Modulatory effects of hydrochlorothiazide and triamterene on resistant hypertension patients

HAIBIN GONG*, YUN LI*, CHENG ZHENG*, TIAN-TIAN DU, BING-QUAN LUO and MIN PANG

Department of Cardiology, Xuzhou Central Hospital, Xuzhou Cardiovascular Disease Institute, Xuzhou, Jiangsu 221009, P.R. China

Received July 4, 2016; Accepted December 28, 2016

DOI: 10.3892/etm.2017.4412

Abstract. The present study explored the modulatory potential of hydrochlorothiazide and triamterene on resistant hypertension patients. The mechanistic information for resistant hypertension was explored by studying the pressure-natriuresis curves between the salt sensitive population and non-salt sensitive population. A cohort of 23 patients with non-hypertension (NH) (13 males and 10 females; aged from 23 to 62 years), 26 patients with controlled hypertension (CH) (14 males and 12 females; aged from 19 to 72 years) and 23 patients with resistant hypertension (RH) (13 males and 10 females; aged from 19 to 76 years) were selected. The patients were divided into two main groups on the basis of salt sensitivity viz. salt sensitive (SS) and non-SS (NSS) groups. These two groups were further classified into four subgroups based on the diuretic drug used. Hydrochlorothiazide-treated subgroups were named as salt sensitive hydrochlorothiazide (SSHy) and non-SSHy (NSSHy) groups. Similarly, triamterene-treated subgroups were named as salt sensitive triamterene (SSTr) and non-SSTr (NSSTr) groups. Treatment continued for 2 weeks and the pressure-natriuresis curves were recorded. Additionally, the plasma aldosterone and renin activity was monitored by radioimmunoassay. The pressure-natriuresis curves of the SS group were shifted towards the right relative to NSS group. On the other hand, hydrochlorothiazide and triamterene treatments reversed the changes of pressure-natriuresis curves. Moreover, significant differences were observed among various important indices including plasma aldosterone, renin activity, office blood pressure as evaluated by the chronic salt load test and diuretic intervention tests. The study concludes that hydrochlorothiazide and triamterene hold good potential as an efficient modulator of resistive hypertension.

Correspondence to: Dr Haibin Gong, Department of Cardiology, Xuzhou Central Hospital, Xuzhou Cardiovascular Disease Institute, 199 Jiefang Road, Xuzhou, Jiangsu 221009, P.R. China
E-mail: ghbxzh@126.com

*Contributed equally

Key words: salt sensitivity, resistant hypertension, pressure-natriuresis curve, diuretics

Introduction

The cardiovascular disease burden worldwide is highly influenced by the major risk factor of hypertension (1). Hypertension is a pathological state responsible for sudden death, stroke, coronary heart disease, heart failure, auricular fibrillation, peripheral vascular disease, and renal insufficiency (2,3). In China, the number of positive patients with hypertension is more than 330 million and in every 3 adults, there is one with hypertension (4,5). The major causative factor responsible for this is a high salt diet and salt sensitivity (6). Salt sensitivity is basically a clinical observation of alterations in blood pressure of the patient with respect to his/her salt intake (7). Moreover, salt sensitive individuals are also affected by endothelial dysfunction, which may be an important contributor of cardiovascular risks of salt sensitive hypertension (8).

Resistant hypertension is the extreme pathological state wherein more than four mediations including diuretic are engaged in order to control blood pressure (9). A diuretic is an indispensable antihypertensive drug utilized worldwide for the treatment of hypertension (10). However, a long-term large-dose administration of diuretics would affect the glucose, lipid metabolism and electrolyte; thus, its role as a first-line antihypertensive drug is limited to some extent. Consequently, the selection of an effective diuretic as well as proper dose is crucial in these cases. Moreover, there is no scientific evidence in evidence-based medicine as to how to choose proper and effective diuretics, especially in the cases of resistant hypertension.

The present study investigated the influences of different diuretics on pressure-natriuresis curves of resistant hypertension patients, in order to provide a research basis for improving the individualized new drug and non-drug therapies for resistant hypertension.

