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Improvement of Cardiac Function by Laparoscopic Adrenalectomy in a Patient with Severe Heart Failure Attributable to Primary Aldosteronism

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Aldosterone affects various systems and organs, including the cardiovascular system, through mineralocorticoid receptors. We here report a primary aldosteronism patient with severe cardiac dysfunction who showed dramatic improvement after laparoscopic adrenalectomy. The 57-year-old man presented with acute heart failure exacerbation. Performance status was 4, and New York Heart Association classification was 4. Echocardiography showed diffuse hypokinetic wall motion with an ejection fraction of 20%. The patient was found to have a high plasma level of brain natriuretic peptide (4,935 pg/mL), hypokalemia (2.7 mEq/L), an extremely elevated plasma aldosterone concentration (1,804 pg/mL), and high aldosterone-to-renin ratio [plasma aldosterone concentration (pg/mL)/plasma renin activity (ng/mL/hr)] (9,002). Computed tomography revealed a tumor 42 mm in diameter in the right adrenal gland. Primary aldosteronism was diagnosed with adrenal venous sampling. Medical treatment for heart failure was continued for several months, but the cardiac function was not sufficiently improved, suggesting the indication of heart transplantation. However, the patient could not be considered a candidate because of the adrenal tumor. Laparoscopic adrenalectomy was therefore performed. Immediately after surgery, echocardiography showed improved wall motion with an ejection fraction of 36%. Performance status and New York Heart Association classification were improved to 0 and 2, respectively. The present case has shown the efficacy of laparoscopic adrenalectomy for primary aldosteronism patients with severe heart failure.

Keywords: ejection fraction; heart failure; laparoscopic adrenalectomy; mineralocorticoid receptor; primary aldosteronism
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Introduction

Aldosterone has been recently recognized to affect various organs through mineralocorticoid receptors. There has been a clinical study examining the factors associated between cardiovascular disease and primary aldosteronism (PA) (Savard et al. 2013). The prevalence of cardiac disease has been reported to be 2.7% in patients with PA (Ohno et al. 2018). Moreover, PA is the most typical cause of secondary hypertension and can be found in 3-10% of the hypertensive patient population (Nishikawa and Omura 2000; Stowasser and Gordon 2004; Williams et al. 2006).

We encountered a patient with heart failure too severe to undergo general anesthesia for adrenalectomy. Here we report a patient with PA and drug-resistant cardiac dysfunction, in whom cardiac function was improved dramatically soon after laparoscopic adrenalectomy (LADX).

Case Report

A 57-year-old man developed heart failure 5 years prior to our first examination and was admitted to a different hospital because of atrial fibrillation and hypertension. The patient received treatment with a beta blocker, diuretics and aldosterone antagonists for about two months. However, he was transferred to the Tohoku University Hospital for advanced treatment because heart failure had not been improved at the previous hospital. On admission, he was 170.0 cm tall and weighed 78 kg (normally 65 kg) with anasarca. Blood pressure was 137/102 mmHg, heart rate was 128 beats/min, and respiratory rate was 18 breaths/

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min with an O_2 saturation of 92% while receiving supplemental oxygen at 2 L/min through a nasal cannula. Heart rhythm was irregular with no cardiac murmur. Chest examination revealed decreased breath sounds with coarse crackles bilaterally. Performance status (PS) (Oken et al. 1982) and New York Heart Association (NYHA) classification (The Criteria Committee of the New York Heart Association 1994) were both 4. Chest radiography showed a butterfly shadow, and cardiothoracic ratio (CTR) was 68.2% (Fig. 1A). Electrocardiography revealed atrial fibrillation, premature ventricular contraction with tachycardia, left ventricular dilatation and diffuse hypokinetic wall motion with an ejection fraction (EF) of 20%. A high plasma level of B-type natriuretic peptide (BNP) of 83,995.3 pg/mL measured by rapid BNP test (the reference range is 0.0 to 18.4 pg/ml in our hospital), renal dysfunction (serum creatinine, 1.84 mg/dL) and hypokalemia (K, 2.7 mEq/L) were noted on admission, as shown in Table 1. Treatment for heart failure was continued in our hospital with intravenous administration of milrinone (0.75 mg/hr),

