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Transforming Growth Factor Beta-1 and Incidence of Heart Failure in Older Adults: The Cardiovascular Health Study

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Abstract

Context—Transforming growth factor-beta1 (TGF-B1) is a highly pleiotropic cytokine whose functions include a central role in the induction of fibrosis.

Objective—To investigate the hypothesis that elevated plasma levels of TGF-B1 are positively associated with incident heart failure (HF).

Participants and Methods—The hypotheses were tested using a two-phase case-control study design, ancillary to the Cardiovascular Health Study – a longitudinal, population-based cohort study. Cases were defined as having an incident HF event after their 1992-93 exam and controls were free of HF at follow-up. TGF-B1 was measured using plasma collected in 1992-93 and data from 89 cases and 128 controls were used for analysis. The association between TGF-B1 and risk

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of HF was evaluated using the weighted likelihood method, and odds ratios (OR) for risk of HF were calculated for TGF-B1 as a continuous linear variable and across quartiles of TGF-B1.

Results—The OR for HF was 1.88 (95% confidence intervals [CI] 1.26 to 2.81) for each nanogram increase in TGF-B1, and the OR for the highest quartile (compared to the lowest) of TGF-B1 was 5.79 (95% CI 1.65 – 20.34), after adjustment for age, sex, C-reactive protein, platelet count and digoxin use. Further adjustment with other covariates did not change the results.

Conclusions—Higher levels of plasma TGF-B1 were associated with an increased risk of incident heart failure among older adults. However, further study is needed in larger samples to confirm these findings.

Keywords

transforming growth factor-beta; heart failure; fibrosis; growth factors; cardiac remodeling

1. Introduction

Longitudinal, community-based studies, have implicated hypertension, diabetes mellitus, and coronary heart disease (CHD) as important risk factors for heart failure (HF) among the elderly, but the pathophysiologic mechanisms of myocardial remodeling in HF remain poorly understood.[1-3] Diabetes, hypertension, and CHD may lead to incident HF, in part, due to the structural and functional changes that result from myocardial fibrosis.[4, 5] Few epidemiologic studies have examined the role of profibrotic growth factors in HF.

Transforming growth factor-beta1 (TGF-B1) is a highly pleiotropic cytokine whose functions include a central role in the induction of fibrosis and an early role in the anti-inflammatory response to injury[6]. TGF-B1, both independently and in conjunction with connective tissue growth factor (CTGF), mediates fibrosis associated with diabetes, hypertension, and CHD. In contrast, researchers hypothesize that the TGF-B1 also plays an essential role in maintaining normal vessel wall structure and the loss of this protective effect can contribute to atherosclerosis.[7] As a result, TGF-B1 has both therapeutic and pathologic potential due to its central role in tissue repair, immune surveillance and suppression, along with its role in extracellular matrix (ECM) regulation.[6] We hypothesized that increasing plasma levels of TGF-B1 are associated with increased risk of HF among older adults.

2. Material and Methods

2.1 Study Design and Participants

The hypotheses were tested using a two-phase case-control study design, ancillary to the CHS. CHS is a population-based, prospective cohort study of risk factors for cardiovascular and cerebrovascular disease in older adults.[8] In brief, participants were recruited from four U.S. communities (Washington County, MD; Pittsburgh, PA; Forsyth County, NC; and Sacramento County, CA) based on a randomly generated sampling frame from Medicare eligibility lists. The cohort consists of 5,201 community-dwelling adults, 65 years of age, who had a baseline visit in 1989 to 1990, and an additional 687 African-American adults, 65 years, recruited to the cohort in 1992-93, yielding a total of 5,888 participants. Follow-

up interviews for events were done at annual in-person visits and through interim 6-month telephone calls. All subjects provided written informed consent to participate, and each site institution's committee on human research approved the study protocol.

