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Original Article

Prognostic value of natriuretic peptides in patients with pheochromocytoma-induced catecholamine cardiomyopathy

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Abstract: To evaluate the prognostic value of atrial and brain natriuretic peptides (ANP and BNP) in patients with adrenal pheochromocytoma (PC)-induced catecholamine cardiomyopathy (CC). A prospective case-control study was conducted from April 2004 to May 2010. Plasma concentrations of ANP and BNP were measured in 132 patients with PC, 75 patients with essential hypertension (EH), and 54 healthy control subjects. After effective antihypertensive therapy, peptide measurements were repeated for patients with PC; laparoscopic adrenalectomy was administered for patients with PC. After surgery, the same procedures were conducted for patients with PC. Patients with CC yielded significantly higher plasma ANP and BNP concentrations than the control subjects, patients with EH, and patients without CC ($P < 0.01$). The control subjects, patients with EH, and patients without CC also showed significantly different ANP and BNP concentrations ($P < 0.01$). Age, tumor size, and disease duration were independent risk factors of CC. Areas under receiver operating characteristic curve of ANP and BNP to predict CC were 0.742 and 0.838, with cutoffs of 148.35 and 451.40 ng/l, respectively. Plasma ANP and BNP concentrations significantly decreased after antihypertensive treatment; these parameters continuously decreased after surgery in patients without CC and patients with CC ($P < 0.01$). Therefore, the two peptides are efficient predictors of cardiovascular mortality among patients with CC, as revealed by univariate Cox proportional hazard regression analyses confirmed using a multivariate model. Plasma ANP and BNP provide important and independent prognostic information of cardiovascular dysfunction induced by CC.

Keywords: Atrial natriuretic peptide, brain natriuretic peptide, catecholamine cardiomyopathy, pheochromocytoma

Introduction

Pheochromocytoma (PC) is a rare, catecholamine-secreting, vascular, neuroendocrine tumor arising from chromaffin cells of the adrenal medulla and shows a prevalence ranging between 0.1% and 0.6% in individuals suffering from hypertension, whereas paraganglioma arises from extra-adrenal tissue of the sympathetic paravertebral ganglia of the thorax, abdomen, and pelvis [1-4]. Few investigations have systematically and prospectively evaluated catecholamine cardiomyopathy (CC) with modern cardiac diagnostic tools in PC patients. With the currently available modalities of early biochemical diagnosis, updated imaging examinations, and routine use of α-adrenergic blockade, previously reported substantial incidence of CC might be higher than the present incidence [5]. Cardiovascular system involvement and hypertension are hallmarks of PC, and may cause perioperative morbidity [6]. In addition to cardiovascular (CV) dysfunction caused by prolonged, severe hypertension and varied clinical and subclinical cardiovascular manifestations, patients with PC may suffer from cardiomyopathy caused by myocardial toxicity of high concentrations of circulating catecholamines, particularly norepinephrine (NE) [7, 8].

The natriuretic peptide system consists of a group of neurohormones, including atrial and brain natriuretic peptides (ANP and BNP), which are involved in an attempt to restore normal circulatory conditions in response to cardiovascular changes [9]. ANP is a 28-amino acid peptide primarily synthesized and released by atrial myocytes in response to atrial distension and

stretch, whereas BNP is a 32-amino acid synthesized within the ventricles and released in response to ventricular stretch or pressure overload [10]. Analysis of transcriptional regulation of ANP and BNP in different animal models of cardiomyopathy demonstrated the two peptides in biomedical research to assess cardiovascular dysfunction in the development of heart diseases, which is in agreement with their extensive application as biomarkers in a broad range of cardiovascular diseases in clinical practice [11]. ANP and BNP can inhibit catecholamine release and increase catecholamine uptake [12]. Some studies using culture of cardiomyocytes (especially from rodents) have demonstrated that the expression of ANP and BNP genes can be regulated by several factors, including catecholamines [13-15]. Therefore, it appears that natriuretic peptides may play an important role in the PC pathophysiology. However, the literature on various echocardiographic changes and CV dysfunction induced by CC is largely limited to case reports and small-sample retrospective studies; few reports have also been provided using large-sample data and long-term follow-up after curative operations.

To evaluate the prognostic value of ANP and BNP among patients with CC induced by adrenal PC, we measured plasma concentrations of these peptides among untreated patients with PC and compared the results with those of patients with essential hypertension (EH) and healthy control subjects. We also determined these parameters among patients with PC after four weeks of effective antihypertensive therapy. We then subjected the patients with PC to laparoscopic adrenalectomy. We further obtained these parameters among patients with PC after two weeks.

Materials and methods

Study subjects

This prospective case-control study was conducted in Renmin Hospital of Wuhan University from April 2004 to May 2010 in accordance with our institutional standards and national regulations; this study was also conducted under the appropriate license of the Ethics Committee of Renmin Hospital. The study groups consisted of 54 healthy control subjects (mean age, 42.0 ± 7.1 years; range, 29-55 years), 75 patients with EH (mean age, 42.7 ± 5.1 years; range, 32-54 years), and 132 patients with sporadic adrenal PC, which included 70 patients without CC (mean age, 40.2 ± 9.0 years; range 20-60 years) and 62 patients with CC (mean age, 43.4 ± 10.7 years; range, 23-63 years). The disease duration of patients with PC was 12.7 ± 7.6 (range 0.2-26.3 months). All of the subjects agreed with the aim of this study and provided informed consent.

Blood pressure (BP) measurement

In accordance with current guidelines [16], normal blood pressure (BP) is characterized by systolic blood pressure (SBP) < 140 mmHg and diastolic blood pressure (DBP) < 90 mmHg. Hypertension is defined as SBP ≥ 140 mmHg or DBP ≥ 90 mmHg, or both.

Arterial BP of the control subjects and the patients with EH was measured using a mercury sphygmomanometer after these subjects underwent at least 30 min of supine rest in a quiet and warm room. The mean of three BP measurements was obtained.

The initial arterial BP of patients with PC was measured using an ambulatory BP monitoring system for at least twenty-four hours. After drugs were administered or surgery was performed, arterial BP was monitored for at least 24 h. The results were analyzed using a computer; the mean BP was used for further analysis.

Routine biochemical and radiological analyses

Routine laboratory and radiological analyses of all of the subjects included the following: blood routine test; urinalysis; serum electrolyte and fasting blood glucose concentration analysis; liver and kidney function tests; serum renin activity test; aldosterone, cortisol, and thyroid hormone concentration analysis; chest roentgenogram; electrocardiogram (ECG); and B-scan ultrasonography of the abdomen, including the liver, cholecyst, pancreas, spleen, kidneys, and adrenal glands. Serum concentrations of epinephrine (E), NE, metanephrine (MN), normetanephrine (NMN), and 24-h E, NE, MN, NMN, and vanillylmandelic acid (VMA) in urine (abbreviated as uE, uNE, uMN, uNMN, and uVMA, respectively), were measured through highly sensitive and specific HPLC with electrochemical detection (HPLC-ECD) [17].

