Plasma Corin Decreases After Coronary Artery Bypass Graft Surgery and Is Associated With Postoperative Heart Failure: A Pilot Study

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Objective: **Corin is a natriuretic peptide-converting enzyme that cleaves precursor pro-B-type natriuretic peptide to active B-type natriuretic peptide (BNP) (diuretic, natriuretic, and vasodilatory properties). Increased plasma BNP is a known diagnostic and prognostic heart failure (HF) biomarker in ambulatory and surgical patients. Recent studies indicate that plasma corin is decreased significantly in chronic HF patients, yet perioperative plasma corin concentrations have not been assessed in cardiac surgical patients. The objectives of this study were to determine the effect of coronary artery bypass graft (CABG) surgery with cardiopulmonary bypass (CPB) on plasma corin concentrations and to assess the association between change in perioperative plasma corin concentration and long-term postoperative HF hospitalization or death. It was hypothesized that plasma corin concentrations decrease significantly from preoperative baseline during postoperative days 1 to 4 and that hospitalization or death from HF during the 5 years after surgery is associated with higher relative difference (preoperative baseline to postoperative nadir) in plasma corin concentrations.**

Design: **Prospective observational pilot study.**

Setting: **Two institutions: Brigham and Women's Hospital, Boston, Massachusetts and the Texas Heart Institute, St. Luke's Hospital, Houston, Texas.**

Participants: **99 patients of European ancestry who underwent isolated primary CABG surgery with CPB.**

Interventions: **Nonemergency isolated primary CABG surgery with CPB.**

Measurements and Main Results: **Plasma corin concentration was assessed preoperatively and at 4 postoperative time points (postoperative days 1-4). HF hospitalization or HF death events during the 5 years after surgery were identified by review of hospital and death records. Postoperative plasma corin concentrations were significantly lower than preoperative baseline concentrations ($p < 0.0001$). Perioperative corin concentrations were significantly higher in males than in females ($p < 0.0001$). Fifteen patients experienced long-term postoperative HF events. Patients who experienced HF hospitalization or HF death during study follow-up had significantly higher relative difference in plasma corin concentration (preoperative baseline to postoperative nadir) than patients who did not experience HF events during study follow-up ($p = 0.03$).**

Conclusions: **Plasma corin concentrations decrease significantly from preoperative concentrations after CABG surgery. HF hospitalization or HF death during the 5 years after CABG surgery with CPB is associated with larger relative decrease in plasma corin concentration from preoperative baseline. Further investigation is warranted to determine the role of corin in postoperative HF biology.**

KEY WORDS: corin protein, human corin, natriuretic peptide, heart failure, coronary artery bypass grafting, biologic markers, cardiac surgery

HEART FAILURE (HF) affects approximately 5.1 million Americans[1] and is associated with increased hospitalization, mortality, and healthcare expenditures.[1,2] Coronary artery bypass graft (CABG) surgery is performed to improve quality of life and survival;[3] however, HF severe enough to result in hospitalization or death occurs in more than 10% of patients during the first 5 years after isolated primary CABG surgery,[4] and remains the leading cause of death after this procedure.[5] Despite advances in HF prevention and treatment,[6] the biology of HF still is not understood completely.

The natriuretic peptide system has counterregulatory natriuretic, diuretic, and vasodilatory properties.[7] The convertase protein corin is a key component of natriuretic peptide processing that cleaves the less biologically active precursor pro-B-type natriuretic peptide (proBNP) into biologically active BNP as well as an inactive NT-proBNP fragment[8,9] (Fig 1). Corin is thought to be produced primarily in the cardiac myocyte but has been shown to be expressed in both the human heart and the kidney,[10] as well as circulating in the bloodstream.[11] Circulating corin levels may be regulated partially by degree of shedding from cardiac myocytes and protein autocleavage.[12] Presently available commercial BNP assays capture within their BNP concentration measurements both the precursor proBNP and the processed and more biologically active BNP.[8,13,14] The less biologically active proBNP has been shown to be elevated preferentially in ambulatory HF patients.[15]

Corin may play a role in HF biology. Ambulatory HF patients have increased plasma concentrations of proBNP in relation to BNP,[15] and plasma corin levels are lower in ambulatory HF patients than in controls.[11,16] Furthermore, the degree of reduced plasma corin concentration in ambulatory patients is correlated with HF severity.[11] Dong et al reported that patients with NYHA class II, III, and IV heart failure had progressively lower levels of circulating plasma corin (450, 377, and 282 pg/mL, respectively).[11] Corin overexpression in mice with dilated cardiomyopathy has been associated with

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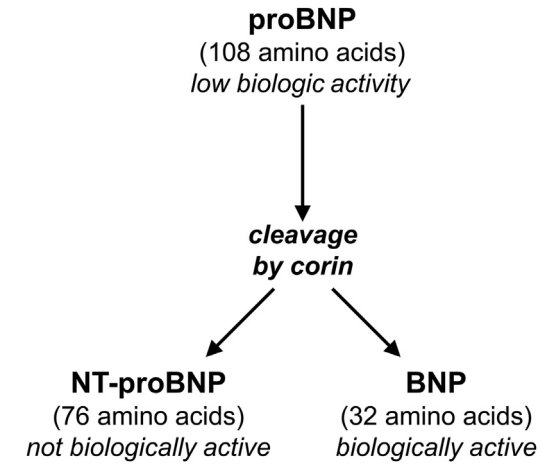