Selection of cases and controls was done using two-phase sampling, a standard technique applicable when collection of new data is limited to a subset of the original study cohort. It involves stratified sampling, with the selection probability depending on case status and other covariates available for the entire cohort.[9] The phase I sample comprised all CHS participants who were alive and free of HF at the time they provided plasma samples in 1992-93 (N=2936). The phase I sample was jointly stratified into 12 strata resulting from the cross classification of case-control status, diabetes status at time of plasma collection in 1992-93 (prevalent diabetes [fasting glucose ≥ 126 mg/dl or the use of anti-diabetic agents], impaired fasting glucose [100 – 125 mg/dl], and fasting glucose levels <100 mg/dl), and angiotensin converting enzyme (ACE)-inhibitor use at time of plasma collection in 1992-93 (yes/no). From within each of the 12 strata, subjects were selected for measurement of TGF-B1. All phase I cases were selected, and controls were preferentially selected based on diabetes status and ACE-inhibitor use. The phase II sample consisted of 431 cases and 469 controls selected for TGF-B1 measurement.

2.2 Clinical Assessments and Measurements

Information on known and hypothesized risk factors for HF was obtained from the 1992-93 visit. These data included demographics, clinical disease (previous coronary heart disease, stroke, transient ischemic attack and atrial fibrillation, adjudicated by a combination of self-report of physician diagnoses and medical record review), traditional cardiovascular disease risk factors, laboratory biomarkers, measures of subclinical disease, and medication use.

2.3 Adjudication of Heart Failure

All HF events were adjudicated by an expert panel who reviewed all pertinent data on the index hospitalization or outpatient visit for HF, including history, physical examination, chest x-ray reports, and medications.[10] [11] Physician diagnosis of HF was confirmed by documentation in the participant's medical records of a constellation of symptoms, physical signs, and by supporting clinical findings. The diagnosis of HF was also confirmed if in addition to having a prior physician diagnosis of HF, the participant was receiving medical therapy for HF. HF events were identified through 30 June 2004. Cases were defined as having an incident HF event after their 1992-93 exam date, and controls were free of HF at time of follow-up in June 2004.

2.4 Measurements of Transforming Growth Factor Beta-1

TGF-B1 was measured on the 900 subjects in the phase II sample, using stored EDTA plasma collected at the 1992-93 visit, on average 5.4 ± 2.8 years before the events. Levels of TGF-B1 were measured by use of a commercially available standard quantitative sandwich ELISA kit (R&D Systems Inc, Minneapolis, MN) and run according to the manufacturer's recommendations. Inter- and intra-assay coefficients of variation (CV) in samples from an established in-house quality-control pool were 8.6% and 3.3%, respectively. Laboratory analyses were conducted by an author (N.L.G.) blinded to the case and control status. TGF-

B1 values for 3 subjects were excluded due to CVs > 15%. Since platelets are a major source of TGF-B1, measurement may be susceptible to artificial increases in plasma levels due to platelet degranulation if the plasma is not platelet poor. Platelet contamination of the plasma was found at three of the study sites and was confirmed by assays of PAI1. Therefore, we restricted our analyses to data from the Pittsburgh clinic (n=217), excluding all samples from the Davis, Johns Hopkins and Bowman Gray sites where platelet contamination occurred.

2.5 Statistical Analyses

Descriptive statistics of demographics, medical conditions, and behavioral risk factors by case-control status and by quartiles of TGF-B1 among controls, were calculated using inverse-probability weighting. Associations between TGF-B1 and risk of HF was evaluated using the weighted likelihood method.[12] Odds ratios for risk of HF were calculated for TGF-B1 as a continuous linear variable and across quartiles of TGF-B1. Potential confounding factors evaluated included age, sex, race, systolic and diastolic (SBP, DBP), treated hypertension, diabetes, stroke/TIA, fasting glucose, low-density lipoprotein, high-density lipoprotein, C-reactive protein, body mass index, platelet count, smoking, digoxin, ACE-inhibitor use, and HMG-CoA reductase inhibitor use. Those not materially altering risk estimates were not included in the final model. STATA (version 9.0, College Station, Texas) and R Survey Package were used for the analyses. P-values less than 0.05 were considered statistically significant.