Blood sampling procedures and hormonal assays

Blood samples were collected early in the morning between 8:00 and 9:00 after an overnight fast. An intravenous catheter was inserted into the antecubital vein of the subject in a supine position. The blood samples were immediately placed in an ice bath, centrifuged (within 1 h of collection) at 3000 rpm at 4°C for 10 min, and stored in polypropylene tubes at -80°C until used for subsequent assays.

Plasma ANP and BNP concentrations were determined through specific immunoradiometric assays for human ANP and BNP (ShionoRIA ANP and BNP kits; Shionogi & Co., Ltd., Osaka, Japan). The accuracies and the detailed methods of these assays have been described previously [18]. The detection limits of ANP and BNP assays were 2.0 and 5.0 ng/l, respectively. The inter- and intra-assay coefficients of variation for ANP were 5% and 7%, respectively, at 96.8 ng/l. The inter- and intra-assay coefficients of variation for BNP were 6% and 8%, respectively, at 287.2 ng/l.

Echocardiographic examination

Patients in experimental and control groups underwent detailed cardiac evaluation with two-dimensional echocardiography and tissue Doppler imaging using a GE Vivid 7 ECHO machine (GE Vingmed Ultrasound, Horten, Norway) to assess cardiac function; this procedure was performed by an independent experienced cardiologist. Left ventricular (LV) dysfunction was determined by speckle tracking, with echocardiogram staff blinded as to other clinical data. LV diastolic filling patterns were assessed by the mitral inflow pulsed-wave Doppler velocity and the following parameters were obtained: LV end-diastolic dimension, posterior wall thickness at end diastole (PWT), and interventricular septum thickness at end diastole (IVST). Left ventricular mass index (LVMI) was derived from the former three parameters. Two-dimensional apical two- and four-chamber views were used for volume measurements, from which the ejection fraction (EF) was derived. LV dysfunction is characterized by LVEF < 55%.

PC localization and CC diagnosis

PC localization was analyzed through computed tomography (CT) indicating a high attenuation on contrast CT (> 10 HU) with < 50% washout at 10 min after administration–of contrast medium or magnetic resonance imaging (MRI) showing remarkable enhancement and high signal intensity on T2-weighted images with a slower washout pattern; PC localization was also evaluated through ^{123}I-*meta*-iodobenzylguanidine (^{123}I-MIBG) diagnostic scintigraphy. Malignant status was determined in terms of the presence of metastatic disease. Positron emission tomography (PET) technology is generally performed when ^{123}I-MIBG results of patients are negative or inconclusive; PET is also conducted to identify metastatic sites. All bilateral diseases or malignant PC were excluded. Imaging examinations of patients with PC showed unilateral solid masses; of the total proportion of the solid masses, 45.5% (60/132) were found in the left adrenal gland and 54.5% (72/132) were detected in the right. Postoperative histopathological findings of the extirpated tumors at surgery were obtained and further showed that the adrenal mass consisted of benign tumor. The tumor size was 4.0 ± 1.4 cm (range 1.0-7.0 cm). Hereditary PC syndromes were ruled out among all of the patients through detection of gene mutations; this procedure showed no identifiable mutations in RET, VHL, NF1, SDHA, SDHB, SDHC and SDHD. CC is defined as catecholamine-mediated myocardial stunning, which was diagnosed in the context of PC and in the presence of the following combination: (1) intermittent or persistent chest discomfort; (2) biochemical evidence of catecholamine hypersecretion, ECG and echocardiographic evidence of myocardial ischemia with left ventricular systolic dysfunction and rapid fluctuation of regional wall motion; (3) MRI evidence of increased signal intensity in T2-weighted black-blood sequences due to myocardial edema matching the regions of abnormal enhancement as a marker of intense myocardial inflammation; and (4) excluding obstructive epicardial coronary artery disease by coronary angiography [19, 20]. Of the total proportion of the masses detected among patients with CC, 50.0% (31/62) were found in the left adrenal gland and 50.0% (31/62) were observed in the right adrenal gland. None of these patients revealed clinical evidence of active infection, malignant cancer of any type, acquired immunodeficiency syndrome, end-stage renal or liver disease, diabetes, pulmonary disease, valvular heart disease, congenital heart

disease, acute myocarditis, angina pectoris, myocardial infarction, EH, or other diseases that could lead to secondary hypertension or cardiomyopathy. Patients with PC had no previous antihypertensive drug treatment or antihypertensive therapy had been washed out for at least two weeks prior to the study. Furthermore, the medications used by the patients should not affect serum and urine concentrations of catecholamines and their metabolites. Healthy controls were age- and gender-matched normotensive subjects who were hospitalized for a healthy checkup.

Antihypertensive treatment and follow-up

After the initial evaluation, 132 patients with PC whose systolic BP was ≥ 140 mmHg or diastolic BP was ≥ 90 mmHg, or both were subjected to antihypertensive therapy with phenoxybenzamine (10-30 mg, bid) to normalize the symptoms and to maintain blood pressure at < 140/90 mmHg. Thirty-five of the 132 patients with PC required nifedipine (10-20 mg, bid) to adequately lower BP. Twenty-four of the 132 patients with PC required atenolol (25-50 mg, bid) to adequately lower BP. A total of 75 patients with EH were subjected to antihypertensive therapy with nifedipine (10-20 mg, tid) to achieve optimal BP and normalized symptoms. Twenty of the 75 patients with EH required atenolol (25-50 mg, bid) to adequately lower BP. ANP, BNP, and other parameters among all of the groups were determined at baseline. After four weeks of effective antihypertensive treatment, patients with PC were subjected to follow-up procedures, including regular laboratory analyses, two-dimensional echocardiography, tissue Doppler imaging, and ANP and BNP quantification; patients with EH underwent laboratory analyses to detect only the concentrations of the two peptides. All of the patients with PC who were suitable for surgery were subjected to transperitoneal laparoscopic adrenalectomy. After two weeks, therapeutic effect was estimated through normalization of catecholamine hypersecretion and complete disappearance of symptoms, as well as the reduction or abstention of antihypertensive therapy among symptomatic patients with PC. The patients with PC were then subjected to the same follow-up measurements. Patients with PC were followed up by the same urologist at an outpatient clinic at an interval of three months for at most five years. The follow-up of patients with PC was 36.6 ± 12.8 (range 12-60 months). No patient without CC died within follow-up; no patient with CC was lost during follow-up. After an independent observer assessed and classified deaths according to CV, the results suggested that all deaths were caused by CC based on medical records, death certificates, and postmortem reports. Follow-up data were collected for five years from the date of enrolment. Outcomes were death and reversal following surgical cure without requiring drug treatment and hospitalization.

