Journal of the American Heart Association

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ORIGINAL RESEARCH

Poorly Controlled Hypertension Alters Coronary Microvascular Contractile Response to Endothelin-1 Before and After Cardiac Surgery

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BACKGROUND: Patients with chronic hypertension have worse outcomes following on-pump (cardioplegia and cardiopulmonary bypass [CP/CPB]) cardiac surgery. Altered vasomotor function of the coronary microvasculature to ET-1 (endothelin-1) and other agonists may underlie these differences.

METHODS: Heart samples were collected from 85 patients undergoing CP/CPB enrolled in this observational study. Ex vivo coronary microvascular responses to ET-1, adenosine diphosphate, and sodium nitroprusside were assessed using video microscopy. Immunoblotting, immunohistochemistry, enzyme-linked immunosorbent assay, and multiomics approaches were also used.

RESULTS: Coronary microvascular contractile response to ET-1 in patients with uncontrolled hypertension was increased compared with the other 2 cohorts pre- and post-CP/CPB ($P<0.05$ across ET-1 10^{-10} to 10^{-7} mmol/L). Adenosine diphosphate-induced coronary microvascular vasodilation was conversely decreased ($P<0.05$ for adenosine diphosphate 10^{-5} and 10^{-4} mmol/L). Post-CP/CPB microvascular responses to ET-1 and adenosine diphosphate were blunted overall ($P<0.05$). Antagonism of pro-vasoconstrictive $endothelin_A$ receptor diminished contractile response ($P<0.05$). Transcriptomics and proteomics showed wide regulation of pro-vasoconstrictive pathways. Regression showed that hypertension status and cardiac mass reliably approximated ET-1-induced coronary microvascular contraction (R^2 0.95 pre-CP/CPB, R^2 0.86 post-CP/CPB), which, in turn, estimated change in ejection fraction pre- and post-CP/CPB ($P<0.05$). Patients with uncontrolled hypertension had –11% change in EF when compared with the other 2 groups pooled ($P<0.05$).

CONCLUSIONS: Altered coronary microvascular vasomotor function in patients with uncontrolled hypertension may jeopardize myocardial perfusion. Hypertension status and cardiac mass may be used to prognosticate this physiology, which, in turn, estimates change in ejection fraction postoperatively. Perioperative endothelin receptor blockers may benefit patients with uncontrolled hypertension and thus warrant further investigation.

Key Words: cardiopulmonary bypass ■ coronary microvascular reactivity ■ hypertension

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This article was sent to Chad E. Grueter, PhD, Associate Editor, for review by expert referees, editorial decision, and final disposition.

The data were presented at American Heart Association Vivien Thomas Early Career Investigator Award Competition, Philadelphia, PA, November 11–13, 2023.

Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.125.045333

For Sources of Funding and Disclosures, see page 19.

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CLINICAL PERSPECTIVE

What Is New?

- Uncontrolled peripheral hypertension is associated with increased coronary microvascular contractile response whereas this response in well-controlled chronic hypertension mirrors the profile of patients without hypertension.
- Cardioplegia and cardiopulmonary bypass are associated with blunted endothelium-dependent vasodilation and endothelin-induced vasoconstriction of the coronary microcirculation.

What Are the Clinical Implications?

- Altered coronary microvascular vasoconstriction related to hypertension may predispose subgroups to myocardial malperfusion; this contractile response in combination with hypertension status and left ventricular mass are significantly associated with change in postoperative ejection fraction.

Nonstandard Abbreviations and Acronyms

CP/CPB	cardioplegia and cardiopulmonary bypass
ET-1	endothelin-1
ET_AR	$endothelin_A$ receptor
ET_BR	$endothelin_B$ receptor
SNP	sodium nitroprusside

Patients with hypertension have worse peri- and postoperative outcomes following cardiac surgery with cardioplegia and cardiopulmonary bypass (CP/CPB) than patients without hypertension.[1–5] Altered coronary microvascular vasomotor tone is a proposed mechanism that may contribute to these worse outcomes, because the coronary microvasculature is a key regulator of myocardial perfusion and is adversely affected by both hypertension and CP/CPB.[6–12]

Dysregulated coronary microvascular function following CP/CPB has been associated with myocardial malperfusion, and alterations in peripheral resistance arterioles have been associated with systemic hypotension.[13–15] Taken together, increased peri- and postoperative pressor support may in turn jeopardize blood flow to the myocardium.[14,16,17] CP/CPB-induced dysregulation of coronary microcirculation may be compounded by comorbidities that independently increase the risk of microvascular dysfunction, including hypertension.[16,18,19] Chronic microvascular remodeling with increased wall stress, changes in vascular myogenic tone, lower shear rate, increased oxidative stress, and maladaptive activation of PKC-α (protein kinase C-α) pathways seen in the setting of chronic hypertension induce endothelial and vascular smooth muscle dysfunction, rendering myocardium more susceptible to ischemia with increases in oxygen demand or reductions in perfusion pressure.[20,21] These changes may clinically manifest in various ways, including altered ejection fraction (EF).

ET-1 (endothelin-1), an isoform of the most potent endogenous vasoconstrictor, is a key modulator of vasomotor tone. ET-1 is dysregulated in the setting of hypertension and CP/CPB.[22–25] ET-1 exhibits clinically significant vasoconstrictive effects by way of interaction with ET_AR ($endothelin_A$ receptor), which is expressed mostly on vascular smooth muscle cells and in myocardium. In contrast, ET_BR ($endothelin_B$ receptor) promotes vasodilation by way of nitric oxide and prostacyclin release from the endothelium and dually functions as a clearance receptor for ET-1 in the local tissue circulation.[26,27] Both ET_AR and ET_BR mediate endothelial dysfunction following ET-1 synthesis and release during the hypertrophic response to hypertension and following CP/CPB-induced microvascular injury.[22,28]

The role of ET-1 in coronary microvascular reactivity in these contexts has yet to be elucidated. Limitations in visualizing and assessing the coronary microvasculature in vivo persist; various contemporary methods indirectly assess this compartment of the coronary circulation by extrapolating microvascular function from measurements of coronary flow reserve or other parameters.[29] Our group performs unique ex vivo experiments using video microscopy that instead directly and precisely assess microvascular reactivity in response to various introduced agents of viable vessels harvested from patients undergoing cardiac surgery. In this study, we used these methods, in addition to multiomics and adjunctive molecular assays, to evaluate differential effects of hypertension on coronary microvascular reactivity and ET-1 molecular signaling pathways following CP/CPB. We hypothesized that patients with poorly controlled hypertension would have increased CP/CPB-induced coronary microvascular vasoconstriction to ET-1 compared with those without hypertension or to those with well-controlled hypertension. We further aimed to identify strong clinical predictors of coronary microvascular reactivity to improve preoperative risk stratification for patients undergoing on-pump cardiac surgery and circumvent the need for invasive means for assessing coronary microvascular function.

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METHODS

Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Design

This study was a prospective cohort study with an observational first phase conducted at a single academic center, during which eligible and consenting patients underwent biopsy of right atrial tissue at the time of operation, before and after cardioplegia and cardiopulmonary bypass. Patients undergoing nonemergent cardiac surgery with CP/CPB were enrolled in our study from 2022 to 2023; exclusion criteria included any aortic repair or reconstructive operation. Both inclusion and exclusion criteria were prospectively established. Patient enrollment, including written informed consent, tissue and blood collections, and sample use for subsequent in vitro studies were approved by the Institutional Review Board of Rhode Island Hospital (IRB #004410, initially approved March 10, 2010, last renewed/reapproved December 21, 2022). Data accrual for this study and any following procedures were in accordance with institutional guidelines.

Statistical Analysis

For sample size calculations, ample preliminary data from our laboratory indicated the SD and functional significance thresholds particular to results derived from their use. Variables included test statistic estimating with a standard normal approximation at a 2-tailed α significance level of 0.02 (=2.57), test statistic estimating with a standard normal approximation at a β error of 0.10 (=1.28), SD of microvessel response assays, and mean altered group response to be compared with mean response of reference group. These variables were used to calculate the minimum n required was ~5 vessels per group to sufficiently determine whether a specific condition (hypertension or cardioplegia/cardiopulmonary bypass) causes a statistically significant alteration in vascular regulation. End points were prospectively identified; advanced statistical testing was completed in collaboration with Biostatistics Core where appropriate statistical corrections were applied. Microvascular reactivity experiments included endothelium-independent control condition to ensure vessel viability (sodium nitroprusside), as substantiated in prior studies performed by our group.

Experimental Design

Our prespecified hypothesis was that patients with poorly controlled hypertension would have increased CP/CPB-induced coronary microvascular vasoconstriction to ET-1 compared with those without hypertension or to those with well-controlled hypertension. We further aimed to identify clinical parameters strongly associated with coronary microvascular reactivity to improve preoperative risk stratification for patients undergoing on-pump cardiac surgery and circumvent the need for invasive means for assessing coronary microvascular function. This translational study involved both prospective clinical cohort design as well as controlled laboratory experiments performed on biopsied myocardial samples. Enrolled patients were divided into 3 groups based on documented history of hypertension, use of prescription antihypertensive medications, and average clinic blood pressure measurements within a year preceding their on-pump cardiac operation. The normotensive/normotension (N) group comprised patients with no documented diagnosis of hypertension, no prescriptions for antihypertensives, and an average blood pressure <130/80 mm Hg. The well-controlled hypertension (C) group comprised patients with documented history of hypertension, prior or active prescription for at least 1 antihypertensive agent, and average blood pressure < 130/80 mm Hg. Patients in the uncontrolled/poorly controlled hypertension (U) group had average blood pressure ≥130/80 mm Hg. Regarding administration of antihypertensive agents, it is the practice of our institution to continue beta-adrenergic receptor blockers and calcium channel blockers through the morning of surgery and to stop angiotensin-converting enzyme inhibitors and angiotensin receptor blockers 48 hours preceding surgery. Prescription for antihypertensive agents was determined using fill history. Laboratory studies using viable tissue necessitated prompt dissection and completion of ex vivo microvascular reactivity studies before the hypertension status of each patient donating samples was known; effectively, the microvascular reactivity studies were performed in a blinded fashion.

