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Editorial Board Member of *World Journal of Hypertension*, Xiao-Ming Gao, MD, Experimental Cardiology Laboratory, Baker IDI Heart and Diabetes Institute, 75 Commercial Road, Melbourne, Victoria 3004, Australia

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World Journal of Hypertension (*World J Hypertens*, *WJH*, online ISSN 2220-3168, DOI: 10.5494) is a peer-reviewed open access academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

WJH covers topics concerning atherosclerosis, atrial fibrillation, blood pressure measurement, cerebrovascular diseases, clinical aspects and trials for hypertension, community cardiovascular practice, diabetes, hypertension education programs, endocrine hypertension, epidemiology of hypertension and metabolic disorders, experimental hypertension, renal hypertension; and hypertension-related heart failure, hemodynamics, imaging procedures, implementation of guidelines, lifestyle changes, microcirculation, molecular biology, neural mechanisms, new therapeutic development, obesity and metabolic syndrome, organ damage, pharmacoeconomics, public health, renin-angiotensin system, sleep apnea, therapeutics and clinical pharmacology. Priority publication will be given to articles concerning diagnosis and treatment of hypertensive disease. The following aspects are covered: Clinical diagnosis, laboratory diagnosis, differential diagnosis, imaging tests, pathological diagnosis, molecular biological diagnosis, immunological diagnosis, genetic diagnosis, functional diagnostics, and physical diagnosis; and comprehensive therapy, drug therapy, surgical therapy, interventional treatment, minimally invasive therapy, and robot-assisted therapy.

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EDITORIAL OFFICE
Jin-Lei Wang, Director
Xiu-Xia Song, Vice Director
World Journal of Hypertension
Room 903, Building D, Ocean International Center,
No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China
Telephone: +86-10-85381891
Fax: +86-10-85381893
E-mail: editorialoffice@wjgnet.com
Help desk: http://www.wjgnet.com/esps/helpdesk.aspx
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REVIEW

Endocrine hypertension: An overview on the current etiopathogenesis and management options

Reena M Thomas, Ewa Ruel, Prapimporn Ch Shantavasinkul, Leonor Corsino

Reena M Thomas, Ewa Ruel, Leonor Corsino, Division of Endocrinology, Metabolism and Nutrition, Department of Medicine, Duke University Medical Center, Durham, NC 27710, United States
Prapimporn Ch Shantavasinkul, Division of Nutrition and Biochemical Medicine, Department of Medicine, Ramathibodi Hospital, Faculty of Medicine, Mahidol University, Bangkok 10400, Thailand
Author contributions: Thomas RM, Ruel E, Shantavasinkul PC and Corsino L had made substantial contributions to the drafting of the article or revising it critically for important intellectual content.
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Correspondence to: Leonor Corsino, MD, MHS, FACE, Assistant Professor of Medicine, Division of Endocrinology, Metabolism and Nutrition, Duke University Medical Center, Box 3451, Durham, NC 27710,
United States. leonor.corsinonunez@dm.duke.edu
Telephone: +1-919-6843841
Fax: +1-919-6681559
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Abstract

Endocrine causes of secondary hypertension include primary aldosteronism, pheochromocytoma, cushing's syndrome, hyperparathyroidism and hypo- and hyperthyroidism. They comprise 5%-10% of the causes of secondary hypertension. Primary hyperaldosteronism, the most common of the endocrine cause of hypertension often presents with resistant or difficult to control hypertension associated with either normo-or hypokalemia. Pheochromocytoma, a great mimicker of many conditions, is associated with high morbidity and mortality if left untreated. A complete history including pertinent family history, physical examination along with a high index of suspicion with focused biochemical and radiological evaluation is important to diagnose and effectively treat these conditions. The cost effective targeted genetic screening for current known mutations associated with pheochromocytoma are important for early diagnosis and management in family members. The current review focuses on the most recent evidence regarding causes, clinical features, methods of diagnosis, and management of these conditions. A multidisciplinary approach involving internists, endocrinologists and surgeons is recommended in optimal management of these conditions.

Key words: Primary aldosteronism; Hyperaldosteronism; Adrenal; Adenoma; Pheochromocytoma

Core tip: This is an invited manuscript to present a summary of the most recent information on the etiology, diagnosis and management of endocrine diseases as a cause of secondary hypertension.

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INTRODUCTION

Secondary hypertension, a term used for the hypertension for which there is an identifiable cause, accounts for 10% of all patients with hypertension[1,2]. Endocrine conditions as a cause of secondary hypertension comprise 5%-10% of all patients with hypertension[2]. Although this form of hypertension is rare, identification and treatment of the underlying cause, might lead to the cure or significant improvement of the hypertension, thereby decreasing the cardiovascular risk and morbidities associated with hypertension.

The endocrine conditions causing secondary hypertension are primary aldosteronism, pheochromocytoma, Cushing's syndrome, acromegaly, hyperparathyroidism, congenital adrenal hyperplasia, hypothyroidism, hyperthyroidism and renin-secreting tumors. Current evidence shows no benefit of screening for endocrine causes of hypertension in all patients presenting with hypertension. However, it is important to maintain a high index of clinical suspicion based on the knowledge of the clinical features and presentation of these conditions.

In this review, we will focus on the etiopathogenesis, diagnosis and treatment of the most common endocrine causes of hypertension-primary hyperaldosteronsim (PAH) and pheochromocytoma.

PAH

Introduction

PAH is one of the most common causes of secondary hypertension[3]. As such, it is recommended that this condition be considered in the differential diagnosis of patients with uncontrolled hypertension. With the advent of more refined testing, it is widely quoted to account for 5%-13% of the population with age of onset between 30 and 60[3]. A recent prospective study of 1180 patients with newly diagnosed hypertension found a prevalence of primary hyperaldosteronism of 4.8%[4]. PAH is due to either idiopathic hyperaldosteronism (IHA) or due to aldosterone producing adenoma (APA). IHA involves bilateral adrenals and accounts for an estimated 60%-66% of diagnosis. APA, the classic case first discovered by Conn over 60 years ago, is a unilateral adrenal adenoma and makes up the majority of remaining cases of primary hyperaldosteronism (30%-35%)[3,5]. However, the prospective study described above found that the exact make up of what constitutes the majority of primary hyperaldosteronism diagnosis varies depending on access to confirmatory testing, notably adrenal vein sampling (AVS). More patients were diagnosed with bilateral than unilateral disease if there was no access to AVS and vice versa[4]. Thus, depending on access to an academic center with AVS expertise, the prevalence of bilateral *vs* unilateral disease will differ. Additionally, 2% of cases of primary hyperaldosteronism involve a unilateral hyperplasia also known as primary adrenal hyperplasia. This is thought to be a micro or macrondular area of hyperplasia in the zona glomerulosa of the adrenal gland that is limited to only one rather than both adrenals[3]. Further, 2% of patients have a familial hyperaldosteronism syndrome type 1 or 2[3]. Type 1 is glucocorticoid-remediable aldosteronism (GRA) and type 2 familial aldosterone-producing adenoma or IHA[6]. These are further discussed in the section on genetic disorders. The remaining rare categories of aldosterone producers (1%) are adrenocortical carcinoma, or ectopic production of aldosterone such as ovarian or renal source[5,7].

Clinical presentation: The classic patient with primary hyperaldosteronism presents with difficult to control hypertension and hypokalemia. If severe, hypokalemia may be accompanied by muscle weakness, cramping, headaches, palpitations, and polyuria. Hypokalemia may be unmasked with the addition of diuretics. The presentation of hyperaldosteronism varies and many patients may present with hypertension without hypokalemia. A higher index of suspicion is necessary in order to make the diagnosis.

Screening for PAH should be considered for hypertensive patients with the following presentation: hypokalemia, difficult to control hypertension on 3 or more anti-hypertensive drugs or hypertension of $\geqslant$ 160 mmHg systolic and $\geqslant$ 100 mmHg diastolic, or those with hypertension and an incidental adrenal mass, young onset of hypertension, or those being evaluated for other causes of secondary hypertension[3]. The Endocrine Society Guidelines published in 2008 echoed these recommendations adding that screening should also include those with hypertension and diuretic-induced hypokalemia, those with family history of early onset hypertension or stroke at age < 40, as well as all hypertensive patients with a first degree relatives with primary hyperaldosteronism[8].

APA: Patients with APA tend to be younger and present with severe symptoms in terms of degree and frequency of hypertension and hypokalemia, respectively. Biochemical analysis reveals higher plasma levels of aldosterone (> 25 ng/dL plasma aldosterone)[9,10].

Cardiovascular and renal effects: Recent evidence has called attention to the increase of cardiovascular events associated with hyperaldosteronism. Specifically, in a study with case matched patients with essential hypertension, those with hyperaldosteronism had more cardiovascular events and increased left ventricular hypertrophy independent of blood pressure levels[11]. These left ventricle changes appeared to be reversible post adrenalectomy[12].

A recent prospective Italian study > 1100 patients found that urine albumin was significantly increased as compared to patients with essential hypertension, presumably highlighting increased renal damage with

PAH[13].

Diagnosis

The biochemical hallmarks of primary hyperaldosteronism are low potassium, high aldosterone, and low renin. Hypokalemia itself, while helpful in recognizing the disease, is not required, with only 9%-37% of patients presenting with hypokalemia[14]. Normal potassium cannot rule out hyperaldosteronism as some patients with primary hyperaldosteronism will have normal potassium levels[15]. Additionally, most patients with hypertension who have hypokalemia do not have PAH[16]. Low renin and elevated aldosterone are hallmarks. However, low renin on its own can be found in patients taking beta-blockers, high sodium intake, steroids, licorice or with low renin essential hypertension[16]. Further, plasma and urine aldosterone levels are subject to confounders including incomplete urine assays, influence of hypokalemia and diurnal variation[16].

The diagnosis for primary hyperaldosteronism traditionally includes the following 3 steps: (1) screening; (2) confirmation; and (3) diagnosis of subtype[3,8]. Debate over exact cutoffs for screening, the need for confirmatory testing and the best way to distinguish APA from other subtypes is ongoing.

Screening: Initial screening of patients suspected to have hyperaldosteronism should be conducted with a morning (preferably 8-10 am) plasma aldosterone and renin values. For proper interpretation, aldosterone and renin testing should be performed in the morning on a seated ambulatory patient[8]. Though plasma aldosterone to renin ratio is considered a screening test, some physicians forgo additional lab testing once this screen is obtained[17]. It is important to note, however, that debate exists over the exact cutoffs for the ratio, with a recent study finding a ratio of 32 ng/mL per hour[18]. Some experts advocate for the use of both a ratio and an aldosterone level. For example, using a plasma aldosterone to plasma renin activity ratio of more than 30 ng/mL per hour and a plasma aldosterone of more than 20 ng/dL combination is 90% sensitive and 91% specific, with a positive predictive value of 69% and negative predictive value of 98%[16]. Physicians need to be aware that false positives and negatives do occur[19]. Testing in general is affected by medications (including many anti-hypertensive, oral contraceptives, and selective serotonin reuptake inhibitors), renal function, upright posture, age, sex and pregnancy[19,20]. Thus, tests should be interpreted with caution and in many cases repeated to confirm results. Additionally, biochemical results may be laboratory and assay dependent. There exists variability in assays and units used in reporting various cut offs[8,20]. Further, laboratories measuring renin must be able to detect renin at its lowest range; this has been found to be a limitation of some laboratories[8]. It is critical that providers become familiar with their own laboratories units and measurement assays while interpreting their results.

Impact of medications on screening: Ideally, hypertensive drugs interfering with renin and aldosterone measurements should be discontinued at least 2 wk prior to laboratory testing. However, for those patients with severe hypertension who are on multiple anti-hypertensives, this may not be safe and tolerable. Several studies suggest that anti-hypertensives need not be discontinued for screening[15,21], but the debate continues. Experts in the field suggest that if discontinuation of all antihypertensive medications is not feasible because of the concern of patient safety, providers should discontinue mineralocorticoid receptor antagonist such as spironolactone, eplerenone and amiloride for at least 4 wk prior to testing and use other medications to control hypertension[8]. The Endocrine Society practice guidelines suggest the following medications (verapamil, hydralazine, prazosin hydrochloride, doxazosin and terazosin) as alternatives during screening because of their minimal impact on screening assays[8].

Confirmatory testing: While an increased ratio of plasma aldosterone to plasma renin is highly suggestive of the diagnosis, some experts advocate for confirmatory testing. For patients with severe cardiac or renal disease, confirmatory testing may not be advised. Currently there are no gold standard confirmatory tests[8]. The Endocrine Society guidelines suggest the following as potential confirmatory test: oral sodium loading test, saline infusion test, fludrocortisone suppression test, and the captopril challenge test[8]. The selection of a confirmatory test should be based on cost, time, morbidity and conflicting data on sensitivity and specificity of the test[17].

A recent study in Japan of 120 cases examined the diagnostic relevance of captopril challenge and saline infusion testing to confirm positive screening test and concluded that most patients with positive screens also had positive confirmatory testing. The study challenges the point that not all cases may require confirmatory testing to establish the diagnosis[22].

Salt loading test is one of the most commonly used confirmatory tests. Once blood pressure is stable and potassium is replete, the patient is given oral salt tablets for 3 d. Subsequently, a 24 h urine aldosterone is measured. Careful monitoring of blood pressure and potassium is required. The test is considered positive when the 24 h urine aldosterone level is > 12 μg/24 h or 33 nmol/d with a concomitant 24 h urine sodium excretion of > 200 mmol/d (approximately 6 g/d). This test provides > 90% sensitivity and specificity[23].

Intravenous saline infusion test involves the infusion 2 L of normal saline over 4 h after an overnight fast and drawing plasma aldosterone level post infusion. Plasma aldosterone levels above 10 ng/dL or 277 pmol/L (as compared to less than 5 ng/dL or 139 pmol/L for controls) is considered confirmatory for a diagnosis of primary hyperaldosteronism[24].

The fludrocortisone suppression test and the captopril challenge test are not widely used in clinical practice due to cardiovascular concerns, the need to follow the patient closely during the test, challenges in interpreting the results, and risk for false negative and equivocal results[25].

Imaging modalities

Localization of the source of primary hyperaldosteronism is key to the treatment. Only unilateral adenomas or APA are treated with surgery. Imaging helps to distinguish between unilateral *vs* bilateral disease. Recent research has focused on how to best utilize computerized tomography (CT) scan *vs* AVS in order to correctly identify those patients who may potentially be cured with surgery[5,26,27].

CT imaging: Adrenal CT imaging alone cannot reliably distinguish a unilateral source of hyperaldosteronism, especially in older patients[5,9]. In a prospective study of 203 patients with primary hyperaldosteronism selected for AVS, CT scan could identify unilateral *vs* bilateral aldosterone source in about half (53%) of the cases[5]. CT can also creates confusion if it reveals normal adrenals, bilateral large nodules or bilateral small < 1 cm adrenal nodules[26]. Specifically, a small growth noted on adrenal gland with another on the other may be falsely categorized a patient as having bilateral hyperplasia whereas in reality the smaller growth is non-functioning and the patient has a unilateral adenoma that warrants referral for surgery[5].

Traditionally, unilateral adenomas appear as small nodules < 2 cm in diameter and are hypodense. In contrast, it should be noted that adrenal carcinomas are usually > 4 cm in diameter and are heterogenous on CT scan. IHA can appear as bilateral nodules on CT scan. However, sometimes, the CT scan can be read as normal. Given the caveats of adrenal CT scans, imaging must often be combined with other test modalities with most favoring AVS for biochemical confirmation of laterality prior to surgical intervention.

Scintigraphy: Scintigraphy iodomethyl-nor-cholesterol (NP-59) uptake also known as dexamethasone-suppression DS adrenal scintigraphy can be considered for adenomas > 1.5 cm in diameter. However, a definitive distinction of unilateral *vs* bilateral source of aldosterone cannot be made as tracer uptake for the most part correlates with tumor volume and less so with tumor secretion[28]. This imaging is not useful in cases with microadenomas. Imaging with scintigraphy does not reliably replace adrenal venous sampling in characterizing nodule function[28].

AVS: Selective AVS is the most reliable technique used to distinguish a true unilateral adenoma (APA) from bilateral disease notably IHA[29]. AVS is critical in categorizing certain patients correctly. In a prospective study of 203 patients selected for AVS to determine if the diagnosis could be made based solely on CT showed that 48 patients (24.7%) would have had inappropriate surgery and 42 patients (21.7%) would have been denied needed for surgery based on CT scan results alone[5]. AVS may be helpful for patients when adrenal CT is normal, shows micronodularity (unilateral or bilateral < 1 cm) or a combination of micro and macronodules[5,26]. In a recent radiological study, matching patients who underwent CT *vs* CT and AVS found that for tumors larger than 1 cm, CT can reliably predict unilateral disease and thus obviate the need for AVS. This study concluded that AVS is helpful when CT study is equivocal or shows bilateral disease[27]. An algorithm based partly on age of more or less than age 40, together with the nodule's appearance, size and uni-laterality as seen on CT scan may best guide next steps, including referral for AVS[26]. Based on this algorithm, it should be noted that patients younger than age 40 with a unilateral hypo-dense nodule > 1 cm on adrenal CT scan who have a very high probability of unilateral adenoma may proceed to surgery without AVS[26]. An expert consensus statement has defined the following exceptions to recommending AVS: age < 40 years with marked PA and a clear uni-lateral adrenal adenoma and a normal contralateral adrenal gland on CT, unacceptable high risks of adrenal surgery (*i.e.*, due to multiple comorbidities), those with suspected adrenocortical carcinoma and those with proven Familial Hyperaldosteronism-Ⅰ or with Familial Hyperaldosteronism-Ⅲ[30].

In AVS, adrenal veins are accessed *via* the femoral vein. Blood samples are taken from both adrenal veins and compared to that found in the inferior vena cava (IVC) at the level below the renal veins. The right adrenal vein may be particularly challenging to access. The left adrenal sample is accessed from the inferior phrenic vein next to the adrenal vein[5]. During the study, cosyntropin or ACTH is infused throughout the procedure to minimize fluctuations in aldosterone levels due to stress[26]. Using a radioimmunoassay, aldosterone and cortisol concentrations of the right and left adrenal glands as well as the IVC are measured. To account for dilution, the aldosterone concentration is then corrected using cortisol so that an aldosterone/cortisol ratio is obtained. The ratios of aldosterone to cortisol from each side are then compared[5]. Traditionally, the cut off for distinguishing a unilateral source of aldosterone is a lateralization ratio of > 5[31]. However, a recent study found a lateralization ratio of more than > 4 as indicative of APA[5]. Others suggest a cortisol-corrected aldosterone ratio from high side to low side more than 4:1 is indicative of unilateral aldosterone excess; a ratio less than 3:1 is suggestive of bilateral aldosterone hypersecretion[8].

