Coronary sinus biomarker sampling compared to peripheral venous blood for predicting outcomes in patients with severe heart failure undergoing cardiac resynchronization therapy: The BIOCRT study

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BACKGROUND A significant minority of patients receiving cardiac resynchronization therapy (CRT) remain nonresponsive to this intervention.

OBJECTIVE This study aimed to determine whether coronary sinus (CS) or baseline peripheral venous (PV) levels of established and emerging heart failure (HF) biomarkers are predictive of CRT outcomes.

METHODS In 73 patients (aged 68 ± 12 years; 83% men; ejection fraction 27% ± 7%) with CS and PV blood samples drawn simultaneously at the time of CRT device implantation, we measured amino-terminal pro-B–type natriuretic peptide (NT-proBNP), galectin-3 (gal-3), and soluble ST2 (sST2) levels. NT-proBNP concentrations >2000 pg/mL, gal-3 concentrations >25.9 ng/mL, and sST2 concentrations >35 ng/mL were considered positive on the basis of established PV cut points for identifying "high-risk" individuals with HF. CRT response was adjudicated by the HF Clinical Composite Score. A major adverse cardiovascular event (MACE) was defined as the composite end point of death, cardiac transplant, left ventricular assist device, and HF hospitalization at 2 years.

RESULTS NT-proBNP concentrations were 20% higher in the CS than in the periphery, while gal-3 and sST2 concentrations were 10% higher in the periphery than in the CS (all $P < .001$). There were 45% CRT nonresponders at 6 months and 16 (22%) patients with MACE. Triple-positive CS values yielded the highest specificity of 95% for predicting CRT nonresponse. Consistently, CS strategies identified patients at higher risk of developing MACE, with >11-fold adjusted increase for triple-positive CS patients compared to triple-negative patients (all $P \leq .04$). PV strategies were not predictive of MACE.

CONCLUSION Our findings suggest that CS sampling of HF biomarkers may be better than PV sampling for predicting CRT outcomes. Larger studies are needed to confirm our findings.

KEYWORDS Biomarker; Coronary sinus; Galectin-3; Soluble ST2; Cardiac resynchronization therapy

ABBREVIATIONS BIOCRT = Biomarkers to Predict CRT Response in Patients With HF; **CRT** = cardiac resynchronization therapy; **CS** = coronary sinus; **CV** = coefficient of variation; **gal-3** = galectin-3; **HF** = heart failure; **LVAD** = left ventricular assist device; **MACE** = major adverse cardiovascular event; **NT-proBNP** = amino-terminal pro-B–type natriuretic peptide; **NYHA** = New York Heart Association; **PV** = peripheral venous; **sST2** = soluble ST2

(Heart Rhythm 2014;11:2167–2175)

This study was supported by NIH/NHLBI K23HL098370. Dr Truong also received support from the NIH L30HL093896. Dr Ajijola was supported by an A.P. Giannini Foundation award. The reagents were provided and assays were performed by Siemens Healthcare Diagnostics, BG Medicine, and Critical Diagnostics. Dr Truong has received grant support from St Jude Medical, the American College of Radiology Imaging Network, and Duke Clinical Research Institute. Dr Januzzi is supported in part by the Roman W. Desanctis Distinguished Clinical Scholar Endowment and has received grant support from Roche Diagnostics, Siemens, BG Medicine, Critical Diagnostics, Singulex, and Thermo Fisher Scientific. Dr Min has served on the medical advisory boards of GE Healthcare, Arineta, Astra Zeneca, and Bristol-Myers Squibb; is on speakers bureau of GE Healthcare; and has received research support from GE Healthcare, Vital Images, and Phillips Healthcare. Dr Singh has received grant support from St Jude Medical, Medtronic, Boston Scientific, Sorin Group, Biotronik, BG Medicine, and Siemens. **Address reprint requests and correspondence:** Dr Quynh A. Truong, Dalio Institute of Cardiovascular Imaging, New York-Presbyterian Hospital and Weill Cornell Medical College, 413 E 69th St, Suite 108, New York, NY 10021. E-mail address: qat9001@med.cornell.edu.