Specimen Collection

Right atrial tissue was harvested before and after CP/CPB from patients undergoing cardiac surgery as previously described.[30] These samples were collected from the right atrial appendage using a double purse-string technique with 3–0 polypropylene sutures. The first, pre-CP/CPB atrial sample was collected during placement of the venous cannula in the right atrium before initiation of CP/CPB. To do this, 2 separate superior/superficial and inferior/deep purse-string sutures were initially placed at the right atrial appendage <1 cm apart. The tip of the right atrial appendage was harvested immediately (pre-CP/CPB atrial sample). The superior suture was tightened to secure the cannula in place while the inferior suture was left loose to allow the remaining atrial tissue between the 2 sutures to be exposed to cardioplegia solution, effects of CP/CPB, and effects of reperfusion. The

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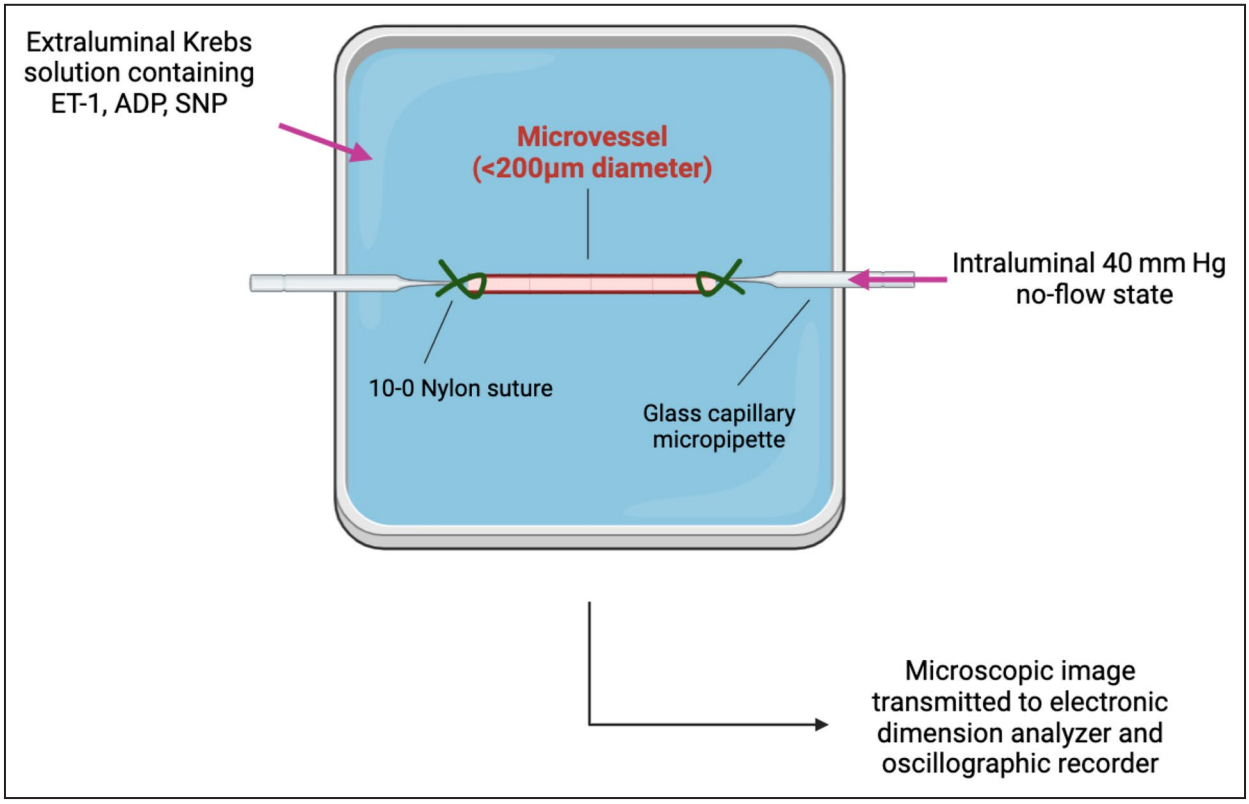


Figure 1. In vitro microvascular reactivity experimental apparatus.
Microvessels (<200 µm in diameter) were dissected from human atrial samples, cannulated with dual glass micropipettes (40–80 µm in diameter), and secured in place with 10-0 nylon monofilament suture. Oxygenated (95% oxygen, 5% carbon dioxide) Krebs buffer solution warmed to physiologic 37 °C was continuously circulated through the chamber. Microvessels were pressurized to 40 mm Hg in a no-flow state and were allowed to stabilize in the chamber for at least 30 min before pharmacologic intervention. With an inverted microscope (40–200×, Olympus CK2, Olympus Optical) connected to a video camera, the vessel image was projected onto a monitor. An electronic dimension analyzer was used to measure the internal lumen diameter in response to ET-1, ADP, and SNP added to the bath solution at varying concentrations. ET-1 indicates endothelin-1; and SNP, sodium nitroprusside.

second, post-CP/CPB atrial sample was collected between the 2 purse-string sutures following cross-clamp removal and termination of CP/CPB but before protamine infusion. This was done by tying the inferior/deep purse-string suture and harvesting the tissue between the 2 purse-string sutures following a brief period of reperfusion (post-CP/CPB atrial sample). This double purse-string technique allowed for assessing the effects of blood cardioplegia and cardiopulmonary bypass rather than unprotected ischemia. Upon collection, atrial samples were immediately sectioned and either preserved in cold Krebs buffer for immediate in vitro microvascular reactivity studies, preserved in 10% formalin or embedded in Optimal Cutting Temperature compound and subsequently processed for immunohistochemistry studies, or stored in locking Eppendorf tubes that were flash frozen in liquid nitrogen and kept at –80 °C for subsequent RNA deep-sequencing, immunoblotting, and proteomics.

Arterial blood was collected in tubes containing either clot activator or anticoagulant. Blood samples were collected before incision (pre-CP/CPB) and following termination of CP/CPB but before protamine infusion (post-CP/CPB). Following collection, blood samples were immediately placed on ice and expeditiously transported to our laboratory for processing. Blood was centrifuged at 4 °C at 1500*g* for 20 minutes. Liquid component (serum or plasma) was promptly separated from red blood cell pellet, flash frozen in liquid nitrogen, and stored at –80 °C.

In Vitro Coronary Microvascular Reactivity Studies

Viable coronary resistance arterioles were dissected from myocardial tissue and studied in vitro in a pressurized no-flow state using video microscopy as previously described (Figure 1).[30–32] Isolated microvessels were placed in a microvessel chamber, cannulated with dual glass micropipettes (40–80 µm in diameter), and secured in place with 10-0 nylon monofilament suture. The microvessel was continuously bathed in oxygenated (95% oxygen and 5% carbon dioxide) Krebs buffer solution warmed to physiologic 37 °C that was

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circulated through the chamber. As each vessel was studied in a no-flow state, the luminal pressure reflected by the micropipettes was maintained at 40 mm Hg to provide distension. Each vessel was equilibrated under these conditions for a minimum of 30 minutes before pharmacologic intervention.

The vessel was visualized, its image was projected to a monitor using an inverted microscope (40–200×, Olympus CK2, Olympus Optical) connected to a video camera, and measurements of internal luminal diameter detected by an electronic dimension analyzer were subsequently transmitted to the oscillographic recorder. The stability of similarly prepared microvessels over several hours has been previously demonstrated.[33]

Vasoconstriction agents ET-1 (CAS No. 117399–94-7) and vasopressin (CAS No. 113–79-1), ET_AR blocker (BQ123), and ET_BR blocker (BQ788) were obtained from Sigma-Aldrich (St. Louis, MO, USA). ET-1 was dissolved in ultrapure distilled water to 10^{-7} mmol/L dilution and stored at –20 °C. BQ123 and BQ788 were dissolved in dimethylsulfoxide to make stock solution and was stored at –20 °C. Vasodilatory agents were ADP (CAS No. 58-64-0) and sodium nitroprusside (CAS No. 13755-38-9).

The baseline diameter ($D_{baseline}$) was measured at the end of the initial equilibration. Each vessel was then subjected to increasing concentrations of ET-1 (10^{-12} mmol/L to 10^{-7} mmol/L) or vasopressin (10^{-8} mmol/L to 10^{-5} mmol/L) introduced into the bath solution for 15 minutes at each concentration to examine dose-dependent responses. Several vessels were pretreated with BQ123 or BQ788 (10^{-7} mmol/L) for 5 minutes before ET-1 (10^{-12} mmol/L to 10^{-7} mmol/L) administration. The internal diameter was measured at each concentration ($D_{constricted}$), and the percentage of constriction was calculated for each microvessel according to the following equation:

$$\%\,\text{constriction} = \frac{D_{baseline} - D_{constricted}}{D_{baseline}} \times 100\%$$

For vasodilation studies, $D_{baseline}$ was similarly measured following initial equilibration. Each vessel was preconstricted with ET-1 until at least 20% constriction achieved, with $D_{constricted}$ recorded. Each vessel was then subjected to increasing concentrations of vasodilatory agents introduced into the bath solution (10^{-9} mmol/L to 10^{-4} mmol/L), with the internal diameter recorded at each concentration ($D_{dilated}$). The percentage dilation (% dilation) adjusted according to ET-1 preconstriction was calculated using the following equation:

$$\%\,\text{dilation} = \frac{D_{dilated} - D_{constricted}}{D_{baseline} - D_{constricted}} \times 100\%$$

Concentration response curves were obtained. Only microvessels that were <200 μm in diameter were included for data analysis. No patient contributed >1 vessel to any group.

Immunoblotting

Myocardial atrial tissue samples (n=22) were solubilized using RIPA Lysis and Extraction Buffer, Halt Protease Inhibitor Cocktail (Thermo Fisher Scientific, Waltham, MA, USA) and an ultrasonic homogenizer as previously described.[30–32] Protein concentration was calculated using a BCA Protein Assay Kit (Thermo Fisher Scientific, Waltham, MA, USA). The protein lysates (40 μg) were fractionated on 4% to 12% Bis-Tris gels (Thermo Fisher Scientific, Waltham, MA, USA) and transferred to nitrocellulose membranes (Thermo Fisher Scientific, Waltham, MA, USA). Membranes were blocked for 1 hour using 5% nonfat dry milk in TBST (Boston BioProducts, Milford, MA, USA), and subsequently incubated overnight with 1:1000 dilutions of rabbit or mouse polyclonal primary antibodies in 3% bovine serum albumin in TBST at 4 °C. Primary antibodies to ET_AR [UMB-8-37-1] (ab178454, Abcam, Cambridge, UK) and ET_BR (ab117529, Abcam, Cambridge, UK) were used. The membranes were subsequently washed and incubated with horseradish peroxidase linked to secondary antibodies to rabbit or mouse (Cell Signaling, Danvers, MA, USA) mixed as 2.5:10000 dilutions in 3% bovine serum albumin in TBST for 1 hour at room temperature. Membranes were then washed and processed for chemiluminescent detection imaged on a ChemiDoc Imaging System (Bio-Rad, Hercules, CA, USA) using ECL Western Blotting Substrate developing agent (Thermo Fisher Scientific, Waltham, MA, USA). All membranes were probed with GAPDH (Cell Signaling, Danvers, MA, USA) to correct for loading error.