Statistical analysis

Continuous data were expressed as mean ± SD and analyzed using SPSS version 19.0 (SPSS Inc., Chicago, IL). Normal distribution data were analyzed by parametric testes whereas non-normal distribution data were analyzed by non-parametric testes. Comparisons between two variables were performed with an unpaired *t*-test or Mann-Whitney *U*-test. Multiple comparisons were evaluated via one-way ANOVA or Kruskal-Wallis method followed by an appropriate post-hoc test. Significant differences between paired variables were determined via a paired *t*-test or Wilcoxon test. Categorical variables were assessed via χ^2 test or Fisher's exact test. Independent risk factors of CC were evaluated through multiple logistic regression analysis. Receiver operating characteristic (ROC) curves was used to determine area under the curve (AUC) and cutoffs of ANP and BNP to efficiently predict CC. The correlation between two variables was performed through linear regression analysis; significance was further confirmed via Spearman's rank test. Kaplan-Meier curves were plotted to compare the five-year survival of patients with CC according to the identified ANP and BNP cutoffs. Differences in survival were compared via the log-rank test. The effects of ANP and BNP on mortality were evaluated via Cox proportional-hazard regression analysis. Two-sided *P* value < 0.05 was considered statistically significant.

Results

The clinical profiles of the study groups are present in **Table 1**. Age and gender distribution did not significantly differ among the four groups. The mean values of SBP and DBP were significantly higher in patients with EH, patients without CC and patients with CC than in the

Table 1. Clinical profiles of study subjects

Parameters	Control (n = 54)	EH (n = 75)	PC (n = 132)	
			Non-CC (n = 70)	CC (n = 62)
Age (years)	42.0 ± 7.1	42.7 ± 5.1	40.2 ± 9.0	43.4 ± 10.7
Gender (male : female)	30:24	39:36	42:28	31:31
SBP (mmHg)	121 ± 8	174 ± 15[a]	178 ± 13[a]	175 ± 15[a]
DBP (mmHg)	77 ± 6	106 ± 8[a]	107 ± 9[a]	109 ± 10[a]
SE (ng/l)	61 ± 15	65 ± 17	471 ± 227[a,b]	518 ± 210[a,b]
SNE (ng/l)	232 ± 50	255 ± 95	1321 ± 430[a,b]	1415 ± 386[a,b]
SMN (ng/l)	37 ± 10	39 ± 14	373 ± 146[a,b]	407 ± 176[a,b]
SNMN (ng/l)	71 ± 22	75 ± 27	759 ± 278[a,b]	843 ± 322[a,b]
uE (μg/24 h)	11 ± 5	12 ± 6	121 ± 33[a,b]	132 ± 39[a,b]
uNE (μg/24 h)	43 ± 16	47 ± 18	418 ± 217[a,b]	485 ± 238[a,b]
uMN (μg/24 h)	49 ± 14	53 ± 15	687 ± 228[a,b]	730 ± 257[a,b]
uNMN (μg/24 h)	204 ± 46	225 ± 86	2086 ± 655[a,b]	2176 ± 767[a,b]
uVMA (mg/24 h)	4 ± 1	4 ± 2	20 ± 7[a,b]	21 ± 6[a,b]
LVEF (%)	81 ± 4	75 ± 8[a]	64 ± 8[a,b]	51 ± 7[a,b,c]
PWT (mm)	7.6 ± 0.5	8.9 ± 1.0[a]	10.2 ± 1.8[a,b]	10.9 ± 1.3[a,b,c]
IVST (mm)	7.9 ± 0.9	9.1 ± 1.2[a]	10.5 ± 1.9[a,b]	11.3 ± 1.3[a,b,c]
LVMI (g/m^2)	114 ± 7	126 ± 10[a]	138 ± 14[a,b]	144 ± 13[a,b,c]

EH, essential hypertension; PC, pheochromocytoma; CC, catecholamine cardiomyopathy; SBP, systolic blood pressure; DBP, diastolic blood pressure; SE, serum epinephrine; SNE, serum norepinephrine; SMN, serum metanephrine; SNMN, serum normetanephrine; uE, urine epinephrine; uNE, urine norepinephrine; uMN, urine metanephrine; uNMN, urine normetanephrine; uVMA, urine vanillylmandelic acid; LVEF, left ventricular ejection fraction; PWT, posterior wall thickness at end diastole; IVST, interventricular septum thickness at end diastole; LVMI, left ventricular mass index. Normal reference values for catecholamines: SE, 0-100 ng/l; SNE, 0-600 ng/l; SMN, 0-60 ng/l; SNMN, 0-150 ng/l; uE, 0-20 μg/24 h; uNE, 0-80 μg/24 h; uMN, 0-120 μg/24 h; uNMN, 0-400 μg/24 h; uVMA, 1-7 mg/24 h. [a]P < 0.01 compared with control. [b]P < 0.01 compared with EH. [c]P < 0.05 compared with non-CC.

control group (P < 0.01). SBP and DBP did not significantly differ among patients with EH, patients without CC and patients with CC.

As expected, patients without and with CC yielded significantly higher mean values of serum E, NE, MN, and NMN and uE, uNE, uMN, uNMN, and uVMA (P < 0.01). In the patients with EH, without CC, and with CC, LVEF was impaired in 3, 11, and 38 respectively, whereas it was normal in 72, 59, and 24 respectively. The abnormal percentage of LVEF in patients with EH significantly differed from that in patients without CC (4.0% versus 15.7%, P < 0.05); likewise, the abnormal percentage of LVEF of patients without CC significantly differed from that of patients with CC (15.7% versus 61.3%, P < 0.01). The mean LVEF was significantly lower in patients with EH, without CC and with CC than in the control subjects (P < 0.01); by contrast, the mean values of PWT, IVST, and LVMI were significantly higher in patients with EH, without CC and with CC than in the control subjects (P < 0.01). LVEF, PWT, IVST, and LVMI in patients with EH significantly differed from those in patients without CC (P < 0.01); likewise, LVEF, PWT, IVST, and LVMI in patients without CC significantly differed from those in patients with CC (P < 0.05).

Plasma ANP and BNP concentrations in the study groups are shown in **Figure 1A**. The mean ANP concentration was significantly higher in patients with CC (171.0 ± 37.8 ng/l) than in patients without CC (133.0 ± 38.6 ng/l), in patients with EH (63.5 ± 14.6 ng/l) (P < 0.01), and in the control subjects (10.7 ± 3.2 ng/l) (P < 0.01). The mean ANP concentration of patients without CC significantly differed from that of patients with EH (P < 0.01); similarly, the mean ANP concentration of patients with EH significantly differed from that of the control subjects (P < 0.01). The mean BNP concentrations of the control subjects, patients with EH, patients without CC, and patients with CC were 15.9 ± 4.2, 132.1 ± 28.8, 375.6 ± 115.3, and 544.7 ± 122.4 ng/l, respectively. The mean BNP concentration was significantly higher in patients with CC than in patients without CC, in patients with EH, and in the control subjects (P < 0.01). The mean BNP concentration of patients without CC significantly differed from that of patients with EH (P < 0.01); similarly, the mean BNP concentration of patients with EH significantly differed from that of the control subjects (P < 0.01).