There are several complications that may occur during AVS. These can be as high as 5%. These complications are: groin hematoma, adrenal hemorrhage, dissection

of adrenal vein and paroxysmal atrial fibrillation. Theoretically, Addisonian crisis could also occur[5]. There is a major limitation of AVS including the access to institutions that perform this specialized, highly skilled procedure. A recent international study of AVS, found that many referral centers worldwide, do not use AVS[32], mainly because of lack of skilled professionals with experience conducting the procedure. In a recent study, the failure rate of AVS was low at 4.4%. However, the study relied on one angiographer to perform the vast majority of procedures[5]. In general, the failure rate can be greater than 25%[33].

Management

Medical management: Medical management should be provided to all patients with demonstrated bilateral disease. Additionally, medical management is an option for patients with unilateral disease who do not undergo surgery. It has been noted that those with IHA are more likely to require multi drug treatment as compared to APA[34].

The main stay of treatment of PAH is spironolactone, a competitive aldosterone receptor antagonist[34]. Spironolactone should be started in patients without contraindications. The starting dose is 12.5-25 mg per day. It is recommended that the prescribing provider follow the patient's blood pressure and potassium levels closely. The follow up should be close for the first couple of weeks after starting this medication. Spironolactone should be titrated slowly until blood pressure is controlled to a maximum dose of 100 mg per day[8]. Spironolactone has multiple side effects that may affect quality of life particularly for male patients, the most notable side effect being gynecomastia. In general, side effects as noted by patients may include breast tenderness, breast engorgement, decreased libido, muscle cramps, erectile dysfunction, menstrual irregularities and loss of axillary hair[35].

Eplerenone, a selective aldosterone receptor antagonist, has fewer side effects as compared to spironolactone but is more costly. Due to minimal affinity for the androgen, estrogen and progesterone receptors, this drug does not result in significant androgen effects such as gynecomastia that is associated with spironolactone. In a small study comparing, blood pressure in patients with bilateral IHA, eplerenone dosed at 50-400 mg per day was shown to be just as effective as spironolactone. Furthermore, 2 patients had gynecomastia reversed by switching from spironolactone to eplerenone[34]. In a recent prospective study evaluating long term follow up of patients and renal function, they included: adrenalectomy (86 cases), eplerenone (18 cases) and spironolactone (65 cases), spironolactone was just a good at preserving Glomerular Filtration Rate (GFR) and urine albumin excretion as patients who had an adrenalectomy, however patients on eplerenone required on average more anti-hypertensive medications[36]. The starting dose for eplerenone is 25 mg per day or twice a day. Both, spironolactone and eplerenone, should be used with caution in patients with chronic kidney disease stage 3 because of the risk of hyperkalemia. They should be avoided in patients with end stage renal disease and chronic kidney disease stage 4. Amiloride, a sodium channel blocker can also correct hypokalemia and improve blood pressure without the side effects of spironolactone. Muscle cramps have been noted as side effect[35].

Calcium channel blockers can decrease aldosterone secretion and have variable success at lowering blood pressure. Angiotensin converting enzyme inhibitors may also improve blood pressure. It is postulated that IHA would be more responsive to treatment since APAs are autonomous and would therefore be less likely to respond to angiotensin Ⅱ. Angiotensin Ⅱ inhibitors have a role as additional agents in treatment[37]. In a small study looking at long term follow up of patients with APA who chose medical therapy, with a follow up time between 5-17 years, blood pressure was at goal for 75% of participants. The majority patients (n = 24) were receiving a potassium-sparing diuretic plus an additional blood pressure medication. All had resolution of hypokalemia. In the time of follow up, none had a malignant transformation and none experienced stroke, myocardial infarction or heart failure[35].

Surgery: Once potassium and blood pressure are controlled, laparoscopic adrenalectomy is indicated for unilateral source of aldosteronism. AVS should be considered prior to surgery as discussed in detail above. The laparoscopic approach is preferred because it offers faster recovery from surgery with associated shorter length of stay and lower morbidity[38].

A recent study, found that adrenalectomy (the majority of which was done laparoscopically) did have lower overall medical costs compared to medical treatment[39]. Further, surgery for APA has been shown to normalize hypokalemia and improve if not normalize blood pressure. In one third to half of patients it can offer a cure by normalizing blood pressure[40].

In contrast, for bilateral disease or IHA, unilateral or bilateral adrenalectomy is not indicated. Surgery for IHA in general does not correct the hypertension. In some select cases of bilateral disease, those with poorly controlled hypertension on more than three drugs, with incomplete lateralization on AVS, a unilateral adrenalectomy may be considered. In some cases, blood pressure may improve and the patient may be able to take fewer anti-hypertensive drugs post surgery[5,41].

Surgical outcome and post-operative follow up: Thirty to 60% of patients with a unilateral aldosterone tumor can be cured and achieve normal blood pressure after surgery. However, many may still require at least one blood pressure medication post surgery[42].

In general, mineralocorticoid receptor antagonist and potassium supplements are discontinued post

op. During the first month post surgery a generous salt diet is encouraged to stimulate the contralateral adrenal gland. Blood pressure normalizes within 6 mo but can take up to one year post surgery[42]. Patients that are more likely to have persistent hypertension despite adrenalectomy include: older age, chronic hypertension > 5 years, larger tumor size, significant family history of hypertension and those with additional secondary hypertension[40,43-47]. Also, one study found that higher creatinine levels also predicts persistent hypertension post surgery[48].

Recently, a score card of low, medium or high likelihood of hypertension resolution post surgery was recently developed using a predictive regression model that compiled data from 100 patients with primary hyperaldosteronism who underwent adrenalectomy. Based on 4 predictors: ⩽ 2 or fewer anti-hypertensive drugs (2 points), body mass index ⩽ 25 kg/m^2 (1 point), hypertension of ⩽ 6 years (1 point) and female sex (1 point), the likelihood of a cure was low (27% cured), medium or high (75% cured)[49]. Using data from 91 Japanese patients, this score card was validated in an Asian population[50].

PAH and associated genetic disorders: A minority of patients (1%-2%) with PAH have a familial syndrome type Ⅰ or Ⅱ. Type Ⅰ is GRA and type Ⅱ familial aldosterone-producing adenoma or IHA[6]. Recently, a new genetic form, familial hyperaldosteronism type Ⅲ has also been identified[51].

Type Ⅰ (GRA) is an autosomal dominant condition characterized by variable degree of aldosterone excess, increased steroids (18-hydroxycortisol and 18-oxocortisol), and suppression of disease with glucocorticoid treatment. It is due to a chimericic gene duplication between the CYP11B1 (11β-hydroxylase) and CYP11B2 (aldosterone synthase) genes. Genetic testing should be targeted to those with hypertension at age < 20 that is resistant, accompanied by hypokalemia, family history of hypertension, and cerebral hemorrhage at a young age[52]. The Endocrine Society guidelines recommend genetic testing to rule out GRA for those patients who have onset of hypertension at age < 20, and those with a family history primary hyperaldosteronism or stroke at age < 40[8].

Type Ⅱ familial hyperaldosteronism is an autosomal dominant condition that does not suppressed with exogenous glucocorticoids and has been linked to locus 7p22[6]. Type Ⅲ familial hyperaldosteronism involves a germline mutation in the gene coding for ion channel KCNJ5[51].

Conclusion

Primary hyperaldosteronism is found in 5%-13% of population[3] Prevalence has increased with the advent of more refined screening and confirmatory studies. However, specific screening cutoffs vary by institution. The majority of patients fall into one of two categories: APA, which is unilateral and should be surgically removed, and IHA which is bilateral and requires medical management.

The cost and morbidity of chronic medication, as well as new evidence that hyperaldosteronism itself aside from blood pressure may increase cardiac events and possibly renal dysfunction, needs to be considered. AVS is the most reliable technique used to distinguish a true unilateral adenoma (APA) from bilateral disease notably IHA. However, this procedure is highly specialized and is not available at every institution. With the advent of safe, less invasive, and shorter surgery, laparoscopic adrenalectomy for APA is preferred as it offers the best chance for a cure.

PHEOCHROMOCYTOMA

Introduction

Pheochromocytoma is a tumor of the adrenal medulla (chromaffin cells) that secretes excess catecholamines, epinephrine, norepinephrine, and dopamine. Paraganglioma is a tumor derived from extra-adrenal chromaffin cells of the sympathetic nervous system. Pheochromocytomas and catecholamine secreting paragangliomas account for 0.2%-0.6% of all causes of hypertension in the population[53-55]. Both of these tumors have similar clinical presentations and management. However, it is important to classify them separately because of the implications of genetic testing, risk of malignancy and associated neoplasms. In this review, we will focus mainly on pheochromocytomas arising from the adrenal gland.

Clinical presentation

Pheochromocytoma is often referred as the great mimicker of other conditions. The average age of presentation of pheochromocytoma is approximately 40-50 years with equally distribution between men and women[56]. Patients can present with different symptoms that can vary greatly between patients as well as within family members in familial syndromes associated with pheochromocytoma. The classic triad for pheochromocytoma: episodic headache, sweating and tachycardia are not always present in most patients[57,58]. The most common sign, found in about 80%-90% of patients with pheochromocytoma, is hypertension[59].

Types of hypertension in pheochromocytoma[54,60]: (1) Sustained hypertension - found in about 50% of the patients with pheochromocytoma; (2) Paroxysmal hypertension - found in 45% of the patients; and (3) Normotension in 5%-15% of the patients.

The type of hypertension is often dependent on the pattern of catecholamine secretion from the tumor - which is either continuous, episodic or both. There is an inversion of the circadian BP rhythm and increased blood pressure variability due to high circulating levels of catecholamines[61].

Paroxysm or "spell" can be triggered by physical activity (exercise or postural changes) as well as from tumor manipulation[60]. In addition, the biochemical phenotype of the tumor, *i.e.*, type of catecholamine secreted influences the type of hypertension. Patient with high levels of norepinephrine and epinephrine more likely have sustained hypertension while patients with high levels of dopamine are often normotensive[62,63]. Orthostatic hypotension may occur more commonly in patients with sustained hypertension than in those with paroxysmal and normotensive hypertension. The mechanism for orthostatic hypotension is thought to be due to decreased blood volume caused by persistent vasoconstriction and diminished sympathetic reflex[64].

Characteristic symptoms include headache (90% of symptomatic patients), pallor and anxiety, feeling of doom, generalized sweating, fever, nausea or vomiting. Rarely secondary erythrocytosis, new onset diabetes mellitus and isolated dilated cardiomyopathy are associated with pheochromocytoma[57,65-68].

Pheochromocytomas represent one of the main causes of hypertensive crisis in the hospital. These crises are precipitated by postural changes, physical stress, surgery and invasive procedures in undiagnosed patients. Further, it can be precipitated by the use of medications such as corticosteroids, histamine, metoclopramide, phenothiazines, tricyclic antidepressants or anesthetic agents[69]. The clinical presentation during a crisis will depend on the effect of the catecholamine release on the target organs[65].

Diagnosis

Clinicians should keep a high index of clinical suspicion in young adults (< 25 years) with new-onset hypertension, people with clinical features typical of pheochromocytoma, a history of resistant hypertension, an incidental adrenal adenoma, severe hypertension during general anesthesia or during sedation, idiopathic cardiomyopathy and in patients with a family history of pheochromocytoma.

The cornerstone for diagnosis of pheochromoctyoma is the measurement of urine and plasma fractionated metanephrines. Most pheochromocytomas have fluctuating levels of catecholamines, but the metabolism of catecholamines into metanephrines is constant[57,70,71].

There is no consensus regarding the "best test" for diagnosis. However, most endocrinologists favor choosing the best test based on the degree of clinical suspicion. If clinical suspicion is high (family history, genetic syndrome, past history of pheochromocytoma, positive adrenal gland imaging characteristics) then plasma fractionated metanephrines are measured (sensitivity is 96%-100% and specificity 85%-89%)[71-73]. If clinical suspicion is low (resistant hypertension, hyperadrenergic spells, no classical imaging characteristics of adrenal gland), then 24-h urinary fractionated catecholamines and metanephrines (sensitivity 98% and specificity 98%) should be measured[72,74,75]. Twenty-four hour urinary creatinine should be measured simultaneously with urinary metanephrines to confirm that urine collection is completed[76]. For plasma metanephrines measurement, blood sample collection in the supine position is recommended after 30 min in recumbent position before sampling[76]. If the blood sample collection is obtained in a seated position, the clinician should be aware of the potential for false positive result from sympathoadrenal activation of the upright position[77,78]. In patients with positive test results from seated sampling, repeat testing with samples obtained in supine position might be necessary[76]. The reference interval of plasma metanephrines should be used as established in the same position of blood draw to avoid the inaccurate interpretation. Caffeine intake and medications that interfere with the catecholamine or metanephrine levels should be avoided at least 24 h before the diagnostic work up for pheochromocytoma[79,80].

Imaging modalities

CT imaging: Adrenal pheochromocytomas with a size larger than 0.5 cm as well as metastatic pheochromocytomas can be detected by CT scan with high sensitivity of 85%-94% (Figure 1)[81]. Ninety-five percent of tumors are within the abdomen and pelvis and 10% of tumors are extra-adrenal[68]. Pheochromocytomas have a varied appearance on a non-contrast CT ranging from low density to soft-tissue attenuation. An attenuation threshold of 10 Hounsfield units (HU) on a non-contrast CT has a sensitivity of 71% and a specificity of 98% to differentiate a benign from malignant tumor[82]. Approximately two thirds of pheochromocytomas are solid and the rest are complex or cystic[83]. Hemorrhage and calcifications in a pheochromocytoma can be found in approximately 10% of all pheochromocytomas and it may increase the density of the pheochromocytoma[83]. CT with low-osmolar contrast is safe in patients with pheochromocytoma not on alpha-or beta-blockers[84]. Pheochromoctyomas can show either homogenous or variable enhancement (depending on the solid and cystic components) on contrast enhanced CT scan. The characteristic appearance seen on contrast CT scan of a pheochromocytoma include increased contrast uptake (40-50 HU) with delayed washout with necrosis and calcifications[81,85].

Magnetic resonance imaging: Magnetic resonance imaging (MRI) are more expensive and lacks the spatial resolution offered by CT scan. The classical imaging description for pheochromocytoma is a "light bulb" bright lesion on T2-weighted imaging comparable to signal intensity of CSF in 11%-65% of pheochromocytomas[86,87]. This variability in the appearance on T2-weighted imaging is due to the water content present in cystic or necrotic components of the tumor. T1-weighted imaging of pheochromocytomas are typically isointense to muscle and hypointense to liver[81]. MRI gadolinium enhancement on MRI is variable

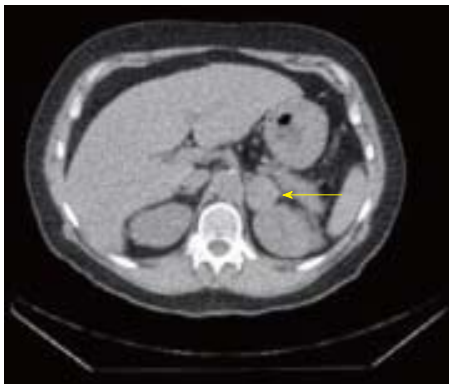

Figure 1 Computerized tomography scan of the abdomen demonstrating left adrenal nodule 3.5 cm.

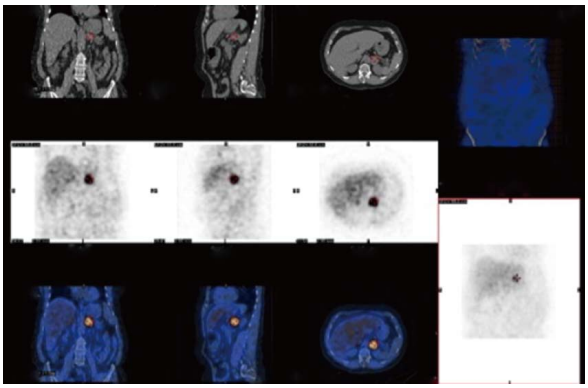

Figure 2 I-123-metaiodobenzylguanidine-SPECT images demonstrated focal increased tracer activity in the left adrenal nodule compatible with metaiodobenzylguanidine avid tumor.

depending on the presence of cystic-necrotic areas, which do not enhance[88].

Functional imaging is indicated in-patient with large (> 10 cm) adrenal pheochromocytomas, extra-adrenal pheochromocytomas, metastatic disease and tumor recurrence assessment. Functional imaging examinations are performed using ^{131}I- and ^{123}I-metaiodobenzylguanidine (MIBG) (Figure 2), ^{111}In-pentetreotide (Octreoscan, Covidien), and several PET ligands including ^{18}F-fluorodopamine, ^{18}F-dihydroxyphenylalanine (DOPA), and ^{18}F-FDG (FDG)[81,89]. FDG-PET is more sensitive than ^{123}I-MIBG and CT/MRI for detection of metastatic disease[90,91].

Management

Pre-operative management: A detailed history, physical examination and cardiac evaluation of patients is necessary as part of the preparation for surgery.

Medical management: Appropriate and optimal pharmacological therapy to block the effects of released catecholamines, is of critical importance in the pre-operative phase of the surgical management of pheochromocytoma[92]. The main goals for therapy includes: normalization of blood pressure, heart rate, restores volume depletion and prevention of intraoperative hypertensive crisis.

Phenoxybenzamine (Dibenzyline), a long lasting, non-selective, irreversible, and noncompetitive alpha-receptor blocker. This medication reduces blood pressure fluctuations, eases vasoconstriction and prevents intra-operative hypertensive crisis[93]. Phenoxybenzamine is usually started at a dose of 10 mg twice a day with increments of 10-20 mg every 2-3 d until clinical symptoms from pheochromocytoma are controlled or side effects of the medication appears, which usually takes 7-14 d. Maximum dose is 1 mg/kg per day[76]. The side effects of this medication are postural hypotension with reflex tachycardia, dizziness, syncope and nasal congestion. Selective, competitive, short-acting alpha-blockers like doxazosin (Cardura), prazosin (Minipress) and terazosin (Hytrin) are preferred in some institutions as they are associated with less reflex tachycardia and a lower incidence of postoperative hypotension as compared to phenoxybenzamine. However, because of the short half life of these selective alpha-1 blockers, these medications should be given on the morning of the surgery. In a study, comparing the use of these different classes of alpha blockers in the preoperative management of laparoscopic resection of pheochromocytoma, phenoxybenzamine use was associated with better decrease in intra-operative hypertension at the expense of prolonged post-operative hypotension requiring the use of vasopressors. In contrast, patients treated with doxazocin had no clinically significant differences in post surgical outcomes[94].