Immunohistochemistry

Atrial samples were initially stored in 10% formalin at room temperature, deparaffinized in xylene and phosphate-buffered saline solution at room temperature within 4 to 8 hours of initial collection, and rehydrated in 70% graded ethanol and kept at 4 °C. Sections were prepared and mounted on slides for staining and immunofluorescence studies as performed by iHisto (Salem, MA, USA). Images were acquired at 20× magnification using the PANNORAMIC Midi II slide scanner (Budapest, Hungary). QuPath software and National Institutes of Health Image J was used to quantify immunofluorescence staining per mm^2 tissue section by identifying 3 to 5 representative vessels per slide, selecting a 0.1 mm^2 area centered around the vessel. Images were exported to Image J for analysis of total area of immunofluorescent staining.

Enzyme-Linked Immunosorbent Assay

ELISA for human ET-1 was performed according to manufacturer's instructions (ab133030, Abcam, Cambridge, UK). All assays were completed in

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duplicate, and the protein levels were calculated using a standard curve derived from known concentrations of ET-1.

RNA Deep-Sequencing

High-throughput RNA deep-sequencing was used to distinguish gene expression profiles of ET_AR, ET_BR, ET-1-related proteins, and PKs.

Total RNA was extracted from frozen samples, and messenger RNA was subsequently purified from total RNA using poly-T oligo-attached magnetic beads followed by genome sequencing as performed by SingulOmics Corporation (New York, NY, USA).

Proteomics

Myocardial tissue samples (n=36) were lysed, homogenized, and digested with trypsin to aliquots of 300 mg. A 1.00 μL of each sample was combined and fractionated via high pH reversed phase fractionation into 40 fractions concatenated to 20 using an UltiMate 3000 HPLC (Thermo Fisher, San Jose, CA, USA). These fractions were analyzed via liquid chromatography-ion mobility-tandem mass spectrometry using data-dependent acquisition in order to generate a data-sourced spectral library of the unenriched data set. The remainder of the samples were phosphopeptide enriched using Fe-NTA kit (Thermo Fisher, PN A32992) and TiO_2 enrichment kit (Thermo Fisher PN A32993). An aliquot of each phosphoenriched sample was combined and fractioned (as described) to similarly generate a data-sourced spectral library of the phosphoenriched samples. Both the phosphoenriched and unenriched digests were then analyzed via liquid chromatography-ion mobility-tandem mass spectrometry using data-independent acquisition with an Evosep One (Evosep, Odense, Denmark) nano-liquid chromatography coupled online to a Bruker timsTOF HT mass spectrometer (Bruker Scientific LLC, Billerica, MA, USA). The samples were searched against the proper spectral library. Data were processed with Bruker's Parallel Database Search Engine in Real-Time (PaSER) and Data-independent acquisition (DIA)-Neural Networks (NN) (DIA-NN) software with a false discovery rate of 1%. Enrichment and pathway analyses were completed using PANTHER Classification System version 18.0 (Los Angeles, CA, USA) and ShinyGo 0.77 (Brookings, SD, USA).

Clinical Parameters Estimating Coronary Microvascular Reactivity and Diastolic Dysfunction

Left ventricular (LV) mass was analyzed for patients who contributed pre- and post-CP/CPB samples for coronary microvascular reactivity assessment. LV mass was calculated based on preoperative echocardiography measurements, according to the Devereux formula (American Society of Echocardiography convention) as follows, where IVS_d is interventricular septum thickness in diastole, $LVID_d$ is LV internal diameter in diastole, and PWT_d is posterior wall thickness in diastole:

$$\text{LV mass} = 0.8 \times 1.04 \times \left[\left(IVS_d + LVID_d + PWT_d \right)^3 - LVID_d{}^3 \right] + 0.6$$

LV mass was then indexed by height$^{2.7}$ according to most appropriate fit based on patient characteristics of body mass index and presence of hypertension.

Change in EF was measured by preoperative echocardiography.

Data Analysis

Baseline characteristics, clinical parameters, and outcomes were compared across all 3 hypertension groups by chi-square test or 1-way Welch's ANOVA.

Data from microvascular reactivity studies were analyzed using 2-way ANOVA with a repeated-measures factor followed by Tukey's multiple comparison test for pairwise contrasts by hypertension group and pre- and post-CP/CPB, across ET-1, vasopressin, and ADP concentrations. Data were reported as mean±SEM. Residuals were inspected for deviations from normality and equal variances. Results of analyses with assumption of sphericity were congruent to results of analyses with sphericity not assumed, which used Greenhouse–Geisser correction to calculate adjusted P values <0.05 for indicated comparisons. Statistics were calculated using Prism 9 (GraphPad Software, San Diego, CA, USA) and SAS (SAS Institute, Cary, NC, USA).

Densitometric analyses of band intensity from immunoblotting and immunohistochemistry were performed using National Institutes of Health Image J software and SAS. Generalized estimating equations were used to test whether samples of tissue from patients having (1) normotension, (2) well-controlled hypertension, or (3) uncontrolled hypertension had differential expression per immunoblotting and localization per immunohistochemistry of ET_AR and ET_BR, or changed differentially pre-CPB versus post-CPB. A Poisson distribution was selected based on model residuals for immunoblotting data, and GAPDH (log) was used as an offset to normalize samples within the statistical model. For immunohistochemistry data, a binomial model was used to restrict the range of the model predictions to within scale of the measurements (0–100). A compound symmetry variance–covariance structure was used, nesting based on correlated error. Classical sandwich estimation was used to adjust for any model misspecification. Nine individual hypothesis tests comparing patient sample pre-CPB (3), post-CPB (3), and changes from pre-CPB to post-CPB (3) were carried out as orthogonal linear estimates, with alpha maintained at 0.05 using the Holm test.

Data from ELISA assay were analyzed using paired t tests with Holm correction in Prism 9 (GraphPad Software, San Diego, CA, USA).

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Data from immunoblotting, immunohistochemistry, and ELISA are presented as median value with interquartile ranges.

Gene expression data were converted to $\log_2$ fold change and presented as volcano plots (versus $\log_{10}$ *P* values) or bar charts. Proteomics data analysis was completed using PaSER as described previously.

Multivariable linear regression was used to estimate slopes for LV mass and mean differences between hypertension groups for % constriction at each concentration of ET-1 both pre- and post-CP/CPB. Models adjusting for age were also constructed. Additional objective clinical parameters analyzed in the regression model included preoperative EF, left atrial volume, left atrial volume index, tricuspid valve peak velocity, and type of chronic antihypertensive agent. These covariates were selected based on previously observed associations with coronary microvascular disease. Group-specific slopes for LV mass and % constriction were estimated by regression models stratified by group. Differences in slopes between groups were tested by including an interaction term between LV mass and group. The normotensive cohort was the reference group and therefore was omitted as a term in each model. *P* values were adjusted for multiple comparisons by the Holm-Bonferroni approach: 16 comparisons for 2 hypertension group contrasts (versus normotensive) and 8 comparisons for LV mass across 4 ET-1 concentrations from 10^{-10} mmol/L to 10^{-7} mmol/L and 2 time points. Model residual plots were inspected for deviations from normality. Change in EF by hypertension group was examined by similar multivariable linear regression models.

A complete case analysis was performed when data were missing. Two-sided probability values <0.05 were considered significant.

RESULTS

Patient Characteristics

A total of 85 patients were consented and enrolled. The patients were divided into 3 groups based on hypertension status as described in Methods. Patient characteristics are listed in Table 1. There were no significant differences in age, sex, and several prevalent comorbidities including coronary artery disease and hyperlipidemia between the 3 groups.

Coronary Microvascular Contractile Response to ET-1 Significantly Increased in Patients With Poorly Controlled Hypertension, and This Effect Persisted Following CP/CPB

Coronary resistance arterioles (80–150 μm in diameter) dissected from patients in each group, those without hypertension (n=8), those with well-controlled hypertension (n=11), and those with uncontrolled hypertension (n=12), exhibited distinct patterns in vasoconstriction to ET-1 but not to vasopressin. Coronary microvessels isolated from patients with uncontrolled hypertension pre-CP/CPB demonstrated a 50% relative increase in contractile response to maximal ET-1 concentrations of 10^{-7} mmol/L when compared with coronary microvascular responses corresponding to those without hypertension and those with well-controlled hypertension (P=0.002) (Figure 2A). Contractile response was significantly increased in the cohort with uncontrolled hypertension at ET-1 concentrations ranging from 10^{-10} mmol/L to 10^{-7} mmol/L when compared with both the cohorts without hypertension (P<0.045) and with well-controlled hypertension (P<0.03). In contrast, there was no significant difference in coronary arteriolar contractile response to vasopressin across the 3 groups pre-CP/CPB (P=0.3).

This increased coronary microvascular contractile response in the group with uncontrolled hypertension persisted following CP/CPB at similar concentrations of ET-1 (10^{-10} mmol/L to 10^{-7} mmol/L) when compared with both the cohorts without hypertension (P<0.02) and with well-controlled hypertension (P<0.03). Contractile response to vasopressin did not vary between the 3 cohorts post-CP/CPB (P=0.3).

Coronary microvascular contractile responses in those with well-controlled hypertension and those without a diagnosis of hypertension were comparable at all ET-1 concentrations both pre- (P>0.99) and post-CP/CPB (P>0.3).

Endothelium-Dependent Coronary Vasodilatory Response to ADP Was Impaired With Uncontrolled Hypertension

Coronary resistance arterioles dissected from patients in each group, those without hypertension (n=5), those with well-controlled hypertension (n=5), and those with uncontrolled hypertension (n=8), exhibited distinct patterns in endothelium-dependent vasomotor function. Vasodilatory response of coronary microvessels to ADP isolated from patients with uncontrolled hypertension decreased by >40% in a dose-dependent manner when compared with both those without hypertension and those with well-controlled hypertension both pre- (P<0.0001) and post-CP/CPB (P<0.0001) (Figure 2C). Pre-CP/CPB vasodilatory responses were significantly decreased in the cohort with uncontrolled hypertension at ADP concentrations ranging from 10^{-6} M to 10^{-4} M when compared with both the cohorts without hypertension (P<0.009) and with well-controlled hypertension (P<0.02). Sodium nitroprusside served as an endothelium-independent control, with no difference in vasodilatory responses when stratified by hypertension status (Figure 2D).