3. Results

3.1 Baseline characteristics of HF cases and controls

There were 122 controls and 95 incident cases included for analysis. TGF-B1 levels ranged from 0.48 ng/ml to 8.0 ng/ml in this population of older adults, with a mean of 1.4 ng/ml. Traditional risk factors for HF, history of cardiovascular disease (CVD), diabetes mellitus and hypertension, were more prevalent in HF cases than in controls (Table 1). Cases were older, had higher levels of C-reactive protein, had lower platelet count, and were more likely to be male, and use diuretics and digoxin.

3.2 Characteristics associated with TGF-B1 levels, among 122 control subjects

Participant characteristics were similar across quartiles of TGF-B1. Controls in the upper quartile of TGF-B1 had higher CRP levels, higher platelet count, and increased use of digoxin, compared to those in the lowest quartile (Table 2). Hypertension, blood pressure levels and prevalent CHD were not associated with TGF-B1. Impaired fasting glucose and diabetes were, however, associated with significantly increased TGF-B1 levels.

3.3 Association of TGF-B1 with risk of incident HF

In multivariate analyses of 217 subjects, higher levels of TGF-B1 were associated with increased risk of HF. TGF-B1 was examined as a continuous variable and was associated with an OR for HF of 1.88 (95% CI 1.26 to 2.81) for each 1-ng increase in TGF-B1, after adjustment for age, sex, CRP, platelet count and digoxin use. The addition of diabetes, race, BMI, smoking, treated hypertension, stroke and/or TIA, atrial fibrillation, SBP, DBP, fasting

glucose, fasting insulin, ACE-inhibitor, diuretic, beta-blocker or HMG-CoA reductase inhibitor use to the models did not change the risk estimate. The ORs for increasing quartiles of TGF-B1 were 1.0 (reference), 1.70 (95% CI: 0.42 – 6.83), 2.46 (95% CI: 0.59 – 10325), 5.79 (95% CI 1.65 – 20.3), after adjustment for age, sex, CRP, platelet count and digoxin use. To evaluate whether there was differential risk for more proximally occurring events, we evaluated the association of TGF-B1 with HF separately for cases occurring within 5 years of plasma collection versus cases occurring after 5 years. Risk estimates for both case groups were similar.

4. Discussion

In this two-phase case control study, high plasma levels of TGF-B1 in blood samples collected on average 5 years before the event were associated with increased risk of HF among older adults. To our knowledge, this is the first prospective study in humans to demonstrate a relationship between elevated plasma levels of TGF-B1 and incident HF.

One previous cross-sectional study examined circulating levels of inflammatory and antiinflammatory cytokines in 38 patients with HF and 21 healthy controls and found that patients with severe HF had decreased serum levels of TGF-B1 compared with healthy controls.[13] However, the authors measured levels of TGF-B1 in serum, rather than plasma, and it was a cross-sectional study of patients with chronic HF with systolic dysfunction secondary to either coronary artery disease or idiopathic dilated cardiomyopathy.

The positive association of TGF-B1 with increased risk of HF in the elderly may be due to the effect of TGF-B1 on fibrosis [6, 14]. HF in the elderly is frequently multifactorial, and TGF-B1 is thought to be up-regulated in the setting of hypertension, diabetes and MI - major risk factors for HF in the elderly[1, 2, 15]. Acute MI stimulates the formation of scar tissue, but diabetes and hypertension can also induce a more diffuse, progressive fibrosis that impairs myocardial filling and contraction[4, 5]. TGF-B1-induced cardiac fibrosis is brought about largely through its actions on the ECM, simultaneously stimulating cells to increase production of ECM proteins, and by inhibiting the degradation of these matrix proteins.[14] It is still unknown how the profibrotic properties of TGF-B1 along with its anti-inflammatory activities may influence the development and progression of HF. TGF-B1 anti-inflammatory effects play an essential role in maintaining normal vessel wall structure and the loss of this protective effect can contribute to atherosclerosis.[7]