Once optimal α-blockade is achieved, β-blockers are used for the management of catecholamine-induced tachyarrhythmias. These medications should not be used in the absence of α-blockers as they will exacerbate epinephrine-induced vasoconstriction by blocking the vasodilator component (β2). The most commonly used β-blockers are the non-selective β-receptor blocker propranolol (Inderal LA) (20-40 mg - 3 times a day) and the cardio selective β-1 blockers atenolol (Tenormin) (25-50 mg per a day)[76].

Calcium channel blockers are the second line anti-hypertensive medications use to supplement α-blockers[95]. They block norepinephrine mediated calcium influx into vascular smooth muscle and help in controlling hypertension and tachyarrhythmia. In addition, they might prevent catecholamine induced coronary vasospasm[96,97]. The calcium channel blockers used are amlodipine (Norvasc) in a dose of 10-20 mg, nicardipine (Cardene) in a dose from 60-90 mg per day, nifedipine SR (Adalat) in a dose of 30-90 mg and verapamil ER (Isoptin SR, Calan SR) in a dose from 180-540 mg per day[98].

Metyrosine (alpha-methyl-para-tyrosine, Demser) is an analog of tyrosine that is a competitive inhibitor of tyrosine hydroxylase, the rate limiting enzyme in catecholamine biosynthesis. Metyrosine is added to α- and β-blockers in patients with extensive metastatic

disease or large tumor burden[99]. This medication incompletely depletes the catecholamine stores after 3 d of treatment. The recommended dose in all surgical candidates is 250 mg orally every 8-12 h with increments of dose by 250 to 500 mg every 2-3 d up to a total of 1.5 to 2 g per day. The medication is usually initiated 1-3 wk prior to surgery[98]. Metyrosine helps to control blood pressure during induction of anesthesia and surgical manipulation of the tumor[100,101]. The side effects of this medication include depression, anxiety, sedation, extra-pyramidal signs, crystalluria and galactorrhea[102].

Optimizing cardiovascular function prior to surgery with normalization of blood pressure 10-14 d prior to surgery, initiating a normal or high-salt diet (usually 3 d after alpha-blockers are initiated) and expansion of blood volume by initiating pre-operative isotonic intravenous fluids minimizes protracted post-operative hypotension or shock from sudden diffuse vasodilatation at time of tumor removal[98]. In patients with resistant hypertension or hypertensive crisis, sodium nitroprusside or phentolamine infusion, can be used preoperatively.

Intra-operative management: The intra-operative management of hypertension or hypertensive crisis along with prevention of postoperative hypotension is important for successful and safe surgical resection of pheochromocytoma. Nitroprusside (Nitropress), an intravenous vasodilator is the preferred medication for intraoperative control of hypertension due to its rapid onset and short duration of action. Nicardipine (Cardene) is a calcium channel blocker that may be used as an alternative. Intravenous magnesium sulfate is used in some centers, in a dose of 40-60 mg/kg before intubation followed by an infusion of 2 g/h. Magnesium sulfate inhibits catecholamine release, enhances vasodilatation, blocks catecholamine receptors and stabilizes the myocardium from arrhythmias[103].

Surgery: Surgical resection is the only curative treatment of pheochromocytomas. Laparoscopic adrenalectomy is a well-established approach in intra-adrenal pheochromocytomas 6 cm or less in diameter, with no malignant features. This approach has been shown to improve surgical outcomes, reduced hospital stay and is better for patient comfort and recovery time compared to open adrenalectomy[104,105]. Laparoscopic adrenalectomy is also often used in tumors above 6 cm in diameter but often these procedures are converted to open procedure intraoperative[106,107]. More recently, experienced surgeons have preferred retroperitoneal endoscopic approach for adrenalectomy, as this provides direct access to the adrenal glands without requiring mobilization of adjacent organs (liver or pancreas), better in bilateral tumors and avoid repositioning as compared to the transabdominal approach[108,109].

Postoperative management: Potential postoperative complications after pheochromocytoma resection include tachyarrhythmias, splenic injury (left sided lesions), renal impairment, hypoglycemia and persistent hypotension. These complications have been shown to correlate with preoperative systolic blood pressure, urinary metanephrines and tumor size[110,111]. Postoperative hypoglycemia is related to catecholamine-induced depletion of glycogen stores, overstimulation of insulin production by pre-operative α-blockade and hyperinsulinemia after loss of catecholamine inhibitory effect on the β2-receptors of the pancreatic islet cell[112,113].

Hemodynamic and blood glucose monitoring with optimal blood pressure, tachyarrhythmia's and intravenous fluids (including glucose) are critical for a smooth postoperative course.

Surgical outcome and post-operative follow up: Surgical removal of pheochromocytoma does not always lead to a long-term cure of hypertension. Some studies report 80% of patients may become normotensive. However, postoperative hypertension may persist due to residual tumor, metastatic disease or intra operative injury to the renal artery or most commonly due to acquired renovascular changes due to pre-operative hypertension.

Plasma fractionated catecholamines or urinary metanephrines should be measured two weeks after surgery, and thereafter every three months for the first year and then annually. Regular blood pressure monitoring and optimal management of hypertension should be done.

Pheochromocytoma and associated genetic disorders: Most of the pheochromocytomas are sporadic although 15%-20% of patients with pheochromocytoma have an associated familial disease. These patients tend to have bilateral adrenal pheochromocytomas or have paragangliomas. The frequency of pheochromocytomas in some of the autosomal dominant familial disorders are 10% to 20% in Von Hippel-Lindau syndrome, 50% in Multiple endocrine neoplasia type 2, and 0.1% to 5.7% in neurofibromatosis type 1. Genetic testing should be considered if a patient has bilateral pheochromocytomas, onset less than 45 years, paragangliomas, family history of pheochromocytomas or clinical findings with strong evidence for hereditary syndrome[114,115]. A sequential genetic testing algorithm, based on these findings, tailored for cost efficacy has been proposed[116].

Pheochromocytoma and pregnancy: Pheochromocytoma is a rare cause of hypertension in pregnancy with a frequency of 0.002% of all pregnancies and untreated it carries a high maternal and fetal mortality of around 50%[117]. Early detection and proper treatment during pregnancy decrease the maternal and fetal mortality to < 5% and 15% respectively. The clinical features of pheochromocytoma in pregnancy are similar to non-pregnant patients. The characteristics of

Table 1 Key clinical features, screening and confirmatory tests, radiological and management modalities for primary aldosteronism and pheochromocytoma

	Primary aldosteronism	Pheochromocytoma
Clinical features	Difficult to control HTN	
Common Symptoms	on 3 or more hypertensive agents	Episodes or paroxysmal hypertension
		Headache
	Young age of onset of HTN	Sweating
		Palpitations
Signs	With or without hypokalemia	
	Asymptomatic *vs* Symptomatic	Hypertension
	Muscle weakness, cramping, headaches, palpitations, and polyuria	Tachycardia
		Orthostatic hypotension
		Heart failure
Screening tests	AM plasma aldosterone to renin ratio > 30	24-h urine fractionated metanephrines
	+/- Aldosterone > 20 ng/dL	Plasma fractionated metanephrines (high suspicion)
Confirmatory tests	Oral sodium loading test with 24 h aldosterone level > 12 μg/24 h	Same as above
	Saline infusion test	
	Fludrocortisone suppression test	
	Captopril challenge test	
Radiology	Adrenal protocol CT	Adrenal protocol CT/MRI
	+/- Scintigraphy	^{123}I-MIBG scan/^{111}In-pentetreotide/FDG-PET
	Adrenal vein sampling	
Treatment	For bilateral disease (or for those with unilateral disease who are unable to undergo surgery)	Pre-op preparation (10-14 d prior to surgery)
Medical		Phenoxybenzamine
	Spirinolactone (best choice)	Alpha-blockers blockers-Doxazocin, Prazocin or Terazocin
	Eplerenone	Calcium channel blockers
	Amiloride	Beta-blockers
		Metyrosine
Surgical	For unilateral source of aldosteronism: Laparoscopic adrenalectomy	Laparoscopic/retro-peritoneal adrenalectomy of adrenal pheochromocytoma

CT: Computed tomography; MRI: Magnetic resonance imaging; FDG-PET: Fluorodeoxyglueose-positron emission tomography.

hypertension that should lead to a clinical consideration of pheochromocytoma are severe hypertension diagnosed in the first and second trimesters, uncontrolled hypertension in the third trimester, unexplained postural hypotension or cardiogenic shock in the antepartum period. Plasma free metanephrines and urinary fractionated metanephrines assessment are the first recommended tests in the diagnostic workup. MRI without gadolinium as well as ultrasonography is imaging modalities of choice. Pre-operative management is similar to non-pregnant adults. Laparoscopic adrenalectomy is the surgery of choice in the first 24 wk of gestation. If the tumor is diagnosed in the third trimester, the patient should be managed until the fetus is viable with medication management and caesarean section with tumor removal in the same session or at a later stage is then preferred since vaginal delivery is possibly associated with higher mortality[117].

Conclusion

In summary, both primary hyperaldosteronism and pheochromocytoma are important causes of endocrine hypertension that carry significant mortality and morbidity, if left untreated. A high index of clinical suspicion, a systematic approach to diagnosis, localization and management of both these conditions is important. Personalized approach with multidisciplinary team of internists, endocrinologists and surgeons is recommended in optimal management of these conditions.

Key clinical features, investigations and management modalities of primary hyperaldosteronism and pheochromocytoma are summarized in Table 1.

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REVIEW

Novel contributions of multimodality imaging in hypertension: A narrative review

Erick Alexanderson-Rosas, Enrique Berríos-Bárcenas, Aloha Meave, Juan Carlos de la Fuente-Mancera, Mariano Oropeza-Aguilar, Alejandro Barrero-Mier, Andrea de Guadalupe Monroy-González, Raul Cruz-Mendoza, Gerardo Yoshiaki Guinto-Nishimura

Erick Alexanderson-Rosas, Juan Carlos de la Fuente-Mancera, Mariano Oropeza-Aguilar, Alejandro Barrero-Mier, Andrea de Guadalupe Monroy-González, Raul Cruz-Mendoza, Gerardo Yoshiaki Guinto Nishimura, Nuclear Cardiology Department, National Institute of Cardiology Ignacio Chávez, Mexico City 14080, Mexico

Enrique Berríos-Bárcenas, Aloha Meave, Cardiac Magnetic Resonance Department, National Institute of Cardiology Ignacio Chávez, Mexico City 14080, Mexico

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Correspondence to: Dr. Enrique Berríos-Bárcenas, MD, Cardiac Magnetic Resonance Department, National Institute of Cardiology Ignacio Chávez, uan Badiano #1. Colonia Sección XVI, Mexico City 14080, Mexico. berrios.md@gmail.com
Telephone: +52-55-54850672
Fax: +52-55-55732111

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Abstract

Hypertension is currently one of the most prevalent illnesses worldwide, and is the second most common cause of heart failure, only behind ischemic cardiomyopathy. The development of novel multimodality imaging techniques in recent years has broadened the diagnostic methods, risk stratification and monitoring of treatment of cardiovascular diseases available for clinicians. Cardiovascular magnetic resonance (CMR) has a great capacity to evaluate cardiac dimensions and ventricular function, is extremely useful in ruling-out ischemic cardiomyopathy, the evaluation of the vascular system, in making the differential diagnosis for resistant hypertension and risk stratification for hypertensive cardiomyopathy and constitutes today, the method of choice to evaluate left ventricular systolic function. Computed tomography (CT) is the method of choice for the evaluation of vascular anatomy, including coronary arteries, and is also able to provide both functional and structural information. Finally, nuclear cardiology studies have been traditionally used to evaluate myocardial ischemia, along with offering the capacity to evaluate ventricular, endothelial and cardiac innervation function; information that is key in directing the treatment of the patient. In this narrative review, the most recent contributions of multimodality imaging to the patient with hypertension (CMR, CT and nuclear cardiology) will be reviewed.

Key words: Cardiac imaging techniques; Multimodality imaging; Magnetic resonance imaging; Multidetector computed tomography; Cardiac-gated single photon

emission computed tomography; Positron emission tomography; Hypertension

Core tip: Diverse imaging modalities are playing a larger role every day in the diagnosis, treatment decisions and follow-up of patients. This is especially true in patients with hypertension. The merger of diverse imaging techniques has led to the rise of Multimodality Imaging, using tools such as cardiovascular magnetic resonance, computed tomography and nuclear cardiology that aid clinicians make the best therapeutic decisions. In this article, we will make a comprehensive review of the most novel contributions of multimodality imaging to patients with hypertension.

Alexanderson-Rosas E, Berríos-Bárcenas E, Meave A, de la Fuente-Mancera JC, Oropeza-Aguilar M, Barrero-Mier A, Monroy-González AG, Cruz-Mendoza R, Guinto-Nishimura GY. Novel contributions of multimodality imaging in hypertension: A narrative review. *World J Hypertens* 2015; 5(2): 28-40 Available from: URL: http://www.wjgnet.com/2220-3168/full/v5/i2/28.htm DOI: http://dx.doi.org/10.5494/wjh.v5.i2.28

INTRODUCTION

Hypertension is one of the most prevalent illnesses worldwide. Data from the NHANES 2007-2010 found that approximately 6% of adults in the United States have undiagnosed hypertension and that in the adult general population; up to one-third might present this illness. It is considered that a 65% of patients presenting with heart failure have a history of Hypertension, and is currently its second most common etiology, only behind ischemic cardiomyopathy[1]. Furthermore, besides its impact on the heart, Hypertension also produces serious damage in blood vessels (including the aorta), kidneys, eyes and brain.

During the last few years, the development of multimodality imaging has contributed to a better understanding of the pathophysiology of cardiovascular diseases, also aiding in its early diagnosis and also monitoring the response to treatment. Traditionally, echocardiogram has been used as the standard imaging method for patient evaluation. However, multimodality imaging has made available a wide array of other imaging techniques [cardiovascular magnetic resonance (CMR), computed tomography (CT), positron emission tomography (PET), single-photon emission computed tomography (SPECT)] for the patient with Hypertension, which might help improve treatment and monitoring of the patients, thus contributing to control this worldwide pandemic. In this review we will touch on the most novel contributions on this subject.

CMR

CMR is an imaging method that does not use ionizing radiation, and can evaluate both cardiovascular anatomy and function with high spatial resolution and diagnostic certainty. Furthermore, with the use of gadolinium-based contrasts, it is possible to evaluate vascular anatomy. The 1.5 tesla (T) machines are the most widely used models around the world, although there have been reports of the usefulness of new 3.0 T machines. Traditionally, the most used sequences in patients with hypertensive cardiomyopathy are: tracers, Steady-state Free Precision (SSFP) cine imaging, weighted T2 STIR (short-tau inversion recovery), fast spin-echo weighted T1 and T2, first step myocardial perfusion with gadolinium, phase contrast sequences, inversion recovery sequences for late enhancement and 3D angiographies. All imaging sequences must be acquired with electrocardiographic (ECG) gating, meaning that patients presenting rhythms other than sinus might generate imaging artifacts or suboptimal images. The complete protocol has a duration of approximately 45-60 min, during which the patient must be able to withstand performing 10-20 s apneas, and must also deal with being enclosed in a tight space. Therefore, the success of the study depends greatly on the appropriate selection of the patients. In case that the patient cannot tolerate the study, the best course of action is to perform the study with the patient under general anesthesia with invasive mechanical ventilation.

The following are the most relevant contributions of CMR to patients with Hypertension.

Measurements of volumes and ventricular mass

Hypertension has a direct impact on the heart, which is most pronounced in patients with poor control. The most common repercussions in cardiac anatomy are left ventricular hypertrophy and left atrial dilation (Figure 1).

The Framingham study demonstrated that left ventricular hypertrophy is associated with higher cardiovascular mortality, independently of the presence of coronary artery disease[2]. CMR is currently considered the gold standard for the quantification of cardiac dimensions, including ventricular mass, since CMR is a highly exact and reproducible method, when compared with 2D echocardiography. In a study that compared these 2 tools in a sample composed of patients with dilated cardiomyopathy, hypertrophic cardiomyopathy and healthy controls, the coefficients of intra-study variability for left ventricular mass were -1.0 ± 7.7 g for CMR and 8.7 ± 25 g for 2D echocardiography ($P < 0.001$)[3]. 3D echocardiography has demonstrated accuracy and reproducibility similar to CMR, however, it is still hindered by the same limitations as 2D echo: the need of a good acoustic window and experienced personnel in the usage of the device[4].

Besides the diagnosis of ventricular hypertrophy,

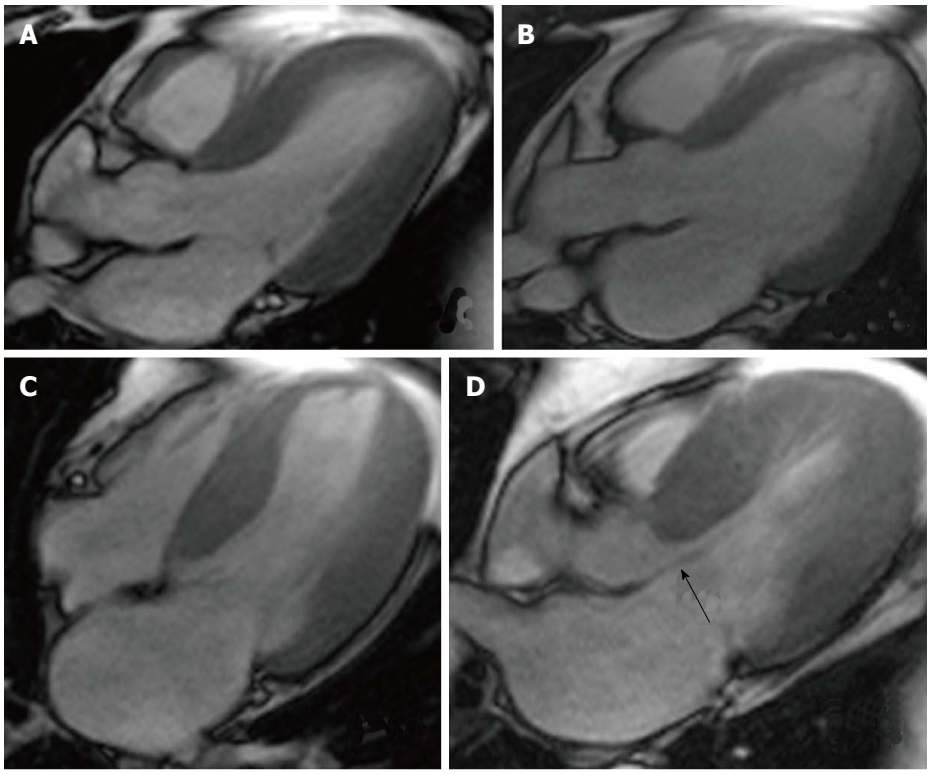

Figure 1 Cardiovascular magnetic resonance showing Steady-state Free Precision Sequences. A: Patient with hypertension presenting slight ventricular hypertrophy (septal wall of 13 mm); B: Patient with hypertensive cardiomyopathy in dilated phase with a LVDD = 70 mm, LVEF = 40%, left atrium = 65 mm; C: 51-year-old male patient with asymmetrical septal hypertrophy, with a maximum thickness of 27 mm; D: Same patient as in C, the arrow shows the anterior systolic movement of the mitral valve, generating outflow tract obstruction.