Materials and methods

Experimental grouping. A cohort of 23 patients with non-hypertension (NH) (13 males and 10 females; aged 23-62 years), 26 patients with controlled hypertension (CH)

(14 males and 12 females; aged from 19 to 72 years) and 23 patients with RH (13 males and 10 females; aged from 19 to 76 years) were selected. Salt sensitivity was measured by utilizing acute/chronic salt load tests. According to the salt sensitive index (SSI) the patients were segregated into two groups viz. salt sensitive (SS) and non-SS (NSS) groups. The two groups were further classified into four subgroups based on the diuretic drug used. Hydrochlorothiazide-treated subgroups were termed SS hydrochlorothiazide (SSHy) and non-SSHy (NSSHy) groups. Similarly, triamterene-treated subgroups were designated as SS triamterene (SSTr) and non-SSTr (NSSTr) groups. Patients received oral administration of diuretics for two weeks in high salt diet period. During the chronic salt load test period, the 24-h natriuresis/kaluresis, serum sodium/potassium, cortisol, plasma aldosterone, renin activity, office blood pressure, 24-h ambulatory blood pressure (ABP), pressure pulse waveform (PWA) and carotid-to-femoral pulse wave velocity (PWVcf) at day 7 were monitored during low salt diet period, balanced salt diet period, high salt diet period and diuretic intervention period. Finally, we drew the pressure-natriuresis curve according to the result of chronic salt load test. The radioimmunoassay was applied to detect the plasma aldosterone and renin activity, and SphygmoCor non-invasive arterial pressure wave analyzer was used to detect PWA and PWVcf.

Requirements of Medical Ethics Committee. This study obtained written informed consents of the enrolled subjects or their family. The study conforms to the Medical Ethics and obtained approval of the Biomedical Research Ethics Committee of the Central Hospital of Xuzhou.

Screening. Screening and treatment of the possible pathogeny of hypertension was performed by using modern diagnosis and treatment technology to screen and exclude secondary hypertension, including renal parenchyma, renal vascular, primary hyperaldosteronism, sleep apnea syndrome and pheochromocytoma.

Acute and chronic salt load tests. The improvised short method was used, which included dripping of 2,000 ml normal saline into the patients, which was immediately followed by the administration of 40 mg furosemide. After 2 h, blood pressure was recorded. This was followed by calculation of growth rate between salt load mean pressure and baseline pressure, and the decreasing rate between mean blood pressure (MBP) (2 h after furosemide) and baseline pressure, the sum of the two values ≥15 mmHg was considered to be salt sensitive. On the other hand, a decreasing rate <5 mmHg was considered to be salt resistive.

Chronic salt load test. Combining the methods of American Nutrition Society 2010 Yatabe and the method proposed by Dr Mou Jianjun under the reference of Jackson 2003 (11,12): Balanced diet (9 g/day, 150 mmol/day Na) x 7 days, 3 g salt in each meal viz. breakfast, lunch and dinner each; then low salt diet (3 g/day, 51.3 mmol/day Na^+) x 7 days, 1 g salt in each meal viz. breakfast, lunch and dinner each; immediately followed by high salt diet (18 g/day, 307.7 mmol/day Na^+) x 7 days, 3 g salt for breakfast and 7.5 g salt for lunch and dinner. We monitored the 24 h ABP, office blood pressure, aldosterone, 24 h natriuresis, 24 h kaliuresis, PWA and PWV. Salt sensitivity was calculated by finding the SSI according to MBP in low salt period and high salt period. SSI = (MBPHs - MBPLs)/MBPLs, SSI >5% was considered to be SS; where SSI <5% was considered to be salt resistant (SR). According to the SSI, the subjects were divided into SS and non-SS (NSS) groups. Then according to complete random design, the patients were further divided into with hypertension salt sensitivity and hypertension non-salt sensitivity into SSHy, SSTr, NSSHy and NSSTr groups. Patients received oral administration of diuretic for two weeks in high salt diet period. During chronic salt load test period, we monitored the 24 h natriuresis/kaluresis, serum sodium/potassium, cortisol, plasma aldosterone, renin activity, office blood pressure, 24 h ABP, PWA and PWVcf at day 7 during low salt diet period, balanced salt diet period, high salt diet period and diuretic intervention period. Then the pressure-natriuresis curve was drawn based on the results of chronic salt load test.

