Endothelin-1 Is a Key Mediator of Coronary Vasoconstriction in Patients With Transplant Coronary Arteriosclerosis

Eric Larose, DVM, MD; Dominik Behrendt, MD; Scott Kinlay, MBBS, PhD; Andrew P. Selwyn, MD; Peter Ganz, MD; James C. Fang, MD

Background—Transplant coronary arteriosclerosis (TCA) is the principal long-term complication in cardiac transplant recipients. The mediators responsible for vascular proliferation and vasoconstriction typical of TCA remain largely unknown. We tested whether endothelin-1 (ET-1), a potent vasoconstrictor and mitogen, contributes to the pathogenesis and manifestations of TCA.

Methods and Results—BQ-123, an ET-1 receptor-A antagonist, was infused into a coronary artery (40 nmol/min for 60 minutes) of 18 subjects, 6±4 years after transplantation. Vasomotor responses were measured in the infused artery and in a noninfused control artery in patients with (n=10) and without (n=8) advanced TCA (108 total coronary segments). Changes in diameters were compared at 15-minute intervals up to 60 minutes. Contribution of ET-1 to coronary constrictor tone was assessed by comparing vasodilation from BQ-123 with that of the maximal vasodilator nitroglycerin (200-µg intracoronary bolus).

BQ-123 dilated coronary arteries of transplanted patients (8.4% at 60 minutes versus 0.4% in noninfused arteries, P<0.001). Dilation was greater for arteries with advanced TCA defined as diameter stenosis ≥15% (dilation 15.2% with versus 0.6% without advanced TCA, P=0.004). Judged against the response to nitroglycerin, ET-1 accounted for 53.2% of coronary tone in advanced TCA but only 12.9% without advanced TCA.

Conclusions—This study shows for the first time in humans that ET-1 is an important mediator of coronary vasoconstriction in TCA and accounts for >50% of the increased vasomotor tone. Therapeutic targeting of ET-1 may retard the development of TCA. (Circ Heart Fail. 2009;2:409-416.)

Key Words: heart transplant ■ transplant coronary arteriosclerosis ■ endothelin

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ET-1 binds to 2 specific receptors: the ET_A receptor, located on vascular smooth muscle cells (SMCs), and the ET_B receptor, located predominantly on vascular smooth muscle and endothelial cells. The vasoconstrictor and mitogenic effects of ET-1 are mediated principally by the ET_A receptor. The selective ET_A receptor antagonist BQ-123 (D-Trp-D-Asp-Pro-D-Val-Leu) reduces mitogenesis9 and reverses ET-1-induced coronary artery vasoconstriction in subjects with native coronary arteriosclerosis.10 For the first time in humans, we investigated the contribution of ET-1 to TCA by testing the hypothesis that ET-1 bioactivity is significantly increased in coronary arteries with coronary arteriosclerosis is the main limitation to the long-term survival of heart transplant recipients.1 Distinct from atherosclerosis in native coronary arteries, transplant coronary arteriosclerosis (TCA) is characterized by diffuse and concentric intimal proliferation involving both epicardial and intramyocardial coronary arteries. Angiographically, TCA is recognized by diffuse and focal narrowings in epicardial arteries, loss of tertiary branches, and by rapid tapering of conduit vessels.2 Although the pathogenesis of TCA is most likely multifactorial involving immunologic, infectious, and traditional risk factors, specific molecular mediators remain to be determined.3 Endothelin-1 (ET-1) is a peptide with potent vasoconstrictor and mitogenic properties4 that may play such a mechanistic role. Plasma ET-1 is increased after organ transplantation5 and immunoreactive ET-1 has been identified at sites of intimal proliferation in animal and human TCA.6,7

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advanced TCA. We compared the vasomotor responses of coronary arteries with selective ETA receptor inhibition in heart transplant recipients with and without advanced TCA.

**Methods**

**Patient Population**

We studied patients, 18 to 75 years of age, undergoing routine annual diagnostic cardiac catheterization after heart transplantation. Patients were divided into 2 groups on the basis of angiographic findings. The first group had at least one &gt;15% diameter stenosis in a major coronary artery determined by quantitative coronary angiography (QCA; advanced TCA group). The second group had angiographically smooth coronary arteries (no advanced TCA group).