We analyzed the risk factors of CC via stepwise multiple logistic regression analysis; the results revealed that age (B = 1.576, OR = 4.838, P =

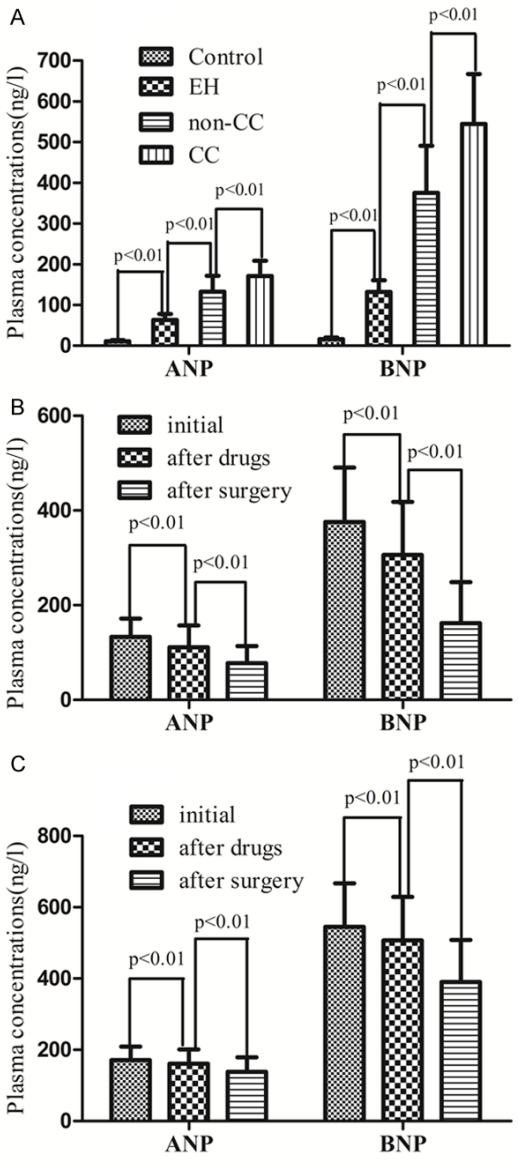

Figure 1. A. Plasma concentrations of ANP and BNP in controls, patients with EH, patients without CC and patients with CC. The mean concentrations of ANP and BNP were significantly higher in the patients with CC than in the patients without CC, patients with EH and controls ($P < 0.01$). The mean ANP and BNP concentrations of patients without CC significantly differed from that of patients with EH ($P < 0.01$); similarly, the mean ANP and BNP concentrations of patients with EH significantly differed from that of the control subjects ($P < 0.01$). B. Plasma concentrations of ANP and BNP at the beginning of the observation period, at four weeks after effective antihypertensive therapy, and at two weeks after surgery in patients without CC. Plasma concentrations of ANP and BNP significantly decreased after drugs; continued decrease was found after surgery ($P < 0.01$). C. Plasma concentrations of ANP and BNP at the beginning of the observation period, at four weeks after effective antihypertensive therapy, and at two weeks after surgery in patients with CC. Plasma concentrations of ANP and BNP significantly decreased after drugs and their continued decrease was detected after surgery ($P < 0.01$).

0.000), tumor size (B = 1.233, OR = 3.431, P = 0.005) and disease duration (B = 1.602, OR = 4.964, P = 0.000), were the most important independent factors of CC when age, gender, tumor site, tumor size, and disease duration were taken into account.

For the diagnosis of CC among patients with PC, the AUC of ANP was 0.742 with a cutoff of 148.35 ng/l. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of the test were 67.7%, 68.6%, 65.6%, and 70.6%, respectively. For the diagnosis of CC among patients with PC, the AUC of BNP was 0.838 with a cutoff of 451.40 ng/l. The sensitivity, specificity, PPV, and NPV of the test were 72.6%, 77.1%, 73.8%, and 76.1%, respectively. The AUCs of ANP and BNP were significantly predictive of CC ($P < 0.01$).

ANP was significantly correlated with SBP, DBP, SE, SNE, SMN, SNMN, uE, uNE, uMN, uNMN, uVMA, LVEF, PWT, IVST, and LVMI of patients with CC ($P < 0.01$; **Table 2**). BNP was also significantly correlated with SBP, DBP, SE, SNE, SMN, SNMN, uE, uNE, uMN, uNMN, uVMA, LVEF, PWT, IVST, and LVMI of patients with CC ($P < 0.01$).

Table 3 shows the clinical parameters of patients without and with CC at diagnosis; **Table 3** also summarizes the changes in these parameters after drugs and after surgery. SBP and DBP in patients without CC and with CC significantly decreased to be normal after drugs and after surgery ($P < 0.01$). SE, SNE, SMN, SNMN, uE, uNE, uMN, uNMN, and uVMA in the two groups did not significantly change after drugs; however, these parameters significantly decreased after surgery ($P < 0.01$). LVEF, PWT, IVST, and LVMI in the two groups were significantly improved after drugs; LVEF, PWT, IVST, and LVMI continuously improved after surgery ($P < 0.01$).

The plasma concentrations of ANP and BNP are depicted in **Figure 1B** and **1C**, respectively, at the beginning of the observation period, at four weeks after effective antihypertensive therapy, and at two weeks after surgery in patients without CC and patients with CC. Plasma ANP and

Table 2. Spearman rank correlation analysis between variables in 62 patients with CC

Variables	SBP	DBP	SE	SNE	SMN	SNMN	uE	uNE	uMN	uNMN	uVMA	LVEF	PWT	IVST	LVMI	*P*
ANP	0.54	0.61	0.67	0.68	0.73	0.75	0.63	0.74	0.65	0.74	0.69	-0.63	0.66	0.56	0.74	< 0.01
BNP	0.67	0.68	0.74	0.74	0.81	0.83	0.75	0.82	0.78	0.83	0.75	-0.74	0.66	0.65	0.78	< 0.01

CC, catecholamine cardiomyopathy; SBP, systolic blood pressure; DBP, diastolic blood pressure; SE, serum epinephrine; SNE, serum norepinephrine; SMN, serum metanephrine; SNMN, serum normetanephrine; uE, urine epinephrine; uNE, urine norepinephrine; uMN, urine metanephrine; uNMN, urine normetanephrine; uVMA, urine vanillylmandelic acid; LVEF, left ventricular ejection fraction; PWT, posterior wall thickness at end diastole; IVST, interventricular septum thickness at end diastole; LVMI, left ventricular mass index; ANP, atrial natriuretic peptide; BNP, brain natriuretic peptide.