Radioimmunoassays and other immune assays. All the radioimmunoassays and other immune assays were performed by the specific kits as per the supplier protocols.

Results

Screening results of resistant hypertension. From October 2012 to October 2014, a total of 593 patients received hypertension screening and treatment in the Central Hospital of Xuzhou, among whom were 62 cases (10.46%) of resistant hypertension. In the above 62 patients, 55 patients were admitted to hospital and received diagnostic classification and had comprehensively individualized treatment. In the 55 admitted patients, 28 patients (50.90%) were diagnosed with essential resistant hypertension, 12 (21.82%) with essential aldosteronism, 5 (9.09%) with obstructive sleep apnea syndrome, 3 (5.45%) with renal parenchymal hypertension, 5 (9.09%) with renal vascular hypertension (4 atherosclerosis and 1 fibromuscular dysplasia), 1 (1.82%) with Cushing's syndrome, 1 (1.82%) with chromaffinoma, and 0 with aortic constriction, 0 with drug-induced hypertension.

Results of acute salt load test. After the acute salt load test, 7 of 16 cases in the NH group were confirmed with salt sensitivity, and the detection rate was 43.75%; 10 of 20 cases in the CH group were confirmed with salt sensitivity, and the detection rate was 50.00%; 8 of 19 cases in the RH group were confirmed with salt sensitivity, with a detection rate of 42.11% (Table I).

Results of chronic salt load test. After the chronic salt load test, 7 of 16 cases in the NH group were confirmed with salt sensitivity, detection rate of 43.75%; 11 of 20 cases in CH group were confirmed with salt sensitivity, detection rate of 55.00%; and 8 of 19 cases in RH group were confirmed with salt sensitivity, with a detection rate of 47.37% (P>0.05) (Table II).

Results of diuretic intervention trial. The NH group received 3-week chronic salt load test, RH and CH groups received 5-week chronic salt load test and diuretic intervention trial. Differences in plasma aldosterone, renin activity, office blood

Table I. Result of acute salt load test result.

Groups	Case	SS detection rate (%)
NH	16	43.75
CH	20	50.00
RH	19	42.11

NH, non-hypertension; CH, controlled hypertension; RH, resistant hypertension.

Table II. Result of chronic salt load test result.

Groups	Case	SS detection rate (%)
NH	16	43.75
CH	20	55.00
RH	19	47.37

NH, non-hypertension; CH, controlled hypertension; RH, resistant hypertension.

pressure (systolic blood pressure, diastolic blood pressure, mean arterial pressure), 24 h ABP, central aortic pressure, and carotid pulse wave conduction velocity among the three groups were observed to be statistically different ($P<0.05$). The results confirmed the ability of diuretics to change the right shift of the pressure-natriuresis curve (Figs. 1-3 and Table III).

Discussion

Resistant hypertension is a particular type of hypertension characterized by high baseline, long course, and many combined risk factors (13). Management of this deadly pathological state involved utilization of 3-4 antihypertensive drugs including diuretics, so as to get the blood pressure of affected patient to normal (14,15). However, random employment of diuretics in the management of this pathological state may result in the obstruction of the epithelial sodium channels or reduce the re-absorption of Na^+ and Cl^- (16). Sensitivity to salt is another key player influencing the use of diuretic therapeutics in resistant hypertension (7,17). Salt sensitivity is the key player that helps in achieving resistance to the treatment during resistant hypertension. In the present study, modulatory potential of two antihypertensive drugs, the triamterene and hydrochlorothiazide, have been studied in resistive hypertension patients.