We excluded patients with left ventricular dysfunction (ejection fraction &lt;40%) and severe renal or hepatic abnormalities for safety reasons. Patients were asked to hold long-acting vasoactive medications for &gt;24 hours before the study. No patient had evidence of active rejection at the time of the study.

Coronary risk factors were assessed from chart review and patient interview. Hypertension was defined by brachial cuff pressure &gt;140/90 mm Hg or the use of blood pressure lowering medications; diabetes was defined by fasting blood glucose &gt;125 mg/dL or the use of oral hypoglycemic agents or insulin; smoking was considered active if there was any smoking documented in the last 30 days. Transplant-related TCA risk factors, such as ischemic time, cytomegalovirus infection, treated rejection, and immunosuppressive drugs, were assessed from chart review. The research protocol was approved by the Investigational Review Board of Brigham and Women’s Hospital, and signed informed consent was obtained from all patients.

**Study Protocol**

After the diagnostic catheterization, one major coronary artery was selected for BQ-123 infusion (BQ-123 infused artery). The infused artery was angiographically smooth, without rapid tapering or loss of tertiary branches in the "no advanced TCA" patients; it contained at least one &gt;15% diameter stenosis (confirmed by QCA) in the patients with advanced TCA. We relied on these strict angiographic criteria to determine the relative severity of TCA and differentiate patients with advanced TCA from those without. Because several extraneous systemic factors including anxiety and ambient conditions may alter vasomotion during the course of the study, another noninfused artery served as a time control in both groups during the 60 minutes of BQ-123 administration (Figure 1).

Intravenous heparin (5000 to 10,000 U) was given, and a 0.014-inch Doppler FloWire (EndoSonics, Rancho Cordova, Calif) was advanced through a 6 Fr guiding catheter into the infused artery. A 2.5F infusion catheter (Mass Transit, Cordis, Miami Lakes, Fla) was advanced over the FloWire to allow for drug administration into a thoracic position throughout the study.

**Epicardial Artery Responses**

The coronary vasomotor responses to BQ-123 and nitroglycerin in patients with advanced TCA and without advanced TCA were assessed by examining 3 coronary segments (proximal, mid, and distal) from the infused coronary artery and 3 segments from the noninfused coronary artery using off-line QCA. In the advanced TCA group, the segment of the infused coronary artery that contained the maximum diameter stenosis was also analyzed (Figure 1).

**Quantitative Coronary Angiography**

End-diastolic cine frames were digitized, and the luminal diameters of the coronary segments were measured by computerized QCA. The percent change in epicardial diameter from baseline in each of the 3 segments was averaged. In the subjects with advanced TCA, the change in the segment that contained the maximum diameter stenosis in the infused artery was also measured.

**Microvascular Tone**

In the infused artery, changes in coronary microvascular tone over the 60 minute infusion of BQ-123 were assessed by measuring coronary blood flow velocity with a 0.014-inch Doppler FloWire. The FloWire was maintained in a stable position throughout the study.

Coronary blood velocity was calculated as APV/2. Coronary blood flow volume was calculated as \((\pi \times \text{diameter}^2) \times \text{(APV/8)}\) where the diameter was measured 5-mm distal to the FloWire tip using QCA. Coronary microvascular resistance was calculated as mean arterial blood pressure/coronary blood flow.