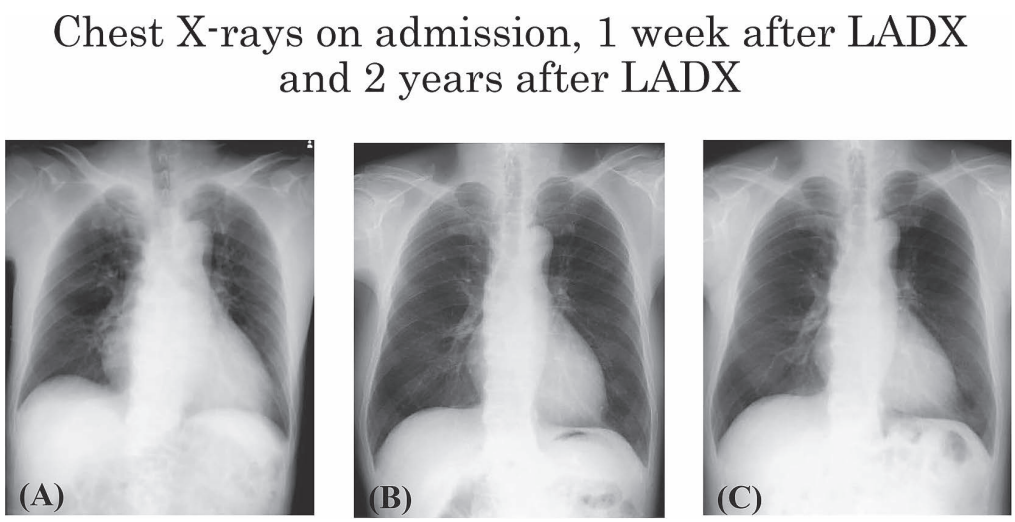

Fig. 1. Changes in the findings of chest radiography after laparoscopic adrenalectomy.
Chest radiography on admission (A), 1 week after laparoscopic adrenalectomy (LADX) (B), and 2 years after LADX (C). Pulmonary congestion and cardiac enlargement found on admission improved immediately after LADX, and remained recovered for two years after LADX.

Table 1. Blood and urine test results on admission.

Blood count	
Leukocytes ($\times 10^3/\mu L$)	6.0
Hemoglobin (g/dL)	15.4
Platelets ($\times 10^9/\mu L$)	15.3
Urinalysis	
pH	8.0
Protein	4+
Glucose	-
Ketone	-
Bilirubin	-
Erythrocytes	3+
Leukocytes	2+
Serum chemistry	
Total Bilirubin (mg/dL)	3.0
Direct Bilirubin (mg/dL)	0.2
Alkaline phosphatase (U/L)	240
γ-Glutamyl transpeptidase (U/L)	39
Aspartate aminotransferase (U/L)	18
Alanine aminotransferase (U/L)	20
Lactate dehydrogenase (U/L)	283
Urea nitrogen (mg/dL)	19
Creatinine (mg/dL)	1.84
Urea (mg/dL)	8.7
Total protein (g/dL)	5.8
Albumin (g/dL)	3.5
Sodium (mEq/L)	145
Potassium (mEq/L)	2.7
Chloride (mEq/L)	103
Calcium (mg/dL)	8.7
Triglycerides (mg/dL)	120
Total cholesterol (mg/dL)	180
Creatine kinase (U/L)	160
Creatine kinase MB (U/L)	11
HDL cholesterol (mg/dL)	31
LDL cholesterol (mg/dL)	130
Fasting plasma glucose (mg/dL)	152
Estimagted glemerular filtration rate ($mL/min/1.72m^2$)	31
C-reactive protein (mg/dL)	0.2
BNP (pg/mL)	3995.3
Coagulation	
Prothrombin time (INR)	22.4
Prothrombin time-international normalized ratio (sec)	2.17
Activated partial thromboplastin time (μg/mL)	42.6
D-dimers	1.0

dobutamine (6 mg/hr) and human atrial natriuretic peptide (hANP) (120 μg/hr). However, additional 2-month treatment only improved NYHA classification to 3, not allowing discontinuation of milrinone and hANP. Forrester classification (Forrester et al. 1976) was 4 and peripheral vascular resistance remained high (Fig. 2).

Taking heart transplantation into consideration as a potential next step of the treatment, myocardial biopsy was performed. Hematoxylin-eosin staining of the myocardial biopsy specimen demonstrated hypertrophic changes of myocytes with variation in myocyte size, and variations in size and deformation of the nuclei of cardiomyocytes (Fig. 3A). Elastica-Masson staining demonstrated marked fibrosis with no myocardial disarray (Fig. 3B). These findings indicate cardiomyopathy.