Triamterene is a water pill that has the ability to control the salt absorption by the body and simultaneously keeps the potassium levels in the normal range (18). It does this by blocking the sodium channels (19). On the other hand, hydrochlorothiazide is a thiazide medication able to cause decline in the retention of water by kidneys (20). The combination of these two drugs in the present study, successfully managed resistant hypertensions by resulting in significant improvement in water-sodium retention in the affected patients. Moreover, in the present study, the mechanism of the therapeutic effects

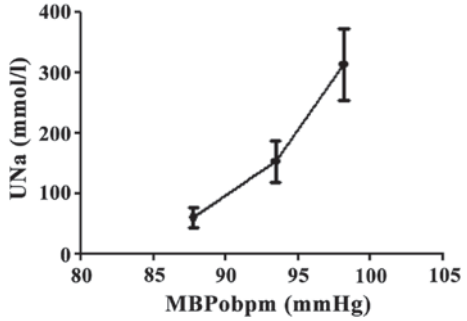

Figure 1. Pressure-natriuresis curve of SS. Pressure-natriuresis curve of SS shifted to right relative to NSS. SS, salt sensitive; NSS, non-salt sensitive.

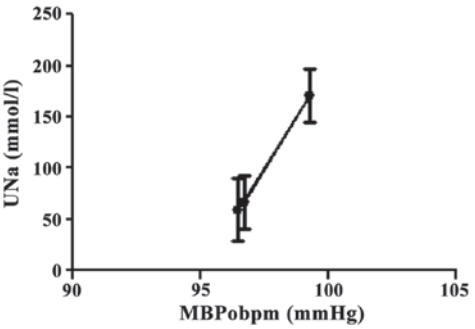

Figure 2. Pressure-natriuresis curve of NSS. Pressure-natriuresis curve of SS shifted to right relative to NSS. SS, salt sensitive; NSS, non-salt sensitive.

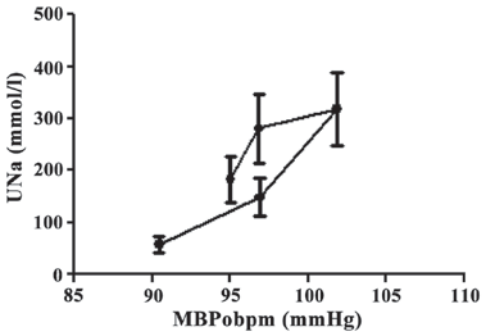

Figure 3. Curve of the influence of diuretic on urinary sodium pressure. Hydrochlorothiazide and triamterene could change the right shift of the pressure-natriuresis curve of resistant hypertension patients.

of this combination was further studied in a novel way by observation of the pressure-natriuresis curve.

Pressure-natriuresis curve has the ability to show an increase of the resistance of afferent glomerular arteriole, the glomerulotubular imbalance and the increase of sodium reabsorption of kidney tubules. In the present study, salt intake constant deduced from pressure-natriuresis curve indicated the blood pressure sensitivity to salt, which also provided a new hypothesis for the study of the salt sensitivity mechanism (21). The urine protein excretion rate of the SS group has been observed to be significantly higher than that of the non-SS group, which directly related the urine protein excretion rate to increasing glomerular capillary pressure (22).

Thus, it is evident from the above observations that the combination of drugs is able to efficiently manage resistant

Table III. Indexes related to chronic salt loading test and diuretic intervention in each group.