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Table 1. Patient Characteristics

Baseline characteristic	Normotension (n=14)	IQR	Well-controlled hypertension (n=32)	IQR	Uncontrolled hypertension (n=39)	IQR	*P* value
Age, y	63±9	15	67±9	21	69±9	6	0.13
Male sex, n (%)	10 (71%)	11	24 (75%)	16	27 (69%)	14	0.87
Systolic blood pressure, mm Hg	117±9	15	119±7	10	140±8	6	<0.001*
Diastolic blood pressure, mm Hg	71±6	7	71±9	13	77±12	6	0.06
Hemoglobin A1c (%)	5.6±0.5	0.65	6.7±1.5	1.7	6.5±1.5	1.6	<0.001*
Hyperlipidemia, n (%)	11 (79%)	7	27 (84%)	16	38 (97%)	16	0.07
Body mass index, kg/m^2	27.0±4.4	7.51	30.0±5.9	7.87	31.0±5.6	7.63	0.04*
Coronary artery disease (significant stenosis)	10 (71%)	7	20 (63%)	6	30 (78%)	10	0.55
Operation, n (%)							0.56
CABG only	9 (64%)	5	17 (53%)	2	28 (72%)	8	
Valve surgery only	4 (29%)	7	10 (31%)	6	7 (18%)	10	
CABG+valve surgery	1 (7%)	11	5 (16%)	18	4 (10%)	16	
Number of vessels bypassed for CABG, n (%)							0.90
1	0 (0%)		2 (9%)		2 (6%)		
2	1 (10%)		5 (23%)		7 (22%)		
3	8 (80%)		11 (50%)		18 (56%)		
4	1 (10%)		4 (18%)		5 (16%)		
Cross-clamp time, min	78±38	48	97±45	49	98±43	52	0.26
Cardiopulmonary bypass time, min	101±47	57	130±57	83	126±53	62	0.17
Antihypertensive drug class							
Angiotensin-converting enzyme inhibitor, n (%)	0 (0%)		17 (55%)		18 (46%)		0.44†
Angiotensin II receptor blocker, n (%)	0 (0%)		7 (23%)		14 (36%)		0.03*,†
Calcium channel blocker, n (%)	0 (0%)		7 (23%)		12 (31%)		0.10†
Beta blocker, n (%)	4 (29%)		23 (74%)		26 (67%)		0.53
Thiazide diuretic, n (%)	0 (0%)		2 (7%)		7 (18%)		0.08†
Loop diuretic, n (%)	1 (7%)		13 (42%)		5 (13%)		0.05
Nitrate, n (%)	0 (0%)		4 (13%)		1 (3%)		0.37†

Categorical variables presented as no. (%). Continuous variables presented as mean±SD. CABG indicates coronary artery bypass grafting surgery; and IQR, interquartile range.

*P<0.05.

†Analyses comparing uncontrolled vs controlled hypertension when n=0 in normotension. One-way ANOVA for continuous variables and chi-square test for binary variables.

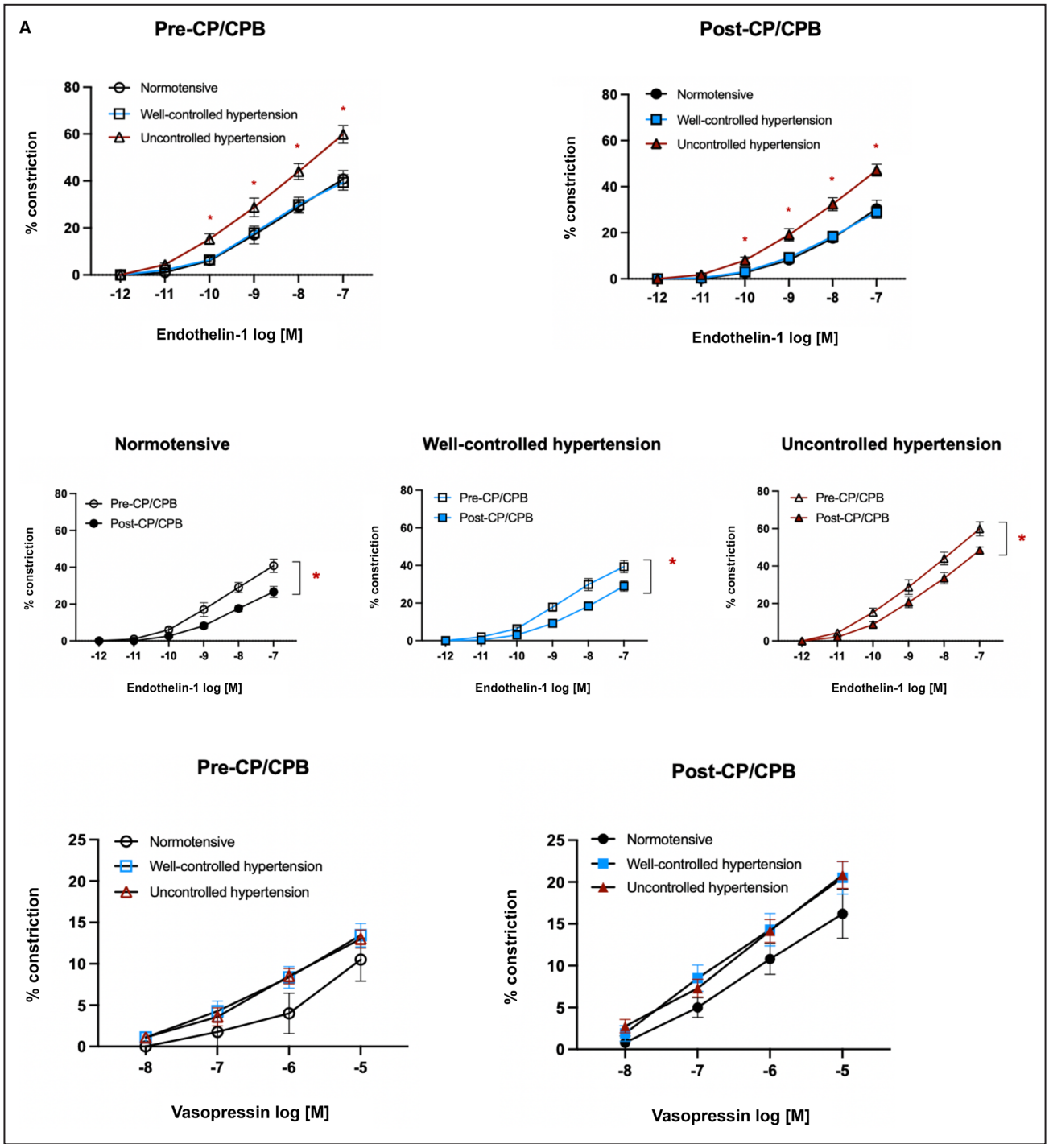
This impaired vasodilatory response in the group with uncontrolled hypertension persisted following CP/CPB at ADP concentrations ranging from 10^{-7} mmol/L to 10^{-6} mmol/L when compared with responses in the group without hypertension (P=0.001), and at higher ADP concentrations between 10^{-5} mmol/L and 10^{-4} mmol/L when compared with both the cohorts without hypertension (P<0.0007) and with well-controlled hypertension (P<0.003).

Coronary microvascular vasodilatory responses in those with well-controlled hypertension and those without a diagnosis of hypertension were comparable at all tested concentrations of ADP (10^{-9} mmol/L to 10^{-4} mmol/L) both pre- (P>0.99) and post-CP/CPB (P>0.3).

CP/CPB Blunted Overall Microvascular Contractile Response to ET-1 and Vasodilatory Response to ADP

Overall, CP/CPB impaired coronary vasomotor contractile response to ET-1 by 30% to 50% regardless of hypertension status (P<0.03 for all groups). Uncontrolled hypertension was still associated with relatively higher coronary microvascular contractile response when compared with the other 2 groups (Figure 2A). CP/CPB was associated with significantly reduced coronary vasodilatory response to ADP by ~20% across all 3 groups (P<0.0008, Figure 2C). Sodium nitroprusside-mediated vasodilation was decreased following CP/CPB across all 3 groups, but

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Figure 2. Coronary microvascular constriction response to ET-1 in vitro with and without endothelin receptor blockade pre- and post-CP/CPB.

Dose-dependent constriction of coronary arterioles in response to ET-1 (10^{-12} mmol/L to 10^{-7} mmol/L) and vasopressin (10^{-8} mmol/L to 10^{-5} mmol/L) in N (n=5), C (n=8), and U (n=8) groups pre- and post-CP/CPB alone (**A**), and following pretreatment with either ET_AR blocker (BQ123, 10^{-7} mmol/L) or ET_BR blocker (BQ788, 10^{-7} M) (**B**) in N (n=5), C (n=6), and U (n=6). Dose-dependent relaxation of coronary arterioles in response to ADP (10^{-9} to 10^{-4} mmol/L) in N (n=5), C (n=8), and U (n=8) groups pre- and post-CP/CPB (**C**). Dose-dependent vasodilation of coronary arterioles in response to SNP (10^{-9} mmol/L to 10^{-4} mmol/L) in N (n=5), C (n=8), and U (n=8) groups pre- and post-CP/CPB (**D**). *P<0.05 as indicated in (**A**). *P<0.05 for ET-1 vs ET-1+BQ123 alone in (**B**). *P<0.05 for uncontrolled hypertension vs normotension in (**C**). **P<0.05 for both ET-1 vs ET-1+BQ123, and ET-1+BQ123 vs ET-1 vs BQ788 in (**B**). **P<0.05 for both uncontrolled hypertension vs normotension and uncontrolled hypertension vs well-controlled hypertension in **C**. Two-way ANOVA with repeated measures factor, post hoc Tukey's test for multiple comparisons ($\mu \pm$SEM). C indicates well-controlled hypertension; CP/CPB, cardioplegia and cardiopulmonary bypass; ET-1, endothelin-1; ET_AR, endothelin$_A$ receptor; ET_BR, endothelin$_B$ receptor; N, normotension; SNP, sodium nitroprusside; and U, uncontrolled hypertension.