**Statistical Analysis**

Clinical characteristics were compared using t tests for continuous variables and \(\chi^2\) or Fisher exact tests for categorical variables. The primary end point of the study was the change in the epicardial diameter of the infused artery to BQ-123 as measured by QCA. The responses to BQ-123 and to nitroglycerin were normally distributed. To analyze the responses during the 60 minutes of BQ-123 infusion, we performed 3 analyses. First, we compared the percent changes in epicardial diameter of the infused arteries with and without advanced TCA with their respective noninfused arteries. The significance of these comparisons was assessed by repeated measures multivariate ANOVA. Second, we compared the percent changes in epicardial diameter from BQ-123 infusion in the advanced TCA arteries with the arteries devoid of advanced TCA, and then the percent change in epicardial diameter from BQ-123 infusion in the segment with...
maximum diameter stenosis with the advanced TCA arteries. Third, we compared the ratio of epicardial diameter change to BQ-123 at 60 minutes with the epicardial diameter change to nitroglycerin to assess the percentage of resting vasomotor tone attributable to ET-1 in the arteries without advanced TCA, with advanced TCA, and the segment with maximum diameter stenosis. A randomized-effects model was used to assess the effect of BQ-123 after adjusting for baseline variables that differed between groups and those potentially related to TCA. Coronary blood flow and microvascular resistance changes were compared with baseline at 15-minute intervals using similar models. All data were analyzed using Intercooled Stata release 9 (StataCorp, College Station, Tex).

Results
We studied 10 patients with advanced TCA and 8 patients with angiographically normal coronary arteries at an average of 6 years after heart transplantation. Clinical characteristics of the study and control groups are presented in Table 1. Only 1 patient in the entire cohort had developed cytomegalovirus infection after transplant. All clinical characteristics were similar between groups, except for serum creatinine which was slightly but significantly more elevated in the group with angiographically normal coronary arteries.

All subjects with advanced TCA had at least one stenosis >15% in the study vessel. All subjects without advanced TCA had angiographically smooth coronary arteries without evidence of any luminal irregularities, rapid tapering of the distal vessel, or loss of tertiary branches. The mean luminal diameter narrowing of the most stenotic segment of the study vessel in the advanced TCA group was 31 ± 14% (P<0.0001, compared with the study vessel of the no advanced TCA group). The study vessel was either the left anterior descending or the circumflex arteries with no significant difference of vessel distribution between groups (left anterior descending study vessel in 60% of patients with advanced TCA and 63% of those without, P=NS).

There was a mild, nonsignificant reduction in mean blood pressure during the 60-minute intracoronary BQ-123 infusion, which was not different between both groups (P=NS). We observed a mild but significant increase in heart rate during the infusion, which was slightly greater in the group without advanced TCA compared with those with advanced TCA (percent increase in heart rate at 60 minutes: advanced TCA 2.3±3.8% versus no advanced TCA 2.9±3.7%, P=0.04, Table 2).

Epicardial Responses to BQ-123
There were no significant differences in baseline diameters between the infused study and control vessels, or between the patients with and without advanced TCA (Table 3). At 60 minutes of BQ-123 infusion only the infused study vessels and the stenotic segments of the subjects with advanced TCA increased in diameter. The vasodilation of the epicardial arteries, expressed as a percent change from baseline at 15 minute increments during intracoronary infusion of BQ-123, is presented in Figure 2. There was no detectable change in the diameter of the noninfused control arteries of either group over 60 minutes. There was no detectable vasodilation of the BQ-123 infused study arteries of the no advanced TCA group (0.6±6.8% at 60 minutes, P=NS). In contrast, the BQ-123 infused study arteries of the advanced TCA group signifi-

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Data are presented as mean (SD) or n (%). LDL indicates low-density lipoprotein; HDL, high-density lipoprotein; ASA, acetylsalicylic acid; ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker. *P<0.05.
Contribution of ET-1 to Epicardial Vasomotor Tone

The vasodilation achieved by BQ-123 was compared with that after intracoronary nitroglycerin, a maximal dilator of epicardial arteries, to determine the relative contribution of ET-1 to the overall resting vasomotor tone. The dilation to nitroglycerin was 12.5±10.3% in the infused artery without advanced TCA, 33.3±17.9% in the infused artery with advanced TCA, and 61.4±69.3% in the infused stenotic segment (P<0.01 for advanced TCA versus no advanced TCA; P=0.03 for stenotic segment versus advanced TCA). The contribution of ET-1 to resting vasomotor tone expressed as the ratio of dilation to BQ-123 over the dilation to nitroglycerin was 12.9±26.3% in the no advanced TCA group with angiographically normal arteries, 53.2±28.6% in the advanced TCA group, and 59.1±29.6% in the stenotic segments of the advanced TCA group (P=0.007 for advanced TCA versus no advanced TCA, and P=NS for advanced TCA versus stenotic segment).