Items	RH (19)	CH (20)	NH (16)	P-value
24 h UNa ls	66.88±23.23	66.38±26.72	58.80±17.41	P>0.05
24 h UNa ms	167.66±38.96	162.39±27.18	160.81±23.95	P>0.05
24 h UNa hs	297.61±56.55	316.40±62.04	300.80±37.38	P>0.05
24 h UNa hs1	297.99±90.56	313.66±79.32		P>0.05
24 h UNa ms2	184.97±39.56	190.01±48.27		P>0.05
24 h urine potassium ls	58.32±38.60	63.56±14.28	49.46±25.36	P>0.05
24 h urine potassium ms	66.98±43.60	62.17±23.89	56.10±34.85	P>0.05
24 h urine potassium hs	65.04±29.59	71.09±20.51	50.24±26.18	P>0.05
24 h urine potassium hs1	69.61±45.79	67.56±24.95		P>0.05
24 h urine potassium ms2	65.25±23.87	64.60±19.79		P>0.05
Serum Na^+ ls	138.91±3.10	139.14±1.78	131.19±32.69	P>0.05
Serum Na^+ ms	132.84±31.31	1.40.70±2.71	139.51±1.79	P>0.05
Serum Na^+ hs	139.82±2.20	143.47±30.56	140.17±2.20	P>0.05
Serum Na^+ hs1	132.23±1.25	133.28±30.52		P>0.05
Serum Na^+ ms2	140.00±3.13	139.86±2.16		P>0.05
Serum K^+ ls	4.28±0.25	4.4±0.22	4.11±0.32	P>0.05
Serum K^+ ms	4.21±0.13	4.26±0.35	4.23±0.23	P>0.05
Serum K^+ hs	4.16±0.25002 4.10±0.30	4.12±0.31		P>0.05
Serum K^+ hs1	4.11±0.30	4.00±0.32		P>0.05
Serum K^+ ms2	4.34±0.43860	4.18±0.21		P>0.05
Aldols	359.61±93.70	349.38±28.46	390.21±59.50	P<0.05
Aldoms	272.41±98.26	269.75±74.15	285.77±133.33	P<0.05
Aldohs	171.17±91.51	166.72±79.31	157.51±81.32	P<0.05
Aldohs1	311.65±.92	240.94±97.28		P<0.05
Aldoms2	263.71±72.81	278.92±123.98		P<0.05
Reninls	2.97±4.74	1.45±1.62	7.18±2.11	P<0.05
Reninms	1.24±1.39	0.57±0.61	1.26±1.78	P<0.05
Reninhs	0.64±0.977	0.26±0.28	0.47±0.354	P<0.05
Reninhs1	1.89±2.12	0.68±0.69		P<0.05
Reninms2	2.14±3.34	1.12±0.80		P<0.05
SBPobpmls	135.68±14.87	128.80±13.48	118.41±9.97	P<0.05
DBPobpmls	81.16±11.46	73.05±9.87	72.24±7.00	P<0.05
MBPobpmls	99.33±11.56	91.63±9.84	87.62±7.52	P<0.05
SBPobpmms	143.26±14.83	133.10±11.09	120.06±9.743	P<0.05
DBPobpmms	88.89±11.827	76.15±9.810	71.29±5.49	P<0.05
MBPobpmms	107.02±12.18	87.54±5.74	87.54±5.74	P<0.05
SBPobpmhs	142.21±9.63	133.95±9.976	123.29±6.96	P<0.05
DBPobpmhs	85.95±9.113	76.15±10.00	74.41±5.94	P<0.05
MBPobpmhs	104.70±8.27	95.41±8.99	90.705±5.37	P<0.05
SBPobpmhs1	141.95±16.708	133.3±10.22		P<0.05
DBPobpmhs1	84.84±15.178	74.11±9.06		P<0.05
MBPobpmms2	103.88±14.38930	93.84±7.46		P<0.05
SBPobpmls	139.00±18.12	130.47±8.72		P<0.05
DBPobpmms2	77.95±10.648	72.89±7.42		P>0.05
MBPobpmms2	98.29±12.18626	92.08±6.46		P<0.05
SBPabpmls	138.32±17.12	129.35±14.324	127.29±11.389	P>0.05
DBPabpmls	85.42±12.02	76.05±8.79	74.12±6.52	P>0.05
MBPabpmls	103.05±13.30518	93.81±9.98	91.84±7.53	P>0.05
SBPabpmms	142.79±15.76	138.10±13.90	125.76±9.19	P>0.05
DBPabpmms	87.05±10.71	79.45±5.85	75.12±6.48	P>0.05
MBPabpmms	105.63±11.57	99.00±7.75	92.00±7.05	P<0.05

Table III. Continued.