CMR can also contribute to the monitoring of these patients. Adequate antihypertensive treatment has demonstrated to revert ventricular hypertrophy, which is associated to a better prognosis, since it prevents the progression to heart failure. These studies have used CMR as the method of choice for serial measurement of ventricular mass[5-7].

However, ventricular hypertrophy is not exclusive of hypertensive cardiomyopathy and can be observed in other illnesses, such as infiltrative diseases (Fabry's disease, cardiac sarcoidosis, and cardiac amyloidosis), hypertrophic cardiomyopathy, aortic stenosis, exercise-induced hypertrophy, *etc.* CMR can readily differentiate between these different diseases and help in making the differential diagnosis in favor of hypertensive cardiomyopathy.

Left atrial dilation correlates with the severity and duration of hypertension. Traditionally, this has been measured by echocardiogram; however, CMR has proven to be a more reliable technique for measuring auricular volumes. The presence of left atrial dilation has been linked to the development of atrial fibrillation and increased mortality[8]. Furthermore, the morphology of the left atrial appendage can differentiate between patients with low and high risk of thrombus formation and subsequent embolic events[9]. Finally, left atrial dilation is related to the chronicity of ventricular diastolic dysfunction, as long as mitral valvular disease has been ruled out. Unlike echocardiography, an area of more than 20 cm^2 indicates an enlarged left atrium, with the enlargement being classified as severe if the area surpasses 40 cm^2[10].

Diastolic function evaluation

The gold standard for the evaluation of diastolic dysfunction has traditionally been the echocardiogram, which evaluates the pattern of the flow across the mitral valve with Doppler technique. CMR is able to obtain very similar information, by realizing ECG-gated sequences of contrast-phase in the around the mitral valve and the pulmonary veins. This way, it is possible to obtain a time/speed curve very similar to that shown by the echo, with similar diastolic dysfunction patterns[10-12]. Also, novel indexes, such as the Normalized average sweep rate, early diastole normalized sweep peak rate and the relationship between the normalized peak sweep rate in early diastole and the normalized peak sweep rate in atrial systole with an area under the curve of 0.93, 0.88 and 0.88 respectively[13].

Ruling out ischemic cardiomyopathy

Coronary artery disease is extremely prevalent in the hypertensive population. The presence of chest pain in patients with hypertensive cardiomyopathy is complex, since most of the times it can be due to the hemodynamic changes that arise as consequence of poor blood pressure control. This is complicated even further since traditional tests, such as the cardiac stress

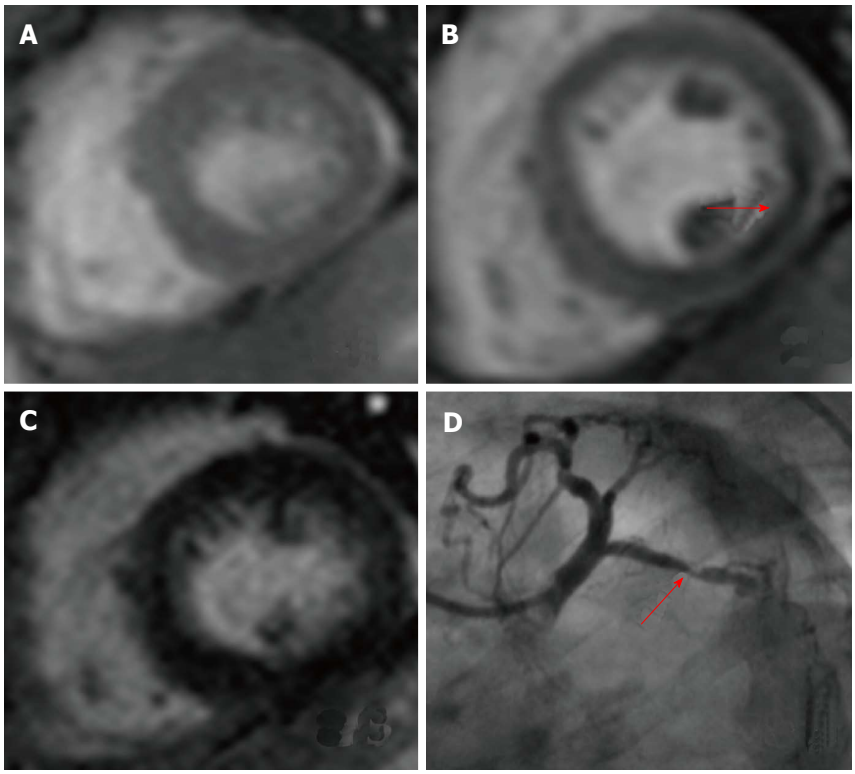

Figure 2 Evaluation of ischemia using cardiovascular magnetic resonance. A: Rest perfusion image using cardiovascular magnetic resonance that doesn't show any defects; B: Same patient post adenosine-induced stress test, the arrow shows a perfusion defect in the inferolateral wall (territory of the circumflex artery); C: Inversion recovery sequence that doesn't show the presence of late enhancement, which demonstrates the absence of infarction in the ischemic area; D: Invasive coronariography of the same patient, which shows a significant plaque in the circumflex artery.

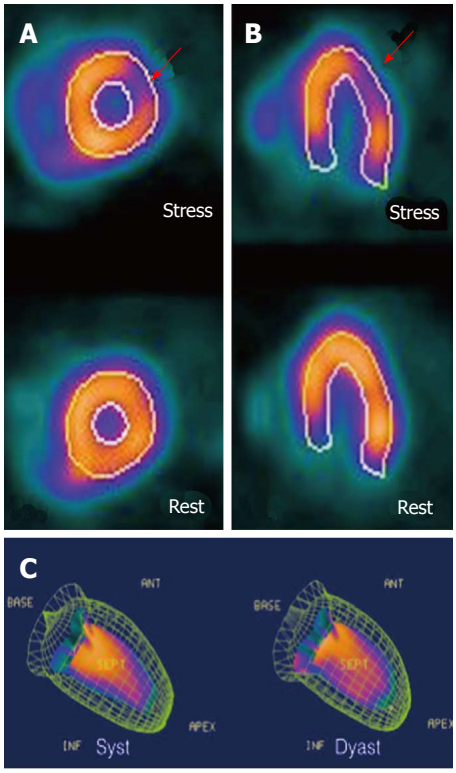

Figure 3 Evaluation of ischemia using single-photon emission computed tomography. A: Short axis view of the left ventricle with a perfusion defect visible after pharmacologic stress test in the anterior lateral wall (territory of the circumflex artery); B: Confirmation of the perfusion defect in the long axis view; C: Gated-single-photon emission computed tomography used to evaluate left ventricular function.

test yields suboptimal results due to the non-ischemic electrocardiographical changes seen in hypertensive patients. CMR has proven itself as a very useful diagnostic aid to rule-out the presence of ischemic cardiomyopathy. Through the use of myocardial perfusion imaging at rest, and after pharmacological stress (Figures 2 and 3), myocardial ischemia can be diagnosed with a sensitivity of 89% and a specificity of 76%[14]. Also, in patients with hypertensive cardiomyopathy and severe systolic dysfunction, the absence of ischemic patterns (transmural or subendocardic) excludes the coexistence of coronary artery disease as the cause of heart failure.

Evaluation of vascular disease

Hypertension exerts direct damage to the great blood vessels, especially the aorta. Magnetic Resonance Angiography is a very exact method to diagnose aortic dilation, and can also be used in the presence of acute aortic syndromes. There are studies that have shown that patients with cardiovascular risk factors (including hypertension) have an increased aortic wall thickness, which directly correlates to the presence of atherosclerosis and a poor prognosis[15]. CMR is able to quantify the atherosclerotic burden and plaque composition.

Furthermore, CMR can detect the presence of vulnerable plaques, mainly by the detection of necrotic lipid cores, calcification and hemorrhage in T1 and T2 sequences, with a sensitivity ranging from 84%-100%, both in autopsy studies and in live patients[16,17]. Recent studies have demonstrated that it is possible to quantify the necrotic lipid core, which does not differ from the pathology findings (23.7% *vs* 20.3%, P = 0.1)[18]. Other findings that can readily be detected by CMR are: plaque fissure, endothelial denudation with

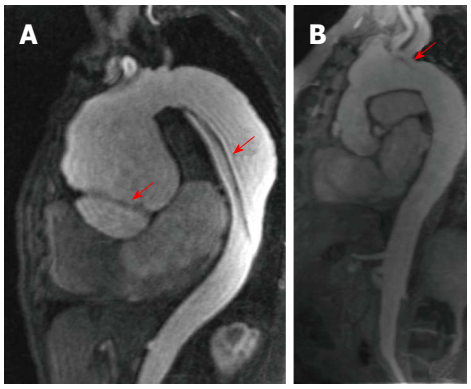

Figure 4 Evaluation of vascular anatomy using cardiovascular magnetic resonance. A: Patient with Marfan's syndrome that presents a Stanford A type dissected aortic aneurysm; the arrows point to the two sites of dissection; B shows post-surgical changes after a Bentall and Bono procedure; the arrow points to a dissection flap in the aortic arch.

platelet adhesion and fibrin deposit, late enhancement in plaques with active inflammatory activity and the severity of vascular stenosis[19].

The study of plaque composition with CMR has been used to demonstrate the beneficial effects of some therapeutic approaches. Lipid apheresis has proven to be statistically significant in diminishing the prevalence of necrotic lipid core in carotid plaques (28.1% *vs* 56.3%, $P < 0.05$)[20]. It also showed it reduced its lipid content (5.0% *vs* 11.6%, $P < 0.05$). Lipid lowering therapy has been shown to reduce the area of the lipid core of the plaques (0.7 mm^2 *vs* 10.2 mm^2, $P = 0.01$), along with the progression of vascular stenosis[21].

As for functional evaluation, there are studies that have demonstrated an increased vascular rigidity in patients with hypertension and diabetes mellitus, measured by the speed of the aortic pulse wave and vascular compliance[22,23]. The severity of the rigidity has also been associated with an increased degree of endothelial injury. The significance of these findings is still being clarified.

Aortic angioresonance has proven to have excellent diagnostic accuracy for the diagnosis of aortic dissection, with a sensitivity and specificity of 98% and an excellent performance compared to transesophageal echocardiography and CT (Diagnostic OR of 6.8, 6.5 and 6.1, respectively)[24]. It also offers a very high spatial resolution that allows an easy differentiation between the false and true aortic lumen and its branches. In dissections involving the aortic root, SSFP cine imaging allows the evaluation of aortic valve function, to assess the presence of regurgitation and at the same time, to measure both ventricular dimensions and function (Figure 4); all of which are vital parameters which directly affect therapeutic decisions in patients with acute aortic syndromes. The presence of liquid with an increased signal output in the pleura or pericardium are highly suggestive of aortic rupture with subsequent presence of free blood.

The fact that CMR does not emit ionizing radiation and its non-invasive nature make it a very attractive alternative to serially evaluate the diameter of aortic aneurysms. CMR has the potential to establish itself as the diagnostic tool of choice in the follow-up of patients with aortic pathology, due to the high reproducibility of its measurements.

In the case of intramural hematomas, the high spatial resolution allows to identify small hematomas that might have been overlooked even by CT. These blood collections are seen as hyperintense thickening in the aortic wall in weighted T1 sequence.

One of the drawbacks of CMR is that it is a study that requires a lot of time, and can be very uncomfortable for a patient in an acute setting.

Detection of intramyocardial fibrosis

The administration of gadolinium allows the evaluation of late enhancement, which correlates with the presence of interstitial fibrosis in hypertensive cardiomyopathy. The characteristic pattern is diffuse, and found mainly in the interventricular septum[25] (Figure 5). The presence of interstitial fibrosis correlates directly with the prognosis, since it is directly associated with an increased ventricular remodeling, systolic dysfunction and malignant arrhythmias[25]. Several small studies have demonstrated that around 45% of the patients with hypertension present late enhancement after gadolinium administration, which is associated with interstitial fibrosis and coronary microangiopathy[26]. However, it is necessary to assess the direct impact these findings have regarding mortality, progression to heart failure and the development of arrhythmias. Hopefully, quantitative evaluation will shed some light on this issue, as it did with hypertrophic cardiomyopathy. At this moment, there is no available evidence that clarifies the usefulness of diagnosing interstitial fibrosis in patients with hypertensive cardiomyopathy using CMR.

Diagnosis of secondary causes of hypertension

Patients who present with resistant hypertension (patients without blood pressure control that are already taking 3 different drugs, one of them being a diuretic) must undergo differential diagnosis in order to rule out a secondary cause of hypertension, which are present in approximately 5% of the population[27]. The majority of secondary causes are due to endocrine dysfunction, for which the first diagnostic step are biochemical panels and hormone level tests, only after those, are imaging methods solicited. However, CMR is a very useful tool used to speed up the diagnosis of these patients. The most common causes of secondary hypertension are: primary hyperaldosteronism, renovascular disease, chronic renal insufficiency and obstructive sleep apnea. Here we will make a very brief summary of the secondary causes that can be evaluated using CMR.

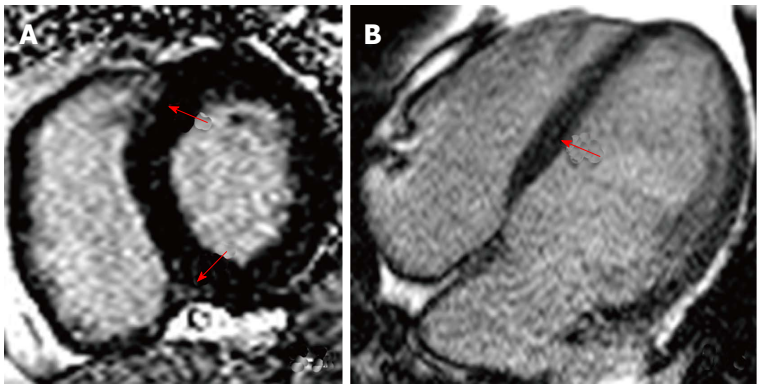

Figure 5 Cardiovascular magnetic resonance using inversion-recovery sequences. A: Patient with chronic hypertension that presents late enhancement in the areas connecting with the right ventricle (shown by red arrows); B: Patient with hypertensive cardiomyopathy in dilated phase, showing linear late enhancement in the septal wall.

PRIMARY HYPERALDOSTERONISM

The prevalence of this disease is still a matter of debate. Some studies report that it might be responsible for up to 6.1% of the cases of hypertension, and this number goes up to 18% when taking into account patients with BP of over 180/110 mmHg. It makes up 20% of the cases of secondary hypertension[28]. Clinical and laboratory findings typical of this disease include hypokalemia and hypertension; however, hypokalemia is only present in around half of the cases, and it's only found in latter stages of the disease[28,29]. A high degree of clinical suspicion is necessary to diagnose this illness, followed by biochemical confirmation (aldosterone/renin relationship in blood serum, confirmed with oral or parenteral sodium overload). The two principal causes of primary hyperaldosteronism are: adrenal adenoma (35%) and bilateral adrenal hyperplasia (65%). In these patients, it is mandatory to realize an imaging study to rule out the presence of neoplasm, since in these cases, surgical removal of the aldosterone producing tumor can cure the patient. Adenomas are usually hypo or isointense in T1 (when compared to the liver) and slightly hyperintense in T2. CMR has demonstrated a sensitivity of 70% and a specificity of 100% for the diagnosis of these tumors[30]; these values are very similar to those offered by CT[31].

RENOVASCULAR DISEASE

Up to 20% of patients who undergo cardiac catheterization present significant unilateral or bilateral renal artery stenosis[32] as an incidental finding; mainly in patients with extrarenal atherosclerosis[33], but it is still unclear how many of these patients have a direct repercussion on their BP. Renovascular disease is responsible for 35% of the cases of resistant hypertension[28]. CMR sequences used to study renal arteries are the same ones used during aortic angio-resonance. CMR with gadolinium has shown a sensitivity of 97% and a specificity of 93% for the diagnosis of renal artery stenosis[34], with the limitation of being contraindicated in patients with a creatinine clearance of less than 30 mL/min per 1.73 m^2. It must be noted that treatment using either balloon angioplasty or stenting has not shown to improve BP control or renal function[35,36] (Figure 6).

Other less frequent causes of secondary hypertension include Cushing's syndrome and pheocromocytoma. Both these entities have very characteristic clinical presentations, so once that there is enough clinical suspicion, a biochemical confirmation must be made. Once both these criteria have been met, CMR might be used; offering a very similar diagnostic capacity to that of CT.

CT

Over the last few decades, impressive technological advances have been made in the field of CT. The rise of machines with a very high spatial and temporal resolution coupled with ECG gating have allowed to obtain high precision coronary artery images, which is currently CT's main use in cardiology. Among the most relevant contributions to patients with hypertension we can find the following:

Coronary artery evaluation

The use of CT for the evaluation of coronary artery disease (CAD) constitutes one of the most important breakthroughs in non-invasive cardiology in the last few decades. The CT machines best suited for the acquisition of these studies are those with 16 detectors or more; nowadays the most used CT scanners have 64 detectors. The acquisition must always be ECG-gated and coordinated with contrast administration. Today, thanks to the various acquisition techniques (prospective protocols, diminished voltage, high pitch, *etc.*) the radiation dose per study has been reduced to around 1-2 mSv.

Coronary CT has shown a great diagnostic certainty when it comes to ruling out CAD with a sensitivity of 85% (95%CI: 79%-90%) and a specificity of 90% (95%CI: 83%-94%), with an area under the curve of 0.93[37]. Furthermore, the result of the Coronary CT has a direct relationship with prognosis, having a 3-year survival of over 95%[38].

