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The Trifecta of Precision Care in Heart Failure:

Biology, Biomarkers, and Big Data*

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Imagine for a moment that you are witnessing a late-breaking clinical trial presentation in a packed auditorium. The disease being studied is anemia, and the randomized therapeutic intervention is liver extract. Several observational studies showed dramatic benefit with liver extract in anemia, and a major governmental funding agency had partnered with thought leaders to perform a definitive large multicenter clinical trial that was adequately powered for clinical outcomes. Unfortunately, the trial is negative, and the investigators conclude in the simultaneous publication that “on the basis of these results, liver extract cannot be recommended for use in patients with anemia.” Without an appreciation of the unique pathophysiology of pernicious anemia, for which liver extract is highly effective and was the basis of the 1921 Nobel Prize in Medicine, a promising therapy might have been discarded and a subset of anemic patients would continue to suffer from a debilitating disease.

This thought experiment is very familiar in heart failure circles, where hundreds of mechanistically promising therapies have been deemed ineffective in the aftermath of large negative clinical trials. For the most part, it is the intervention rather than the trial design that has shouldered responsibility, leaving a decades-old paradigm for studying heart failure unchanged. In the meantime, however, advances in molecular biology have generated a veritable “tsunami” of biomarkers that can objectively capture distinct aspects of heart

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failure pathophysiology and logarithmic increases in computing power can extract information from large clinical datasets in a manner previously impossible with traditional statistics (1). This combination of greater precision medicine tools and the growing statistical implausibility of sequential negative heart failure trials has led to a breaking point realization: perhaps the fault lies in our current approach to heart failure rather than deficiencies in prior therapeutic strategies. It is therefore timely that this issue of the *Journal* has published an exciting paper that re-examines heart failure by applying advanced analytics to a rich dataset of biomarkers in a well-phenotyped cohort of patients, with the goal of understanding the molecular pathways that are both unique and different between the 2 key therapeutic groups in heart failure: those with reduced and those with preserved ejection fraction (2).

WHAT DID THE STUDY SHOW?

The stated aim of the investigators was to identify biological mechanisms that are unique to the 2 clinically pertinent subgroups of heart failure: those with preserved and reduced ejection fraction. For this, they used data from the BIOSTAT-CHF project (A systems BIOlogy Study to TAilored Treatment in Chronic Heart Failure), a European cohort that was specifically designed to probe the systems biology of heart failure. Deriving results from 1,544 Scottish patients, they validated their findings in 808 mainland Europeans. All the included patients had 92 protein-based biomarkers measured that represented a wide range of biological pathways ranging from inflammation to metabolism. After statistically distilling and validating data on individual biomarkers, they were left with 65 protein–protein correlations. The majority of these overlapped between the left ventricular ejection fraction–derived subgroups of heart failure, with only 8 specific to reduced and 6 to preserved ejection fraction. Finally, they performed a network analysis on these pathways and surmised that biological pathways uniquely up-regulated in heart failure with reduced ejection fraction were related to cellular growth and metabolism, whereas those for heart failure with preserved ejection fraction reported on inflammation and extracellular matrix organization. Specifically, in the case of reduced ejection fraction, the following biomarkers formed central “nodes,” signifying essential biological pathways: N-terminal pro-B-type natriuretic peptide (NT-proBNP), growth differentiation factor (GDF)-15, Interleukin-1 receptor-like type 1 (IL1RL1—also known as ST2, suppressor of tumor-genicity 2), and activating transcription factor (ATF2). Heart failure with preserved ejection fraction, on the other hand, did not yield clear-cut nodes; after statistical enrichment of the data with a priori knowledge of protein–protein interactions, integrin subunit $\beta 2$ (ITG $\beta 2$) and β -catenin were found to be important hubs.

WHAT IS NETWORK ANALYSIS AND HOW CAN IT HELP MAKE SENSE OF COMPLEX SYNDROMES?