Multivariate Analysis

We assessed the effects of serum creatinine and change in heart rate, which differed mildly but significantly between the groups with and without advanced TCA (Tables 1 and 2), on dilation to BQ-123. There was no independent effect of serum creatinine or change in heart rate on the response of infused arteries to BQ-123. We also assessed the effects of potentially significant variables, which did not differ between groups, including donor gender and history of rejection. There was no independent effect of donor gender and history of rejection on the response of infused arteries to BQ-123.

Coronary Microvascular Response

Coronary blood flow was measured in all patients by Doppler FloWire. There was no significant change in coronary blood flow velocity over the 60-minute infusion of BQ-123 in either angiographically normal or advanced TCA groups (advanced TCA +5.7±17.6%, versus no advanced TCA +0.8±18.8% at 60 minutes, P=NS). However, greater epicardial coronary artery dilation in the advanced TCA group led to a significantly greater increase in coronary blood flow compared with the group without advanced TCA (advanced TCA +41.0±35.4%, no advanced TCA +0.6±19.5% at 60 minutes, P=0.05). Coronary microvascular resistance significantly decreased with BQ-123 infusion in the advanced TCA group compared with the group without advanced TCA (advanced TCA −26.9±16.1% versus no advanced TCA −0.4±26.7% at 60 minutes, P=0.05).

Discussion

In this study, we observed a striking degree of basal coronary artery vasoconstriction in patients with advanced TCA, evidenced by a robust vasorelaxation in response to nitroglycerin. This pronounced resting vasoconstriction seems to be characteristic of advanced TCA. Moreover, we have demonstrated that the bioactivity of ET-1, measured through its constriction of coronary arteries, is markedly augmented in patients with advanced TCA. This increased bioactivity is manifest by relaxation of epicardial and intramyocardial arteries in patients with advanced TCA when the ETA receptor is blocked with BQ-123. The increase in ET-1 activity is particularly pronounced at sites of coronary luminal irregularities or stenoses. In patients with advanced TCA, ET-1 contributes to half or more of the resting coronary tone, whereas it contributes little if at all to the resting coronary tone.
töne of patients without advanced TCA. As ET-1 is a potent mitogen and a vasoconstrictor, these findings support a key role for the ET-1 in the pathogenesis of TCA.

The Pathogenesis of TCA Is Not Well Defined

Cardiac transplantation remains the treatment of choice for patients with end-stage cardiac disease and severe functional limitations. Despite important successes in improving patient survival, late graft failure and death due to TCA present a continuing challenge. TCA is demonstrated by angiography in 30% to 50% of patients within 5 years of transplantation, a prevalence that has not decreased with improvements in immunosuppressive regimens. Intravascular ultrasound studies suggest that most patients are affected within 3 years of transplantation, a prevalence that has not decreased with improvements in immunosuppressive regimens. Intravascular ultrasound studies suggest that most patients are affected within 3 years of transplantation. TCA is also difficult to assess clinically because the denervated donor heart commonly does not produce angina when ischemia is present: TCA more commonly presents with congestive heart failure, myocardial infarction, or death. Once identified, angiographically significant TCA carries a >50% mortality rate at 2 years. Although pharmacological interventions such as diltiazem, antioxidant vitamins, statins, gangliclovir, and sirolimus may slow the progression of TCA, the only definitive therapy in severe TCA is retransplantation.

The mechanisms underlying TCA are incompletely understood but likely include processes that are both similar and distinct from native coronary atherosclerosis. For example, coronary endothelial dysfunction is characteristic of both TCA and native coronary atherosclerosis. However, in contrast to native coronary atherosclerosis, a disease of focal eccentric plaques composed of lipid deposits and a fibrous cap, TCA leads to diffuse concentric intimal thickening of the major epicardial vessels and their intramyocardial branches. Histopathologic analysis demonstrates an intima composed of SMCs and abundant lymphocytes and macrophages. Allogeneic immune responses between the host and the recipient coronary endothelium play an important role in TCA. Despite these insights, specific molecular mediators that initiate or perpetuate vascular smooth muscle proliferation and inflammation in TCA are not well-defined in humans.