The presence of coronary artery tortuosity has been related to female gender and the presence of chronic hypertension[39]. It is believed that these changes are

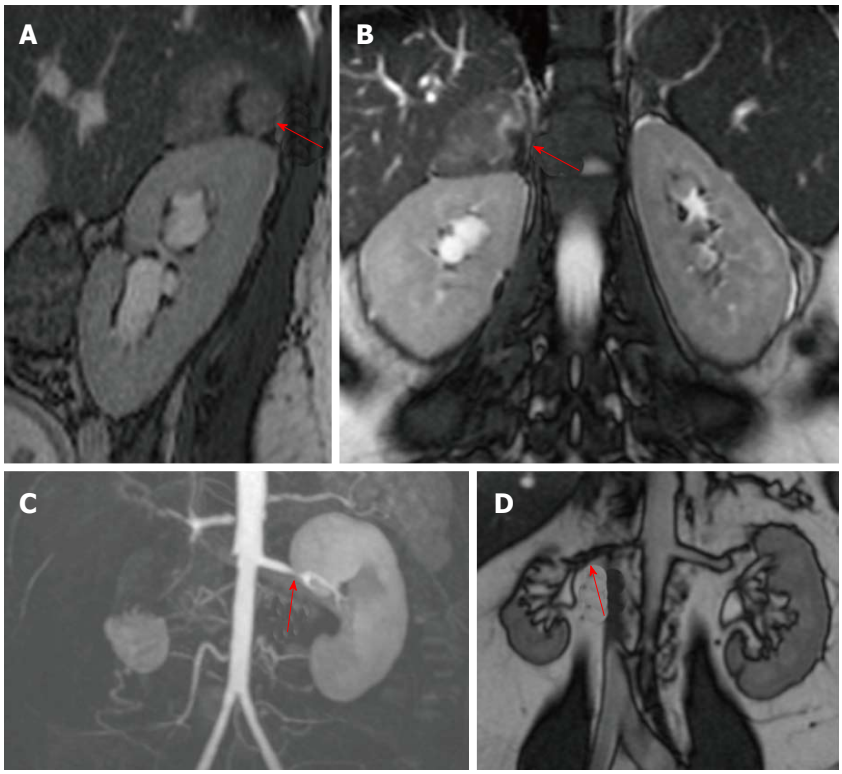

Figure 6 Evaluation of secondary hypertension. Cardiovascular magnetic resonance T2- sequences. Above is show a study taken in a 27-year-old female patient that presented with hypertension and a 5 cm × 4 cm adrenal mass, hyperintense when compared to the liver (marked by red arrows). On the bottom panels we see the contrast angiography study and T2 sequence, which show significant bilateral renal artery stenosis.

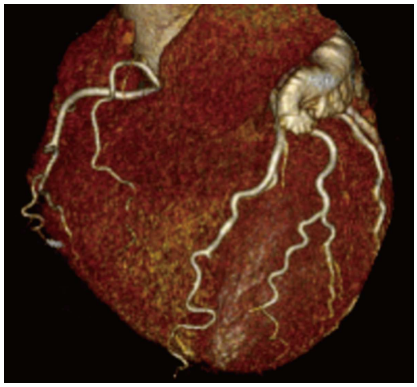

Figure 7 Coronary computed tomography of an 81-year-old hypertensive patient that demonstrates the presence of coronary tortuosity without atherosclerotic plaques.

due to an increase in the pressure and volume load in coronary vessels, therefore these changes can be seen as a consequence of hypertension[40]. There are studies that have related coronary tortuosity with diastolic dysfunction[41]; however, this finding has not been linked with worsening in the prognosis. The relevance of the presence of coronary artery tortuosity in coronary CT studies is still being debated (Figure 7).

Coronary calcium

Coronary calcium quantification currently is made with CT machines with prospective ECG-gating capacity, which translates to reduced radiation dosage per study (1-2 mSv). CT has a sensitivity of 96% and a positive predictive value of 80% for coronary calcium, with the drawback being that it only has a specificity of 46%[42]. Patients with an Agatston score of under 100 have a very good prognosis, with a very low probability of having a positive SPECT scan[43]. The risk for coronary disease increases linearly as the Agatson score rises[44-48]; the same is seen with mortality[49].

It is known that hypertension is an important risk factor for the development of atherosclerosis. Recently, a study included 8238 asymptomatic subjects and then divided them by category of BP (according to JNC-7), demonstrating that the risk of subclinical atherosclerosis, non-calcified coronary plaques and coronary calcium score of over 100 AU increase linearly as BP levels rise[50]. Previous studies have demonstrated that the progression of coronary calcification was significantly slower in patients with adequate BP control[51]. Erbel *et al*[52] have shown that as BP levels rise, so does coronary calcium scores (mainly in men) as does the rate of major adverse cardiovascular events. This suggests that in patients with a stage 2 hypertension (BP > 160/100) might be candidates for a CT study to rule out subclinical atherosclerotic. However, the impact of this strategy must be evaluated in future studies.

Ventricular volume and mass quantification

Retrospective protocols with radiation modulation have allowed the evaluation of volumes, dimensions and mass of cardiac structures. CT offers the advantage of being able to evaluate cardiac cavities with a great temporal and spatial resolution, along with the possibility of 3D volumetric visualization. A meta-analysis comprising 27 comparative studies between CT and CMR demonstrated excellent correlations in the measurement of telesystolic, telediastolic, ejection

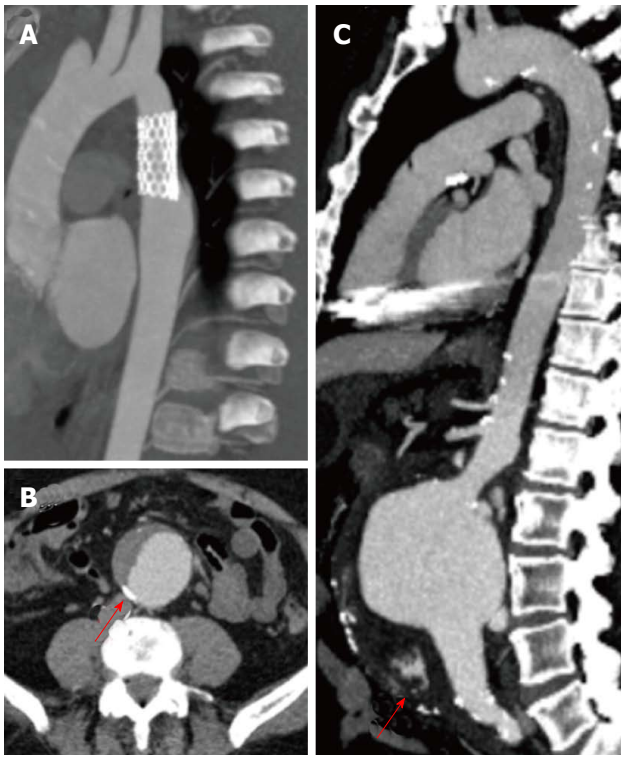

Figure 8 Aortic computed tomography. A: Patient with vascular endoprothesis, without vascular leaks; B: Dissected abdominal aortic aneurysm, arrow points to calcified atherosclerotic plaques; C: Ruptured infrarenal aortic aneurysm, seen as hyperdense material in the abdominal cavity (arrow).

fraction and left ventricular mass volumes (r = 0.93, 0.95, 0.93, 0.86 respectively)[53]. In hypertensive patients, the acquisition of this data has a direct impact on prognosis.

Right ventricular function has also been compared to CMR in several studies, showing good correlation between the 2 imaging modalities (r = 0.88), with an even higher reproducibility in CT[54,55]. However, the exactitude of the measurement of the right ventricle depends on the quality of the attenuation of right cavities, being necessary at least 175 HU to achieve a good measurement[56].

Vascular disease evaluation

CT is currently the method of choice to evaluate vascular anatomy, playing a key role in the diagnosis, risk stratification and treatment of aortic disease[57]. ECG-gated studies allow the acquisition of precise aortic root images free of movement artifacts. Also, CT is a diagnostic tool that is present in most hospital centers and unlike CMR, the acquisition times are very short.

The traditional CT protocol must include non-contrast images, mainly when an acute coronary syndrome is suspected, since this sequence allows the detection of intramural hematomas. Afterwards, ECG-gated angiography is performed using contrast, allowing the evaluation of vascular anatomy. Finally, in patients with vascular implants, late images can identify vascular leaks (Figure 8). In general, CT has a great performance in the diagnosis of aortic disease (up to 92%), including its main branches[58].

In Korean hypertensive patients of over 65 years, CT studies have shown a prevalence of thoracic aortic aneurysms in 36.5% and abdominal aortic aneurysms in 6%[59]. In another study, high coronary calcium scores correlated with an increased abdominal aortic diameter and a higher incidence of aneurysms (14%) when the score was > 400 AU, especially when this coincided with other cardiovascular risk factors[60]. However, due to the scarce evidence regarding this issue, there is currently no recommendation about screening studies in these patients.

Diagnosis of causes of secondary hypertension

The advantages of CT for the diagnosis of renovascular disease or adrenal adenomas have been mentioned previously: good spatial resolution, short acquisition times and widely available in many hospital centers. CT has demonstrated a sensitivity of 85%-87% and a specificity of 82%-93% for the diagnosis of adrenal adenomas[31]. In the evaluation of resistant hypertension, the usage of either CT or CMR can be used interchangeably, since their diagnostic accuracy is very similar.

NUCLEAR CARDIOLOGY

Nuclear cardiology is the most studied non-invasive cardiovascular imaging modality, only behind echocardiogram. Since the 1970's, SPECT established itself as the most widely diffused imaging technique to evaluate the presence of myocardial ischemia all around the world; today, PET and hybrid imaging offer valuable information used in everyday cardiologic practice.

Myocardial perfusion evaluation

Both SPECT and PET have developed protocols for the evaluation for myocardial ischemia, which is extremely useful in hypertensive patients with angina and multiple cardiovascular risk factors. Both techniques use protocols that involve image acquisition in rest and stress, either physical or pharmacological. In a meta-analysis, the validity for SPECT to detect myocardial ischemia has shown a sensitivity of 88% (95%CI: 88%-89%) with specificity of 61% (95%CI: 59%-62%) and an area under the curve of 0.86[14]. Regarding PET, it showed a better diagnostic capability, with a sensitivity of 84% (95%CI: 81%-87%) with a specificity of 81% (95%CI: 74%-87%) and an area under the curve of 0.92[14]. When merging different techniques, a modality called hybrid imaging, SPECT/CT has shown a sensitivity of 94%-96%, specificity of 92%-95% and a negative predictive value of 97%-99%. Finally, PET/CT has shown a slightly better performance over other imaging techniques, with a sensitivity of 93% and a specificity of 99% when using ^{15}O-H_2O radioisotope[61] (Figure 9).

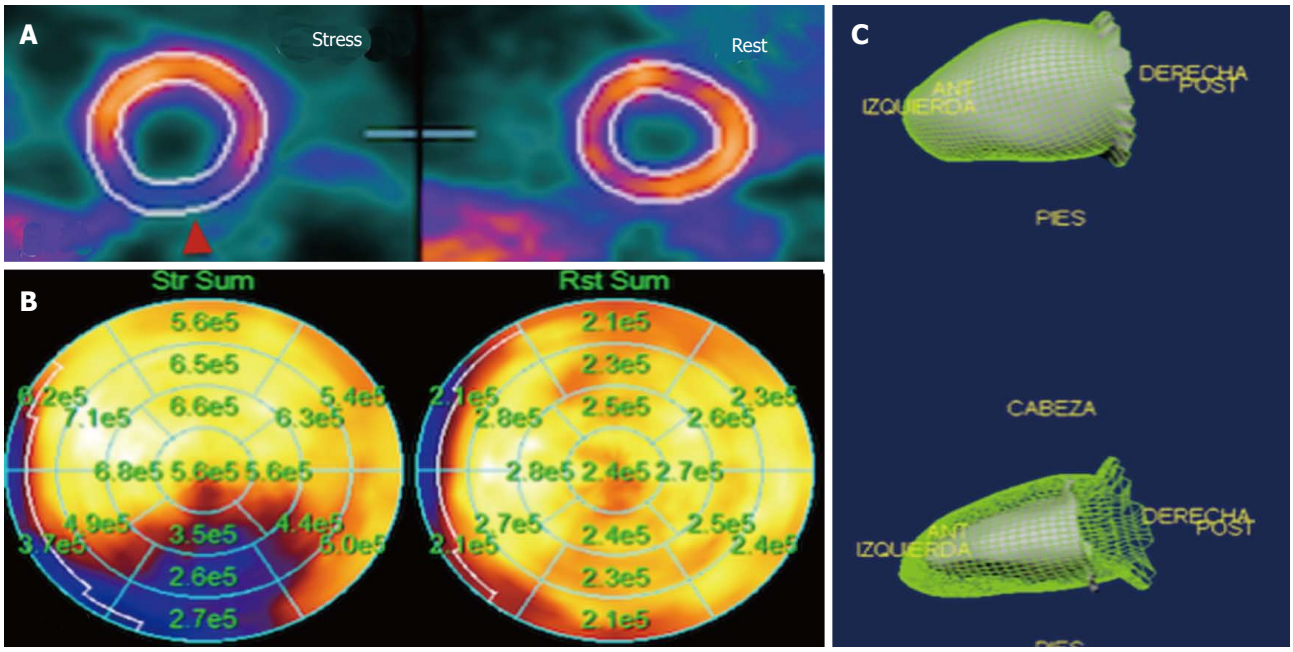

Figure 9 Myocardial perfusion positron emission tomography. A shows a perfusion defect in the posterior wall during stress; B shows flow quantification; the regional flows during stress are significantly increased in all areas, except in the inferior wall (territory of the right coronary artery), where the increase is significantly diminished; C shows a Gated-positron emission tomography to evaluate left ventricular function.

Patients with several risk factors can present with silent ischemia. A study of hypertensive patients without angina demonstrated that, when evaluated with pharmacologic stress-SPECT, the prevalence of reversible perfusion defects was of 27.7% and increased to 41.4% in patients with diabetes (P = 0.001), many of these being moderate to severe defects. In a sub-analysis of the same study, dyspnea and proteinuria were found to be independent predictors of silent ischemia[62].

Evaluation of ventricular function

The incorporation of cardiac-gating allowed evaluating left ventricular function at the same time as myocardial perfusion without the need of performing an additional radioisotope ventriculography, which implied a longer study time and radiation exposure. The calculation of the left ventricular ejection fraction (LVEF) is done automatically by software, without human intervention, which makes it a highly reproducible method.

Furthermore, it has shown to have a very good correlation with CMR (r = 0.82), without being statistically significant in the Bland-Altman analysis and high reproducibility[63-65]. LVEF calculation with Gated-PET has shown to have a good correlation with CMR (r = 0.76)[66], however, it has been observed that it underestimates both telesystolic and telediastolic volumes. Today, the clinical implications of this method are limited to complementing the myocardial perfusion study, with isolated LVEF measurement being reserved for investigation protocols exclusively.

Evaluation of endothelial lesion

Nuclear cardiology studies have been able to demonstrate the presence of endothelial lesions in patients with hypertension. A study made by our group evaluated the endothelial function using a triphasic protocol of 13N-Amonia PET (rest, cold pressor test and adenosine induced-hyperemia) in patients with recent diagnosis of hypertension, compared with a healthy control group. We found that 84% of the hypertensive patients had endothelial dysfunction measured by an ENDEVI score < 1.5 (Endothelial-dependent Vasodilation Index) and 58% presented vasomotor abnormalities measured by a CFR (coronary flow reserve) of < 2.5. These findings might be early findings of coronary artery disease[67]. Another similar study also found more significant endothelial dysfunction in patients with dyslipidemia, when compared with a healthy control group. Notably, the study group showed improvement after 8 wk of treatment with ezetimibe-simvastatin[68]. The findings of this study are very promising, especially regarding its implications in vascular risk screening, therapeutic decision-making and patient follow-up. However, more information is needed before this method demonstrates its usefulness in daily practice.

Sympathetic innervation

The autonomic sympathetic nervous system plays a fundamental role in the maintenance of hormonal and hemodynamic harmony in the cardiovascular system. In hypertensive patients, the increase in this system's activity leads to the development of hypertensive cardiomyopathy. The synaptic vesicles contain adrenaline, noradrenaline and the false neurotransmitter, an analogue of noradrenaline, guanetidine. This last one can be radioactively marked, transforming itself into meta-iodinebenylguanidine (^{123}I-*m*IBG) which,

when found in a great enough concentration can be measured by conventional gamma-cameras[69]. There are studies that have shown altered myocardial retention of ^{123}I-*m*IBG in hypertensive patients that also present left ventricular hypertrophy, mainly in the lateral and inferior left ventricular wall[70-72]. This translates to an abnormal neuroadrenergic cardiac function, which might be related to hypertension-induced myocardial damage.

This neurohormonal unbalance, diagnosed with ^{123}I-*m*IBG SPECT has shown to be related with the prognosis of patients in other diseases. In patients with heart failure, a heart/mediastinum ratio (H/M) < 1.6 is related with a higher mortality, progression of disease and arrhythmias[69]. These findings have been used to evaluate the appropriateness of the therapeutic choice, mainly concerning beta-blocker therapy, although there are studies that involve ACE/ARB inhibitors and spironolactone[69]. However, the role of sympathetic innervation evaluation in hypertensive patients hasn't been clearly defined.

Evaluation of causes of secondary hypertension

In patients with hypertension of renovascualr origin, the abnormalities in sympathetic innervation diagnosed with ^{123}I-*m*IBG SPECT are independent of the development of ventricular hypertrophy, which is a key aspect in which it differs from patients with essential hypertension. This might be due to the fact that myocardial injury due to hypertension of renal origin occurs earlier in the history of the disease compared with essential hypertension[73].

The use of FDG-PET in hyperaldosteronism is focused in the evaluation of adrenal masses, which show no retention of the tracer in the setting of a benign mass, unlike malignant tumors. A meta-analysis reported that FDG-PET showed an excellent diagnostic capacity to differentiate between benign and malignant adrenal masses, with a sensitivity of 97% (95%CI: 93%-98%) specificity of 91% (95%CI: 87%-94%) and an area under the curve of 0.96%[74]. When studying adrenal hyperplasia, it was seen that it did not demonstrated FDG activity.

Regarding pheochromocytoma, the vast majority showed activity when using both FDG and ^{123}I-*m*IBG, though the latter was found to be unable to diagnose pheochromocytomas associated with Von-Hippel-Lindau syndrome.

CONCLUSION

Multimodality imaging studies have helped to improve the understanding of a vast number of cardiovascular illnesses, including hypertension. Among the most recent contributions we can find the evaluation of dimensions and ventricular function using CMR, CT and Gated SPECT/PET studies, the ability to exclude the presence of coronary artery disease using non-invasive methods with a high diagnostic certainty; risk stratification in hypertensive cardiomyopathy using late enhancement techniques with the aid of gadolinium contrast in CMR or the evaluation of sympathetic innervation and the evaluation of different causes of resistant hypertension. The use of these techniques is still not commonplace in everyday clinical practice, and further studies are needed before they become a standard of common clinical practice; however, the future is certainly very promising.

