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CLINICAL RESEARCH

Transcriptomic Analysis Identifies the Effect of Beta-Blocking Agents on a Molecular Pathway of Contraction in the Heart and Predicts Response to Therapy

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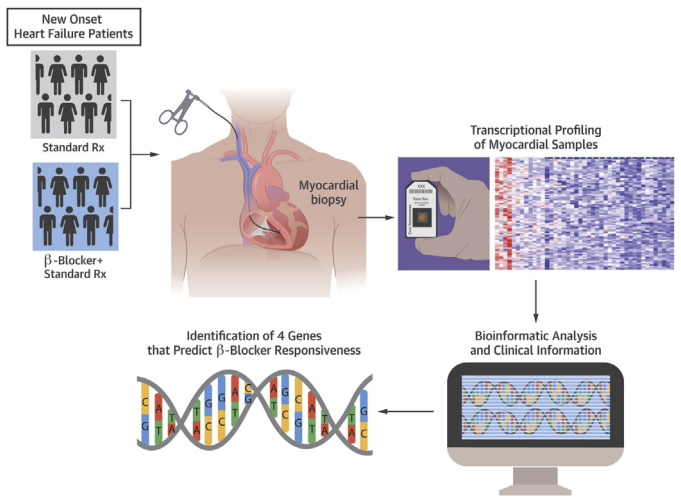
VISUAL ABSTRACT



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HIGHLIGHTS

- **Endomyocardial biopsy obtained from patients with new onset heart failure.**
- **Patients are followed long-term to determine clinical outcome and prognosis.**
- **Total RNA is purified from the endomyocardial biopsy specimen and subjected to microarray analysis.**
- **Pathway discovery and development of transcriptomic biomarkers are determined that predict clinical response to beta-adrenergic antagonists.**

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*Dr. Baughman is deceased.

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SUMMARY

Over the last decades, beta-blockers have been a key component of heart failure therapy. However, currently there is no method to identify patients who will benefit from beta-blocking therapy versus those who will be unresponsive or worsen. Furthermore, there is an unmet need to better understand molecular mechanisms through which heart failure therapies, such as beta-blockers, improve cardiac function, in order to design novel targeted therapies. Solving these issues is an important step towards personalized medicine. Here, we present a comprehensive transcriptomic analysis of molecular pathways that are affected by beta-blocking agents and a transcriptomic biomarker to predict therapy response.

G-protein-coupled receptors are the most commonly targeted proteins of recently designed drugs in the cardiovascular field, making them a key component of pharmacogenomic investigations and genetic variability studies (1). One of the best studied G-protein-coupled receptors is the beta-adrenergic receptor (AR) (1), with β1- and β2-AR both being expressed on human cardiomyocytes. Stimulation of ARs, in particular the β1-AR, induces increased cardiac inotropy and chronotropy (1). The β3-ARs have been shown to have negative regulatory functions on inotropy and cardiac reserve (2,3) through Gi coupling to cyclic guanine monophosphate-nitric oxide (4). Although beta-adrenergic stimulation is a major compensatory mechanism in the acute setting such as traumatic hypovolemia, it appears to worsen ventricular function and outcome in conditions with limited metabolic and physiological reserves, such as heart failure (HF) (1). Accordingly, beta-blocking agents were developed to partially antagonize beta-adrenergic "excess" of norepinephrine at the cardiomyocyte level (1).

ABBREVIATIONS AND ACRONYMS

AR = adrenergic receptor
EF = ejection fraction
EMB = endomyocardial biopsy
GO = gene ontology
HF = heart failure
MiPP = Misclassified Penalized Posteriors
MYH = myosin heavy chain
SAM = significance analysis of microarrays
SERCA = sarcoplasmic reticulum calcium-dependent ATPase
TBB = transcriptomic-based biomarker

Since the first discovery of beneficial effects of beta-blocker therapy in a small case series of 7 patients with HF by Waagstein et al. (5) in 1975, a sequence of large clinical trials (5–9) has confirmed clinical improvement with beta-blockade in HF and suggested various hypotheses on how beta-blockade in the failing heart may improve outcomes. These hypotheses included effects of beta-blockade through activation of myocardial contractile proteins and sarcoplasmic reticulum calcium-dependent ATPase (SERCA) activity, as well as alteration of gene expression (10–12).

In the field of gene expression analysis, Lowes et al. (10) made the important observation that functional improvement during beta-blocker therapy measured by improved ejection fraction (EF) (increase by 18.8 ± 1.8%) was associated with overexpression of SERCA and α-myosin heavy chain (MYH), whereas there was a decrease in expression levels of β-MYH. Yasumura et al. (11) made a similar observation in a clinical study, in which they treated patients with dilated cardiomyopathy for 4 months with beta-blockers. Improvement of EF during therapy with beta-blocking agents was associated with overexpression of SERCA and phospholamban.

While the previously mentioned investigational approaches used polymerase chain reaction (PCR) to gain valuable information about the molecular effects of beta-blocking agents on specific candidate genes, our group sought to expand the current knowledge by applying microarrays, a technology that evaluates expression levels of all genes in a given individual. Therefore, it allows the discovery of new genes and pathways in a more comprehensive approach (13–18) that has proven useful to delineate diagnosis and prognosis in HF populations (15,16,18). While typically only genes of interest or candidate genes are investigated with polymerase chain reaction, microarray technology analyzes the entire transcriptome of about 30,000 genes in 1 experiment (19) and, therefore, provides a less biased approach of gene discovery.

METHODS

PATIENT POPULATION. To identify genes that undergo expression changes during treatment with beta-blocking agents, we first analyzed endomyocardial biopsies (EMBs) obtained from patients with new-onset HF (n = 43), who were treated with beta-blockers (n = 30) versus alternative standard therapy (n = 13). This cohort has been previously described and analyzed for prognostic information (15). EMBs were obtained from a biorepository containing samples from patients with new-onset HF (15,16,18). In brief, transvenous EMBs were obtained from the right interventricular septum and