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Research Article

Low plasma renalase concentration in hypertensive patients after surgical repair of coarctation of aorta

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Abstract

The study aimed to evaluate plasma renalase level, a recently discovered kidney-derived catecholamine-metabolizing enzyme in patients after successful repair of aortic coarctation, with special consideration of arterial hypertension in the context of underlying process of arterial remodeling. This case–control study covered 50 consecutive patients after Dacron patch repair of aortic coarctation (31 men; median age 33 [26; 40]; age at surgery 10 [5; 16] years), matched in terms of age and gender with 50 controls. Both groups were stratified depending on the presence of hypertension and assessed in terms of renalase, C-reactive protein, and carotid intima-media thickness. Additionally ultrasound and tonometric markers of vascular remodeling were obtained in the study group. Hypertension was found in 21 patients (42%) in the study group and 29 (58%) in the control group ($P = .11$). Renalase level was significantly lower in patients in the study than control group (5825.1 vs. 6592.7 ng/mL; $P = .041$). Significant difference in terms of renalase concentration between hypertensive and normotensive patients was confirmed both in subjects with coarctation of aorta ($P = .027$) and in control group ($P < .0001$). Renalase level inversely correlated with serum creatinine ($r = -0.36$) and arterial blood pressure in the whole population, and with central systolic ($r = -0.29$) and diastolic pressure ($r = -0.35$) in study group. Multivariate regression revealed that serum creatinine and pulse pressure were independent predictors of renalase. Surgical intervention >7 years was linked to lower renalase ($P = .018$) and unfavorable vascular parameters. Renalase level <4958 ng/mL accurately predicted presence of hypertension in patients after coarctation of aorta repair (odds ratio, 3.8; $P = .032$). Renalase deficiency is associated with the presence of hypertension in both patients after surgical repair of aortic coarctation and the control group. In coarctation of aorta, its action is probably parallel to underlying arterial remodeling. J Am Soc Hypertens 2014;8(7):464–474.

Keywords: Aortic coarctation; arterial hypertension; arterial remodeling; catecholamine metabolism.

Introduction

A growing number of adult patients after correction of congenital heart defects becomes a challenge for health care practitioners.[1] Despite successful repair of aortic coarctation, patients require meticulous long-term follow-up.[2] The cornerstone of coarctation of aorta consists in a systemic vasculopathy, not only related with the narrowing of the aortic isthmus itself but also related with widespread remodeling of arterial vascular bed.[3] Large body of evidence suggests that complex cytokine interactions, involving members of transforming growth factor beta (TGF-β) superfamily,[4]

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lead to profibrotic and antiapoptotic propensity inside the arterial wall, which, in turn, results in stiffening of arteries[3,5–8] in addition to endothelial[5] and baroreceptor dysfunction.[9] The effect of long-term renal ischemia in coarctation of aorta on patients' health status after successful repair is poorly recognized. Experimental studies showed the development of tubulointerstitial inflammation in the kidneys that usually is followed by irreversible fibrosis.[10] This may disturb the neuroendocrine kidney function, even without any significant deterioration of excretory function, and may contribute to the persistence of hypertension after the repair of coarctation of aorta.

Arterial hypertension develops in 30–50% of patients with coarctation of aorta,[11] regardless of timely successful surgical intervention.[3,7,12,13] In due course, sequelae of coarctation of aorta include coronary artery disease and neurovascular incidents,[8,14–16] eventually leading to notable shortening of lifespan,[17] even in normotensive individuals.[14,15,18]

A search for reliable cardiovascular risk markers in patients with coarctation of aorta is under way. Recent discovery in the field of cardionephrology shed light on the role of renalase in the bilateral cross talk between heart and kidneys.[19,20] This flavin adenine dinucleotide–dependent oxidase was shown to catabolize circulating catecholamines to aminochromes.[19,20] Its expression is triggered by high plasma catecholamine level[21] and downregulated by dietary sodium intake.[22] Animal studies demonstrated that renalase knockout mice have higher blood pressure (BP) and are more vulnerable to inducible myocardial damage.[23] Renalase level inversely correlated with systolic BP,[24] while two single nucleotide polymorphisms within its gene were linked to essential hypertension,[25] ventricular hypertrophy, systolic and diastolic left ventricular dysfunction,[26] impaired exercise capacity, and inducible ischemia.[26]

We speculated that plasma renalase, as a key player in catecholamine equilibrium and renal regulator of sodium excretion, might help explore the mechanisms responsible for hypertension development in patients after correction of aortic coarctation and compare them to those related with essential hypertension in the general population. The rationale for performing the study was the hypothesis that, potentially due to chronic renal ischemia, patients with coarctation of aorta are characterized by lower plasma renalase than healthy population despite successful correction of coarctation of aorta and that late surgical repair is related with further renalase deficiency and impaired vascular parameters. We thus aimed to evaluate plasma renalase concentration in patients after surgical repair of coarctation of aorta and healthy and hypertensive controls, jointly with numerous sonographic and tonometric vascular parameters.

Methods

The project was carried out as a case–control study and covered 50 asymptomatic patients admitted to outpatient clinic for routine follow-up visit after successful Dacron patch repair of coarctation of aorta. The study group was further divided into patients with postprocedural hypertension, which developed despite successful surgical intervention (group 1) and normotensive subjects (group 2). The control group was matched in terms of age and gender with the study group and consisted of 50 subjects, who were further stratified into hypertensive (group 3) and normotensive individuals (group 4). Patients after repair of coarctation of aorta (groups 1 and 2) were further categorized depending on timing of the surgery (at the age $>$ 7 years).

Hypertension was diagnosed in line with the 2007 European Society of Cardiology Guidelines[27] (BP $>$ 140/90 mm Hg on two separate visits or antihypertensive therapy). BP was measured with the use of arm-size adjusted sphygmomanometer cuff in all participants after 15 minutes of rest in sedentary position. The values of BP constituted the arithmetic means of three measurements conducted twice on two separate visits (six measurements altogether). Estimated glomerular filtration rate (eGFR) was calculated according to Modification of Diet in Renal Disease formula.

All the study participants were meticulously interviewed and previous medical history was revised to exclude following factors that could possibly impede on the results: active neoplastic disease, inflammatory disease within past 3 months, cigarette smoking, history of diabetes mellitus, chronic kidney disease (CKD) with eGFR $<$60 mL/min/1.73 m^2, proteinuria $>$200 mg/L, liver dysfunction (any hepatic aminotransferase $>3\times$ upper reference limit), valvular heart disease (moderate or severe), left ventricle ejection fraction $<$45%, congestive heart failure, coronary artery disease (angina or coronary angiography positive), peripheral artery disease, and idiopathic cardiomyopathy.

The study complied with the Declaration of Helsinki and was approved by the local Ethics Committee. On admission all patients gave their written consent to personal medical data processing for the purpose of this study.

Laboratory Tests

Blood samples were collected from antecubital or radial vein. Renalase, high sensitivity C-reactive protein (CRP), along with standard blood tests were evaluated both in study and control group. Previously mentioned analyses were performed using enzyme-linked immunosorbent assay using commercially available 96-well kits (USCN Life, Wuhan, China). The assay employs monoclonal antibody specific for plasma renalase. According to data provided by manufacturer, it is characterized by the minimum detectable concentration of $<$1.44 ng/mL, minimum detection range of 3.125–200 ng/mL, plasma recovery rate of about 78–101% (ethylenediaminetetraacetic acid) or 82–96% (heparin), and an acceptable intra-assay (coefficient of variation $<$ 10%) and inter-assay (coefficient of variation $<$ 12%)