Table 3. Parameters of patients without CC and patients with CC at diagnosis and their changes after drugs and after surgery

Parameters	Non-CC (*n* = 70)			CC (*n* = 62)		
	At diagnosis	After drugs	After surgery	At diagnosis	After drugs	After surgery
SBP (mm Hg)	178 ± 13	126 ± 8[a]	125 ± 7[a]	175 ± 15	127 ± 9[a]	128 ± 10[a]
DBP (mm Hg)	107 ± 9	76 ± 4[a]	77 ± 5[a]	109 ± 10	79 ± 6[a]	78 ± 5[a]
SE (ng/l)	471 ± 227	474 ± 237	70 ± 21[a,b]	518 ± 210	516 ± 222	79 ± 24[a,b]
SNE (ng/l)	1321 ± 430	1312 ± 457	324 ± 111[a,b]	1415 ± 386	1399 ± 510	364 ± 114[a,b]
SMN (ng/l)	373 ± 146	380 ± 164	54 ± 17[a,b]	407 ± 176	414 ± 186	62 ± 20[a,b]
SNMN (ng/l)	759 ± 278	778 ± 304	85 ± 35[a,b]	843 ± 322	833 ± 335	103 ± 41[a,b]
uE (μg/24 h)	121 ± 33	125 ± 41	15 ± 7[a,b]	132 ± 39	128 ± 44	18 ± 8[a,b]
uNE (μg/24 h)	418 ± 217	411 ± 229	54 ± 19[a,b]	485 ± 238	493 ± 246	61 ± 21[a,b]
uMN (μg/24 h)	687 ± 228	693 ± 241	64 ± 23[a,b]	730 ± 257	715 ± 273	73 ± 27[a,b]
uNMN (μg/24 h)	2086 ± 655	2122 ± 705	308 ± 102[a,b]	2176 ± 767	2213 ± 829	319 ± 108[a,b]
uVMA (mg/24 h)	20 ± 7	19 ± 8	6 ± 3[a,b]	21 ± 6	20 ± 9	7 ± 4[a,b]
LVEF (%)	64 ± 8	68 ± 9[a]	74 ± 10[a,b]	51 ± 7	54 ± 9[a]	58 ± 13[a,b]
PWT (mm)	10.2 ± 1.8	9.8 ± 2.0[a]	9.3 ± 1.9[a,b]	10.9 ± 1.3	10.6 ± 1.4[a]	10.4 ± 1.3[a,b]
IVST (mm)	10.5 ± 1.9	10.0 ± 2.0[a]	9.4 ± 1.8[a,b]	11.3 ± 1.3	11.0 ± 1.7[a]	10.6 ± 1.7[a,b]
LVMI (g/m^2)	138 ± 14	133 ± 15[a]	127 ± 13[a,b]	144 ± 13	141 ± 14[a]	138 ± 15[a,b]

CC, catecholamine cardiomyopathy; SBP, systolic blood pressure; DBP, diastolic blood pressure; SE, serum epinephrine; SNE, serum norepinephrine; SMN, serum metanephrine; SNMN, serum normetanephrine; uE, urine epinephrine; uNE, urine norepinephrine; uMN, urine metanephrine; uNMN, urine normetanephrine; uVMA, urine vanillylmandelic acid; LVEF, left ventricular ejection fraction; PWT, posterior wall thickness at end diastole; IVST, interventricular septum thickness at end diastole; LVMI, left ventricular mass index. [a]*P* < 0.01 compared with subjects at diagnosis. [b]*P* < 0.01 compared with subjects after drugs.

BNP concentrations in patients without CC significantly decreased after drugs (from 133.0 ± 38.6 ng/l to 111.2 ± 45.8 ng/l and 375.6 ± 115.3 ng/l to 306.2 ± 111.9 ng/l, respectively; *P* < 0.01). Plasma ANP and BNP concentrations continuously decreased after surgery (111.2 ± 45.8 ng/l to 77.6 ± 36.3 ng/l and 306.2 ± 111.9 ng/l to 162.3 ± 86.5 ng/l, respectively; *P* < 0.01). Similar changes in plasma concentrations of ANP and BNP among patients with CC were detected after drugs (171.0 ± 37.8 ng/l to 161.0 ± 40.3 ng/l and 544.7 ± 122.4 ng/l to 506.9 ± 121.9 ng/l, respectively; *P* < 0.01) and after surgery (161.0 ± 40.3 ng/l to 138.0 ± 40.8 ng/l and 506.9 ± 121.9 ng/l to 390.0 ± 118.5 ng/l, respectively; *P* < 0.01).

We also analyzed the plasma concentrations of ANP and BNP initially and four weeks after effective antihypertensive therapy in patients with EH when BP was normal. Plasma ANP and BNP concentrations were significantly decreased after drugs (63.5 ± 14.6 ng/l to 34.4 ± 8.9 ng/l and 132.1 ± 28.8 ng/l to 88.1 ± 19.8 ng/l, respectively; *P* < 0.01).

Kaplan-Meier survival curves of patients with CC were subdivided into two groups according to the cutoffs of ANP and BNP in plasma (**Figure 2**). The respective survival rates were 68.0% (17/25) and 61.9% (13/21) in the two groups whose ANP and BNP concentrations were higher than the cutoffs; by contrast, the respective survival rates were 94.6% (35/37)

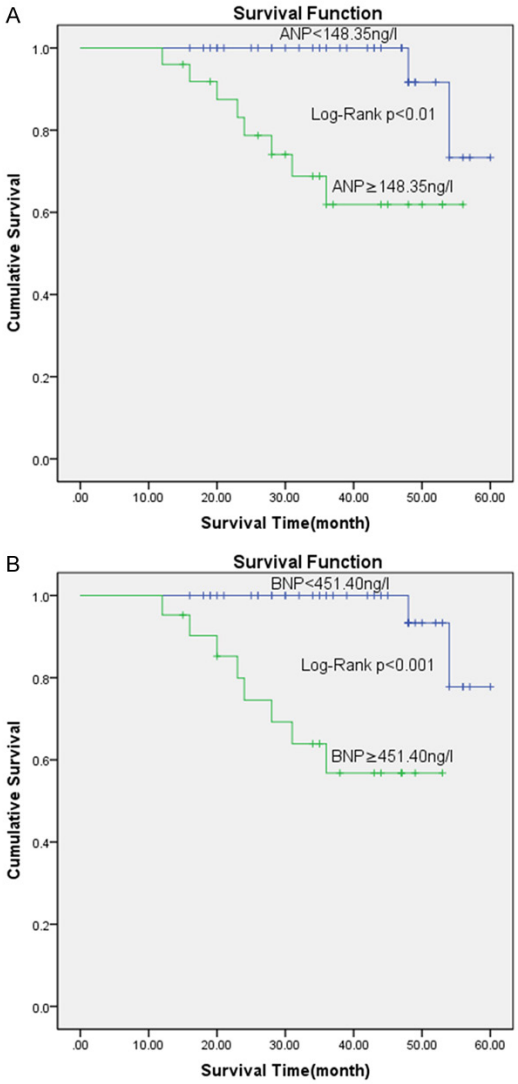

Figure 2. A. Kaplan-Meier survival curves for 62 patients with CC subdivided into two groups according to the cutoff of ANP in plasma (148.35 ng/l). Patients with ANP < 148.35 ng/l significantly differed from patients with ANP ≥ 148.35 ng/l ($P < 0.01$). B. Kaplan-Meier survival curves for 62 patients with CC subdivided into two groups according to the cutoff of BNP in plasma (451.40 ng/l). Patients with BNP < 451.40 ng/l significantly differed from patients with BNP ≥ 451.40 ng/l ($P < 0.001$). Vertical lines represent censor times.