Role of ET-1 in Atherosclerosis of Native Coronary Arteries

ET-1 is a polypeptide that is cleaved from big endothelin by ECE-1. In normal coronary arteries, ET-1 is expressed only in the endothelium. In coronary arteries with atherosclerosis, ET-1 is expressed in the endothelium and strongly in the subendothelium or deep intima, most notably by SMCs and macrophages. ET-1 expression is increased in atherosclerotic compared with normal vessels. Through interaction with the receptor ETA, ET-1 is a potent vasoconstrictor. We have shown that in human atherosclerotic native coronary arteries, ET-1 accounts for nearly all the heightened vasoconstrictor tone, whereas it contributes only modestly to resting coronary tone in normal human arteries. In addition to its important vasoactive properties, ET-1 is chemotactic for macrophages and stimulates neutrophil rolling and adhesion (through P-selectin) as well as platelet activation. ET-1 also stimulates reduced nicotinamide adenine dinucleotide (phosphate) oxidase in human endothelial cells, thereby increasing reactive oxygen species and endothelial injury. Consistent with these proatherogenic actions of ET-1 ex vivo, biological activity of ET-1 is measured as coronary vasoconstriction correlates with the presence and burden of atherosclerotic disease in vivo.

Role for Endothelin-1 in TCA: Animal Studies

Animal models of TCA have demonstrated increased ET-1 immunoactivity in the arterial intima and media as well as the myocardial parenchyma. Increased ET-1 expression by lymphocytes and macrophages seems to be a key step in vascular SMC proliferation leading to the thickened neointima characterizing TCA in a murine model. In the cardiac allograft rejection model, the major ET-1 expressing cell type...
is the mononuclear inflammatory cell in the neointima.\textsuperscript{35} Pharmacological inhibition of ET-1 receptors reduces the abundance of SMCs and macrophages in the neointima\textsuperscript{36} and ameliorates the development of TCA in rat cardiac allografts.\textsuperscript{6}

**ET-1 Expression in Human TCA**

In humans, ET-1 mRNA is increased in cardiac biopsy specimens after transplantation.\textsuperscript{37} ET-1 peptide expression is increased in coronary artery endothelial and myointimal cells of biopsy specimens of patients with TCA.\textsuperscript{7} Interstitial ET-1 expression in human cardiac biopsies at 3 months after transplantation is associated with the subsequent development of angiographic TCA.\textsuperscript{38} However, the findings of ET-1 mRNA or peptide in cardiac biopsies do not provide information about its biological activity. Although the presence of ET-1 in cardiac biopsies suggests an association between ET-1 and TCA, these observations cannot determine whether there is a causal relationship between ET-1, development of TCA and subsequent clinical outcomes.\textsuperscript{38} Furthermore, plasma ET-1 levels (which are elevated in cardiac transplant recipients) do not correlate with the presence of TCA,\textsuperscript{39} partly because ET-1 is produced at many sites outside of the transplanted organ and partly because the majority of endothelin is released abuminally not luminally.\textsuperscript{40} Thus, data about the biological activity of ET-1 in human coronary arteries after cardiac transplantation and the relationship of any biologically active ET-1 to the presence of TCA are needed.