The strengths of this study include prospectively collected blood, population-based data on clinical characteristics as well as incident events. We measured TGF-B1 levels blinded to case-control status, minimizing differential laboratory error. Several limitations should be noted. The number of study subjects was modest and we had limited ability to investigate effect modification or differences in risk of HF type (systolic vs. diastolic). However, fibrosis can result in both LV diastolic and systolic dysfunction, the major physiologic mechanisms underlying HF in older adults. Because of the observational nature of the study, we cannot eliminate the possibility of residual confounding by imprecisely measured risk factors or unmeasured risk factors. Samples were collected in EDTA, without other major

platelet inhibitors and could exhibit artefactually high values for TGF-B1 if platelet removal was incomplete. While the CHS protocol called for handling that should be sufficient for removing platelets, we found that samples from three of the CHS clinic sites may have had incomplete platelet removal, so we did not use TGF-B1 values from those sites. Plasma levels of TGF-B1 were measured at a single point, and it is unknown how stable human plasma TGF-B1 levels are over time or whether circulating plasma levels reflect biologically active levels in the myocardium.

5. Conclusions

We found that higher levels of plasma TGF-B1 were associated with an increased risk of incident HF among older adults. Given the limitations of the study and small sample size, our results should be viewed as preliminary data. If confirmed, these findings suggest that elevated circulating levels of TGF-B1 may be involved in the development HF in older adults and a key mediator of cardiac fibrosis.

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Highlights

- We examined the association between plasma TGF-B1 with incident heart.
- Higher TGF-B1 levels were associated with an increased risk of heart failure.
- Elevated circulating levels of TGF-B1 may be a key mediator of cardiac fibrosis.

Table 1
Characteristics of HF cases and controls at time of blood collection (92-93 visit)

Characteristic	HF Cases (n=95)	Controls (n=122)
	Weighted % or population mean $\pm$ SE	Weighted % or population mean $\pm$ SE
Age, y	77 $\pm$ 0.6	75 $\pm$ 0.2
Female, %	48	67
White, %	92	89
BMI, kg/m ²	26.9 $\pm$ 0.5	25.3 $\pm$ 0.2
Former smoker, %	55	51
Current smoker, %	13	9
History of CHD*, %	38	21
History of Stroke or TIA, %	19	4
History of Atrial Fibrillation, %	10	1
Treated hypertension, %	49	24
SBP, mm Hg	136 $\pm$ 2	126 $\pm$ 1
DBP, mm Hg	71 $\pm$ 1	69 $\pm$ 1
Low density lipoprotein, mg/dL	125 $\pm$ 3	127 $\pm$ 1
High density lipoprotein, mg/dL	48 $\pm$ 1	56 $\pm$ 1
Impaired glucose tolerance, %	43	11
Treated DM or glucose >125 mg/dL, %	18	2
Glucose (fasting), mg/dL	117 $\pm$ 3	95 $\pm$ 0.3
Insulin (fasting), uIU/ml	11 $\pm$ 1	9 $\pm$ 0.2
C-reactive protein, mg/L	6.8 $\pm$ 1.1	3.9 $\pm$ 0.3
Creatinine, mg/dL	1.2 $\pm$ 0.04	1.0 $\pm$ 0.01
Cystatin-C, mg/L	1.2 $\pm$ 0.04	1.1 $\pm$ 0.01
Uric acid, mg/dL	6.2 $\pm$ 0.2	5.3 $\pm$ 0.1
Albumin, mg/dL	3.9 $\pm$ 0.03	3.9 $\pm$ 0.01
Platelet count, /cc.mm	225 $\pm$ 7	247 $\pm$ 3
IL-6, pg/ml	2.3 $\pm$ 0.2	1.8 $\pm$ 0.1
LV mass by ECG, grams	160 $\pm$ 4	144 $\pm$ 2
ACE-inhibitor use, %	11	1
Diuretic use, %	32	13
Beta-blocker use, %	10	9
Statin use, %	5	6
Digoxin use, %	23	5
TGF-B1, ng/ml	1.7 $\pm$ 0.1	1.4 $\pm$ 0.1