Since blood biochemistry tests showed hypokalemia, we examined endocrinological tests on suspicion of PA (Table 2). Endocrine examinations showed an extremely elevated plasma aldosterone concentration (PAC) of 1,804 pg/mL and an aldosterone-to-renin ratio [PAC in pg/mL/

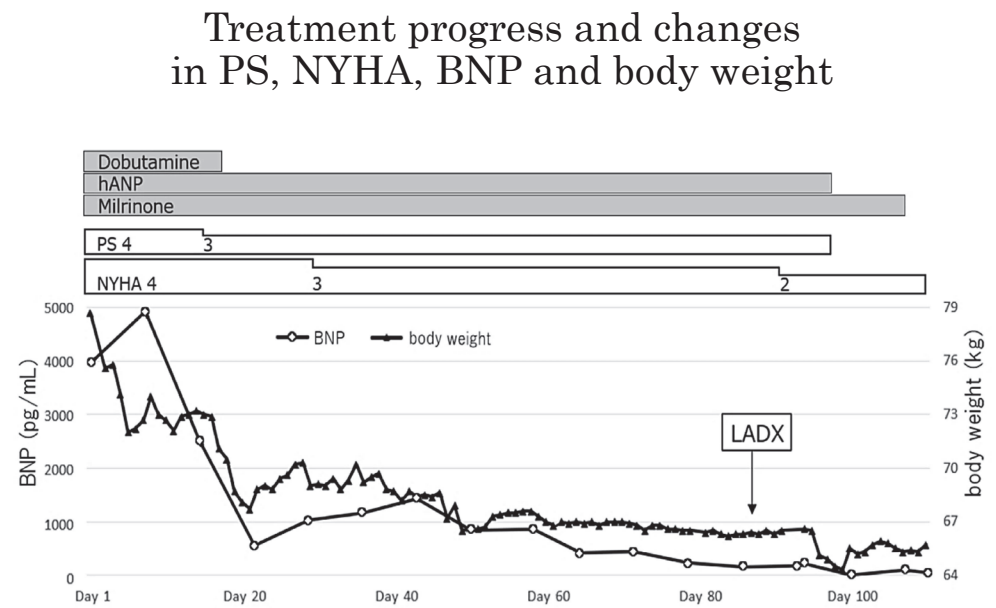

Fig. 2. Timeline of treatments and the changes of patient's conditions.
Shown are the timeline of treatments and the changes in performance status (PS), New York Heart Association (NYHA) classification, plasma levels of B-type natriuretic peptide (BNP) and body weight during admission.
Upper lines show treatment progress of pharmacotherapy, changes in PS and NYHA during hospitalization. Lower graph shows changes in BNP (open circle) and body weight (closed triangle) during admission. Pharmacotherapies with dobutamine, hANP and milrinone for heart failure were initiated after admission. After treatment, BNP and body weight improved until discontinuation of dobutamine. However, hANP and milrinone were needed to be continued, because PS and NYHA improved only to 3 each. All pharmacotherapies were able to be discontinued immediately after laparoscopic adrenalectomy (LADX).

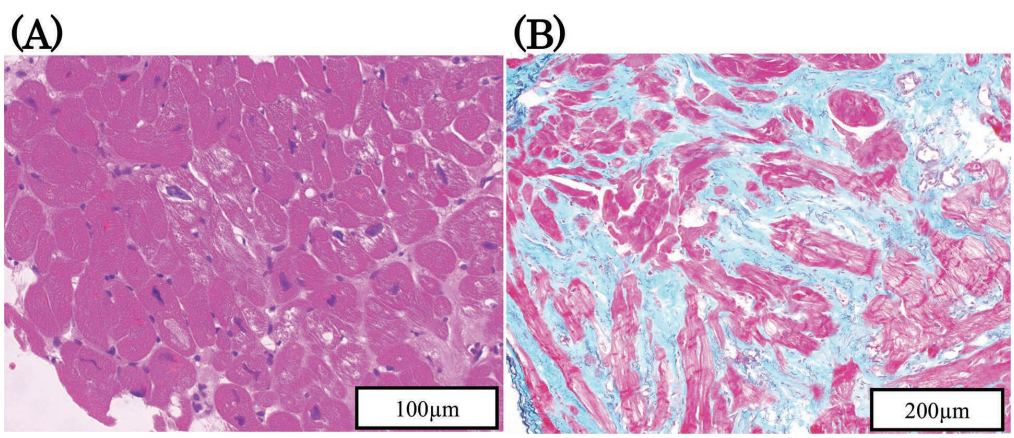

Fig. 3. Histopathological findings of myocardial biopsy specimen.
Hematoxylin-eosin staining demonstrated hypertrophic changes of myocytes with variation in myocyte size, and variations in size and deformation of the nuclei of cardiomyocytes (A). Elastica-Masson staining demonstrated marked fibrosis with no myocardial disarray (B). These findings indicate cardiomyopathy.

