Atherosclerosis 221 (2012) 154–159

Contents lists available at SciVerse ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Adrenalectomy improves increased carotid intima-media thickness and arterial stiffness in patients with aldosterone producing adenoma

Yen-Hung Lin[a], Lian-Yu Lin[a], Aaron Chen[d], Xue-Ming Wu[e], Jen-Kuang Lee[f], Ta-Chen Su[a], Vin-Cent Wu[a], Shih-Chieh Chueh[c,g], Wei-Chou Lin[b], Men-Tzung Lo[h], Pa-Chun Wang[i], Yi-Lwun Ho[a,*], Kwan-Dun Wu[a], The TAIPAI Study Group

[a] Department of Internal Medicine, National Taiwan University Hospital and National Taiwan University College of Medicine, Taipei, Taiwan
[b] Department of Pathology, National Taiwan University Hospital and National Taiwan University College of Medicine, Taipei, Taiwan
[c] Department of Urology, National Taiwan University Hospital and National Taiwan University College of Medicine, Taipei, Taiwan
[d] School of Medicine, St. Geroge's University, London, United Kingdom
[e] Department of Internal Medicine, Taoyuan General Hospital, Taoyuan, Taiwan
[f] Department of Laboratory Medicine, Far Eastern Memorial Hospital, Ban Ciao, Taipei, Taiwan
[g] Department of Urology, Cleveland Clinic, Cleveland, OH, USA
[h] Center for Dynamical Biomarkers and Translational Medicine, National Central University, Chungli, Taiwan
[i] Quality Management center, Cathay General Hospital, Taipei, Taiwan

ARTICLE INFO

Article history:
Received 3 October 2011
Received in revised form 2 December 2011
Accepted 2 December 2011
Available online 8 December 2011

Keywords:
Primary aldosteronism
Adrenalectomy
Carotid intima media thickness
Pulse wave velocity
Aldosterone producing adenoma

ABSTRACT

Context: Primary aldosteronism (PA) is the most frequent cause of secondary hypertension, and is associated with more prominent vascular stiffness and atherosclerosis. However, the effect of adrenalectomy on reversibility of vascular damage is unclear.
Objective: Our objective was to investigate the vascular changes and possibility of reversibility after adrenalectomy in PA patients.
Methods: We prospectively analyzed 20 patients with aldosterone producing adenoma (APA) that received adrenalectomy from October 2006 to December 2008 and 21 patients with essential hypertension (EH) were enrolled as the control group. Carotid intima media thickness (CIMT) measurement by B-mode ultrasound of the right common carotid arteries and pulse wave velocity (PWV) measurement including brachial–ankle PWV (baPWV) and heart–ankle PWV (haPWV) were performed in both groups. The follow-up measurements were performed one-year after adrenalectomy in APA group.
Results: APA patients had significantly higher diastolic blood pressure, plasma aldosterone concentration (PAC) and aldosterone-renin ratio (ARR), but lower serum potassium level and plasma renin activity (PRA) than EH patients. APA patients had significantly higher CIMT (0.64 ± 0.13 vs. 0.53 ± 0.10 mm, $p = 0.006$), higher baPWV (1589 ± 296 vs. 1405 ± 187 cm/s, $p = 0.024$) and haPWV (1095 ± 150 vs. 987 ± 114 cm/s, $p = 0.013$) comparing with EH patients. One-year after adrenalectomy, CIMT reduced significantly from 0.64 ± 0.13 mm to 0.59 ± 0.14 mm ($p = 0.014$), and baPWV and haPWV also showed significant reduction (baPWV, 1589 ± 296 to 1463 ± 188 cm/s, $p = 0.035$; haPWV, 1095 ± 150 to 1017 ± 109 cm/s, $p = 0.019$).
Conclusion: APA patients have higher degree of early atherosclerosis and vascular stiffness. Adrenalectomy not only corrects the high blood pressure and biochemical parameters but also reverse adverse vascular change in APA patients.

1. Introduction

Primary aldosteronism (PA) is characterized by overproduction of aldosterone by adrenal glands. It has caught more and more attention in recent studies due to the fact that its prevalence among secondary hypertension subjects was beyond previous belief, about 5–13% of hypertensive patients of any causes [1]. Long-term exposure to high aldosterone levels, independent of blood pressure level, could eventually lead to cardiovascular and renal structural and functional damage, including progressive left ventricular morphological changes, increasing collagen deposition in myocardium, renal hyperfiltration, and proteinuria [2–9].

These changes give PA patients a greater risk to develop left ventricular hypertrophy, myocardial fibrosis, and diastolic

* Corresponding author at: Department of Internal Medicine, National Taiwan University Hospital, No. 7, Chung-Shan S. Road, Taipei 100, Taiwan.
Tel.: +886 2 23123456x62152; fax: +886 2 23515811.
E-mail address: ylho@ntu.edu.tw (Y.-L. Ho).

0021-9150/$ – see front matter © 2012 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.atherosclerosis.2011.12.003

dysfunction than essential hypertensive (EH) patients [4–6,10,11]. Besides, excessive aldosterone is known to induce endothelial dysfunction, increase arterial stiffness, and atherosclerosis [7,12–14]. In vascular smooth muscle cells study, aldosterone contributed to increase collagen synthesis [15]. Moreover, compared to EH patients, PA patients have shown to have increasing arterial stiffness measured by pulse wave velocity (PWV) [14], and greater carotid intima-media thickness (CIMT) [12,16].