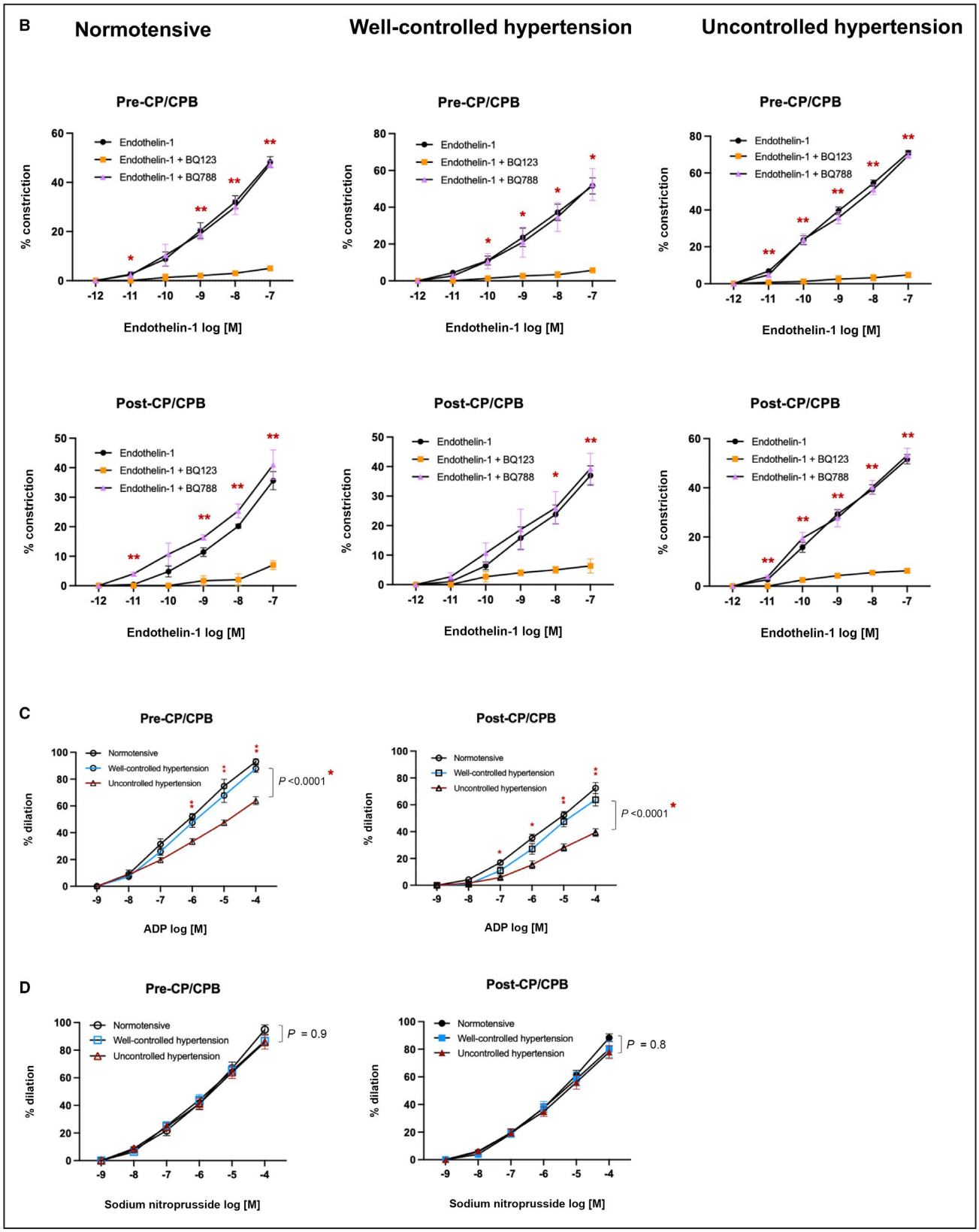


Figure 2. **(Continued)**

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significantly only in patients with poorly controlled hypertension (P=0.001, Figure 2D).

Endothelin Receptor A Blockade Resulted in Near-Complete Reduction in ET-1-Induced Coronary Microvascular Contractile Response

Pretreatment with ET_AR antagonist (BQ123) resulted in significantly diminished coronary microvascular contractile responses to ET-1 both pre- and post-CP/CPB across all cohorts (Figure 2B). Coronary microvessels isolated from both the cohorts without hypertension and with well-controlled hypertension exhibited an absolute reduction in contraction of 50% pre-CP/CPB and an absolute reduction in contraction of 40% post-CP/CPB with ET_AR blocker pretreatment. Coronary microvascular contractile responses in the poorly controlled hypertension cohort diminished sharply from 50% to 70% to <10% both pre- and post-CP/CPB with ET_AR antagonist administration. In contrast, pretreatment with ET_BR blocker (BQ788) had minimal effect on coronary microvascular contractile response profiles across all cohorts.

Patients With Uncontrolled Hypertension Had Relative Upregulation of the Gene Encoding ET-1 Vasoconstrictive Receptor (ET_AR) and Downregulation of the Gene Encoding ET-1 Vasodilatory Receptor (ET_BR)

RNA deep-sequencing showed changes in gene expression between those with poorly controlled hypertension and those without hypertension both pre- and post-CP/CPB (Figure 3A). Patients with chronic uncontrolled hypertension had relative upregulation of *EDNRA*, the gene encoding vasoconstrictive ET_AR, and relative downregulation of *EDNRB*, the gene encoding vasodilatory ET_BR (Figure 3B). Post-CP/CPB, the gene encoding ET-1 (*EDN1*) was relatively increased compared with pre-CP/CPB in this comparison of cohorts.

Endothelin Pathway Intermediate Signaling Molecules Were Significantly Increased in the Cohort With Uncontrolled Hypertension Compared With the Cohort Without Hypertension

Bottom-up quantitative proteomics showed significant upregulation of 86 proteins and downregulation of 110 proteins in patients with uncontrolled hypertension compared with controls without hypertension pre-CP/CPB (Figure 3C). Pathway analysis showed significant activation of the endothelin signaling pathway, with increased intermediate signaling molecule cAMP-dependent PK catalytic subunit γ (P<0.0001). Similar activation of endothelin signaling pathway and cAMP-dependent PK catalytic subunit γ (P=0.03) persisted post-CP/CPB.

Proteomics of the phosphoenriched fraction showed significant global upregulation of 16 proteins and downregulation of 156 proteins in patients with uncontrolled hypertension compared with controls without hypertension pre-CP/CPB. Again, the endothelin signaling pathway was significantly activated, with increases in intermediate signaling molecules PKC-δ (P=0.04) and cAMP-dependent PK catalytic subunit-β (P=0.03). In contrast, endothelin signaling was significantly downregulated post-CP/CPB, with decreases in regulatory subunits of intermediate signaling molecule cAMP-dependent PK (P<0.001).

Total Myocardial Levels of Vasodilatory ET_BR Were Decreased Whereas Vasoconstrictive ET_AR Total Myocardial Levels Trended to an Increase in Patients With Uncontrolled Hypertension

Myocardial expression of vasodilatory ET_BR was significantly decreased in those with poorly controlled hypertension compared with both controls without hypertension (P=0.03) and those with well-controlled hypertension (P=0.04) post-CP/CPB. There was a trend toward increased vasoconstrictive ET_AR in the group with uncontrolled hypertension compared with the group without hypertension (P=0.07) pre-CP/CPB (Figure 4A and 4B). Uncropped Western blots were used for Figure 4A.

Perivascular Expression of Vasoconstrictive ET_AR Trended Toward an Increase Whereas Perivascular Expression of Vasodilatory ET_BR Trended Toward a Decrease in Patients With Uncontrolled Hypertension

Though perivascular expression of vasoconstrictive ET_AR trended toward an increase and perivascular expression of vasodilatory ET_BR trended toward a decrease in patients with poorly controlled hypertension compared with the other groups, there was no significant difference in receptor localization pre-CP/CPB or post-CP/CPB among the 3 groups (Figure 4C and 4D).

Plasma Concentrations of ET-1 Within 1 to 5 Hours Following CP/CPB Were Not Significantly Changed

Plasma ET-1 was not significantly increased across all cohorts between 1 and 5 hours after initiation of CP/CPB (P=0.18).

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Left Ventricular Mass and Hypertension Status Accounted for the Majority of the Variability in Maximal Contractile Response of Coronary Microvasculature to ET-1

Mean LV masses indexed by height$^{2.7}$ (g/m$^{2.7}$) for patients with well-controlled hypertension (μ 50 g/m$^{2.7}$, SD 13 g/m$^{2.7}$) and poorly controlled hypertension (μ 45 g/m$^{2.7}$, SD 15 g/m$^{2.7}$) were elevated compared with LV mass of normotensive controls, where LV hypertrophy is defined as LV mass ≥50 g/m$^{2.7}$ in men and ≥47 g/m$^{2.7}$ in women.[34,35] Patients without hypertension had relatively lower mean LV mass (μ 34 g/m$^{2.7}$, SD 12 g/m$^{2.7}$).

Multivariate regression modeling showed both LV mass indexed by height$^{2.7}$ and hypertension status independently estimated ex vivo contractile response of the coronary microvasculature to ET-1 (Figure 5). At baseline, every 10-unit increase in LV mass resulted in an increase of 7% increase in constriction to ET-1. Uncontrolled hypertension (when compared with no diagnosis of hypertension) resulted in an additional 12% increase in constriction to ET-1 pre-CP/CPB. The regression equation for this relationship is described by: % constriction = 0.66 (LV mass) + 11.7 (uncontrolled hypertension) + 18.2 with R^2 0.95; *P* value for LV mass parameter estimate: *P*<0.0001, and *P*-value for uncontrolled hypertension versus normotension parameter estimate: *P*=0.0004.

Post-CP/CPB, every 10-unit increase in LV mass resulted in an increase of 3% constriction to ET-1, whereas uncontrolled hypertension (versus no diagnosis of hypertension) resulted in an additional 18% contractile response to ET-1. The regression equation for this relationship is described by: %constriction = 0.33 (LV mass) + 18.1 (uncontrolled hypertension) + 15.2 with R^2 0.86; *P* value for LV mass parameter estimate: *P*=0.007, and *P*-value for uncontrolled hypertension versus normotension parameter estimate: *P*<0.0001.

Peri- and Postoperative Clinical Parameters and Outcomes

Clinical parameters and outcomes of the larger cohort of 85 patients are enumerated in Table 2. There was a significant difference in preoperative EF (*P*=0.02) and change in EF (*P*<0.001) between the 3 groups. Preoperative and postoperative creatinine values were significantly higher in both the cohorts with well-controlled and uncontrolled hypertension than in those without hypertension (*P*=0.002, *P*=0.01), but acute kidney injury rates were not significantly different between groups (*P*=0.13). There were no significant differences in hematocrit, new postoperative atrial fibrillation, length of stay, postoperative cardiac shock, or death.

Increased Coronary Microvascular Constriction to ET-1 Was Associated With More Negative Change in Ejection Fraction