plasma renin activity (PRA) in ng/mL/hr, ARR] of 9,002 with normal concentrations of cortisol and catecholamine. Computed tomography (CT) revealed a tumor 42 mm in diameter in the right adrenal gland (Fig. 4). Fluorodeoxyglucose positron emission tomography showed hypometabolic activity in the adrenal tumor with a maximum standardized uptake value of 2.7, suggesting adenoma. Adrenal venous sampling revealed an elevated PAC in the right adrenal central vein (PAC, 26,482.0 pg/mL; cortisol, 1,016.3 μg/mL), compared with that in the left adrenal vein (PAC, 110.0 pg/mL; cortisol, 8.6 μg/mL) (Fig. 5). Consequently, PA caused by the right aldosterone-secreting adrenocortical tumor was diagnosed.

Because his heart dysfunction was too severe, the patient represented a potential candidate for heart transplantation. However, heart transplantation in Japan is only approved for patients without tumors, irrespective of malignancy. We consulted with cardiologists, anesthesiologists and endocrinologists regarding perioperative risks and decided on laparoscopic adrenalectomy (LADX) to provide an opportunity for heart transplantation. The procedure was performed by an experienced surgeon acquainted with laparoscopic surgery, monitoring cardiac function by transesophageal echocardiography and Swan-Gantz's catheter under the supervision of cardiologists. The procedure for LADX was performed under a transperitoneal approach with 4 ports, maintaining intraabdominal pressure under 10

Table 2. Hormonal test results.

	On admission	After surgery	Reference values
PAC	1,804	57	(36-240) pg/mL
PRA	0.2	0.8	(0.2-2.7) ng/mL/hr
ARR	9,002	71.3	n/a
ACTH	16.7	87.9	(4.4-48.0) pg/mL
DHEA	407	457	(38-313) ng/mL
cortisol	11.7	9.2	(4.5-21.1) µg/dL
BNP	3995.3	83.2	(0-18.4) pg/mL

PAC, plasma aldosterone concentration; PRA, plasma renin activity; ARR, aldosterone-to renin ratio; DHEA, dehydroepiandrosterone; BNP, B-type natriuretic peptide; n/a, not available. ARR was calculated as PAC in pg/mL / PRA in ng/mL/hr.

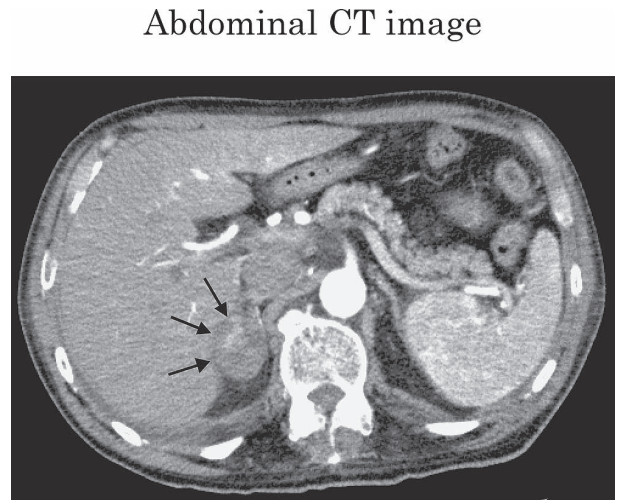

Fig. 4. Abdominal computerized tomography (CT) image.
An abdominal CT image demonstrates a comparatively low-density tumor measuring 42 mm in diameter at the right adrenal gland (arrows).