Fig 1. Illustration of precursor proBNP processing by corin to NT-proBNP (inactive fragment) and BNP (biologically active fragment).

enhanced myocardial contractile function, reduced HF signs, and decreased mortality.[17] It has been hypothesized that active corin deficiency, which could manifest as decreased circulating plasma corin, leads to decreased natriuretic peptide processing with a resulting relative overabundance of less biologically active proBNP and a deficiency of the processed active BNP fragment.[18]

Natriuretic peptides have been studied in cardiac surgical populations. Plasma BNP concentration is known to rise significantly after CABG surgery compared with preoperative baseline.[19,20] The authors previously have shown that both increased preoperative and peak postoperative[20] BNP concentrations are associated with increased short-term and long-term postoperative morbidity and mortality, including increased long-term HF-related hospitalization or death during the 5 years after on-pump CABG surgery.[4,19–21]

Although corin has been studied both in animal models and in ambulatory HF cohorts, the perioperative response pattern of plasma corin concentration to surgical stress has yet to be defined in CABG surgical patients. Furthermore, no study has assessed for an association between a decline in perioperative corin concentration and increased postoperative HF. Therefore, an exploratory pilot study of 99 patients of European ancestry who underwent isolated primary CABG surgery with cardiopulmonary bypass (CPB) was performed to (1) characterize the perioperative pattern of plasma corin concentrations, and (2) assess for an association between decreased postoperative plasma corin concentration and the occurrence of HF hospitalization or HF death up to 5 years after surgery. It was hypothesized that plasma corin concentrations decrease significantly from preoperative baseline during postoperative days 1 to 4 and that hospitalization or death from HF during the 5 years after surgery is associated significantly with higher relative difference (preoperative baseline to postoperative nadir) in plasma corin concentrations.

METHODS

Study Population

A total of 1,922 patients who underwent cardiac surgery with CPB at Brigham and Women's Hospital or the Texas Heart Institute were enrolled prospectively between August 2001 and February 2009 in an ongoing observational parent cohort study known as the CABG Genomics Program, which has the overall aim of identifying genetic and biomarker predictors of adverse events after cardiac surgery (http://clinicaltrials.gov/show/NCT00281164). Institutional review board approvals were obtained, and each study participant provided written informed consent before study initiation. Patients from the overall CABG Genomics Program cohort were not considered for inclusion in the current study if any of the following clinical criteria were present: Emergency surgery, concurrent valve surgery, prior cardiac surgery, preoperative inotropic support or intra-aortic balloon pump, surgery without CPB or aortic cross-clamp, preoperative hemodialysis, or a preoperative creatinine >3 mg/dL.

The 99 patients included in the present study's analysis initially were selected from 100 patients who were included in a pilot study assessment of a genetic hypothesis. Therefore, patients who declared themselves not to be of Northern or Southern European ancestry were excluded to avoid potential influence of population stratification. Those without genotyping data also were excluded to allow comparison of perioperative corin concentrations in minor allele carriers of a *CORIN* gene intronic single nucleotide polymorphism (SNP) rs12645164 versus noncarriers of this SNP. Of the 1,238 CABG Genomics participants (after exclusions for clinical factors, non-European ancestry, and available genotyping), 14 patients were homozygous for the minor allele of rs12645164. A total of 100 patients, therefore, were selected for the pilot study by matching each of the 14 minor allele homozygotes 3:1 with both heterozygotes and major allele homozygotes, with one subject of older age matched 4:1 (matching was performed according to age, sex, study institution, and left ventricular ejection fraction). This genetic pilot study did not identify a significant difference in corin concentrations between minor allele carriers and noncarriers of rs12645164.

For the present study analysis, the authors assessed 99 of these pilot study patients (1 subject excluded for missing preoperative corin concentration) in order describe overall pattern of perioperative plasma corin release (preoperative and postoperative days 1-4), the influence of sex on pattern of perioperative plasma corin release, and the association between decline in perioperative plasma corin concentration and the occurrence of HF hospitalization or HF death up to 5 years after on-pump CABG surgery. A schematic outlining patient selection for this study's analysis is shown in Figure 2.

Blood Collection

Preoperative and postoperative day 1-to-day 4 plasma Ethylenediaminetetraacetic acid samples were collected and assessed, with plasma corin concentrations measured using enzyme-linked immunosorbant assay (R&D Systems, Minneapolis, MN) at a single laboratory.

Data Collection

Perioperative data were collected prospectively using a standard case report form that included demographic information, preoperative medications, medical history, surgical characteristics, and postoperative course. Data regarding need for hospitalization during the 5 years after primary CABG surgery were obtained via questionnaires that were sent to patients 6 weeks, 6 months, and annually on postoperative years 1 to 5, as well as via follow-up telephone interviews and review of study institution electronic medical records. Hospital records were obtained for any patient who was identified as having postoperative hospitalizations for possible cardiac or pulmonary reasons. Deaths were identified using the Social Security Death Index. Cause of death information was obtained from death certificates or National Death Index files for any patient who was found to have died during the study period. Hospitalization and death data were collected for the subject cohort through 5 years after surgery or through July 15, 2012 if that