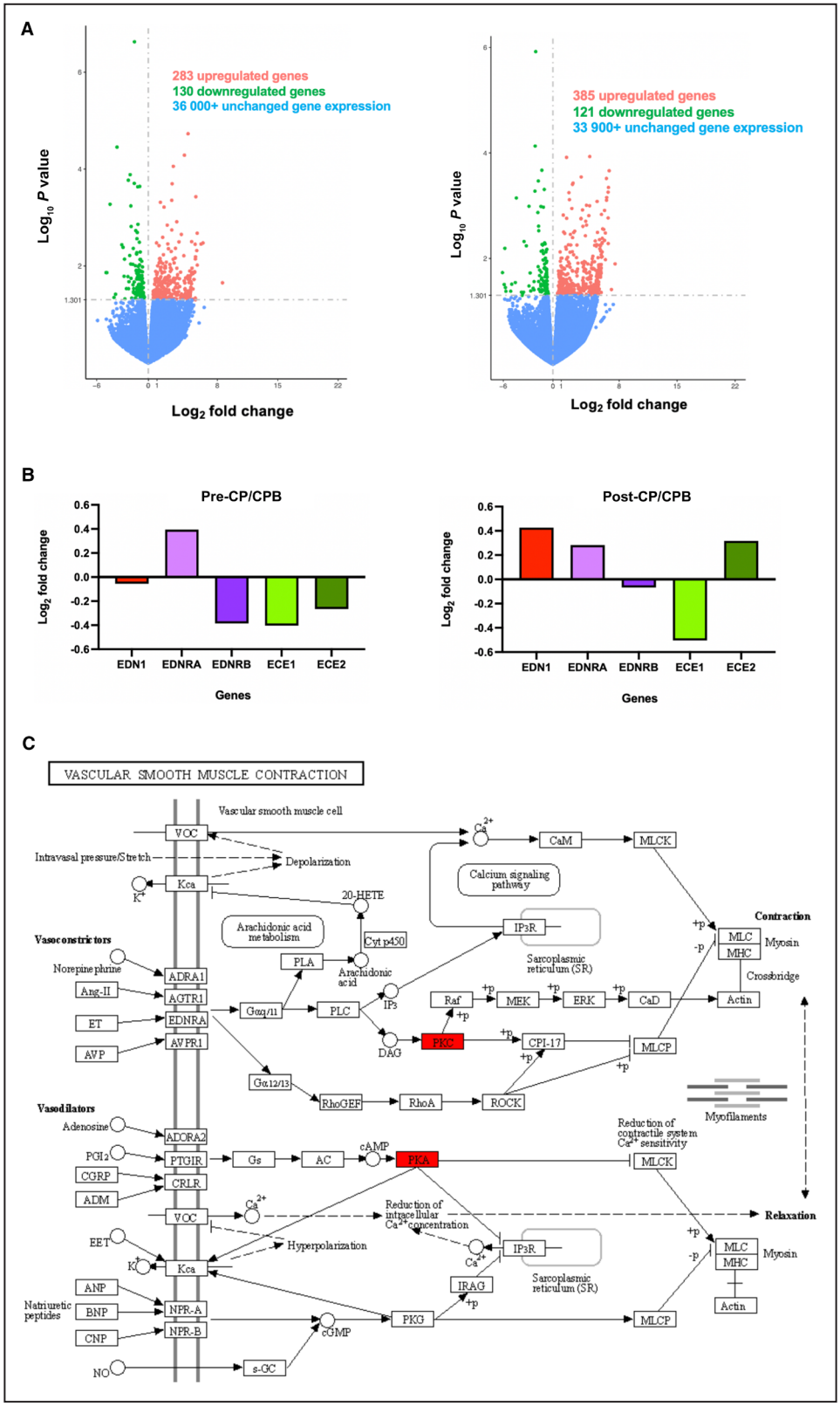
Regression modeling showed both hypertension status and coronary microvascular contractile response to ET-1 estimated change in EF (n=17). Every 10% increase in vasoconstriction to ET-1 pre- (*P*=0.04) or post-CP/CPB (*P*=0.007) projected 3% to 5% decrease in EF. Uncontrolled hypertension (when compared with well-controlled hypertension or no diagnosis of hypertension) resulted in an additional 11% decrease in change in EF (*P*=0.04).

Change in Ejection Fraction Was Significantly Greater in Magnitude and More Negative in Patients With Uncontrolled Hypertension

In the larger cohort (n=85), patients with well-controlled hypertension had significantly lower EF at baseline when compared with the other groups (*P*=0.02, Table 2). Although there was no significant difference

Figure 3. Multiomics of myocardial samples from patients with uncontrolled hypertension vs normotension.
RNA deep-sequencing showed changes in overall gene expression pre- vs post-CP/CPB between U and N (n=4 per group) (**A**). Transcriptomics further showed relative changes in expression of genes involved in endothelin-1 signaling (**B**). Proteomics showed significant activation of endothelin pathway with upregulation in postreceptor signaling molecules in U relative to N (n=6 per group). Proteomics of the phosphoenriched fraction showed significant upregulation of PKC and PKA (*red*) in vascular smooth muscle contraction signaling pathway pre-CP/CPB (**C**). 20-HETE indicates 20-hydroxyeicosatetraenoic acid; AC, adenylate cyclase; ADM, adrenomedullin; ADORA2, adenosine receptor A2; ADRA1, alpha-1 adrenergic receptor; AGTR1, angiotensin II type 1 receptor; Ang II, angiotensin II; ANP, atrial natriuretic peptide; AVP, arginine vasopressin; AVPR1, arginine vasopressin receptor 1; BNP, B-type atrial natriuretic peptide; C, well-controlled hypertension; CaD, caldesmon; CaM, calmodulin; CGRP, calcitonin gene related peptide; CNP, C-type atrial natriuretic peptide; CP/CPB, cardioplegia and cardiopulmonary bypass; CPI-17, protein kinase C-potentiated inhibitor protein of 17 kDa; CRLR, calcitonin receptor-like receptor; Cyt 450; cytochrome 450; DAG, diacylglycerol; ECE1, gene encoding endothelin converting enzyme-1; ECE2, gene encoding endothelin converting enzyme-2; EDN1, gene encoding ET-1; EDNRA, gene encoding endothelin$_A$ receptor; EDNRB, gene encoding endothelin$_B$ receptor; EET, epoxyeicosatrienoic acid; ERK, extracellular signal-regulated kinase; ET-1, endothelin-1; IP$_3$, inositol trisphosphate; IP$_3$R, inositol trisphosphate receptor; IRAG, inositol 1,4,5-trisphosphate receptor-associated cyclic GMP kinase substrate; Kca, calcium-activated potassium; MEK, Map/Erk kinase; MHC, myosin heavy chain; MLC, myosin light chain; MLCK, myosin light chain kinase; MLCP, myosin light chain phosphatase; N, normotension; NO, nitric oxide; NPR, natriuretic peptide receptor; PG12, prostaglandin I2; PKA, protein kinase A; PKC, protein kinase C; PKG, cGMP-dependent protein kinase; PLA, phospholipase A; PLC, phospholipase C; PTGIR, prostaglandin I2 receptor; RhoA, Ras homolog family member A; RhoGEF, Rho guanine nucleotide exchange factor; ROCK, Rho-associated protein kinase; s-GC, soluble guanylate cyclase; U, uncontrolled hypertension; and VOC, voltage-operated channel.

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in postoperative EF among the 3 groups, there was a significant difference in the change in EF (P<0.001). Patients with uncontrolled hypertension had a significant decrease in EF postoperatively compared with preoperative baseline values. In contrast, patients with well-controlled hypertension, despite having lower

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preoperative EF than patients in the other groups, had improved EF postoperatively. Patients without hypertension had similar improvement in EF postoperatively.

Systolic hypertension was significantly associated with change in EF (P=0.02), whereas diastolic hypertension did not (P=0.27). Patients with uncontrolled hypertension had an average 8% reduction in EF following on-pump cardiac surgery when compared with patients with well-controlled hypertension (P<0.001) and an average 7% reduction in EF postoperatively when compared with patients without hypertension (P=0.03).

Adjusting for other variables, including age, sex, hyperlipidemia, diabetes status, body mass index, hemoglobin A1c, most antihypertensive medication classes, cross-clamp time, CPB time, hematocrit change, preoperative EF, and preoperative atrial fibrillation, did not significantly affect the association between hypertension status and change in EF. Among the variables included in the multivariate model that were significantly different between the 3 groups in the larger cohort (hypertension status, hemoglobin A1c, angiotensin II receptor blocker use, and loop diuretic use), hypertension status most reliably estimated change in EF. Patients with uncontrolled hypertension still had −8% change in EF postoperatively when compared with those with well-controlled hypertension (P<0.001) and −6% decrease in change in EF when compared with those without hypertension (P=0.09) after adjusting for 4 additional variables and accounting for all 3 pairwise comparisons between groups based on hypertension status.

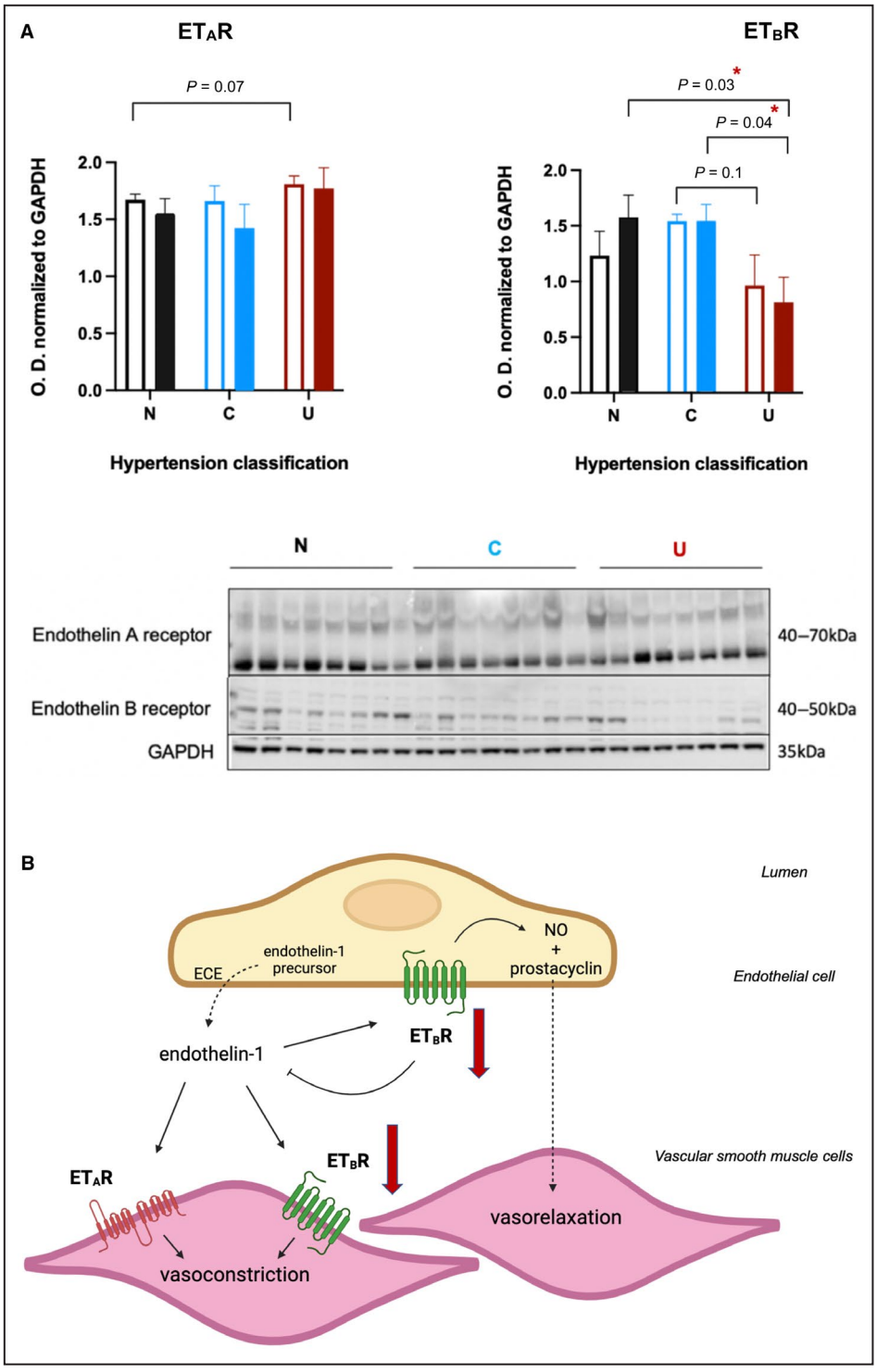
DISCUSSION

Our study demonstrated several novel findings. Poorly controlled chronic hypertension was associated with net increased coronary microvascular vasomotor tone at baseline as assessed by contractile response of coronary microvessels to direct stimulation by ET-1 and vasodilatory response to endothelium-dependent ADP. These differences in vasomotor responses between the groups persisted following CP/CPB, though all responses were blunted overall. The coronary microvascular reactivity profiles between those with well-controlled hypertension and those without hypertension were indistinguishable pre- and post-CP/CPB. Acute administration of ET-1 receptor blocker markedly attenuated the coronary microvascular contractile response across all 3 groups. Notably, coronary microvascular contractile response to ET-1 estimated change in EF postoperatively. We identified 2 readily accessible clinical parameters, hypertension status and LV mass, that accounted for up to 95% of the variability in contractile response of the coronary microvasculature to ET-1, allowing for prognosticating myocardial malperfusion risk in patients. In the larger cohort, patients with uncontrolled hypertension experienced close to a 10% decrease in EF following on-pump cardiac surgery when compared with patients with well-controlled hypertension.

