Machine Learning Analysis of Identifies Polyunsaturated Fatty Acid Metabolites Predictive of Adverse Outcomes In Heart Failure with Preserved Ejection Fraction Patients

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Background: Pulmonary hypertension (PH) in heart failure with preserved ejection fraction (HFpEF; PH-HFpEF) is associated with adverse clinical outcomes; however, the pathophysiology of disease is unknown. The development of PH is a continuum of disease processes initiated by HFpEF, where patients initially develop isolated postcapillary PH (ipc-PH) which can transform to combined pre and postcapillary PH (cpc-PH). This transformation of PH does not occur in all patients, is not explained by traditional risk factors alone, and is associated with significant morbidity and mortality suggesting the need to examine novel regulatory mechanisms. Polyunsaturated Fatty Acid (PUFA) metabolites play a vital role in cardiovascular health by regulating balance between anti-inflammatory and pro-resolutory lipid mediators and imbalances have been previously shown to predispose PH.

Objective: We sought to characterize PUFA-derived mediators that can serve in cardiovascular risk stratification in patients with HFpEF.

Methods: Venous serum samples were collected from 88 HFpEF patients without PH (control, n=40), HFpEF with ipc-PH (ipc-PH-HFpEF, n=30), and HFpEF with cpc-PH (cpc-PH-HFpEF, n=18). 143 PUFA metabolized were analyzed using mass spectroscopy with Multiple Reaction Monitoring. A machine learning model (Anaconda v2022.05) was conducted after ANOVA feature selection to assess

which molecules were associated with future risk of either all cause death or a combined adverse outcome of death or rehospitalization in the setting of HFpEF.

Results: In patients with HFpEF, increased levels of 9(10)-Epome, 15(R)-PGE1, 17-oxoRvD1, TXB3, RvD3, 5(S),15(S)-DiHETE, and 11dh-2,3-dinor TXB2 at baseline were predictive of all cause mortality (all $p<0.05$). Increased baseline levels of 8-oxoRvD1, MaR1(n-3DPA), PGE3, and 5,6-DiHETrE were predictive of the combined adverse outcome of death or rehospitalization (all $p<0.05$).

Conclusion: These findings support the hypothesis that distinct PUFA metabolites play a significant role in mediating cardiovascular disease in HFpEF. Our study introduces a novel lipidomics framework for the diagnostic and prognostic assessment of cardiovascular risk in HFpEF patients.