Items	RH (19)	CH (20)	NH (16)	P-value
SBPabpmhs	143.37±14.72	144.05±12.57	121.59±8.38	P>0.05
DBPabpmhs	86.00±12.12	81.85±7.06	71.94±4.61	P<0.05
MBPabpmhs	105.12±12.39	102.58±7.84	88.49±5.77	P>0.05
SBPabpmhs1	143.58±17.734	138.05±10.14		P>0.05
DBPabpmhs1	88.05±12.04	81.20±7.79		P>0.05
MBPabpmmhs1	106.56±13.23	100.15±7.74		P>0.05
SBPabpmms2	140.68±19.17	134.75±10.43		P>0.05
DBPabpmms2	84.05±11.02	78.90±7.290		P>0.05
MBPabpmms2	102.93±13.00	97.51±7.51		P>0.05
PWASBPls	128.82±16.21	119.35±13.09	108.18±9.16	P<0.05
PWASBPms	132.24±14.53	123.30±11.29	107.65±9.13	P<0.05
PWASBPhs	123.94±10.61	124.05±11.82	105.29±6.743	P<0.05
PWASBPhs1	133.88±14.85	123.21±10.26		P<0.05
PWASBPms2	126.94±14.355	120.05±7.70		P<0.05
PWVcfls	9.91±1.30	9.06±2.29	7.11±1.431	P<0.05
PWVcfms	10.11±1.89	9.90±2.08	7.38±1.33	P<0.05
PWVcfhs	11.71±1.78	10.98±2.219	8.10±1.41	P<0.05
PWVcfhs1	9.8±1.89	9.67±1.63		P>0.05
PWVcfms2	10.60±3.02	9.84±1.48		P>0.05

RH, resistant hypertension; CH, controlled hypertension; NH, non-hypertension.

hypertension as indicated by the information recorded in the pressure-natriuresis curve. Use of pressure-natriuresis to check salt sensitivity in patients is a good hypothesis for selecting individual combination of antihypertensive drugs for more efficient treatments with minimal side effects. However, more studies are required in the clinical settings making this approach the gold standard in resistant hypertension patients.

Acknowledgements

This study was partly financed by the Jiangsu Provincial Special Program of Medical Science (BL2012019).