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REVIEW

Hypertensive cardiomyopathy: A clinical approach and literature review

Kishio Kuroda, Tomoko S Kato, Atsushi Amano

Kishio Kuroda, Tomoko S Kato, Atsushi Amano, Department of Cardiovascular Surgery, Juntendo University, Bunkyo-ku, Tokyo 113-8431, Japan
Author contributions: Kuroda K and Kato TS contributed same amount to this work; all authors contributed to this work.
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Correspondence to: Tomoko S Kato, MD, PhD, FAHA, Department of Cardiovascular Surgery, Juntendo University, Heart Center, Building 9, 1F-Room124A, 2-1-1 Hongo, Bunkyo-ku, Tokyo 113-8431, Japan. rinnko@sannet.ne.jp
Telephone: +81-3-38133111
Fax: +81-3-38155228
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Abstract

Hypertensive cardiomyopathy (HTN-CM) is a structural cardiac disorder generally accompanied by concentric left ventricular hypertrophy (LVH) associated with diastolic or systolic dysfunction in patients with persistent systemic hypertension. It occurs in the absence of other cardiac diseases capable of causing myocardial hypertrophy or cardiac dysfunction. Persistent systemic hypertension leads to structural and functional myocardial abnormalities resulting in myocardial ischemia, fibrosis, and hypertrophy. HTN-CM is predominantly a disease of impaired relaxation rather than impaired contractility, so patients are usually asymptomatic during resting conditions. However, their stiff left ventricles become incapable of handling increased blood volume and cannot produce appropriate cardiac output with the slight change of circulating volume that may occur during exercise. Importantly, the accompanying LVH is itself a risk factor for mortality and morbidity. Therefore, early detection of LVH development in patients with hypertension (referred to as HTN-CM) is critical for optimal treatment. In addition to pathological findings, echocardiography and cardiac magnetic resonance imaging are ideal tools for the diagnosis of HTN-CM. Timely diagnosis of this condition and utilization of appropriate treatment are required to improve morbidity and mortality in hypertensive patients. This review article presents an overview of the multidimensional impact of myocardial disorder in patients with hypertension. Relevant literature is highlighted and the effects of hypertension on cardiac hypertrophy and heart failure development are discussed, including possible therapeutic options.

Key words: Hypertension; Diagnosis; Cardiomyopathy; Hypertrophy; Risk assessment

Core tip: Hypertensive cardiomyopathy is a structural cardiac disorder generally accompanied by left ventricular hypertrophy associated with diastolic and/or systolic dysfunction in patients with persistent systemic hypertension, in the absence of other cardiac diseases. Because regression of myocardial hypertrophy is associated with a reduction in cardiovascular risk along with the improvement of cardiac function, timely diagnosis of the disease-specific pathophysiology and appropriate treatment strategy including maintaining optimal blood pressure control is very important in the care of patients with hypertension. In the present review manuscript, we have described the outline of hypertensive cardiomyopathy,

pathophysiological feature of the disease, diagnosis and the treatment.

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INTRODUCTION

Hypertensive cardiomyopathy (HTN-CM) is a structural cardiac disorder generally accompanied by concentric left ventricular hypertrophy (LVH) associated with diastolic or systolic dysfunction in patients with persistent systemic hypertension. HTN-CM is difficult to distinguish from other cardiac diseases that cause myocardial hypertrophy, such as hypertrophic cardiomyopathy, Fabry disease, or cardiac amyloidosis. However, when other causes are ruled out, leaving hypertension the only possible cause for LVH development, this is considered to be HTN-CM.

Hypertension (HTN) is a major global health issue, accounting for approximately 50% cases of both stroke and ischemic heart disease, and approximately 13% of the total deaths worldwide[1]. Persistent hypertension can cause structural and functional myocardial abnormalities. LVH and remodeling, frequently seen in patients with hypertension[2], is initially an adaptive response of a normal heart to an increased afterload. Hypertension leads to interstitial myocardial fibrosis[3], which has been linked to LVH development and diastolic dysfunction[4].

The renin-angiotensin-aldosterone system (RAAS) is also an important determinant of the hypertrophic response[5-7]. A relationship between angiotensin Ⅱ and development of myocardial fibrosis has been described as well[8]. Importantly, the Framingham Heart Study revealed that LVH is a risk factor for cardiovascular morbidity and mortality, independent of other cardiovascular risk factors, including elevated blood pressure itself[4,9,10]. In addition, patients with persistent hypertension and LVH are susceptible to sudden death[11]. These observations emphasize the importance of early diagnosis and effective treatment of hypertension to prevent cardiac complications[12].

In this review article, we summarize the pathophysiology, mechanism, diagnostic evaluation, and management options of HTN-CM. We have focused on human studies in order to emphasize the importance of early identification and optimization of treatment in patients with hypertension.

EPIDEMIOLOGY

The prevalence of LVH varies with the severity of hypertension, ranging from 20% in mild to almost 100% in severe or complicated hypertension[13]. Cuspidi *et al*[14], who performed a review of the echocardiographic data of 37700 individuals, reported that the prevalence rate of LVH was 19%-48% in untreated hypertensive cohorts and 58%-77% in high-risk hypertensive patients.

The development of LVH is a relatively early response to hypertension, particularly in children and adolescents[15]. Transient hypertension induced by mental stress as well as extensive elevation of blood pressure during exercise can also induce LVH[16,17]. The Framingham Heart Study showed that the left ventricular (LV) mass can be increased prior to the development of overt hypertension[18]. LVH in patients with hypertension predominantly results not only from a chronic increase in LV afterload but also a genetic component such as the DD genotype of the angiotensin-converting-enzyme (*ACE*) gene and B2 bradykinin receptor polymorphism[19-22].

Devereux *et al*[23] reported that the prevalence of LVH among hypertensive patients is influenced by gender, obesity, and possibly age. Sex-specific criteria for LV mass index identify LVH in more women than men with systemic hypertension[24].

MYOCARDIAL REMODELING AND PATTERNS OF LVH IN HTN-CM

Conventional echocardiography provides useful morphological information of LVH patterns. For example, patients with hypertrophic cardiomyopathy (HCM) frequently show asymmetrical septal hypertrophy of the LV; this is the most characteristic finding[25]. In contrast, LVH associated with hypertension or HTN-CM is characterized by symmetrical (concentric) LV hypertrophy. However, 13%-31% of patients with HCM show symmetrical hypertrophy[26,27], whereas 4%-47% of hypertensive patients manifest asymmetrical septal hypertrophy[27,28].

LV remodeling/hypertrophy in HTN-CM may represent an adaptive response to hemodynamic overload imposed by systemic hypertension[2]. This compensatory response can be explained by the Laplace law (Figure 1, reproduced from[2,29]). Sustained elevated blood pressure leads to an increase in LV wall stress, which is a major determinant of myocardial oxygen demand. In response to increased LV wall stress, the LV wall thickens and the LV mass increases, thereby resulting in the normalization of wall stress and development of a structural pattern known as concentric hypertrophy. Alternatively, an increase in blood volume could lead to an increase in the chamber radius, resulting in eccentric hypertrophy[2].

Ganau *et al*[24] investigated patterns of LVH and geometric remodeling in patients with essential hypertension. They reported that LV mass index and relative wall thickness were normal in 52% of the patients,

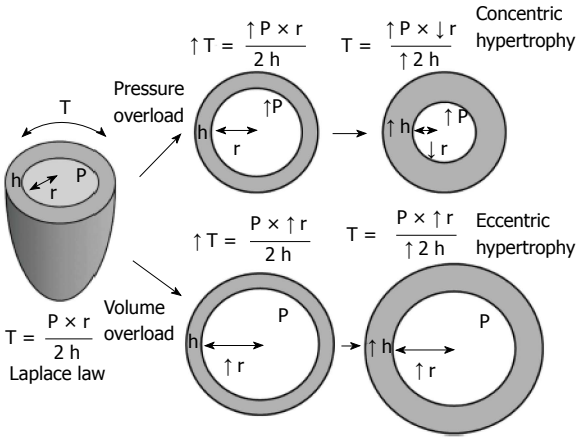

Figure 1 The Laplace law and how it may explain the development of concentric and eccentric left ventricular hypertrophy in response to pressure and volume overload, respectively. Reproduced from Nadruz and Hum[2], 2015; Frolich and Susic[29], 2012. T: Tension or stress in the LV wall; P: LV pressure; r: Radius of the chamber; h: LV wall thickness.

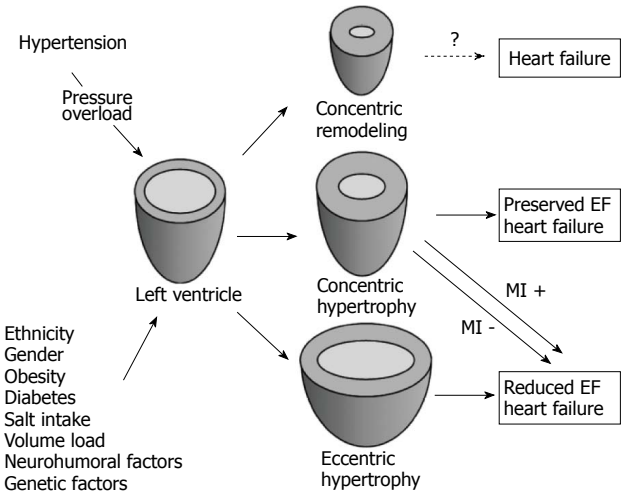

Figure 2 Pathways of left ventricular remodeling progression secondary to systemic hypertension. Reproduced from Nadruz and Hum[2], 2015. EF: Ejection fraction; MI: Myocardial infarction.

whereas 13% had increased relative wall thickness with normal ventricular mass (concentric remodeling), 27% had increased mass with normal relative wall thickness (eccentric hypertrophy), and only 8% had "typical" hypertensive concentric hypertrophy (increase in both variables). Cuspidi *et al*[14] also reported that concentric LV hypertrophy is not the most frequent geometric pattern and is less commonly seen than is eccentric hypertrophy in the hypertensive subjects. Indeed, the geometric pattern of LVH affects the prognosis[30]. Patients without an increase in absolute mass, but with an increase in relative wall thickness or in the wall thickness-to-cavity diameter ratio (concentric remodeling) have the same adverse risk as those with an increase in both mass and relative wall thickness (concentric hypertrophy)[24]. Velagaleti recently reported that the data from the Framingham Heart Study revealed that heart failure risk varied by LV geometric pattern, with eccentric and concentric hypertrophy predisposing to heart failure with reduced and preserved ejection fraction, respectively, after a mean follow-up of 21 years[31].

Recent reports[32,33] have described that a transition from LV concentric hypertrophy to dilation and systolic dysfunction is not a common finding, especially in the absence of coronary heart disease[2]. Observation of over one thousand patients with concentric LV hypertrophy and normal ejection fraction by Milani *et al*[32] revealed only 13% who progressed to systolic dysfunction by three years follow-up and this transition occurred after myocardial infarction in 42.5% of the patients. The various pathways of LV remodeling progression among hypertensive subjects are well described by Nadruz (Figure 2, reproduced from[2])

Interestingly, Khouri *et al*[34] recently suggested that concentric or eccentric LVH can each be subclassified into two subgroups using cardiac magnetic resonance imaging. This yields four distinct geometric patterns: eccentric non-dilated, eccentric dilated, concentric non-dilated, and concentric dilated[34]. They found that dilated type LVH was more frequently associated with low ejection fraction and elevated troponin levels. Their findings were also supported by the investigation using echocardiography performed by Bang *et al*[35]. This newly suggested re-classification of hypertensive patients with LVH into four groups according to the LV dilatation and increased concentricity may provide new insights into the hemodynamic and LV functional alteration in this population.

CLINICAL MANIFESTATION IN PATIENTS WITH HTN-CM

Persistent systemic hypertension induces LVH, fibrosis, diastolic dysfunction, and an increase in the activation of the RAAS, which leads to congestive heart failure[36,37]. One of the mechanisms of heart failure in patients with hypertension is LV diastolic dysfunction. LV diastolic dysfunction associated with hypertension is morphologically characterized by LV wall thickening and increased left atrial (LA) volume. In particular, LA volume is related to LV filling pressure or LA pressure, and is a prognostic marker of various cardiac diseases[38,39]. In advanced stages, hypertension induces eccentric LVH and LV systolic dysfunction[40]. Data from the Framingham Heart Study revealed that LVH is consistently identified as an independent risk factor for cardiovascular morbidity and mortality[4,9,10]. Further, hypertensive LVH or HTN-CM is associated with atrial fibrillation: the incidence increases by 40%-50% in the presence of hypertension[41]. Messerli *et al*[42] documented a strong correlation between hypertensive LVH or HTN-CM and an increased frequency of ventricular arrhythmias. This emphasizes the importance of understanding of the clinical manifestations of HTN-CM.

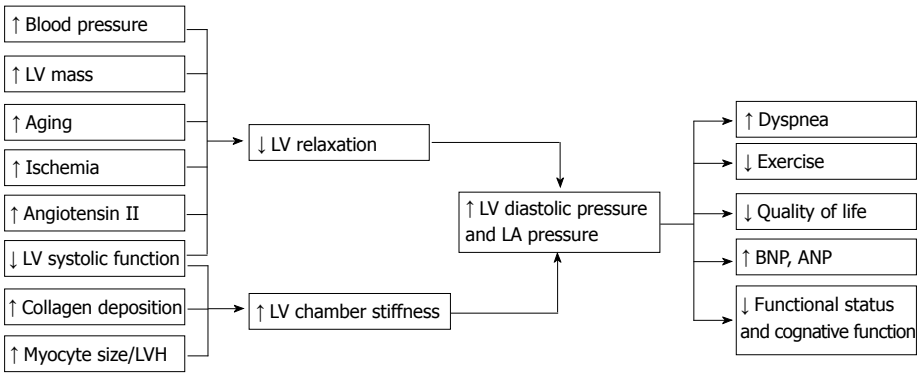

Figure 3 Causes of left ventricular diastolic dysfunction and its clinical consequences. Reproduced from Phillips and Diamond[48], 2001. ANP: Atrial natriuretic peptide; BNP: Brain natriuretic peptide; LA: Left atrial; LVH: Left ventricular hypertrophy.

LVH

The pathophysiological mechanism by which LVH develops in patients with persistent systemic hypertension has been described in the previous sections. Both hypertension and LVH are affected by the same factors, such as angiotensin II, norepinephrine and epinephrine, and an increased peripheral and cardiac sympathetic drive[43,44]. LVH is a significant predictor for heart failure development and is associated with increased mortality[4,9,10]. Notably, patients with persistent hypertension causing HTN-CM often concomitantly have other atherosclerotic risk factors, such as obesity and diabetes. Although hypertension is the leading risk factor for LVH development, substantial evidence indicates that diabetes can also trigger this pathological remodeling response[45]. Obesity is associated with an increased risk of concentric LVH independent of elevated blood pressures[23]. Hypertensive LVH can lead to ventricular diastolic dysfunction; it is also a risk factor for myocardial infarction, which is a principal cause of LV systolic dysfunction[46,47].

Diastolic dysfunction

In addition to LVH, diastolic dysfunction is a major factor contributing to hypertensive heart disease and the progression to "symptomatic" congestive heart failure[48]. Approximately 40% of patients with hypertensive heart disease have normal systolic function but abnormal diastolic function[48,49]. In fact, LV diastolic dysfunction is the main cause of symptomatic heart failure development in patients with hypertension[50]. LV diastolic dysfunction in HTN-CM is morphologically characterized by LV wall thickening and a persistent elevation of LV end-diastolic pressure, causing increased LA volume. The increased LA volume is the result of elevated LV filling pressure or LA pressure, which presents as exercise intolerance in patients with HTN-CM.

Ischemia is also an important factor leading to diastolic impairment in HTN-CM. Hypertension itself accelerates arteriosclerosis in both systemic and coronary arteries[11,51]. Furthermore, a long-standing increase in LV wall stress and workload causes LVH, and is associated with an increase in the diameter of myocardial cells without a proportional proliferation of the capillary vasculature[11]. Therefore, myocardial tissues in patients with persistent hypertension suffer from ischemia, the so-called mismatch between coronary circulation and oxygen requirement of the myocardium. This underlying myocardial ischemia and hypertrophy leads to the association of HTN-CM rather predominantly with relaxation abnormalities. The impairment of LV pressure/volume reserve means that patients with HTN-CM who have impaired relaxation are usually asymptomatic during resting conditions, but a slight change in circulating volume or an elevation of systemic vascular resistance, such as occurs during exercise, renders their stiff LV incapable of handling the increased blood volume and it cannot produce appropriate cardiac output. This can lead to a progressive decline in ventricular function and ultimately congestive heart failure. Phillips *et al*[48] described the mechanisms underlying LV diastolic dysfunction and the clinical consequences of this dysfunction in patients with hypertensive LVH or HTN-CM (Figure 3, reproduced from[50]).

Systolic dysfunction

The Framingham Heart Study reported that severe LV systolic dysfunction occurs in 3%-6% of hypertensive patients[40]. An eccentric pattern of hypertrophy is a particularly strong risk factor for LV systolic dysfunction, as shown by the Cardiovascular Health Study[52]. Severe LV systolic dysfunction [ejection fraction (EF) < 30%] occurred in 6% in the Framingham Heart Study[52]; however, hypertensive LV remodeling/hypertrophy is certainly followed by chamber dilation and heart failure if not treated appropriately. Although LV function may be initially compensatory, it is followed by progressive worsening of symptoms that ends with cardiac death[2,53]. This phenomenon was consistently reproduced in animal models of pressure overload due to aortic banding, as well as in humans with aortic stenosis and hypertrophic cardiomyopathy[53].

DIAGNOSIS OF HTN-CM

Pathological findings of HTN-CM

Pathological evaluation is important in the differential

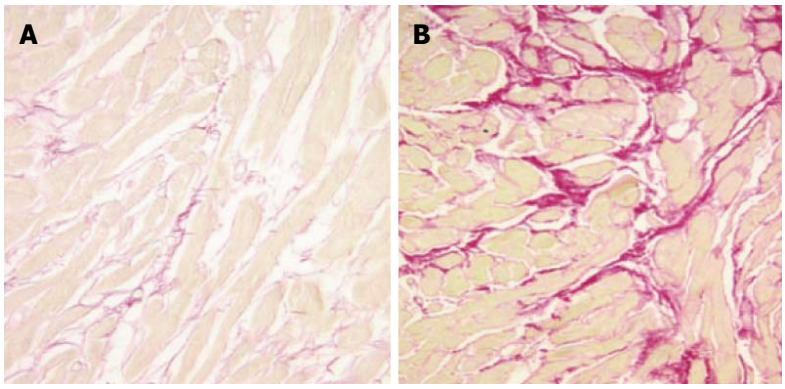

Figure 4 Comparison of collagen fibers in endomyocardial tissue. A: Specimen from a normotensive person; B: Specimen from a patient with hypertensive heart disease. The sections were stained with picrosirius red. Collagen fibers are stained red. Reproduced from Deiz *et al*[54], 2005.