Increased coronary microvascular vasospasm with impaired vasorelaxation observed in our study portends myocardial hypoperfusion in patients with chronic blood pressure ≥ 130/80 mm Hg, as this compartment of the microvascular network may no longer be able to increase coronary blood flow to meet the needs of the working myocardium during periods of increased demand, such as during peri- and postoperative periods.[20,36] Optimal blood pressure control with chronic antihypertensive treatment shifted the phenotype in patients with well-controlled hypertension to reflect coronary microvascular reactivity in patients without a diagnosis of hypertension. This overlap in dose–response curves occurred both at baseline and following CP/CPB even though patients with well-controlled hypertension had more similar degree of microvascular dysfunction secondary to diabetes as did patients with uncontrolled hypertension given similarly elevated hemoglobin A1c values in these 2 cohorts. These findings suggest that maintaining blood pressure <130/80 mm Hg for at least 1 year before on-pump cardiac surgery normalizes coronary microvascular contractile response to endothelium-independent ET-1 and endothelium-dependent ADP, in spite of multiyear

Figure 4. Total myocardial and perivascular expression of ET_AR and ET_BR in atrial samples.
Total myocardial levels of ET_BR were decreased in patients with poorly controlled hypertension. N (n=7), C (n=7), U (n=8) in total, n=4 per group shown in representative immunoblotting images (**A**). Schematic summarizing changes in putative receptors in endothelin-1 signaling in patients with poorly controlled hypertension (**B**). Representative section of human atrial tissue with immunofluorescent staining (**C**) demonstrated expression of ET_AR (green) and ET_BR (purple) on microvessel walls as stained by α-SMA (orange). Nuclei stained with DAPI (blue). Negative control stained only with secondary antibody, showing relatively low level of background fluorescence without ET_AR or ET_BR signals. Images obtained at 20× magnification. Trends toward increased perivascular vasoconstrictive ET_AR expression and decreased vasodilatory ET_BR expression in the uncontrolled cohort U (n=13) compared with N (n=7) and C (n=4) did not reach significance pre- or post-CP/CPB (**D**). Upper and lower borders of each line represent upper and lower quartiles, middle circle on each line represents median. Generalized linear model, binomial distribution, 2-way interactions. *P<0.05 as indicated. Generalized linear model, Poisson distribution, 2-way interactions ($\mu \pm$SEM). C indicates well-controlled hypertension; CP/CPB, cardioplegia and cardiopulmonary bypass; ECE, endothelin-converting enzyme; ET-1, endothelin-1; ET_AR, endothelin$_A$ receptor; ET_BR, endothelin$_B$ receptor; N, normotension; NO, nitric oxide; ns, not significant; OD, optical density; U, uncontrolled hypertension; and α-SMA, alpha smooth muscle.

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duration of hypertension /or diabetes. Additional studies investigating other durations of optimized preoperative blood pressure are warranted. These results may also reflect changes in microvascular function that occur in the context of other major, noncardiac operations where various organ system microcirculations may be similarly affected by systemic intraoperative changes. Study of various other microcirculations in the context of noncardiac operations, including mesenteric, renal, or cerebral microcirculations using animal models, may be another promising future direction.

Our multiomics, immunoblotting, and histologic data suggest that increase in endothelin signaling pathway intermediates (including PKC-δ and cAMP-dependent

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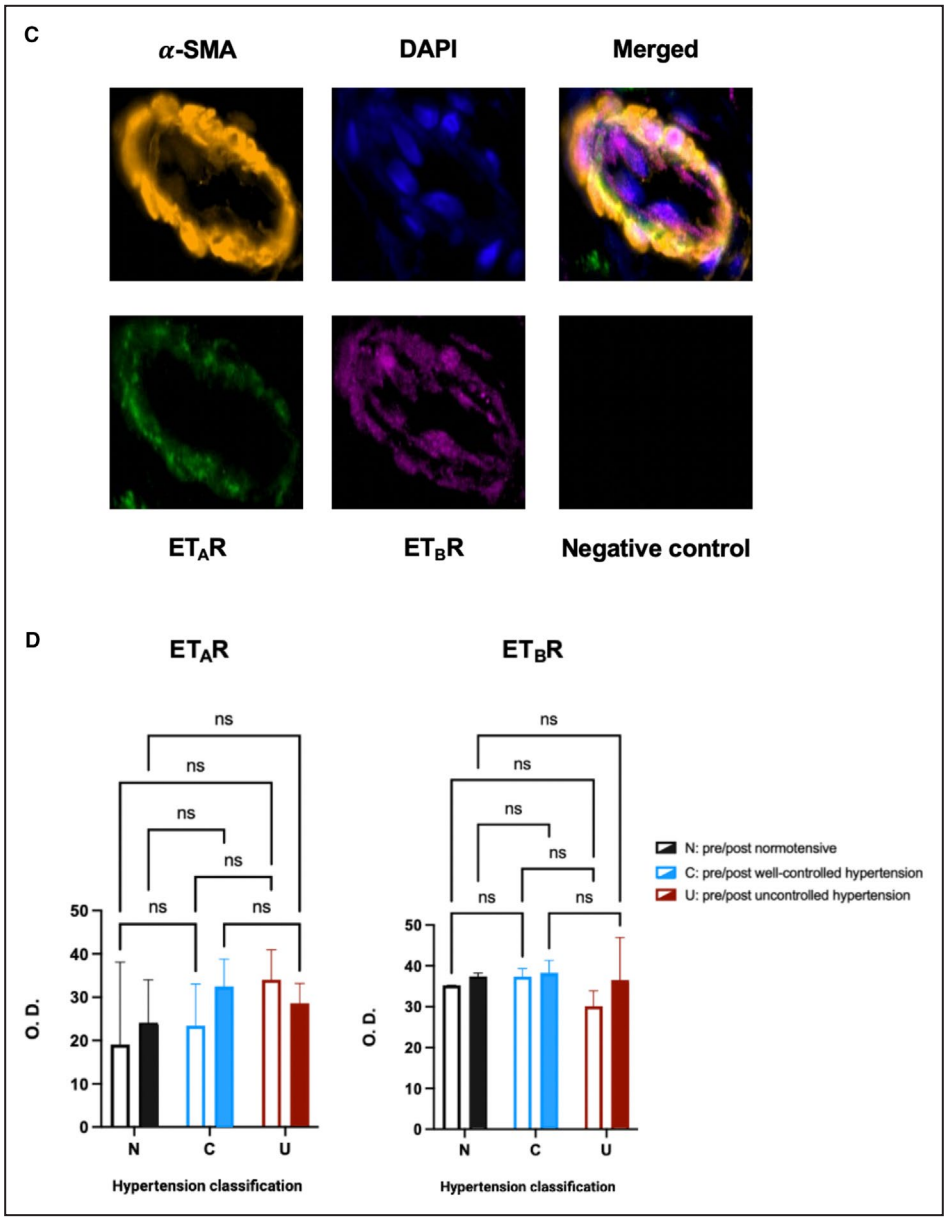


Figure 4. **(Continued)**

PK-β) in the cohort with uncontrolled hypertension and, to a lesser extent, decreased vasodilatory ET_BR levels, may underlie the observed phenotype of pronounced coronary arteriolar vasospasm. Relatively increased ET_AR, as reflected by relatively increased expression of gene encoding ET_AR as well as the trend in relatively increased total myocardial and perivascular ET_AR may also contribute. The peri- and postoperative period following CP/CPB is characterized by an increase of several magnitudes in plasma levels of ET-1, starting 6 hours postoperatively and persisting beyond 24 hours.[23] Taken together, the vasoconstrictive effects of elevated circulating ET-1 levels may be further compounded by the effects of increased vasoconstriction and decreased vasodilation related to increased baseline ET_AR expression reduced baseline ET_BR expression, respectively, in patients with poorly controlled hypertension.

Impaired coronary microvascular reactivity following CP/CPB may be due in large part to damage of downstream contractile mechanisms mediated by mitogen-activated PK and PKC-α,[8,33] dysregulated relaxation related to increased oxidative stress,[19] reactive oxygen species,[15] neutrophil activation,[37] and receptor desensitization.[38] Additionally, the inflammatory response to CP/CPB can induce release of nitric oxide, complement, cytokines, reactive oxygen species, and prostaglandins, all of which may contribute to vasomotor dysfunction through altered vasodilation.[8–10,13,14] Although purinergic receptor P2Y12 for ADP on platelets functions to induce