and 95.1% (39/41) in the two groups whose ANP and BNP values were less than the cutoffs. The survival rates significantly differed between the groups with ANP and BNP concentrations higher and lower than the cutoffs ($P < 0.01$).

Table 4 shows the results of Cox regression analyses of the association between background variables and survival time of patients with CC. Univariate Cox proportional hazard regression analyses showed that ANP and BNP were significant predictors of long-term prognosis of patients with CC. The results were further confirmed by multivariate analysis when age, gender, tumor site, tumor size, disease duration, and ANP, and BNP concentrations were taken into account.

Discussion

PC is a rare neuroendocrine disease with catecholamine hypersecretion; this condition possibly leads to CV dysfunction in the form of left ventricular hypertrophy, heart failure, cardiomyopathy, dysrhythmia, angina, and myocardial infarction, which are important to be recognized to minimize perioperative morbidity and mortality [21-23]. Personalized preoperative management with evaluation and treatment by multidisciplinary teams with appropriate expertise may prevent perioperative complications and ensure favorable outcomes [3]. Natruretic peptides are implicated in catecholamine release; furthermore, these peptides are of pathophysiological diagnostic, and prognostic significance in CV dysfunction [18, 24-26]. CC has been investigated but limited to anecdotal cases, although a few retrospective and prospective studies have reported echocardiographic abnormalities and CV dysfunction in 20-50% patients with PC [22, 27-31]. Reports and investigations generally document the reversibility of catecholamine-induced CV dysfunction. No large-sample prospective long-term follow-up studies have been conducted to systematically document whether patients with catecholamine-induced CV dysfunction cannot be reversible. This prospective case-control study is arguably the first to investigate the nature and extent of CV dysfunction induced by CC; this study is also the first to describe partial reversal and non-reversal of catecholamine-induced CV dysfunction after surgery. Two control groups were used as reference of objective echocardiography, tissue Doppler imaging, and plasma estimations of ANP and BNP. During the five-year follow-up, the survival rate of patients with CC and CV dysfunction was recorded and the prognostic value of ANP and BNP among patients with CC was evaluated.

The abnormal percentage of LVEF of patients with EH did not significantly differed from that of control subjects. The most likely explanation is that the disease duration of patients with EH is not long and their hearts are generally in

Table 4. Cox regression analyses of association between background variables and survival time in 62 patients with CC

Covariates	Univariate models			Multivariate model		
	B	SE	P	B	SE	P
Age (years)	0.703	0.699	0.314	1.453	0.833	0.081
Gender (male : female)	-0.075	0.637	0.906	-0.111	0.803	0.891
Side (left : right)	-0.036	0.636	0.955	0.235	0.804	0.770
Size (cm)	0.177	0.696	0.800	0.110	0.786	0.889
Duration (months)	-0.011	0.694	0.987	-0.142	0.837	0.866
ANP (ng/l)	2.091	0.801	0.009	2.052	0.942	0.029
BNP (ng/l)	3.069	1.076	0.004	3.195	1.127	0.005

CC, catecholamine cardiomyopathy; ANP, atrial natriuretic peptide; BNP, brain natriuretic peptide.

compensatory stage. ANP and BNP have been used as a diagnostic marker in clinical settings to monitor the severity of cardiovascular diseases, such as hypertension, heart failure, valvular stenosis and coronary artery disease [32]. Plasma ANP and BNP concentrations are important prognostic biomarkers of myocardial damage; these peptides are used to monitor left ventricular dysfunction [26, 33]. In our paper, the abnormal percentage of LVEF of patients with EH significantly differed from that of patients without CC. Mean LVEF was lower and mean PWT, IVST, and LVMI were higher in patients with EH and patients without CC than in the control subjects. Plasma ANP and BNP concentrations were also higher in patients with EH and patients without CC than in the control subjects. These results are consistent with those described in our previous study (unpublished data). It can be inferred that CV dysfunction is probably caused by not only EH but also PC-induced secondary hypertension. This situation can simultaneously be aggravated by catecholamine hypersecretion in the latter. Moreover, mean LVEF, PWT, IVST, and LVMI and plasma ANP and BNP concentrations of patients without CC significantly differed from those of patients with CC. However, SBP, DBP, SE, SNE, SMN, SNMN, uE, uNE, uMN, uNMN, and uVMA did not significantly differ between the two groups. Our data suggested that patients with CC experienced more serious CV dysfunction than patients without CC. Logistic regression analysis results also revealed that age, tumor size, and disease duration were the most important risk factors of CC. Therefore, elderly patients or patients with long-term PC likely suffer from cardiomyocyte impairment, which is induced by exposure to high plasma catecholamine concentrations. To the best of our knowledge, no previous study has systematically compared subjects without CC subjects with patients with CC.

In this study, the AUCs of plasma ANP and BNP concentrations were 0.732 and 0.838, respectively; therefore, these parameters were of diagnostic value in CC. The AUC of plasma BNP concentration was evidently higher than that of plasma ANP; this finding indicated that the diagnostic value of BNP was superior to that of ANP. However, further studies should be conducted to elucidate the superiority of high plasma BNP concentration to ANP concentration. This superiority may be related to different biological properties of BNP compared with ANP; for instance, the former exhibits higher biological stability with a longer half-life than the latter [33]. After catecholamine induction occurs, plasma BNP concentration increases in an earlier stage than plasma ANP concentration.