1547-5271/$-see front matter http://dx.doi.org/10.1016/j.hrthm.2014.07.007

Introduction

Heart failure (HF) is a leading cause of morbidity and mortality in the United States, with 50% mortality at 5 years.[1] Several candidate HF biomarkers, including the established amino-terminal pro-B–type natriuretic peptide (NT-proBNP) and emerging markers of galectin-3 (gal-3) and soluble ST2 (sST2), have been used in a multimarker strategy for the assessment of patients with dyspnea and in patients with acute HF for predicting mortality using peripheral venous (PV) samples.[2–4]

Cardiac resynchronization therapy (CRT) is a device therapy that exerts considerable benefit,[5–9] but where approximately one-third of the patients are nonresponders despite optimal selection and adjustment of pacing parameters.[10,11] Thus, prognostication of these HF patients that would benefit from this effective but nonetheless costly therapy is desirable to provide patients and caregivers with realistic expectations.

There is, however, a paucity of data examining the effect of biomarkers obtained via coronary sinus (CS) blood sampling on CRT response. Of note, the CS blood sample can be easily drawn during the implantation of the left ventricular pacing lead within the coronary venous tree. In this study of CRT patients, we examined the differences in the CS and PV levels of 3 HF biomarkers (NT-proBNP, gal-3, and sST2) and evaluated their diagnostic accuracy for predicting CRT nonresponse and prognostic value for predicting major adverse cardiovascular events (MACEs) individually and in multimarker strategies.

Methods

Study population and protocol

The Biomarkers to Predict CRT Response in Patients With HF (BIOCRT; Clinical Trials.gov # NCT01949246) study is a prospective observational study consisting of New York Heart Association (NYHA) functional class II-IV patients undergoing CRT device implantation from a single tertiary hospital, in whom blood samples were drawn from the CS and PV during the time of device implantation. Inclusion and exclusion criteria are detailed in Table 1. We included 73 participants with baseline-matched CS and PV samples for all 3 candidate biomarkers (NT-proBNP, gal-3, and sST2) drawn during CRT device implantation between December 2007 and July 2012.

Before device implantation, baseline evaluation included evaluation of medical history, NYHA class, 12-lead electrocardiography, and 2-dimensional transthoracic echocardiography for the measurement of left ventricular volumes and diameters, and left ventricular ejection fraction by using the modified biplane Simpson's method. During device implantation, invasive coronary venography was used to guide left ventricular pacing lead placement. After CRT device implantation, study participants return for regular clinic visits at 1, 3, and 6 months and were followed for events through a time horizon of up to 2 years. Echocardiography-guided optimization of the CRT devices was uniformly performed on all patients at 1 month. The Social Security Death Index was searched between April 11, 2013, and May 3, 2013, for date of death. Our institutional review board approved the study protocol, and all patients provided written informed consent.

Blood collection and storage

At the time of device implantation, baseline CS blood was drawn from the CS guiding catheter before delivering the CRT lead and PV blood was drawn simultaneously from one of the upper extremity veins. Blood was collected into tubes containing ethylenediaminetetraacetic acid and tubes without anticoagulant. Samples were immediately centrifuged, and the aliquot portions of plasma and serum were stored in microcentrifuge tubes at −80°C until assayed. Anonymized specimens were sent to independent laboratories (Siemens Healthcare Diagnostics, BG Medicine, and Critical Diagnostics) for analysis. In addition to being blinded to the clinical history, the laboratories were blinded to the knowledge of whether the samples were CS or PV samples. All analyses were performed on a first freeze-thaw cycle.

Table 1 Inclusion and exclusion criteria for the BIOCRT study

Inclusion criteria
- Study participant with an approved indication for a CRT or CRT-D system
  - NYHA class II-IV heart failure unresponsive to drug therapy
  - EF <35%
  - QRS duration >120 ms
- Patient receiving optimal medical therapy, including ACE inhibitor or ARB, β-blocker, and diuretics
- Patient with history of significant congestive decompensation events in the last 12 mo

Exclusion criteria
- NYHA class I heart failure
- Comorbidities that may limit life span to <6 mo
- Severe aortic stenosis (valve area <1.0 cm^2)
- History of cardiac surgery or intervention in the last 90 d
- History of moderate to severe COPD, defined as needing chronic oxygen therapy, or recent (within 30 d) hospitalization for COPD flare-up
- Pregnancy
- History of primary pulmonary hypertension
- Patient receiving continuous or intermittent infusion therapy for heart failure

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BIOCRT = Biomarkers to Predict CRT Response in Patients With HF; COPD = chronic obstructive pulmonary disease; CRT = cardiac resynchronization therapy; CRT-D = cardiac resynchronization therapy-defibrillator; EF = ejection fraction; NYHA = New York Heart Association.