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Research Article

Long-term renin–angiotensin blocking therapy in hypertensive patients with normal aorta may attenuate the formation of abdominal aortic aneurysms

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Abstract

Renin–angiotensin system (RAS) has been implicated in the pathogenesis of abdominal aortic aneurysm (AAA). Angiotensin II type 1 receptor blocker (ARB), when given with angiotensin II prevents AAA formation in mice, but found ineffective in attenuating the progression of preexisting AAA. This study was designed to evaluate the effect of chronic RAS blockers on abdominal aortic diameter in hypertensive patients without known aortic aneurysm. Consecutive hypertensive outpatients (n = 122) were stratified according to antihypertensive therapy they received for 12 months or more, consisting of ARB (n = 45), angiotensin converting enzyme inhibitor (ACE-I; n = 45), or nonARB/nonACE-I (control therapy; n = 32). Abdominal ultrasonography was performed to measure maximal subrenal aortic diameter. Eighty-four patients were reexamined by ultrasonography 8 months later. The correlation between the different antihypertensive therapies and aortic diameter was examined. Aortic diameters were significantly smaller in ARB than in control patients in the baseline and follow-up measurements ($P = .004$; $P = .0004$, respectively). Risk factor adjusted covariance analysis showed significant differences between ARB or ACE-I treated groups and controls ($P = .006$ or $P = .046$, respectively). Ultrasound that was performed 8 months later showed smaller increases in mean aortic diameters of the ARB and ACE-I groups than in controls. Both ARB and ACE-I therapy attenuated expansion of nonaneurysmal abdominal aorta in humans. These results indicate that RAS blockade given before advancement of aortic medial remodeling may slow down the development of AAA. J Am Soc Hypertens 2014;8(8):571–577.

Keywords: Angiotensin II; leptin; vascular remodeling.

Introduction

Aging is associated with progressive dilatation of the aorta in humans. This process has been attributed to the continuous breakdown of the extracellular matrix because of the long-term harmful effects of numerous factors on the vessel wall, including endogenous angiotensin (Ang) II, oxidative stress, matrix metalloproteinases, and fibrinolytic activity.[1–4] When provided exogenously, Ang II augments atherosclerotic-like lesions in hyperlipidemic mice and promotes the formation and progression of abdominal aortic aneurysm (AAA).[5] Previous studies have shown the presence of Ang II and angiotensin converting enzyme (ACE) in the vessel wall,[6,7] suggesting a role for the renin–angiotensin system (RAS) in tissue remodeling and aortic aneurysm pathogenesis. Ang II promotes aortic aneurysmogenesis through activation of

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angiotensin type 1 receptor. This occurs, at least in part, through the modulation of transforming growth factor β (TGF-β) signaling.[8] Ang II infusion in *ApoE*-deficient mice promotes medial degeneration, as demonstrated by rapid stiffening of the aorta[9] and decreased circumferential strain in aortic segments prone to develop aneurysm. Aortic aneurysms usually develop in the suprarenal aorta or the aortic arch in Ang II induced mouse models.[10,11] Notably, aortic aneurysms can be attenuated by co-infusion of Ang II with losartan, an angiotensin II type 1 receptor blocker (ARB).[12] This observation implied an analogous situation in human AAA pathogenesis. However, a recent report from the RESCAN Collaborators, England, on angiotensin converting enzyme inhibitor (ACE-I) versus nonACE-I receivers in more than 4000 AAA patients found no significant preventative effects for these treatments.[13] A similar approach of enrolling patients with small aortic aneurysms has been taken in an ongoing Aortic Aneurysmal Regression of Dilation Value of Ace-inhibition on RisK trial of perindopril.[14] We assume that numerous experimental protocols have been attempted within the last few years, but only one retrospective analysis, reporting 25 years of AAA progression surveillance, presented evidence for statistically significant inhibition of AAA growth because of ARB therapy.[15] Surprisingly, there has been no clinical study examining the effects of chronic blockage of the RAS axis, as antihypertensive therapy, on simultaneous aneurysmal dilatation. We therefore examined the effects of long-term ARB or ACE-I therapy on the abdominal aortic diameter of hypertensive patients specifically showing no signs of AAA.

Patients and Methods

Patients

Patients were recruited from the hypertension clinic at The Sheba Medical Center, Tel Hashomer, Israel. Of the 880 patients who were seen in the clinic during the year 2012, we enrolled 122 consecutive hypertensive patients with no known history of AAA, who received medical therapy for 12 months or more (1–9 years), were compliant with their regimen, and gave their consent. Patients were stratified according to their antihypertensive treatment; ARB (n = 45), ACE-I (n = 45), or nonARB/nonACE-I therapy (n = 32). Recorded blood pressure levels were retrieved from each patient's file. The reported levels are the average of all recorded measurements in the office during the year before the initiation of the study. Demographic data and cardiovascular risk factors associated with AAA were assessed in all patients, including age, gender, family history of AAA, diabetes mellitus (DM), body mass index, ischemic heart disease, statin therapy, smoking (past and current), and hypercholesterolemia. There was no family history of aortic aneurysm or connective tissue disease in any of the enrolled patients.

Evaluation of Aortic Diameter

All patients underwent abdominal duplex/ultrasound, measuring maximal end-systolic diameter of the subrenal aorta (outer-to-outer diameter), using a Philips iU22 xMA TRIX ultrasound system. This system has a resolution of 0.1 mm. All patients were in ambulatory status and received no food in the 3 hours before the examination. Eighty-four patients underwent sonographic reevaluation at the same subrenal location to assess the abdominal aortic diameter 8 months into the study. This included 37 ARB and 28 ACE-I receivers, and 19 members of the control group. All sonographies were performed in a blind experiment by a single examiner. For each patient, each sonographic assessment included a duplicate examination at the same aortic location, performed 15 minutes later. A paired t test applied to analyze the intraobserver differences between parallel per-patient measurements demonstrated no statistical significance ($P = .922$). Mean paired difference between the two measurements (per patient) was 0.0004. Interobserver analysis data from 15 consecutive patients, performed by three additional examiners substantiated the adequacy of our intraobserver's analysis.

Statistical Analysis

All measured variables and derived parameters were tabulated by descriptive statistics. For continuous variables, summary tables were provided giving sample size, arithmetic mean, and standard deviation by study group. For categorical variables, summary tables were provided giving sample size, absolute and relative frequency by study group. Analysis of variance model was applied to test the measured differences in abdominal aortic diameter between all study groups and between each of the treatment groups to the reference control group (nonARB/nonACE-I). Analysis of covariance model was applied for testing the differences in measured abdominal aortic diameter, differences between all three groups, and between each of the treatment groups to the reference control group (nonARB/nonACE-I), with adjustment to the following covariates: age, gender, DM, statin therapy, current smoking, and hypercholesterolemia. A chi-square test was used to analyze AAA-related risk factors between the groups. All tests were two tailed, and a P value of $\leq 5\%$ was considered statistically significant. The data were analyzed using the SAS version 9.1 (SAS Institute, Cary NC, USA).

Results

Patients' Characteristics

Assessment of demographic parameters and several AAA-related risk factors revealed no significant difference between the groups, in family history of AAA, mean age, body mass index, DM, and ischemic heart disease