Our study showed that plasma ANP concentration was positively correlated with SBP, DBP, SE, SNE, SMN, SNMN, uE, uNE, uMN, uNMN, uVMA, PWT, IVST, LVMI but negatively correlated with LVEF. Plasma BNP concentration was also significantly correlated with SBP, DBP, SE, SNE, SMN, SNMN, uE, uNE, uMN, uNMN, uVMA, PWT, IVST, LVMI, and LVEF. ANP and BNP are mainly synthesized by and released from atrial and ventricular cardiomyocytes, respectively [34]. In addition, ANP and BNP do not counterbalance pressure changes in circulation; instead, these peptides regulate oxygen transport locally and systemically by causing volume contraction (diuresis, natriuresis and plasma shift), thereby leading to hemoconcentration and increase in oxygen-carrying capacity per unit volume of blood [35-37]. Therefore, atrial and ventricular cardiomyocytes are sensitive to high plasma catecholamine concentrations; ventricular cardiomyocytes are more sensitive than atrial cardiomyocytes. High circulating ANP and BNP concentrations may also participate in compensatory and protective mechanisms to regulate oxygen transport because

catecholamines can locally and systemically increase basal metabolic rate and oxygen consumption. However, ANP and BNP can elicit catecholamine exocytosis in cardiac synaptosomes and in nerve growth factor (NGF)-differentiated PC12 cells, which bear a sympathetic nerve-ending phenotype [24]. CV dysfunction caused by cardiac sympathetic overstimulation is not improved by administering recombinant BNP, despite the predicated beneficial effects of natriuretic peptides [38]. Therefore, further studies should be conducted to clarify the interaction between natriuretic peptides and catecholamines.

After pharmacological α-blockade occurred among patients without and with CC, echocardiographic parameters and plasma ANP and BNP concentrations significantly improved. After curative surgery, all of the clinical parameters and plasma ANP and BNP concentrations were markedly improved two weeks post-operation. Our findings on patients without CC are comparable to those in our previous study (unpublished data). The results of patients with CC are also similar to those described in previous reports [21, 29, 39, 40]. Therefore, reversibility possibly occurs even though CV dysfunction is severe after patients undergo surgery and hyperadrenergic state is resolved. Increased ANP and BNP concentrations significantly decreased after drugs in patients with EH; this finding is consistent with our previous reports [41]. These trends indicated that ANP and BNP may also participate in compensatory and protective mechanisms to counteract further increase in blood pressure in the cardiovascular system.

Despite significant improvements in baseline echocardiographic parameters and plasma ANP and BNP concentrations after surgery, survival rates of patients with CC whose plasma ANP and BNP concentrations were lower than cutoff significantly differed from those of patients whose plasma ANP and BNP concentrations were higher than cutoff based on AUCs. These results demonstrated that ANP and BNP are strong predictors of adverse outcomes among patients with CC. Many patients with CC can exhibit reversible outcomes; by contrast, some of these patients suffer from exacerbated conditions or even die within five-year follow-up. ANP and BNP concentrations were identified as independent parameters related to survival rates when age, gender, tumor site and size, disease duration, and plasma ANP and BNP concentrations were considered in univariate Cox regression analysis; this finding was further confirmed by a multivariate Cox model.

Our study has several limitations. First, the age- and gender-matched control groups did not consist of patients with non-PC adrenal tumors. Second, all bilateral tumors and malignant PC were excluded in the research subjects. Third, the number of events was limited; as such, a possible overestimation of the predictive value of biomarkers could not be excluded. Therefore, a multicenter large-sample study with non-PC adrenal tumors, bilateral tumors and malignant PC should be performed to investigate CC.

In conclusion, subclinical and overt cardiac dysfunctions are likely common in PC. Various cardiac indices are improved even when traditional α-blockade is induced by phenoxybenzamine; these changes remain after surgical cure in patients with CC. Detailed echocardiography and plasma ANP and BNP evaluation among patients with CC can be helpful in preoperative optimization of cardiac risk; these procedures may also provide valuable prognostic information. Nevertheless, further studies are necessary to identify specific pathophysiological significance and exact pharmacokinetics of ANP and BNP and their interactions with each other and with catecholamines in CC.

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Disclosure of conflict of interest

None.

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References

[1] Tsirlin A, Oo Y, Sharma R, Kansara A, Gliwa A and Banerji MA. Pheochromocytoma: a review. Maturitas 2014; 77: 229-238.

[2] Domi R and Laho H. Management of pheochromocytoma: old ideas and new drugs. Niger J Clin Pract 2012; 15: 253-257.

[3] Lenders JW, Duh QY, Eisenhofer G, Gimenez-Roqueplo AP, Grebe SK, Murad MH, Naruse M, Pacak K and Young WF Jr. Pheochromocytoma and paraganglioma: an endocrine society clinical practice guideline. J Clin Endocrinol Metab 2014; 99: 1915-1942.

[4] Conzo G, Pasquali D, Colantuoni V, Circelli L, Tartaglia E, Gambardella C, Napolitano S, Mauriello C, Avenia N, Santini L and Sinisi AA. Current concepts of pheochromocytoma. Int J Surg 2014; 12: 469-74.

[5] Kassim TA, Clarke DD, Mai VQ, Clyde PW and Mohamed Shakir KM. Catecholamine-induced cardiomyopathy. Endocr Pract 2008; 14: 1137-1149.

[6] Loosli N, Kohler BB, Pechere-Bertschi A, Karenovics W and Triponex F. [Pheochromocytoma and paraganglioma: basics for the general practitioner]. Rev Med Suisse 2014; 10: 1650-1652, 1654-1655.

[7] Stolk RF, Bakx C, Mulder J, Timmers HJ and Lenders JW. Is the excess cardiovascular morbidity in pheochromocytoma related to blood pressure or to catecholamines? J Clin Endocrinol Metab 2013; 98: 1100-1106.

[8] Prejbisz A, Lenders JW, Eisenhofer G and Januszewicz A. Mortality associated with phaeochromocytoma. Horm Metab Res 2013; 45: 154-158.

[9] Federico C. Natriuretic Peptide system and cardiovascular disease. Heart Views 2010; 11: 10-15.

[10] Argyra E, Theodoraki K, Rellia P, Marinis A, Voros D and Polymeneas G. Atrial and brain natriuretic peptide changes in an experimental model of intra-abdominal hypertension. J Surg Res 2013; 184: 937-943.

[11] Sergeeva IA and Christoffels VM. Regulation of expression of atrial and brain natriuretic peptide, biomarkers for heart development and disease. Biochim Biophys Acta 2013; 1832: 2403-2413.

[12] Porzionato A, Macchi V, Rucinski M, Malendowicz LK and De Caro R. Natriuretic peptides in the regulation of the hypothalamic-pituitary-adrenal axis. Int Rev Cell Mol Biol 2010; 280: 1-39.

[13] Wann BP, Audet MC and Anisman H. Impact of acute and chronic stressor experiences on heart atrial and brain natriuretic peptides in response to a subsequent stressor. Horm Behav 2010; 58: 907-916.

[14] de Bold AJ. Cardiac natriuretic peptides gene expression and secretion in inflammation. J Investig Med 2009; 57: 29-32.

[15] Goetze JP. Biosynthesis of cardiac natriuretic peptides. Results Probl Cell Differ 2010; 50: 97-120.