An explosion of high-throughput biological data has allowed detailed phenotyping of complex syndromes and revealed that clinical and biological phenotypes do not always overlap (3). Traditional statistical approaches can easily measure correlations between 2 measured biomarkers, but only recently has computational power reached a point where the

interactions between multiple variables can be adequately represented—this science of “interactome” modeling is still in its infancy but has already led to substantial advances in the understanding of cellular physiology and biological processes (4). Network analysis, a subset of graph theory, allows for the calculation of multiple biologically-relevant features of the inter-actome. These include the betweenness-centrality of a given protein (how central it is to the rest of the network), as well as the clustering coefficient of a group of proteins (how “tightly knit” a given group is). The implication of these analyses is that causative biological processes can be identified in a data-driven way, bypassing traditional knockdown/knockout studies that have previously been key to describing protein–protein interactions. In the present study, network analysis was stratified by the subtype of heart failure—a choice that assumes that there are fundamental differences in the physiological underpinnings of heart failure with reduced and preserved ejection fraction. Although the results suggest that that choice was a reasonable one—it was not strictly necessary—network analysis can be performed in an unbiased manner to reveal protein–protein interactions that can potentially phenotype patients more accurately than the current heart failure paradigm allows.

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

On the wards, the complexity of individual heart failure patients makes it difficult to imagine that they might share dysfunction in fundamental biological pathways. Furthermore, clinicians tend to cloak a lack of knowledge about the mechanisms underlying this phenotypic heterogeneity in subjective and imprecise measures of the syndrome (e.g., bedside hemodynamic profiling of heart failure patients as cold/wet/warm/dry). This study shows us that the molecular pathways underlying clinically identified subgroups of the syndrome have the potential to give us novel insights into disease process and therapeutic strategies. The ease by which these biomarkers can be measured at the bedside and the current state of computing power makes it entirely plausible that clinician decision making and drug development could soon be augmented by molecular data. The investigators also confirm the widely acknowledged notion that heart failure with preserved ejection fraction is a far more heterogeneous disorder than heart failure with reduced ejection fraction and is therefore unlikely to be successfully treated as a singular disease—a fact that has borne out in numerous negative clinical trials.

WHERE ARE WE ON THE PATH TO PRECISION MEDICINE IN HEART FAILURE?

This study is a key step in the right direction on the path towards bringing precision medicine to patients with heart failure. However, we have significant challenges to traverse, several of which are deeply entrenched in the fabric of modern medicine. Although the authors of this study deserve immense commendation for their work, we believe that meaningful advances will require a rethinking in our fundamental approach and be driven by validated biomarkers, advanced analytics, targeted clinical trials, and continuous feedback (Figure 1).

EJECTION FRACTION: A PARADIGM IN NEED OF CHANGE.

To suggest that description of a syndrome as complex as heart failure could be whittled down to an inexact measure of left ventricular function is rather ambitious (5). However, the dual constraints of history and prior clinical trials have imprisoned us into a construct that is “not a clinical disorder with distinguishable features; it is the artifact of the arbitrary compartmentalization of the numerical values of a very poor biomarker” (6). Moving forward, we need to redefine heart failure from the ground up as even the most objective of measures of disease are meaningless if anchored in imprecise classification schemata (7). The BIOSTAT-CHF cohort is especially well suited for this endeavor because it contains detailed phenotypic data on patients that could be used to reverse engineer a more objective taxonomy of heart failure.

HEART FAILURE BIOMARKERS: A PRICE FOR ENTRY.

Whereas the biomarker panel tested in this study is comprehensive, the field of heart failure biomarkers has evolved rapidly over the last decade, and numerous well-validated biomarkers were not represented in this study (8). For example, the panel omitted biomarkers of cardiac necrosis and renal dysfunction, 2 pathways that are central to heart failure pathophysiology and would likely have emerged as major nodes in the network analysis. Other validated biomarkers of heart failure are shown in Table 1. Furthermore, it is unclear whether the assay used to quantify biomarkers has acceptable measures of biological variation and low analytical imprecision. In future multimarker approaches to describing heart failure, it is imperative that we use quality control measures to determine biomarker inclusion criteria because these decisions are likely to have a multiplicative effect on the output (9).