Arterial stiffness is conventionally estimated by a non-invasive parameter, PWV. It is a measure of stiffness of the aorta, usually as a predictor of coronary heart diseases and stroke [17]. Increased CIMT is an intermediate phenotype for early atherosclerosis [18]. Various studies have demonstrated that CIMT has high correlation with incidence of cardiac events, such as myocardial infarction and angina pectoris, and cerebrovascular events, like stroke or transient ischemic attack [19]. Therefore, measuring PWV and CIMT may indicate the change of vascular structures and risks of development of cardiovascular or cerebrovascular disorders in PA patients.

Unilateral aldosterone producing adenoma (APA) is the most common subtype that can be cured by adrenalectomy, which significantly corrects hypertension, hypokalemia and biochemical parameters in those patients [6,20]. Besides, adrenalectomy also regressed the increased left ventricular mass [6,20–22], and myocardial fibrosis [22]. However, there are limited studies reporting the aldosterone effect on vascular changes in human subjects [12,14], post-operative changes lacking in particular [23]. To our best knowledge, there is only one study reveal that arterial stiffness improved after adrenalectomy [23]. However, efficacy of adrenalectomy on CIMT has not been examined. Therefore, we conduct this study to investigate the vascular changes in APA patients and the possibility of reversibility after adrenalectomy.

2. Subjects and methods

2.1. Patients

This prospective study enrolled 20 patients diagnosed as APA and received adrenalectomy from October 2006 to December 2008. In addition, another 21 patients with EH were enrolled as control group. The diagnosis of EH was made by exclusion, through appropriate clinical and biochemical investigations of all detectable forms of secondary hypertension. All patients were evaluated and registered in the Taiwan Primary Aldosteronism Investigation (TAIPAI) database, constructed for quality assurance in the main National Taiwan University Hospital, Taipei (NTUH) and its three branch hospitals in different cities, including NTUH Yun-Lin branch in Yun-Lin, Far-Eastern Memorial Hospital in Taipei and Tao-Yuan General Hospital in Tao-Yuan [20,24–26]. Medical history, including demography and medication, was thoroughly recorded. The biochemistry study was analyzed at the first evaluation of these patients in NTUH: plasma aldosterone concentration (PAC) was measured by radioimmune assay with commercial kits (Aldosterone Maia Kit; Adaltis Italia, Bologna, Italy), and plasma renin activity (PRA) was measured as the generation of angiotensin-I in vitro using a commercially available radioimmune assay kit (Cisbio, Bedford, MA). Blood pressure determinations were taken in the right arm after being seated for 5 min by a trained research assistant with a mercury sphygmomanometer. The blood pressure was measured twice at 5-min intervals and the average value was used for analysis. CIMT and PWV measurements were performed within 3 months before and one-year after the surgery in PA patients and within 3 months when enrollment in EH patients. This study was approved by the Institutional Review Board of National Taiwan University Hospital, and all subjects were given informed consent.

2.2. Diagnosis of APA

The diagnosis of APA was validated by the "modified four-corner approach" requesting all of the following criteria being met [4,27,28]: (1) evidence of autonomous excess aldosterone production based on an post captopril ARR > 35, (2) lateralization of aldosterone secretion at adrenal vein sampling or during dexamethasone suppression adrenocortical scintigraphy, (3) evidence of adenoma at CT scan, and (4) post-saline loading (PAC > 10 ng/dl) and/or pathologically-proved adenoma after adrenalectomy and cure of hypertension without antihypertensive agents or improved hypertension, potassium, PAC and PRA. All antihypertensive medications were discontinued for at least 21 days before PAC and PRA determination. Diltiazem and/or doxazosin were administered for control of marked high blood pressure when required [24,29].

2.3. Adrenalectomy

The indication for operation was evidence of adenoma at CT scan. All of the operations were performed using the lateral transperitoneal approach, and were performed by a single experienced laparoscopic surgeon to ensure that the principles of adrenal gland surgery were strictly followed [30].

2.4. Histopathologic studies

All of the operated adenomas were blindly re-evaluated by a histo-pathologist. The histological diagnosis of adenoma was based on well-defined, encapsulated tumors, predominately consisting of foamy clear cells [31]. Adenoma appeared as nodules of clear cells in sheets or nests that were sharply demarcated by a pseudo-capsule and was compressing the non-neoplastic uninvolved adrenal gland. Adenomas are differentiated from nodular adrenal hyperplasia by their solitary and well-circumscribed nature [32].

2.5. Measurement of CIMT

A Hewlett-Packard SONO 5500 ultrasound system (Andover, MA, USA), equipped with a 3–11 MHz real-time B-mode scanner was used for the evaluation. Imaging of the right common carotid artery (CCA) was performed with the subjects turning their head 45° to the left. Two measures of maximal IMT at the right CCA 5–15 mm proximal to the carotid bifurcation were obtained. The intraclass correlation coefficients of the intra-observer were approximately 0.70–0.87 for CIMT measurements as reported previously [33].

2.6. Measurement of PWV

PWV was measured in a supine position after 15 min of rest using an automatic waveform analyzer (Colin VP-2000, Omeron Inc., Japan) as described previously [34]. The instrument recorded bilateral brachial and tibial arterial pressure wave forms, a phonocardiogram, and electrocardiogram (lead I) simultaneously. Occlusion cuffs which connected to oscillometric sensors and plethysmographic sensors were placed around arms and ankles for blood pressure and pulse wave measurements and analysis. Distance between ankles and arms was determined upon individual height. Wave front velocity theory was applied to estimate traveling time of arterial pressure between brachial points and ankle points. The brachial–ankle PWV(baPWV) was calculated from the ratio of arm–ankle distance and arm–ankle time difference in both right and left. The heart–ankle PWV (haPWV) was measured with the same protocol.