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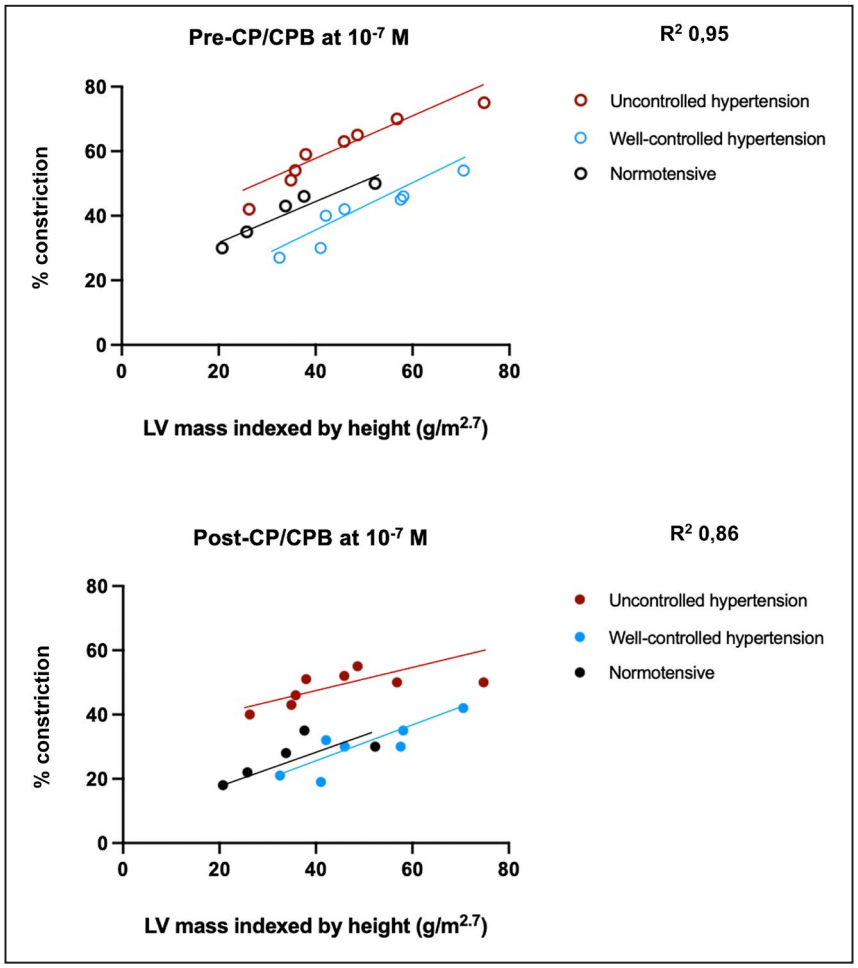


Figure 5. Clinical prognosticators of coronary microvascular tone.
Pre-CP/CPB regression equation: % constriction = 0.66 (LV mass) − 10.6 (well-controlled hypertension) + 11.7 (uncontrolled hypertension) + 18.2. Holm *P* value for LV mass parameter estimate: *P*<0.0001, Holm *P*-value for uncontrolled hypertension vs normotension parameter estimate: P=0.0004. Post-CP/CPB regression equation: % constriction = 0.33 (LV mass) − 2.0 (well-controlled hypertension) + 18.1 (uncontrolled hypertension) + 15.2. Holm *P* value for LV mass parameter estimate: *P*=0.007, Holm *P* value for uncontrolled hypertension vs normotension parameter estimate: *P*<0.0001. Multivariable linear regression models included LV mass and hypertension group as main effects, with N as the hypertension reference group. R^2 values were computed for each model, and Holm-Bonferroni correction was applied when testing coefficients. Differences in slopes for LV mass by hypertension group were tested by product interaction terms (*P*>0.05 for all). Residual plots were inspected for deviations from normality. The models included 20 patients: 5 with normotension, 7 with well-controlled hypertension, and 8 with uncontrolled hypertension. CP/CPB indicates cardioplegia and cardiopulmonary bypass; and LV, left ventricular.

inflammation in chronic hypertension, it has a number of functions in the coronary microvasculature. It may trigger nitric oxide release in larger arterioles resulting in endothelium-dependent vasodilation, while maintaining resistance in smaller arterioles to ensure adequate myocardial perfusion through ADP-mediated activation of P2Y12 receptor on coronary vascular smooth muscle cells.[39] Our results suggest endothelium-independent vasoconstriction may be offsetting endothelial-dependent vasodilation in coronary microvasculature. Investigating the role of P2Y12 receptor in this context may be an interesting future avenue. Changes in ET-1- and ADP-induced vascular response of the coronary microcirculation may affect downstream vascular beds. Moreover, vasomotor function in microvasculature pertaining to various other organ systems, including renal and peripheral systems, may closely follow patterns seen in the coronary microcirculation following CP/CPB, and study of these vascular reactivity profiles warrants further investigation.

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Table 2. Perioperative Clinical Parameters and Outcomes

Clinical outcome	Normotension (n=14)	Well-controlled hypertension (n=32)	Uncontrolled hypertension (n=39)	*P* value
Ejection fraction, %				
Preoperative	53±16	46±13	55±12	0.02*
Postoperative	55±14	50±15	51±14	0.51
Change in ejection fraction	2±7	3±9	-5±8	<0.001*
Hematocrit, %				
Preoperative	39±5	40±5	40±6	0.58
Postoperative	29±6	32±6	31±6	0.27
Postoperative acute kidney injury, n (%)	1 (7%)	7 (22%)	13 (33%)	0.13
Atrial fibrillation, n (%)				
Preoperative	0 (0%)	6 (19%)	10 (26%)	0.11
Postoperative	4 (29%)	18 (56%)	17 (44%)	0.21
Total postoperative LOS, d	8.5±8.3	7.8±5.1	9.4±9	0.65
Intensive care unit LOS, d	4.5±4.6	4.3±4.4	5.7±9.2	0.72
Cardiac shock, n (%)	0 (0%)	4 (13%)	2 (26%)	0.38
Death, n (%)	0 (0%)	2 (6%)	1 (3%)	0.76

Categorical variables presented as no. (%). Continuous variables presented as mean±SD. One-way ANOVA for continuous variables and chi-square test for binary variables. LOS indicates unit length of stay.

*$P<0.05$.

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The dominant vasoconstrictive effect of ET-1 is mediated by ET_AR found on vascular smooth muscle cells, which is nominally the principal receptor for regulating contractile vasomotor tone. Our unique in vitro studies allow for direct assessment of changes in vasomotor tone with exposure to ET-1. We showed that pretreatment with ET_AR blocker (BQ123) attenuated contractile tone of the coronary microvasculature to ET-1, whereas ET_BR blocker (BQ788) pretreatment had minimal effect. The use of pharmacologic inhibitors rather than loss-of-function studies (ie, through RNA interference) allowed for the study of acute vasomotor response to ET-1 without significant alteration in membrane-bound receptor composition that may be present with chronic treatment. Multiple studies have demonstrated the beneficial resistance-lowering effects of several ET-1-directed therapies that result in ET_AR blockade when taken chronically in patients with heart failure.[40–43] Shorter-duration treatment with ET_AR antagonist (BQ123) has been associated with longer recurrence-free survival in patients with ST-elevation acute myocardial infarction.[44] Our findings provide a mechanism by which ET_AR blockade may exert clinical benefits in the acute setting, and focused study of perioperative use of ET_AR antagonists in patients with poorly controlled hypertension is warranted. Conversely, our results suggest minimizing peri- or postoperative use of vasoconstricting agents that concomitantly reduce myocardial perfusion may be an important consideration in this target population, and this also warrants further investigation.

In vivo assessment of coronary microvascular function continues to be a challenge. Unique, invasive ex vivo microvascular reactivity studies performed by our group allow for more detailed assessment of changes in specific vasomotor pathways than do indirect, in vivo measurements of organ perfusion parameters used as proxies for coronary microvascular function. Correlation of results from these ex vivo studies with in vivo measurements may offer an important functional context for observed changes in microvascular reactivity which may otherwise not be readily apparent. In this study, we characterized the ex vivo contractile response of the coronary microvasculature to ET-1 and correlated these physiologic measurements with clinical variables that, like coronary microvascular dysfunction, also lead to diastolic dysfunction. We identified 2 readily accessible clinical parameters, a patient's hypertension status and LV mass as estimated by preoperative echocardiography measurements, that predict up to 95% of variability in observed coronary microvascular contractile tone in response to ET-1. These 2 factors can therefore be used for preoperative patient risk stratification and may be meaningful measures for prognosticating the impact on myocardial perfusion.

Pronounced coronary vasomotor tone may underlie the observed reduction in EF postoperatively seen in patients with uncontrolled hypertension when compared with both other groups. Despite patients with well-controlled hypertension had significantly decreased preoperative EF compared with the other groups, they still experienced an increased in postoperative EF, and this increase was similar to the magnitude of increase

in EF in patients with no diagnosis of hypertension. In contrast, patients with poorly controlled hypertension, though starting with preoperative EF similar to that of the group without hypertension, experienced a near 10% decrease in EF postoperatively. Other variables affecting microvascular function, including hyperlipidemia, age, sex, and hemoglobin A1c, did not significantly affect the association between hypertension status and change in EF.

Conclusions

This study has several important limitations. Small sample size limits the ability to complete detailed outcomes analyses. The small group sizes, particularly when making comparisons across 6 different groups in a single experimental design, may not be powered enough to detect important differences in receptor expression or localization. Alternate, endothelium-dependent mechanisms not assessed in this study may further characterize coronary microvascular dysfunction seen with long-standing hypertension. Despite this limitation, our study investigated the effects of ET-1, the most potent endogenous vasoconstrictor dually elevated both with hypertension and perioperatively following on-pump cardiac surgery; and its effect on coronary microvascular contractile response has a substantial and clinically relevant effect on myocardial perfusion. Several patients were prescribed multiple antihypertensive agents from various drug classes, complicating regression analyses used to identify potential associations between specific antihypertensive drug classes and coronary microvascular contractile response to ET-1. The increased heterogeneity inherent in the human population further limits delineation of clinical outcomes attributable to changes in microvascular reactivity. Our analyses identified change in EF was significantly associated with regression model variables but not overall EF. This finding, in part, reflected prior clinical trial data reporting LV dysfunction and other adverse outcomes in the context of isolated systolic hypertension.[4] Clinical analyses assessing other adverse cardiovascular outcomes implicated in large clinical trials, including nonfatal myocardial infarction, nonfatal stroke, and death, were limited.[1,3] Although we attempted to characterize baseline characteristic distributions and clinical outcomes pertinent to coronary microvascular disease (including sex, age, body mass index, hemoglobin A1c, presence of hyperlipidemia, significant coronary artery disease, antihypertensive use, operation type and duration, and length of stay), there may be other unaccounted for comorbidities affecting microvascular tone and clinical outcome. Our findings are confined to our study that relates these parameters (LV mass, degree of contractile response, and change in EF) in patients with poorly controlled hypertension, and our correlation studies do not prove direct causation. Notwithstanding our sample size per group and inherent heterogeneity in our target population, our clinical model still consistently revealed that 2 clinical parameters could account for up to 95% of the variability in ET-1-induced coronary microvascular contractile response at several different concentrations and both before and after cardioplegic arrest and cardiopulmonary bypass.

ARTICLE INFORMATION

Received July 24, 2025; accepted August 31, 2026.

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Sources of Funding

This work was supported by National Institutes of Health grant T32GM065085 (Debolina Banerjee); National Institutes of Health grant F32HL160063 (Sharif A. Sabe); National Institutes of Health grants 1R01HL127072-01A1, 1R01HL136347-01, 1R01HL179089, and R01HL136347-04S1 (Jun Feng); and National Institutes of Health grants NIH R01-HL46716 and R01HL128831 (Frank W. Sellke).

Disclosures

Dr. Sellke is co-founder of XM-Therapeutics. No relationship with current study.

Supplemental Material

Unedited Gels

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