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**Insulin-like Growth Factor Binding Protein 2:
A prognostic biomarker for heart failure hardly redundant with natriuretic peptides**

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Insulin-like Growth Factor Binding Protein 2 (IGFBP2) is a member of the IGFBP family which is present in the heart; cardiac IGFBP2 mRNA levels have furthermore been shown to rise in animal models of ischemia-induced heart failure (HF) ¹. The group of Dr. P. Rouet previously showed that IGFBP2 is a powerful diagnostic biomarker for HF whose accuracy for identifying acute HF is a valuable adjunct to brain natriuretic peptide (BNP)¹: The area under the curve of the receiver operating characteristic (ROC) curve for HF was 0.908 (0.830-0.958) for IGFBP2 versus 0.857 (0.770-0.921) for BNP. In addition, IGFBP2 improved the model's accuracy in predicting HF as well as the net reclassification index (NRI) (0.574 (0.340-0.750) p<0.001) on top of BNP.

The group of Dr. Rouet now reports the results of an elegant study to assess the prognostic value of IGFBP2 in 870 patients with known HF from 3 independent international cohorts². In this study, their results show that the highest quartile of IGFBP2 was associated with mortality in the Maastricht cohort and in the combined Atlanta and Toulouse cohorts with Hazard Ratios > 1.5. More importantly, adding IGFBP2 to survival models significantly increased the NRI for death in the 3 pooled cohorts on top of clinical variables (0.404, p=0.01 at 1 year, 0.315, p=0.02 at 3 years) as well as on top of clinical variables and BNP (0.404, p=0.0005 at 1 year, 0.285, p=0.01 at 3 years).

These results emphasize the vast potential of IGFBP2 in the field of HF both for diagnostic and prognostic purposes. However, our understanding of the exact role of IGFBP2 in HF is still lacking. The fact that IGFBP2 surprisingly and notably adds to the diagnostic and prognostic value of BNP suggests that IGFBP2 features a different pathophysiological background than natriuretic peptides. Yet, achieving a comprehensive

view on the current evidence regarding IGFBP2 and its link with natriuretic peptides and HF remains challenging: complex network analysis is an increasingly used³ analysis strategy allowing such integrated view of available evidence.

In order to gain a better understanding of the interplay between IGFBP2, BNP and HF, we used the graph knowledge box (GKBox) developed within the FIGHT-HF program (<https://www.inicrct.org/en/ini-crct-partner-hospitalo-universitaire-rhu-fighting-heart-failure-fight-hf-research-program-9>). The GKBox integrates data from over 20 public biological databases such as UniProt, DisGeNET or String. In this instance, the GKBox can be used to better understand the mechanisms underpinning the association between IGFBP2, BNP and HF by better positioning the biomarkers in their biological context and identifying underlying pathways or mechanism(s) of action.

Specifically, we built a network diagram (Figure, panel A) representing proteins (in grey) associated with HF and directly linked to either IGFBP2 or BNP, and Gene Ontology biological processes connecting at least 2 proteins (in blue). From this diagram, it appears that there is no overlapping biological process emerging from both BNP and IGFBP2. In addition, the proteins emerging from these Gene Ontology terms are distinct between the BNP and the IGFBP2 components of the diagrams (respectively ANP and ANP receptors for BNP and Hypoxia-inducible factor 1-alpha [HIF1A] and Insulin-like growth factor 1 [IGF1] for IGFBP2). There are only 5 Gene Ontology terms linking the ANP/ANP receptor to IGFBP2/HIF1A/IGF1, most of which are hardly specific (response to hypoxia and to insulin, cellular protein metabolic process, signal transduction and female pregnancy). BNP is related to the Gene Ontology term associated with congestion (body fluid secretion, regulation of vascular permeability, positive regulation of renal sodium excretion) whereas IGFBP2 is currently predominantly related to the Gene Ontology evocative of glucose metabolism (regulation of glycolytic process) and cellular death (regulation of apoptotic process and activated T cell proliferation). Of note, such associations with hypoxia and apoptotic process echo previous findings of IGFBP2 being overexpressed in an experimental model of ischemic HF.

In a second more detailed network diagram (Figure, panel B), we plotted the proteins linked to HF and indirectly linked to IGFBP2 or BNP through a Gene Ontology biological process term (in blue). This large diagram allows gaining a more comprehensive view of current biological evidence linking IGFBP2/BNP with HF. In this panel, a number of proteins are related to both BNP and IGFBP2 (in the center of the diagram), some of which are associated with the renin angiotensin aldosterone system, while a large number of proteins are related to only IGFBP2 (on the right of the diagram). Additional Gene Ontology terms not included in the panel A diagram are considered in this diagram, showing that, in the context of HF, IGFBP2 is related to the response to mechanical stimulus, aging, as well as to the response to various hormonal stimuli (steroid, estrogens, estradiol, glucocorticoid, insulin).

From these complex network representations, it can be seen that there is little interconnection between BNP and IGFBP2, probably explaining why IGFBP2 conveys additional value on top of BNP. In addition, there is evidence of IGFBP2 being linked to mechanical stimulus, which may be underpinning its strong diagnostic value for acute HF. Lastly, the association of IGFBP2 with hormonal response and apoptotic mechanisms is possibly related to its good prognostic value in HF patients. It should nevertheless be emphasized that the lack of

interconnection between BNP and IGFBP2 in the diagrams provided herein only indicates that these links are not currently reported in the literature (but could be in the future following additional research).

All in all, IGFBP2 is a promising biomarker for HF which needs further investigation. The prognostic value of changes in IGFBP2 in HF patients could further strengthen the evidence supporting its clinical use, along with natriuretic peptides and other biological and imaging markers of congestion^{4,7}. Obviously, as for any HF biomarker, designing trials tailoring HF medication to repeat IGFBP2 measurements would indubitably represent the ultimate proof of its usefulness in the management of HF.

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