Research Letter

Hemodynamic Determinants of Right Heart Failure are Associated with Impaired T Cell Activation in Advanced Heart Failure

To the Editor:

The role of inflammation in the development and progression of heart failure has been well described.[1,2] Our group has recently found that decreased immune cell function carries adverse prognostic implications for patients with heart failure who have been referred for cardiac transplantation.[3] Right ventricular dysfunction is a marker of poor prognosis in heart failure with preserved and reduced ejection fraction.[4,5] We hypothesized that right ventricular failure would be associated with decreased immune cell function.

This was a retrospective single-center study that included patients referred for advanced heart failure therapies evaluation to the Cleveland Clinic between 2010 and 2016 and who underwent right heart catheterization (RHC) and had a cell-mediated function assay performed within 30 days of RHC as part of their routine workups. We excluded patients who had had their RHCs or immune function assays performed as inpatients, were on IV inotropes or pressors at the time of RHC evaluation for multiorgan transplantation, had congenital or acquired immunodeficiency, including immunosuppressive drug therapy, had amyloidosis, or had any type of mechanical circulatory support.

Patients were grouped in the following predefined hemodynamic categories: Group A: right atrial pressure $\leq$ 15 mmHg; Group B: right atrial pressure $>$ 15 mmHg and central venous pressure/pulmonary capillary wedge pressure $<$ 0.63; Group C: right atrial pressure $>$ 15 mmHg and central venous pressure/pulmonary capillary wedge pressure $\geq$ 0.63. We used a cell-mediated immune function assay (IFA) (Immuknow; Cylex, Columbia, MD) to estimate the degree of cell-mediated immunity. The test measures the increase of intracellular adenosine triphosphate (ATP) in CD4 cells after being activated by a mitogen (phytohemagglutinin). Released ATP is measured by a luciferase in ng ATP/mL. Values are expressed as the median and interquartile range. Differences between medians were detected by the Wilcoxon rank-sum test with 2-tailed p values of $<$ 0.05. We performed a multivariable linear regression model adjusted by age, gender, blood urea nitrogen, creatinine, bilirubin, and ischemic etiology.

During the study period, 1002 patients were evaluated; of those, 261 were included in the present report. The mean age was 56.7, and 70% of the patients were male. The median time between RHC and IFA testing was −1 day (range −28 to +30). There were 199, 28 and 34 patients who met the definition of hemodynamic groups A, B and C, respectively. There were no statistically significant differences in age or gender among the groups. Patients in group C had higher ejection fraction than patients in groups A and B (A: 24.5 ± 12.9; B: 19.1 ± 9.4; C: 32.6 ± 17.8; p<0.001) and were less likely to have ischemic cardiomyopathy (A: 49%; B: 54%; C: 24%; p = 0.023). There were no significant differences in comorbidities, such as diabetes mellitus, chronic obstructive pulmonary disease, hypertension, or chronic kidney disease. Patients in group C had higher blood urea nitrogen levels (mg/dL) (A: 23.2 ± 11.8; B: 22.2 ± 9.9; C: 33.2 ± 20.2; p < 0.001); creatinine levels (mg/dL) (A: 1.20 ± 0.43; B: 1.15 ± 0.33; C: 1.53 ± 1.15; p = 0.007); and bilirubin (mg/dL) (A: 0.84 ± 0.54; B: 0.86 ± 0.47; C: 1.18 ± 0.84; p = 0.010) as compared to patients in group A or B. Of note, there were no statistically significant differences in levels of other biomarkers, such as N-terminal pro-brain natriuretic peptide, troponin T, myeloperoxidase, or immunoglobulin.

Pulmonary artery pulsatility index (A: 3.93 ± 3.98; B: 1.60 ± 0.53; C: 1.24 ± 0.50; p =<0.001) and right ventricular stroke work index (mmHg x mL/m^2) (A: 622 ± 255; B: 604 ± 234; C: 426 ± 276; p = <0.001) were significantly lower in the patients in group C. Patients in group C had the lowest value of IFA (ng ATP/mL) when compared to the other groups (A: 389.0 ± 154.6; B: 397.4 ± 150.2; C: 294.1 ± 129.6; p = 0.003 Fig. 1). In a multivariable linear regression model, group C had significantly lower IFA values than the other groups (group C vs A, −90.6 [−30.7 to −150.4]; p = 0.003; group C vs B, −104.7 [−23.8 to −185.5]; p = 0.011). Linear correlation between IFA and the right ventricular stroke work index was poor but statistically significant (R2 0.009, p < 0.001).

The main finding of our study is that patients with predominant hemodynamically defined right ventricular failure have decreased T-cell activation as measured by IFA. Our findings have to be interpreted in the light of the limitations of retrospective studies and the small sample size. It is important to emphasize that this assay does not represent a detailed analysis of cell-mediated immunity, and prospective studies are needed to validate these findings. Prospective studies in patients with right heart failure that characterize T-cell subsets, evaluate T-cell function using phytohemagglutinin and other stimulants (eg, exogenous interleukin-2, soluble anti-Cd3+), and assess the interaction

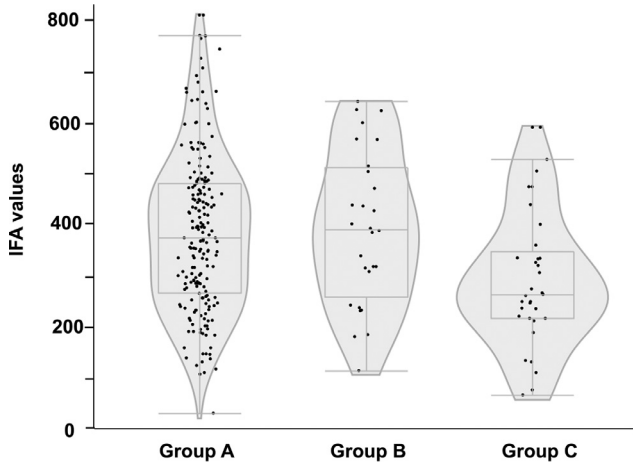

Fig. 1. Intracellular ATP level (IFA) among pre-defined Hemodynamic Subgroups Caption: Group A: RA ≤ 15 mmHg, Group B: RA > 15 mmHg and CV/PCWP < 0.63. Group C: RA > 15 mmHg and CVP/PCWP ≥ 0.63.

of T-cell function and native immunity will be helpful to validate our findings and to better understand the mechanisms of T-cell function in right heart failure.[6]

Supplementary Data

Supplementary data related to this article can be found at doi:10.1016/j.cardfail.2019.06.005.

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