BIG DATA IN HEART FAILURE: OUR GOAL IS A LEARNING HEALTH CARE SYSTEM.

Chronic illnesses are not static processes, but the current process of knowledge generation tends to treat them as such. Snapshots of the heart failure patient are assumed to represent the entirety of their disease; gathered data are curated and analyzed over prolonged periods of time and disseminated after a drawn-out period of peer review. In many instances, research findings modify practice, but this is not generally widespread until they have percolated into the guidelines. Ironically, and in almost a quantum twist, by the time this happens the patients to which they apply are meaningfully different. The potency of advanced analytic methods therefore lies in permitting a learning health care system where insights from large patient data-sets are the engine for continuous and iterative improvement. Because several extrabiological factors such as socioeconomic status and geographical location determine outcomes from heart failure, the construct created by the authors of this study should be extended to include a more comprehensive set of patient variables along with continual feedback to treating centers based on real-time analytics (10). Therefore, a team science approach that includes patients, clinicians, molecular biologists, health care organizations, and computer scientists is needed to bring precision medicine to heart failure.

CONCLUSIONS

A century ago, Dr. Paul Dudley White, arguably the father of American cardiology, bemoaned the widespread lack of a “complete cardiac diagnosis” in the care of heart failure patients, and described the problem as an undue focus on the “structural and functional changes” of the failing heart with “too little consideration given to the factors responsible for heart disease” (11). Unfortunately, despite spectacular advances in our understanding of heart failure biology, this predicament remains unchanged today: clinical care and trials still rely on New York Heart Association classification or left ventricular ejection fraction cutpoints. The work by Tromp et al. (2) represents an important initial step toward what is gravely needed—an intelligent and learning health care system where research and care delivery are integrated and advanced analytics along with state-of-the-art biomarker testing continually augment our ability to make personalized decisions for the individual heart failure patient.

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FIGURE 1. Our Current System of Clinical Care and Trials in Heart Failure Patients Is Imprecise, Inaccurate, and Not Cost-Effective

To bring precision medicine to heart failure patients will require a rethinking of our fundamental approaches to the syndrome and be driven by validated biomarkers, advanced analytics, targeted clinical trials, and continuous feedback. For this to occur, we will need a team science approach to the problem that involves patients, clinicians, molecular biologists, health care organizations, and computer scientists—all working toward the goal of creating a learning health care system. HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction.

TABLE 1

Key Validated Biomarkers Classified According to Broad Categories of Processes Involved in the Development and Progression of Heart Failure

Pathophysiological Process	Key Biomarkers
Myocardial stretch/stress	NT-proBNP/BNP, sST2, GDF-15
Extracellular matrix remodeling	Gal-3, IL-6, osteopontin, syndecan-1, IGFBP-7
Renal function/kidney injury/volume status	Cystatin-C, NGAL, KIM-1, NAG, CEA-125
Myocardial injury	High-sensitivity troponin
Inflammation	CRP, procalcitonin
Neurohormonal activation	Copeptin, MR-proADM

The biomarkers included here are not an exhaustive list and are derived from studies that vary in quality. Furthermore, there are significant overlaps in the biomarkers representing each of the pathophysiological processes.

BNP = B-type natriuretic peptide; CEA = carbohydrate antigen; CRP = C-reactive protein; Gal = gelatinase associated lipocalin; GDF = growth differentiation factor; IGFBP = insulin-like growth factor-binding protein; IL = interleukin; KIM = kidney injury molecule; MR-proADM = midregional proadrenomedullin; NAG = *N*-acetyl- β -D-glucosaminidase; NGAL = neutrophil gelatinase-associated lipocalin; NT-proBNP = N-terminal pro-B-type natriuretic peptide; sST = soluble suppressor of tumorigenicity.