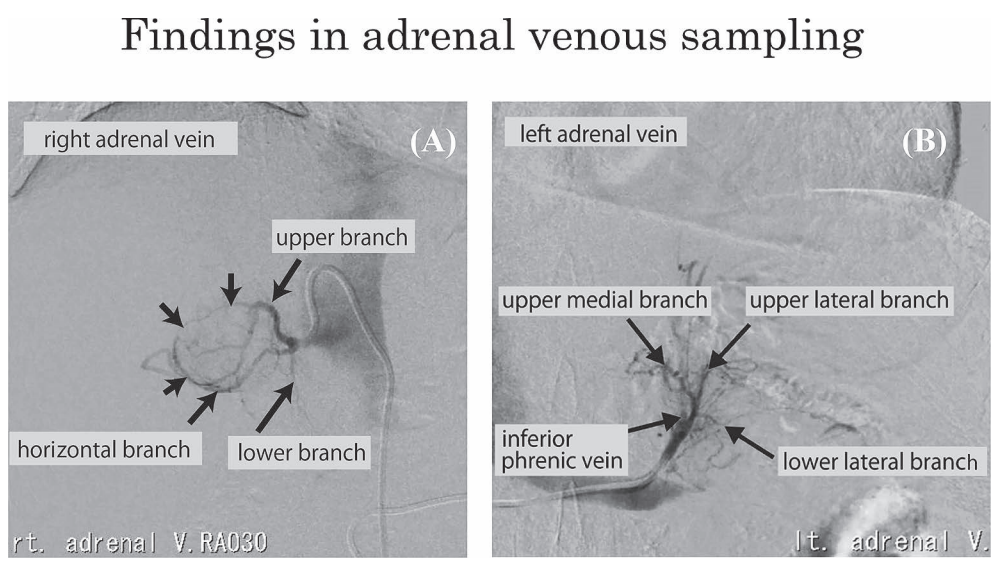

Fig. 5. Findings in adrenal venous sampling.
Contrast media was injected into a right adrenal vein, and upper branch, lower branch and horizontal branch surrounding the right adrenal tumor were identified (A). Contrast media was injected into a left adrenal vein, and upper lateral branch, upper medial branch, and lower lateral branch were identified (B). Plasma concentrations of aldosterone and cortisol were 26,482.0 pg/mL and 1,015.3 μg/mL, respectively, at the right adrenal central vein, while they are 110.0 pg/mL and 8.6 μg/mL, respectively, at the left adrenal vein. We therefore diagnosed right unilateral aldosterone-secreting adrenocortical tumor.

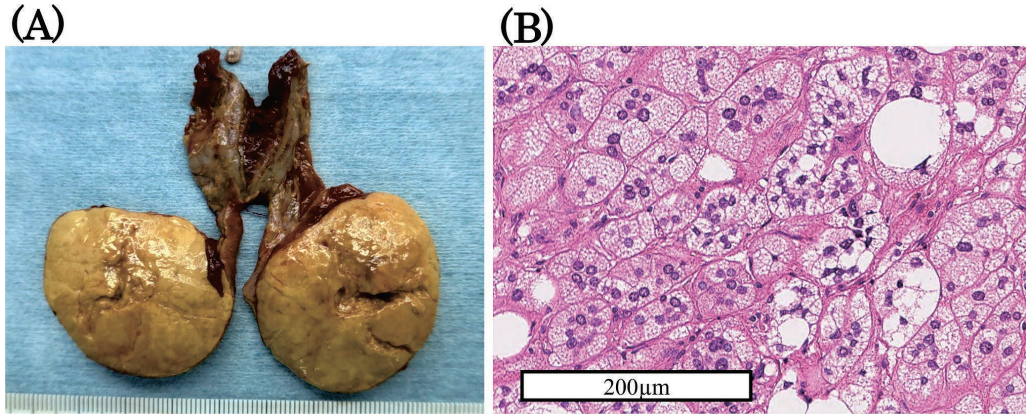

Fig. 6. Macroscopic and microscopic findings of adrenal tumor.
The tumor specimen showed distinct borders and a yellowish spherical nodule measuring 23 × 44 × 23 mm and weighing 26.5 g (A). Histopathologic examinations showed cortical adenoma with lipid-rich clear cells resembling the zona fasciculata of normal adrenal gland. Nuclear mitoses, necrosis and venous invasion were not seen, and Weiss criteria score was 1, indicating a benign adrenocortical adenoma (B).

mmHg CO_2. LADX was completed in a standard surgical procedure with an operative time of 121 min and 9 mL of intraoperative bleeding without any problems, including changes in circulatory dynamics. On gross examination, the tumor specimen removed from the right adrenal gland was a yellowish spherical nodule measuring 23 × 44 × 23 mm and weighing 26.5 g. On microscopic examination, the adrenal tumor showed the growth of clear cells and no malignancy, consistent with benign adrenocortical adenoma (Fig. 6).