**ET-1 Biological Activity in TCA**

To the best of our knowledge, this study is the first to demonstrate markedly increased biological activity of ET-1 in the epicardial and intramyocardial arteries of patients with TCA. Although the mitogenic activity of ET-1 is difficult to establish in vivo, we have confirmed increased biological activity by demonstrating remarkably greater coronary artery vasomotor tone attributable to ET-1 when TCA is present. Similar to our observations in native coronary arteries, per segment analysis reveals that local ET-1 activity is incrementally greater as local disease severity increases, indicating either greater local production or alternately increased sensitivity to ET-1 effects.\textsuperscript{10} Notably, ET-1 synthesis is upregulated by many of the factors thought to contribute to TCA including reactive oxygen species,\textsuperscript{41} cytokines (interferon γ and tumor necrosis factor α),\textsuperscript{42} and growth factors (tumor necrosis factor β).\textsuperscript{43} In contrast, blocking the ET\textsubscript{A} receptor did not elicit any vasomotor effects in the absence of TCA, suggesting modest if any biological activity in nondiseased coronary arteries. The observed effects in epicardial coronary vasomotor tone may extend into the smaller intramyocardial vessels because BQ-123 produced significant changes in coronary blood flow and microvascular resistance.

**Endothelial Dysfunction and TCA**

The overall resting coronary vasomotor tone also increased markedly with the angiographic burden of TCA as surmised from greater nitroglycerin-induced vasodilator responses. ET-1 is not entirely responsible for this increased tone. We have shown previously that loss of nitric oxide bioavailability in coronary arteries is another characteristic of TCA\textsuperscript{23} and portends more rapid progression of TCA.\textsuperscript{44,45} It is likely that excess activity of ET-1 coupled with the loss of nitric oxide act in synergy to increase the coronary tone and promote vascular proliferation in TCA in humans. Endothelial dysfunction is part of a continuous spectrum of dysfunction, from minor to large changes in vascular tone. Our study shows a graded response where areas with advanced TCA have greater contribution of coronary vasoconstrictor tone mediated by endothelin than areas without.

**Limitations**

We defined advanced TCA by angiography rather than by intravascular ultrasound, a more sensitive technique to quantify TCA in its early stages. Nonetheless, the validated angiographic criteria for advanced TCA used here define a group of patients with progressive arteriopathy and poor clinical outcomes.\textsuperscript{46} Although not as sensitive as intravascular ultrasound for detecting TCA in its earliest stages, angiography identifies advanced TCA by luminal irregularities, rapid tapering of the distal vessel, and loss of tertiary branches that correlate well with disease burden and clinical outcomes. Our study demonstrates convincingly that advanced burden of TCA detectable by angiography is characterized by a marked endothelin-induced vasoconstrictor tone. In addition, we studied a limited number of patients. However, most complex coronary physiology studies in humans typically study small numbers of patients because of the invasive and highly technical nature of the investigations.\textsuperscript{10} This limitation is particularly relevant in the unique and limited population of cardiac transplant recipients.\textsuperscript{18} Nevertheless, the findings in our study were robust biologically and highly significant statistically.

**Therapeutic Implications**

This study has important therapeutic implications in defining a potential new target in preventing or treating TCA. Given the increased bioactivity of ET-1 in TCA and the known mitogenic and proinflammatory properties of ET-1, inhibitors of ET-1 might be expected to slow the progression of TCA.

In conclusion, local endogenous ET-1 bioactivity is increased in the epicardial and intramyocardial coronary arteries of patients with advanced TCA and accounts for >50% of basal coronary vascular tone in a diseased artery. These findings implicate ET-1 in the pathophysiology of TCA. Therapies that inhibit ET-1 activity to prevent or treat TCA should be evaluated in controlled clinical trials.

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**Disclosures**

None.
References


Larose ET-1 Bioactivity in TCA


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**CLINICAL PERSPECTIVE**

Transplant coronary arteriosclerosis (TCA) is the principal long-term complication after cardiac transplantation. Treatment remains elusive as the underlying mechanisms are incompletely understood. In cardiac transplant recipients undergoing annual surveillance catheterization, we blocked the actions of endothelin-1, a vasoconstrictor and mitogen proposed to mediate TCA. We found that endothelin-1 accounts for much of the coronary vasoconstrictor tone in TCA. By inference, as endothelin-1 is a mitogen and a vasoconstrictor, it might be responsible for vascular proliferation that characterizes TCA. Controlled clinical trials are now much needed to assess whether currently available endothelin-1 antagonists could be used as a treatment of TCA.
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