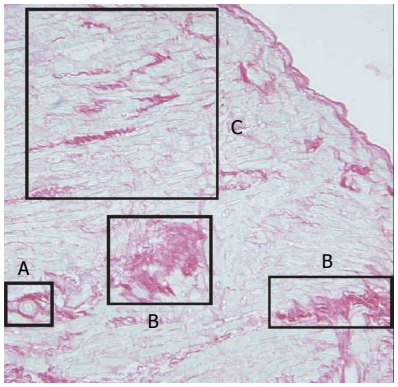

Figure 5 Endomyocardial tissue from a hypertensive patient with left ventricular hypertrophy. A: Perivascular fibrosis; B: Microscopic scarring; C: Interstitial fibrosis. Sections were stained with picrosirius red. Collagen tissue is stained red. Reproduced from Diez[56] 2007.

diagnosis of HTN-CM. Invasive endomyocardial biopsy (EMB) remains a powerful tool for obtaining a specific diagnosis in HTN-CM patients. A histopathological study revealed myocyte hypertrophy and moderate interstitial fibrosis, which was consistent with HTN-CM[54,55]. Cardiomyocyte hypertrophy in HTN-CM occurs as a result of structural remodeling of the myocardium. It is a consequence of a number of pathologic processes that are mediated by mechanical, neurohormonal, and cytokine routes and take place in the cardiomyocyte and noncardiomyocyte compartments of the heart[54]. An exaggerated accumulation of fibers within the myocardial interstitium and surrounding intramural coronary arteries and arterioles has been consistently found in postmortem human hearts and biopsy samples from patients with HTN-CM[55-57].

The collagen volume fraction is significantly increased in the hearts of patients with HTN-CM when compared with normotensive patients (Figures 4 and 5, reproduced from[54,56]). Several clinical observations support the possibility that fibrosis occurs by mechanical stress. Tanaka *et al*[58] reported that the collagen volume fraction of the LV free wall probably reflects transmural gradients of wall stress. Rossi found that the extent and severity of ventricular fibrosis paralleled the enlargement of cardiomyocytes[59]. Querejeta *et al*[60] reported that the collagen volume fraction correlated with systolic blood pressure and pulse pressure in the myocardium of patients with hypertension.

The RAAS and ACE activity may be an important determinant of the hypertrophic response[5-7]. The effect of angiotensin Ⅱ may be a factor in the promotion of myocardial fibrosis[61]. Myocardial disarray (defined as bundles of myocytes oriented perpendicularly or obliquely to each other or interspersed in different directions), which is generally seen in patients with HCM, may also appear in patients in HTN-CM, although the distribution of myocardial disarray is relatively smaller in HTN-CM than in HCM. A previous study by Kato et *al*[62] classified patients as HCM if they showed > 33% myocyte disarray in at least one of the cross sections examined. Patients with no or < 5% myocyte disarray in all cross sections examined were classified as HTN-CM (Figure 6, reproduced from[62]).

HTN-CM arises as the result of an increase in the quantity of myocardium but it also emerges due to alterations in myocardial quality (*i.e.*, fibrosis)[54]. Mechanical stress and hormones such as RAAS lead to fibrosis, which in turn leads to chronic heart failure.

Echocardiography

Echocardiography is a powerful tool that provides morphological information about the LVH pattern in patients with hypertension. LVH can be detected with both electrocardiography and echocardiography[63]. The sensitivity of electrocardiography for LVH diagnosis is relatively low; therefore, echocardiography should be performed to evaluate LV morphology in patients with persistent hypertension. Levy *et al*[64] reviewed electrocardiographic criteria for LVH in 4684 subjects of the Framingham Heart Study and detected echocardiographic LVH in 290 men (14.2%) and 465 women (17.6%), although they found electrocardiographic features of LVH in only 2.9% of men and 1.5% of women[64]. Indeed, a prevalence of echocardiographic LVH was reported in 40% of patients with hypertension[4,65].

LV mass (LVM), LV mass index, and relative wall thickness (RWT) are the most common measurements employed in evaluation of LVH in hypertensive patients[66]. LV geometry is classified into 4 groups based on LVM and RWT: concentric LVH (increased mass and increased RWT), eccentric LVH (increased mass and normal RWT),

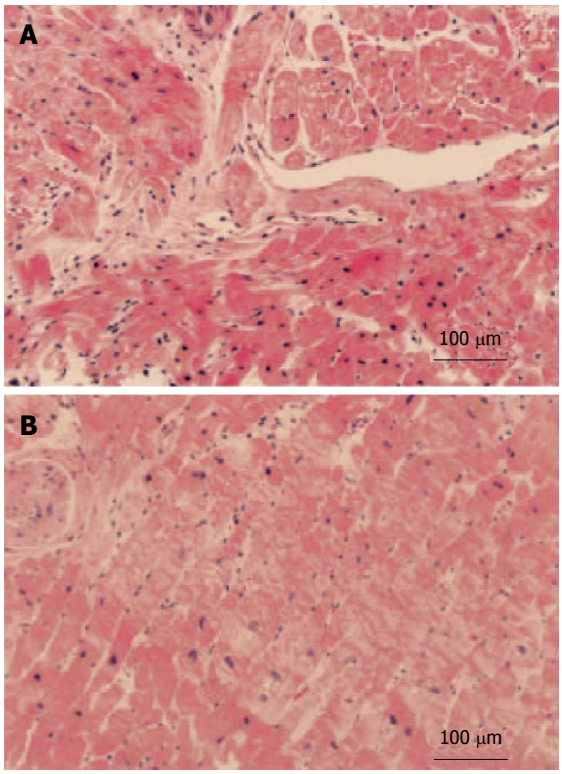

Figure 6 Representative cross sections of myocardial biopsy specimens. A: Hypertrophic cardiomyopathy showing disorganized arrangement of hypertrophic myocytes; B: Hypertensive cardiomyopathy patients showing parallel alignment of hypertrophic myocytes. Sections were stained with hematoxylin-eosin. (Reproduced from Kato *et al*[62], 2004).

concentric remodeling (normal mass and increased RWT), and normal geometry (normal mass and normal RWT)[4,65,66].

Several formulas are used to estimate LV mass. The original calculations from Troy were the first to be recommended as a standard for estimating LVM from M-mode measurements (Formula 1)[67].

Formula 1: LV mass = 1.05 [(LVIDD + PWTD + IVSTD)^3 - (LVIDD)^3] g.

Where: LVIDD = LV Internal Diameter in Diastole

PWTD = Posterior Wall Thickness in Diastole

IVSTD = Interventricular Septum Thickness in Diastole

Devereux added a slight modification by using the Penn convention as the border definition criteria (Formula 2)[68].

Formula 2: LV mass = 1.04 [(LVIDD + PWTD + IVSTD)^3 - (LVIDD)^3] - 13.6 g.

Subsequently, Devereux proposed a new, adjusted equation (validated on necropsy findings of 52 individuals)[69] that used the ASE convention and accounted for this discrepancy (Formula 3).

Formula 3: LV mass = 0.8 {1.04 [(LVIDD + PWTD + IVSTD)^3 - (LVIDD)^3]} + 0.6 g.

Relative wall thickness (RWT) is measured in clinical studies as:

RWT = (IVST + PWTD)/LVIDD

The usual reference cutoff value for increased RWT, derived from upper limits of normal samples, is 0.45[4]. The RWT provides information regarding LV geometry independent of other calculations[70], thereby precluding a requirement for most corrections. Nevertheless, significant LVH can occur without major changes in RWT, particularly when simultaneous pressure and volume overload are present; these conditions can be seen in patients with hypertension.

The American Society of Echocardiography with the European Association of Echocardiography has issued the following criteria for LVH using the modified Simpson's rule[71]: Estimated LVM of 201-227 g (103-116 g/m^2) for men and 151-171 g (89-100 g/m^2) for women is mildly abnormal; Estimated LVM of 228-254 g (117-130 g/m^2) for men and 172-182 g (101-112 g/m^2) for women is moderately abnormal; Estimated LV mass of > 255 g (> 131 g/m^2) for men and > 193 g (> 113 g/m^2) for women is severely abnormal.

Assessment of diastolic dysfunction by echocardiography is also important in the management of patients with HTN-CM. Diastolic dysfunction is seen in approximately 50% of patients with hypertension[72]. The changes in conventional Doppler echocardiographic parameters, such as peak early filling velocity (E), late diastolic filling velocity (A) and its ratio, as well as deceleration time, should be monitored. Patients with long-standing hypertension and advanced stage of HTN-CM may show a pseudonormalization of E/A ratio, known as restrictive physiology.

Tissue Doppler imaging (TDI) allows quantitative assessment of ventricular function and early diastolic mitral annular velocity (E'); the ratio of E/E', which is a parameter with correction of preload. This is a useful tool to assess the severity of diastolic dysfunction in patients with HTN-CM[73]. Kasner *et al*[73] performed both invasive and noninvasive assessment of diastolic dysfunction and identified the LV filling index of E/E' (lateral) as the best index for detection of diastolic dysfunction in patients with heart failure with normal ejection fraction.

Strain and strain rate parameters derived from TDI, as well as speckle tracking echocardiography have also been reported as useful tools for detection of diastolic dysfunction, and these can aid in discriminating patients with HTN-CM from those with other causes of LVH[62,74]. The abnormalities in strain parameters may occur in a stage of subclinical diastolic dysfunction in hypertensive patients[75,76] making this a useful strategy for disease prevention[4].

Cardiac magnetic resonance

Cardiac magnetic resonance imaging (CMR) offers a unique opportunity for noninvasive quantitation of both LVH with high reproducibility and myocardial fibrosis with high spatial and contrast resolution[77]. Takeda *et al*[78] described the power of CMR for distinguishing among cardiac amyloidosis, hypertrophic cardiomyopathy, and hypertensive heart disease, all of which present with LVH and heart failure.

Advances in CMR provide the potential to address all

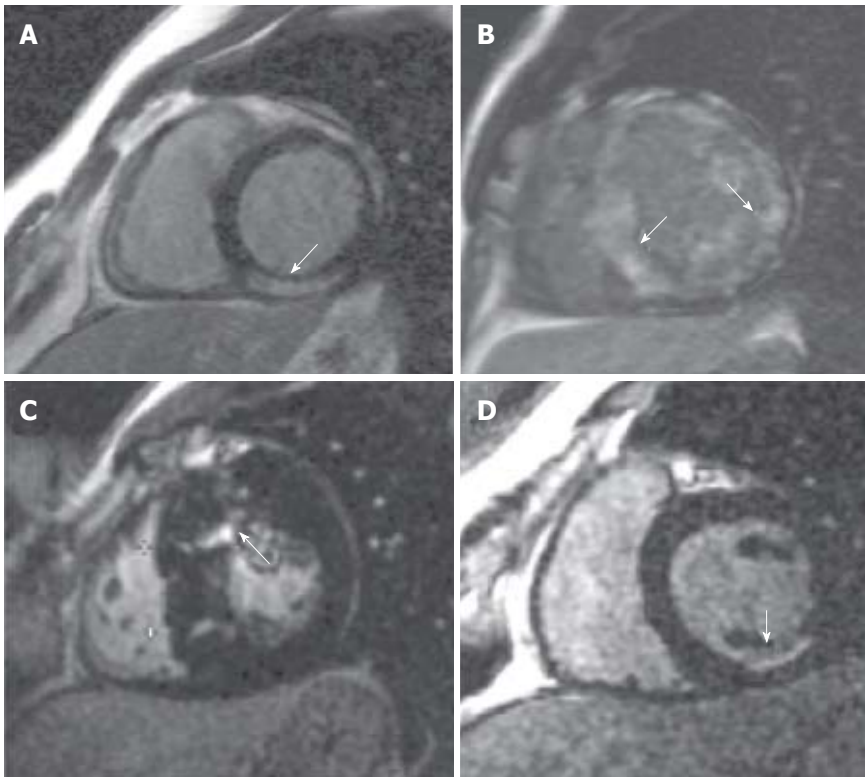

Figure 7 Diagnostic patterns of late gadolinium enhancement distribution pattern and location of late gadolinium enhancement. These features contribute to the differential diagnosis of hypertensive cardiomyopathy (HCM) and non-ischemic cardiomyopathy. (A) sub-epicardial fibrosis following myocarditis, (B) circumferential diffuse enhancement in amyloidosis, (C) patchy fibrosis in affected hypertrophied segments in HCM and a typical ischemic sub-endocardial enhancement (D). (Reproduced from Parsai *et al*[80], 2012).

these important issues in a single scan setting, thereby complementing other noninvasive tools and genetic testing[79]. CMR can provide three-dimensional data on cardiac anatomy, function, tissue characterization, coronary and microvascular perfusion and valvular disease without the use of ionizing radiation. Myocardial fibrosis or infiltration can be assessed following administration of gadolinium, an extracellular agent that accumulates in areas of interstitial expansion (*i.e.*, due to myocardial fibrosis, edema, or infiltration). Late gadolinium enhancement (LGE) imaging detects accumulation of contrast in areas of infarction or fibrosis due to the slower contrast kinetics and greater volume of distribution in the extracellular matrix. The extent and pattern of LGE establish the correct diagnosis between HCM and HTN-CM (Figure 7, reproduced from[80]).

The use of CMR in HTN-CM diagnosis allows reproducible assessment of wall thickness and LV mass with greater accuracy when compared to echocardiography. This is particularly important for assessing small LV mass changes over time as a consequence of treatment. In addition, this capability is also of prognostic value as it represents an independent predictor of cardiac mortality[81,82]. Up to 50% of hypertensive patients display LGE[77,83]. Although no typical pattern of LGE has been described, focal nonsubendocardial distribution predominates. No correlation was found between presence of LGE and LVEF or LV end-diastolic dimensions; however, patients displaying LGE had, in general, a greater LV mass[81]. The LGE patterns in HTN-CM offer new insights into risk stratification. This modality can identify patients with HTN-CM who are at risk of diastolic heart failure as a known relationship exists between myocardial fibrosis and diastolic heart failure. This clearly can be of use in therapeutic decision making[84].

TREATMENT OF HTN-CM

Hypertensive cardiomyopathy (HTN-CM) is a result of a complex interaction of genetic and hemodynamic factors inducing structural and functional adaptations[85]. LVH in HTN-CM is a recognized risk factor for congestive heart failure, dysrhythmia, and sudden death[4,9,10]. Better elucidation of the mechanisms producing cardiovascular end-organ damage should lead to treatment targeted at reducing the effects of hypertension on the heart and vascular system. Most antihypertensive treatments promote regression of LVH and reversal of diastolic dysfunction, which may decrease symptoms of congestive heart failure and improve survival rates[85]. LV mass regression improves survival rates in hypertensive patients[86] and is associated with reduced rate of complications of essential hypertension[87].

The RAAS is implicated in the development of cardiac hypertrophy associated with pressure overload[5-7,32,35,88]. Brilla *et al*[57] indicated ACE inhibition with lisinopril can regress myocardial fibrosis, regardless of LVH regression, and is accompanied by improved LV diastolic function. The Losartan Intervention for Endpoint Reduction (LIFE) study showed that the angiotensin Ⅱ type 1 (AT1) receptor antagonist, Losartan, reduced LV mass and improved systolic performance, despite only a small drop in blood pressure[89]. Furthermore, in their animal study, Nagata *et al*[90] revealed the beneficial cardiac effects of eplerenone, which attenuates myocardial oxidative stress and coronary vascular inflammation induced by

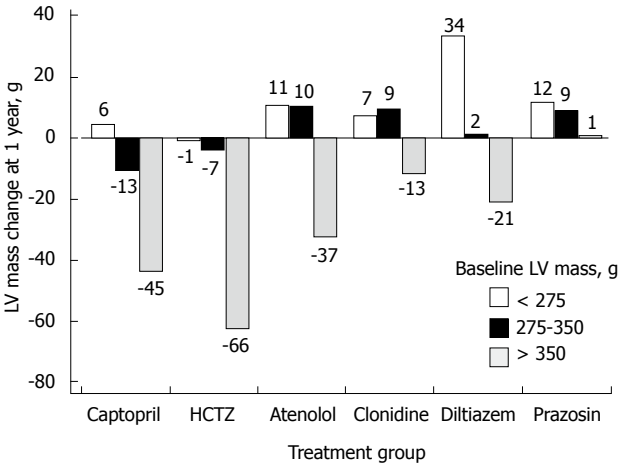

Figure 8 Effect of randomized treatments with single-drug therapy on left ventricular mass. In this group of 493 hypertensive patients, the 1-year change in left ventricular (LV) mass from baseline is shown for each of three baseline mass tertiles. The highest baseline tertile shows significant reductions with hydrochlorothiazide (HCTZ), captopril, and atenolol ($P < 0.05$). (Reproduced from Diamond *et al*[85], 2003; Gottdiener *et al*[91], 2007).

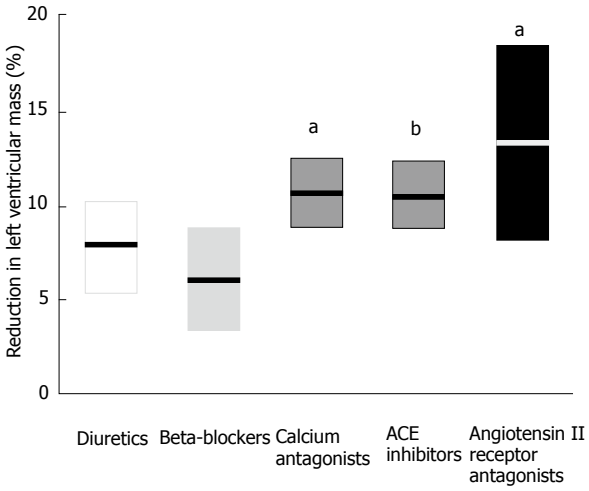

Figure 9 Change in left ventricular mass index (as percentage from baseline) with antihypertensive treatment by drug class. Data represent the mean values and 95% confidence intervals, adjusted for change in diastolic blood pressure and treatment duration. The $^{a}P < 0.05$ *vs* beta-blockers, and $^{b}P < 0.01$ *vs* beta-blocker (after Bonferroni correction). ACE: Angiotensin-converting-enzyme. (Reproduced from Klingbeil *et al*[97], 2003).

glucocorticoid-activated mineralocorticoid receptors. Gottdiener *et al*[91] showed that hydrochlorothiazide administration was associated with greater overall reduction of LA size when compared with other drugs used for the treatment of hypertension. In this study, an ACE inhibitor was nearly as beneficial as hydrochlorothiazide therapy (Figure 8, reproduced from[85,91]). Past studies indicated treatment with statins also reduces ACE activity in the cardiac tissue of rats.