Plasma electrolyte and hormonal levels were normalized immediately after LADX, enabling easy control of blood pressure and weight. Chest radiography showed reduction in CTR from 68.2% to 47.1% and no pulmonary congestion (see Fig. 1B). Echocardiography showed improved wall motion and improvement of EF to 36%. Administration of milrinone and hANP was terminated 1 week after LADX. PS was improved from 4 to 0, and NYHA classification was improved from 3 to 2 (see Fig. 2). Consequently, he was discharged on foot on day 19 after LADX. Two years after LADX, EF was improved up to 67%, and the chest radiography showed a CTR of 50.6% and no pulmonary congestion (see Fig. 1C). The patient remains free from heart failure and is no longer a candidate for heart transplantation.

Discussion

A major target of aldosterone is the distal tubule of the kidney, and aldosterone acts through mineralocorticoid receptors (MRs) on epithelial cells of the renal tubules. Recently, MRs have been reported to exist in various organs, indicating that aldosterone would act directly on those organs. PA patients have been reported to be accompanied by complications such as heart failure, cardiac infarction, and severe arrhythmia (Yoshimoto and Hirata 2007; Alvarez and Mohan 2018). Through MR expression on myocardial cells, aldosterone could cause myocardial fibrosis regardless of elevated blood pressure (Kayes-Wandover and White 2000; Catena et al. 2014). Myocardial fibrosis leads to ventricular remodeling under systolic and diastolic functional depression, and finally to severe heart failure (Leopold 2011).

MRs are also found on peripheral vascular endothelial cells and vascular smooth muscles (Lyngso et al. 2016). These cells show reduced production of nitric oxide under the effects of aldosterone. Consequently, decreased blood vessel relaxation could lead to elevated blood pressure (Nguyen Dinh Cat et al. 2010; McCurley et al. 2012).

As described above, excessive aldosterone causes cardiovascular diseases by activating MR. This means MR-dependent impact on cardiovascular system by aldosterone. On the other hand, MR-independent impacts on the cardiovascular system by aldosterone are already known as non-genomic action (Kritis et al. 2016). Aldosterone directly affects the cardiovascular system to cause cardiac hypertrophy by activating various signaling pathways, including ERK1/2, JNK and PKC (Okoshi et al. 2004). Aldosterone is associated with reactive oxygen species (ROS), and under circumstances of high oxidative stress, increases in ROS cause cellular injury and vascular dilation (Landmesser et al. 2003). Both MR-dependent and -independent impacts could affect the cardiovascular system to cause severe heart failure in our case.

Moreover, we need to consider that anti-aldosterone drugs could be insufficient for the patient because PRA was suppressed to 0.2 ng/mL/hr during the hospital stay (Hundemer et al. 2018). However, taking the non-genomic actions of aldosterone independent of MR into consideration, anti-aldosterone drugs could not be effective from the beginning of cardiac dysfunction. Since needle biopsy of cardiac muscle showed strong fibrosis despite long-term medical therapy, excessive aldosterone was considered to promote dilated cardiomyopathy to severe heart failure. Our case suggests that normalizing aldosterone level by

LADX could be the most effective for PA with cardiovascular diseases intractable to medical therapy with anti-aldosterone drugs.

In our case, LADX was not easy to perform because we were anxious about the risk of severe heart failure and tolerance of general anesthesia. However, LADX was performed safely by experienced urologists under the supervision of cardiologists, anesthesiologists and endocrinologists. Within a week after LADX, normalized PAC with fluid balance normalization achieved improvement of EF and heart failure. His general condition got better day by day with improved PS and NYHA classification. These consequences suggested the impact of normalizing PAC on the cardiovascular system. In addition, cardiac function continued to improve over the long term, probably because gradual reversal of ventricular remodeling might continue to occur under conditions of decreased ventricular and vascular resistance. Francis and Tang (2003) reported that left ventricular reverse remodeling was characterized by a reduction in left ventricular diameter and a normalized cardiac configuration, and gradual left ventricular reverse remodeling led to improve heart pumping and prognosis (Francis and Tang 2003; Hoshikawa et al. 2011). Although limited studies have shown the association between PAC and left ventricular reverse remodeling in PA patients, normalizing PAC by LADX may be important to achieve left ventricular reverse remodeling in this PA patient with heart failure.

In conclusion, we report the case of a possible candidate for heart transplantation because of drug-resistant severe heart failure caused by PA. The patient showed significant improvement of cardiac function following LADX. Through this case, we suggest that normalizing PAC by LADX contributes to the improvement of cardiac function and the prognosis of patients with PA accompanied by heart failure.

Conflict of Interest

The authors declare no conflict of interest.

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