References

1. Ah YM, Lee JY, Choi YJ, Kong J, Kim B, Choi KH, Han N, Yu YM, Oh JM, Shin WG, *et al*: Influence of initial angiotensin receptor blockers on treatment persistence in uncomplicated hypertension: a nation-wide population-based study. Clin Exp Hypertens 38: 325-330, 2016.
2. Mancia G, De Backer G, Dominiczak A, Cifkova R, Fagard R, Germano G, Grassi G, Heagerty AM, Kjeldsen SE, Laurent S, *et al*; Management of Arterial Hypertension of the European Society of Hypertension; European Society of Cardiology: 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 25: 1105-1187, 2007.
3. Vidt DG, Lang RS, Seballos RJ, Misra-Hebert A, Campbell J and Bena JF: Taking blood pressure: too important to trust to humans? Cleve Clin J Med 77: 683-688, 2010.
4. Ong KL, Cheung BM, Man YB, Lau CP and Lam KS: Prevalence, awareness, treatment, and control of hypertension among United States adults 1999-2004. Hypertension 49: 69-75, 2007.
5. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, Jones DW, Materson BJ, Oparil S, Wright JT Jr, *et al*; Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. National Heart, Lung, and Blood Institute; National High Blood Pressure Education Program Coordinating Committee: Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension 42: 1206-1252, 2003.
6. Costanzo F and Brasseur JG: The invalidity of the Laplace law for biological vessels and of estimating elastic modulus from total stress vs. strain: a new practical method. Math Med Biol 32: 1-37, 2015.
7. Amendment Committee of Guidelines for Prevention and Treatment o Hypertension in China. Chinese J Hypert 19: 701-742, 2011.
8. Oliveras A, Armario P, Hernández-Del Rey R, Arroyo JA, Poch E, Larrousse M, Roca-Cusachs A and de la Sierra A: Urinary albumin excretion is associated with true resistant hypertension. J Hum Hypertens 24: 27-33, 2010.
9. Calhoun DA, Jones D, Textor S, Goff DC, Murphy TP, Toto RD, White A, Cushman WC, White W, Sica D, *et al*: Resistant hypertension: diagnosis, evaluation, and treatment. A scientific statement from the American Heart Association Professional Education Committee of the Council for High Blood Pressure Research 51: 1403-1419, 2008.
10. Salles GF, Cardoso CRL, Fiszman R and Muxfeldt ES: Prognostic importance of baseline and serial changes in microalbuminuria in patients with resistant hypertension. Atherosclerosis 216: 199-204, 2011.
11. Mou JJ: Progress of research in relationship between salt and hypertension. Chin J Frontiers Med Sci 3: 22-25, 2011 (In Chinese).
12. Yatabe MS, Yatabe J, Yoneda M, Watanabe T, Otsuki M, Felder RA, Jose PA and Sanada H: Salt sensitivity is associated with insulin resistance, sympathetic overactivity, and decreased suppression of circulating renin activity in lean patients with essential hypertension. Am J Clin Nutr 92: 77-82, 2010.
13. Viera AJ: Resistant hypertension. J Am Board Fam Med 25: 487-495, 2012.

14. Patterson E, Lazzara R, Szabo B, Liu H, Tang D, Li YH, Scherlag BJ and Po SS: Sodium-calcium exchange initiated by the Ca^{2+} transient: an arrhythmia trigger within pulmonary veins. J Am Coll Cardiol 47: 1196-1206, 2006.
15. Stafford RS, Bartholomew LK, Cushman WC, Cutler JA, Davis BR, Dawson G, Einhorn PT, Furberg CD, Piller LB, Pressel SL, *et al*; ALLHAT Collaborative Research Group: Impact of the ALLHAT/JNC7 Dissemination Project on thiazide-type diuretic use. Arch Intern Med 170: 851-858, 2010.
16. Takase H, Sugiura T, Ohte N and Dohi Y: Urinary albumin as a marker of future blood pressure and hypertension in the general population. Medicine (Baltimore) 94: e511, 2015.
17. Tsuruda T, Kato J, Kitamura K, Kuwasako K, Imamura T, Koiwaya Y, Tsuji T, Kangawa K and Eto T: Adrenomedullin: a possible autocrine or paracrine inhibitor of hypertrophy of cardiomyocytes. Hypertension 31: 505-510, 1998.
18. Tu W, Decker BS, He Z, Erdel BL, Eckert GJ, Hellman RN, Murray MD, Oates JA and Pratt JH: Triamterene enhances the blood pressure lowering effect of hydrochlorothiazide in patients with hypertension. J Gen Intern Med 31: 30-36, 2016.
19. Busch AE, Suessbrich H, Kunzelmann K, Hipper A, Greger R, Waldegger S, Mutschler E, Lindemann B and Lang F: Blockade of epithelial Na^+ channels by triamterenes - underlying mechanisms and molecular basis. Pflugers Arch 432: 760-766, 1996.
20. Wagstaff AJ: Valsartan/hydrochlorothiazide: a review of its use in the management of hypertension. Drugs 66: 1881-18901, 2006.
21. Mozumdar A and Liguori G: Persistent increase of prevalence of metabolic syndrome among U.S. adults: NHANES III to NHANES 1999-2006. Diabetes Care 34: 216-219, 2011.
22. Flegal KM, Carroll MD, Kit BK and Ogden CL: Prevalence of obesity and trends in the distribution of body mass index among US adults, 1999-2010. JAMA 307: 491-497, 2012.