[16] Mancia G, De Backer G, Dominiczak A, Cifkova R, Fagard R, Germano G, Grassi G, Heagerty AM, Kjeldsen SE, Laurent S, Narkiewicz K, Ruilope L, Rynkiewicz A, Schmieder RE, Boudier HA, Zanchetti A, Vahanian A, Camm J, De Caterina R, Dean V, Dickstein K, Filippatos G, Funck-Brentano C, Hellemans I, Kristensen SD, McGregor K, Sechtem U, Silber S, Tendera M, Widimsky P, Zamorano JL, Erdine S, Kiowski W, Agabiti-Rosei E, Ambrosioni E, Lindholm LH, Viigimaa M, Adamopoulos S, Agabiti-Rosei E, Ambrosioni E, Bertomeu V, Clement D, Erdine S, Farsang C, Gaita D, Lip G, Mallion JM, Manolis AJ, Nilsson PM, O'Brien E, Ponikowski P, Redon J, Ruschitzka F, Tamargo J, van Zwieten P, Waeber B and Williams B. 2007 Guidelines for the Management of Arterial Hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). J Hypertens 2007; 25: 1105-1187.

[17] Peaston RT and Weinkove C. Measurement of catecholamines and their metabolites. Ann Clin Biochem 2004; 41: 17-38.

[18] Grzywa-Celinska A, Celinski R, Kwasniewska K, Dyczko M, Prystupa A and Mosiewicz J. [The usefulness of natriuretic peptides measurements in the diagnostics of chosen cardiovascular diseases]. Pol Merkur Lekarski 2013; 34: 232-234.

[19] Bybee KA and Prasad A. Stress-related cardiomyopathy syndromes. Circulation 2008; 118: 397-409.

[20] Cummings KW, Bhalla S, Javidan-Nejad C, Bierhals AJ, Gutierrez FR and Woodard PK. A pattern-based approach to assessment of delayed enhancement in nonischemic cardiomyopathy at MR imaging. Radiographics 2009; 29: 89-103.

[21] ter Bekke RM, Crijns HJ, Kroon AA and Gorgels AP. Pheochromocytoma-induced ventricular tachycardia and reversible cardiomyopathy. Int J Cardiol 2011; 147: 145-146.

[22] Zelinka T, Petrak O, Turkova H, Holaj R, Strauch B, Krsek M, Vrankova AB, Musil Z, Duskova J, Kubinyi J, Michalsky D, Novak K and Widimsky J. High incidence of cardiovascular complications in pheochromocytoma. Horm Metab Res 2012; 44: 379-384.

[23] Varghese RT, John AM and Paul TV. Catecholamine induced cardiomyopathy in pheochromocytoma. Indian J Endocrinol Metab 2013; 17: 733-735.
[24] Chan NY, Seyedi N, Takano K and Levi R. An unsuspected property of natriuretic peptides: promotion of calcium-dependent catecholamine release via protein kinase G-mediated phosphodiesterase type 3 inhibition. Circulation 2012; 125: 298-307.
[25] Giannakoulas G, Dimopoulos K, Bolger AP, Tay EL, Inuzuka R, Bedard E, Davos C, Swan L and Gatzoulis MA. Usefulness of natriuretic Peptide levels to predict mortality in adults with congenital heart disease. Am J Cardiol 2010; 105: 869-873.
[26] Irzmanski R, Pawlicki L, Charlusz M and Kowalski J. Concentration of natriuretic peptides in patients suffering from idiopathic arterial hypertension and left ventricular diastolic dysfunction confirmed by echocardiography. Clin Exp Hypertens 2012; 34: 530-540.
[27] Jang SY, Yang DH, Lee SH, Kim JH, Park SH, Park HS, Cho Y, Chae SC, Jun JE and Park WH. Recurrent catecholamine-induced cardiomyopathy in a patient with a pheochromocytoma. Korean Circ J 2009; 39: 254-257.
[28] Lopes A, Sousa C, Correia MJ, Junior C, Rocha J and Pinto F. [Cardiomyopathy: first clinical manifestation of a pheochromocytoma--case report]. Rev Port Cardiol 2010; 29: 1065-1069.
[29] Agarwal G, Sadacharan D, Kapoor A, Batra A, Dabadghao P, Chand G, Mishra A, Agarwal A, Verma AK and Mishra SK. Cardiovascular dysfunction and catecholamine cardiomyopathy in pheochromocytoma patients and their reversal following surgical cure: results of a prospective case-control study. Surgery 2011; 150: 1202-1211.
[30] Satendra M, de Jesus C, Bordalo e Sa AL, Rosario L, Rocha J, Bicha Castelo H, Correia MJ and Nunes Diogo A. Reversible catecholamine-induced cardiomyopathy due to pheochromocytoma: case report. Rev Port Cardiol 2014; 33: 177, e171-176.
[31] Giavarini A, Chedid A, Bobrie G, Plouin PF, Hagege A and Amar L. Acute catecholamine cardiomyopathy in patients with phaeochromocytoma or functional paraganglioma. Heart 2013; 99: 1438-1444.
[32] Battistoni A, Rubattu S and Volpe M. Circulating biomarkers with preventive, diagnostic and prognostic implications in cardiovascular diseases. Int J Cardiol 2012; 157: 160-168.
[33] Gaggin HK and Januzzi JL Jr. Biomarkers and diagnostics in heart failure. Biochim Biophys Acta 2013; 1832: 2442-2450.
[34] Kuhn M. Endothelial actions of atrial and B-type natriuretic peptides. Br J Pharmacol 2012; 166: 522-531.
[35] Arjamaa O and Nikinmaa M. Natriuretic peptides in hormonal regulation of hypoxia responses. Am J Physiol Regul Integr Comp Physiol 2009; 296: R257-264.
[36] Arjamaa O and Nikinmaa M. Hypoxia regulates the natriuretic peptide system. Int J Physiol Pathophysiol Pharmacol 2011; 3: 191-201.
[37] Arjamaa O and Nikinmaa M. Oxygen and natriuretic peptide secretion from the heart. Int J Cardiol 2013; 167: 1089-1090.
[38] Chan NY, Robador PA and Levi R. Natriuretic peptide-induced catecholamine release from cardiac sympathetic neurons: inhibition by histamine H3 and H4 receptor activation. J Pharmacol Exp Ther 2012; 343: 568-577.
[39] Szwench E, P Czkowska M, Marczewski K, Klisiewicz A, Micha Owska I, Ciuba I, Januszewicz M, Prejbisz A, Hoffman P, Januszewicz A. Phaeochromocytoma in a 86-year-old patient presenting with reversible myocardial dysfunction. Blood Press 2011; 20: 383-386.
[40] Leissner KB, Mahmood F, Aragam JR, Amouzgar A and Ortega R. Catecholamine-induced cardiomyopathy and pheochromocytoma. Anesth Analg 2008; 107: 410-412.
[41] Hu W, Zhou PH, Zhang XB, Xu CG and Wang W. Plasma concentrations of adrenomedullin and natriuretic peptides in patients with essential hypertension. Exp Ther Med 2015; 9: 1901-1908.