGFR

4. Discussions

The strength of the study is a proper methodical selection of participants, i.e. inclusion of patients only with primary ADHF and secondary kidney dysfunction, but due to the small number of participants (which is a main limitation), no statistically significant results had been obtained. Although not significant, the effect size is considerable – Pearson correlation test has shown a moderate downhill (negative) relationship between CVP and eGFR (r = -0.48), while correlation between LVEF and eGFR has been weaker (r = 0.12). These results would suggest that CVP, rather than LVEF could be directly associated with impaired renal function in patients with Cardio-Renal Syndrome type 1. Further research with more participants is needed to achieve the statistical significance and to verify the correlation. Sample size for the bigger study (N=32) has been calculated using the

following parameters: α (two-tailed) = 0.050, β = 0.200, r = -0.480, N = [(Zα+Zβ)/C]2 + 3 = 32.

5. Conclusions

Preliminary results this retrospective cross-sectional study suggest that CVP, rather than LVEF could be directly associated with impaired renal function in patients with CRS type 1, thus providing a good background for a larger study that can theoretically have a significant impact on understanding and management of Cardio-Renal syndrome type 1.

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