* CHD = MI, angina, CABG, PTCA

Table 2
Characteristics of 122 controls, by TGF- β 1 quartiles

Characteristic	TGF- β 1 (ng/ml)			
	<0.85 (n=20)	0.85-1.1 (n=27)	1.2-1.6 (n=34)	1.7-8.0 (n=41)
Characteristic	Weighted % or population mean $\pm$ SE			
Age, y	73 $\pm$ 1	76 $\pm$ 1	78 $\pm$ 1	74 $\pm$ 1
Female, %	71	60	74	74
White, %	88	78	94	89
BMI, kg/m ²	23.9 $\pm$ 1.3	28.2 $\pm$ 1.4	24.8 $\pm$ 0.8	29.6 $\pm$ 1.0
Former smoker, %	28	58	32	49
Current smoker, %	9	11	3	14
History of CHD*, %	8	27	24	7
History of Stroke or TIA, %	2	9	9	3
History of Atrial Fibrillation, %	0	0	3	4
Treated hypertension, %	37	49	27	40
SBP, mm Hg	132 $\pm$ 10	124 $\pm$ 4	125 $\pm$ 4	131 $\pm$ 4
DBP, mm Hg	70 $\pm$ 5	67 $\pm$ 2	75 $\pm$ 2	70 $\pm$ 2
Low density lipoprotein, mg/dL	112 $\pm$ 9	138 $\pm$ 7	131 $\pm$ 9	121 $\pm$ 7
High density lipoprotein, mg/dL	51 $\pm$ 3	55 $\pm$ 4	50 $\pm$ 3	51 $\pm$ 2
Impaired fasting glucose (100-125), %	30	23	29	46
Treated DM or glucose >125 mg/dL, %	4	21	10	17
Glucose (fasting), mg/dL	98 $\pm$ 3	113 $\pm$ 4	100 $\pm$ 3	113 $\pm$ 4
Insulin (fasting), uIU/ml	9 $\pm$ 1	11 $\pm$ 1	10 $\pm$ 2	13 $\pm$ 2
C-reactive protein, mg/L	3.2 $\pm$ 0.8	4.1 $\pm$ 0.7	4.2 $\pm$ 0.9	7.4 $\pm$ 1.5
Creatinine, mg/dL	1.0 $\pm$ 0.05	1.0 $\pm$ 0.04	1.0 $\pm$ 0.06	0.9 $\pm$ 0.06
Cystatin-C, mg/L	1.0 $\pm$ 0.04	1.1 $\pm$ 0.1	1.1 $\pm$ 0.08	1.0 $\pm$ 0.06
Uric acid, mg/dL	4.9 $\pm$ 0.4	6.1 $\pm$ 0.2	5.3 $\pm$ 0.4	5.4 $\pm$ 0.2
Albumin, mg/dL	3.9 $\pm$ 0.1	4.0 $\pm$ 0.04	3.8 $\pm$ 0.1	4.0 $\pm$ 0.1
Platelet count, /cc.mm	210 $\pm$ 12	240 $\pm$ 11	250 $\pm$ 16	258 $\pm$ 9
IL-6, pg/ml	1.3 $\pm$ 0.2	2.0 $\pm$ 0.3	2.1 $\pm$ 0.3	2.1 $\pm$ 0.4
LV mass by ECG, grams	129 $\pm$ 12	155 $\pm$ 7	144 $\pm$ 11	157 $\pm$ 6
ACE-inhibitor use, %	4	8	8	11
Diuretic use, %	5	35	11	11
Beta blocker use, %	21	5	8	3
Statin use, %	17	3	4	2
Digoxin use, %	1	4	5	27

* CHD = MI, angina, CABG, PTCA

[†] median values for each quartile