The 3-hydroxy-3-methylgutaryl-CoA (HMG-CoA) reductase inhibitors, commonly referred to as statins, are well-known and potent lipid-lowering agents that reduce the incidence of myocardial infarction and ischemic stroke. In addition to their primary effects, the statins have pleiotropic effects on the cardiovascular system[92], including anti-inflammatory, anti-oxidative, and endothelial protective effects, and thus have been tested as therapeutic agents in heart failure[93]. Chang *et al*[93] showed that Rosuvastatin therapy attenuated myocardial fibrosis and LV stiffness. Saka *et al*[94] suggested that the effects of pitavastatin on load-induced cardiac hypertrophy and fibrosis are independent of its cholesterol lowering action and may be mediated, at least in part, through inhibition of RhoA-ERK-SRF signaling, which activates stretch-induced hypertrophy.

Considering these drug therapies, the most important issues in the treatment of HTN-CM are appropriate blood pressure control, weight loss, and dietary sodium restriction[12,13,95]. Regression of LVH and, more importantly, the prognosis of patients with HTN-CM, are both highly related to the antihypertensive response as well as the therapy used[13]. Regression of LVH continues gradually over time and may be associated with complete reversal of LVH and other abnormalities induced by hypertension, such as LA enlargement and diastolic dysfunction[96].

A meta-analysis published in 2003 evaluated the relative efficacy of different antihypertensive drugs for their ability to reverse LVH in patients with hypertension (Figure 9, reproduced from[97]). Notably, after statistical adjustments for duration of therapy and degree of blood pressure lowering, angiotensin Ⅱ receptor blockers, calcium channel blockers, and ACE inhibitors showed more significant regression of LVH than did beta-blockers. Note that regression of LVH is associated with improvement in both systolic and diastolic function[85], as well as with a reduction in cardiovascular risk[95].

CONCLUSION

To summarize, HTN-CM is characterized by LVH and LVH-induced diastolic dysfunction rather than systolic dysfunction. This is associated with increased risk of heart failure, arrhythmias, and death. LVH itself is a risk factor for mortality and morbidity, independent of other cardiovascular risk factors, including high blood pressure. Therefore, early detection of LVH development in patients with hypertension is important in order to start effective treatment when the myocardial damage is still reversible. Echocardiography, rather than electrocardiography alone, would be an ideal tool for detection of LVH in its early stage, along with advanced measurements such as tissue Doppler and strain parameters. CMR represents another powerful tool for detection and discrimination of patients with HTN-CM from those with other LVH diseases. Because the regression of LVH is associated with a reduction in cardiovascular risk and improved cardiac function, achieving good blood pressure control is very important in the treatment of patients with HTN-CM. This can be achieved with the use of antihypertensive agents (ACE inhibitors, angiotensin receptor blockers, and

aldosterone receptor antagonists), which can be effective for reverse remodeling of the myocardium, weight loss, and sodium restriction.

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REVIEW

Antihypertensive effects of foods

Kehima Hieda, Yoichi Sunagawa, Yasufumi Katanasaka, Koji Hasegawa, Tatsuya Morimoto

Kehima Hieda, Yoichi Sunagawa, Yasufumi Katanasaka, Tatsuya Morimoto, Division of Molecular Medicine, School of Pharmaceutical Sciences, University of Shizuoka, Shizuoka 422-8526, Japan
Yoichi Sunagawa, Yasufumi Katanasaka, Tatsuya Morimoto, Shizuoka General Hospital, Shizuoka 420-8527, Japan
Yoichi Sunagawa, Yasufumi Katanasaka, Koji Hasegawa, Division of Translational Research, Clinical Research Institute, Kyoto Medical Center, National Hospital Organization, Kyoto 612-8555, Japan
Author contributions: Hieda K and Sunagawa Y contributed equally to this work; all authors contributed to this work.
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Correspondence to: Tatsuya Morimoto, MD, PhD, Division of Molecular Medicine, School of Pharmaceutical Sciences, University of Shizuoka, 52-1 Yada, Suruga-ku, Shizuoka 422-8526, Japan. morimoto@u-shizuoka-ken.ac.jp
Telephone: +81-54-2645763
Fax: +81-54-2645764
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Abstract

Hypertension is one of the major risk factors for arteriosclerosis, which leads to cardiovascular disease and stroke. Several clinical trials revealed that control of the blood pressure is useful to reduce the morbidity and mortality associated with these diseases. However, the protective efficacy against these complications still remains at less than 50% even if the high blood pressure is treated by current medical drugs. Healthy diets are expected to not only prevent but also treat lifestyle-related diseases. Improvement of the dietary life, including low-salt diets, appropriate alcohol consumption, and calorie restriction, is important for the prevention of hypertension. In addition, green tea, which has been drunk on a daily basis in Japan and China since ancient times, possesses an antihypertensive effect, and it was revealed that its components with this effect are catechins. Many studies have been performed on the antihypertensive effects of foods. Therefore, functional foods and their ingredients, reported to possess antihypertensive effects in animal experiments and human clinical trials, are summarized in this review. Blood pressure might be controlled by improvement of the daily eating habits based on evidence regarding these functional foods, and a healthy longevity can be expected.

Key words: Foods; Hypertension; Antihypertensive effect; Cardiovascular disease; Renin

Core tip: Management of the blood pressure leads to decreases in morbidity and mortality associated with arteriosclerosis-related diseases. It is well known that the improvement of eating habits, including a low-salt diet, appropriate alcohol drinking, and calorie restriction, has marked effects for the prevention of hypertension. In this review, we have summarized functional foods and their components whose antihypertensive effects have already been reported in animal experiments and human clinical trials. The evidence indicates that hypertension could be effectively controlled by daily functional food intake and healthy longevity could be achieved.

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INTRODUCTION

Hypertension is one of the major risk factors of cardiovascular disease (CVD), stroke, and renal failure. Therefore, management of the blood pressure decreases the risk of morbidity and mortality. In 2008, approximately 40% of adults aged 25 or older had been diagnosed with hypertension globally; the number of people with the condition rose from 600 million in 1980 to 1 billion in 2008[1]. Of the 57 million global deaths in 2008, 36 million (63%) were primarily due to noncommunicable diseases and 17.3 million (30%) were due to CVDs. Death from cardiovascular disease is primarily due to stroke and heart disease, and it has been reported this number will increase to 23.3 million in 2030[2,3]. Therefore, it has become a serious global problem. This assessment of the situation shows that CVD has a high rank regarding disease-related mortality in the world. Hypertension is one of the major risk factors for CVD. The heart is one of the target organs of hypertension. Increasing pressure overload leads to coronary artery endothelial dysfunction, cardiac hypertrophy, and myocardial remodeling. They increase the risk of coronary sclerosis and myocardial ischemia. Several large-scale trials targeting cardiovascular high-risk patients revealed that when their systolic blood pressure (SBP) dropped to 160 mmHg and diastolic blood pressure (DBP) to 90 mmHg, the morbidity and mortality due to CVD decreased[4]. Hypertension is defined as 140/90 mmHg or above. The Hypertension Optimal Treatment study revealed that cardiovascular benefit is maximized when the blood pressure drops to 139/83 mmHg. Survey data of clinics targeting the general population have suggested that the lower the blood pressure, the lower cardiovascular event onset rate. Also, it has been estimated that a 5 mmHg reduction in the population average reduces mortality from stroke by 14%, coronary artery disease by 9%, and total mortality by 7%[5]. In this way, hypertension is one of the highest risk factors for CVD and stroke. Control of the blood pressure is indispensable to improve the prognosis. In hypertension guidelines, diet and exercise therapy are important along with drug therapy. In the future, hypertension will be further improvement by consuming functional foods and lifestyle reconsideration. We expect them to make a contribution to the development of preventive medicine.

Japan has the longest lifespan in the world. One of the reasons is that the balanced diet in Japan is markedly reduces stroke and tuberculosis. Furthermore, Mechnikov, who was awarded the Nobel Prize, reported that large numbers of healthy and long-lived people in the vicinity of Bulgaria may be due to the habit that they have of consuming a large quantity of yogurt. It has also been reported that few Inuk living mainly on a diet of fish contract heart disease or show hardening of the arteries. For these reasons, the diet and healthy longevity are considered to be closely related. Research on the relationship between food and health has been conducted throughout the world. As a result, it has been indicated that the ingredients in some foods have effects on biological regulation, such as on the immune, endocrine, and nervous systems, and also on digestion, absorption, and circulatory systems. That is, in certain foods, there are substances which have significant effects on the regulatory function of the body. It has been clarified that these ingredients have the ability to prevent various diseases developing because of an abnormal biological regulatory system. Foods with effects like this are called functional foods, and they have attracted global attention[6]. Diseases such as hypertension, hypercholesterolemia, and hypertriglyceridemia are lifestyle-related diseases. They are caused by inadequate lifestyle, such as an unbalanced diet, lack of exercise, drinking, and insufficient sleep. In developed countries with increasing lifestyle-related diseases and aging of the population, people have an increased awareness of self-medication, the act of taking care of yourself. Attention has been focused on functional foods. Functional foods having particularly beneficial effects on hypertension in animal experiments (Table 1) and human clinical trials (Table 2) are summarized in this paper. This manuscript is focusing on clinical findings than experimental ones. Moreover, we emphasize interventional studies yielded results with statistical significance. Functional foods reduce the blood pressure by different mechanisms, such as rennin-angiotensin-aldosterone system (RAAS) inhibition, antioxidant effect, diuretic effect, NOS production-promoting effect. And there are also some foods with multiple mechanisms (Figure 1).

CATECHINS

Green tea is a beverage that has been found to be useful for maintaining and recovering health. People have continued to drink it on a daily basis from ancient times in East Asia such as Japan and China. Using stroke-prone spontaneously hypertensive rats (SHRSP), treatment of black tea polyphenols or green tea polyphenols showed significant reductions of SBP and DBP. Moreover, several experiments indicated that the regular consumption of black and green tea may also provide some protection against hypertension in humans[7]. The major active constituents of tea are polyphenols such as catechins and tannins. In recent years, many studies have reported that catechins have a variety of actions, such as antihypertensive effects[8-10]. The action mechanism of catechins for their antihypertensive effect is considered to be through an antioxidant action. That is, reduction of oxidative stress in the vascular endothelium increases the bioavailability of NO, which enhances the vasodilatory action. Also, it is related to the diuretic action of caffeine contained

Table 1 Antihypertensive effects of functional foods in animal experiments

Functional foods	Active ingredients	Animal experiments	Results	Ref.
Tea	Catechin Flavonoid	Taking the green tea polyphenol water containing 3.5 g/L catechins, 0.5 g/L flavonols and 1 g/L polymetric flavonoids to SHRSP	Decreases in SBP and DBP	[7]
GABA	GABA	Single oral administration of GABA (0.5 mg/kg) to SHR and normotensive Wistar-Kyoto rats	Decrease in SBP in SHR rats, but not in normotensive rats	[16]
Stevia	Stevioside	Intraperitoneally administration of stevioside (50, 100 and 200 mg/kg) to normotensive Wistar-Kyoto rats (NTR), SHR, DOCA-NaCl, DHR and RHR	Hypotensive effect was noted in different strains of rats at the dose of 50 mg/kg. The dose of 100 and 200 mg/kg caused slow and persistent lowering of blood pressure in SHR and NTR Blood pressure decreased in a dose-dependent manner in SHR	[22]
Black vinegar	Acetic acid Black vinegar-derived peptides	Single (3 g/kg body weight) and continuous administration (8 wk; 10% (w/w) of diet) of black malt vinegar to SHR	Decrease in SBP in the administration of either	[32]
Goma	Sesamin	Taking a sesamin-containing diets (0.1, 1 w/w%) to DOCA-salt hypertensive rats for 5 wk	Decrease in SBP	[34]
Fish oil	EPA DHA	Daily oral administration of 30 to 300 mg/kg EPA to SHR and normotensive rats for eight weeks	Treatment of 30, 100, and 300 mg/kg EPA decreased mean SBP in SHR	[40]
Garlic	S-allyl cysteine (SAC), Allicin	Daily oral administration of 50 mg of aqueous extract of garlic totwo-kidney-one-clip hypertensive rat for 4 wk	SBP and ACE activity in serum and different tissues such as aorta, heart, kidney and lung decreased	[46]
		5/6 nephrectomized rats were treated with SAC (200 mg/kg ip) or aged garlic extract (1.2 mL/kg ip) every other day for 30 d	SBP and renal failure decreased, SOD activity increased	[47]
Onion	Quercetin	Taking a 5% dried onion diet to L-NAME induced-hypertensive rats and SHRSP for 4 wk	SBP decreased from 1 wk in both rats, and TBARS decreased at 4 wk Urinary nitrite, NOS activity was increased in SHRSP rats	[58]
Pea	PPH	Oral administration of the PPH to spontaneously hypertensive rats (SHR) at doses of 100 and 200 mg/kg	Decrease in SBP	[64]

A list of animal experiments. Hypotensive actions have been confirmed in multiple types of rat, mainly SHR. GABA: G-aminobutyric acid; PPH: Pea protein hydrolysate; DOCA-NaCl: Deoxycorticosterone acetate-salt; DHR: Sensitive hypertensive rats; RHR: Renal hypertensive rats.

in green tea. Studies on the hypotensive action of green tea have been conducted throughout the world. Clinical trials in humans reported that hypertensive patients with obese who consumed green tea extract for 3 mo showed significant decreases in their SBP and DBP compared with a placebo group[11]. In addition to this, it was reported that subjects who were classified as being healthy but had a slightly high blood pressure or mild hypertension consumed Benifuuki tea from a tea bag containing 2 g of Benifuuki leaves [containing 25 mg of epigallocatechin-3-O-(3-O-methyl) gallate, EGCG] for 8 wk, leading to significant decreases in SBP and DBP[12]. Overweight or obese male subjects with a BMI of 28-38 who took 400 mg of EGCG twice daily for 8 wk showed a DBP reduction below 2.8 mmHg[10]. Mildly hypertensive patients with type 2 diabetes mellitus showed a decreased SBP after drinking green tea three times a day 2 h after each meal for 4 wk[13]. No adverse effects were observed either study. From the above, it has been suggested that polyphenols such as catechins contained in green tea have not only a hypotensive action but also improve lifestyle-related diseases. Although the causal relationship is unknown, the elderly in Shizuoka Prefecture, considered the home of green tea in Japan, consume large amounts of green tea and show a healthy longevity that is a longer compared with other prefectures. Green tea may therefore play a role for health and longevity.

GABA

GABA is γ-aminobutyric acid, a kind of amino acid, and one of a large number of inhibitory neurotransmitters in the central nervous system such as the brain, cerebellum, and spinal cord. In recent years, GABA has been found to improve blood flow and metabolism in the brain. In addition to being produced by the brain during sleep, GABA can be obtained from food. GABA is included in trace amounts in rice, vegetables, tea, and fermented food. Especially, sprouted brown rice contains about 10 times more GABA than rice. GABA is produced from glutamic acid decarboxylase (GAD) synthesized by lactic acid bacteria. Therefore, it is also abundant in pickles which is a lactic acid fermentation product made from plants[14,15]. Antihypertensive mechanisms of GABA have been considered as follow: an inhibitory effect on the sympathetic nervous system and peripheral sympathetic ganglia, a diuretic effect by the inhibition of anti-diuretic hormone secretion, and angiotensin converting enzyme (ACE) activity inhibition[16,17]. Some

Table 2 Antihypertensive effects of functional foods in human clinical trials

Functional foods	Human clinical trials		Ref.
	Targets	Study designs	
Tea	Obese (BMI ⩾ 30), hypertensive subjects	Taking 379 mg of Green Tea extract (including 208 mg of EGCG) for 3 mo. (randomized double-blind, placebo-controlled trial)	[11]
	Overweight or obese subjects (BMI > 28)	Taking 400 mg of EGCG twice daily for 8 wk. (randomized double-blind, placebo-controlled trial)	[10]
GABA	Subjects with high normal blood pressure	Drinking 100 mL of fermented milk containing 12.3 mg of GABA for 12 wk. (randomized double-blind, placebo-controlled trial)	[17]
	Mildly hypertensive subjects	Drinking 100 mL of fermented milk product containing 10-12 mg of GABA for 12 wk. (randomized single-blind, placebo-controlled trial	[18]
	Subjects with high-normal blood pressure	Taking less-sodium soy sauce containing 120 mg of GABA once daily for 12 wk. (double-blind, placebo-controlled trial	[19]
Stevia	Subjects with mild to moderate essential hypertension	Taking 250 mg of stevioside 3 times daily for 1 yr. (randomized double-blind, placebo-controlled trial)	[25]
	Subjects with mild essential hypertension	Taking 500 mg of stevioside 3 times daily for 2 yr. (randomized double-blind, placebo-controlled trial)	[26]
Black vinegar	Subjects with high normal, mild hypertension	Taking a drink containing 15% black vinegar or 15% apple vinegar for 10 wk (double-blind, placebo-controlled trial)	[29]
	Subjects with high normal, mild hypertension	taking a drink containing tomato vinega (750 mg/100 g per day) for 12 wk (double-blind placebo-controlled trial)	[30]
	Subjects with mild to moderate hypertension	Taking a drink containing apple vinegar (acetic acid 0.75 g/100 mL) or acetic acid (acetic acid 1.5 g/100 mL) for 8 wk (three groups parallel, placebo-controlled trial)	[31]
Goma	Subjects with mild hypertension	Taking 60 mg of sesamin for 4 wk (double-blind, cross-over, placebo-controlled trial)	[37]
Fish oil	Subjects with essential hypertension	Taking 2.7 g of EPA for 8 wk (randomized double-blind, cross-over, placebo-controlled trial)	[41]
	Subjects with hypertension and/or hypercholesterolemia	Taking a 2 g of DHA for 5 wk (randomized double-blind, placebo-controlled trial)	[45]
Garlic	Subjects with uncontrolled systolic hypertension (SBP ⩾ 140 mmHg)	Taking aged garlic extract (240/480/960 mg containing 0.6/1.2/2.4 mg of S-allylcysteine) for 12 wk (randomized double-blind, placebo-controlled trial)	[51]
	Subjects with uncontrolled hypertension	Taking 960 mg of aged garlic extract containing 2.4 mg S-allylcysteine daily for 12 wk (randomized double-blind, placebo-controlled trial)	[55]
Onion	Subjects with prehypertension and stage 1 hypertension	Taking 730 mg quercetin for 4 wk (randomized double-blind, cross-over, placebo-controlled trial)	[63]
Pea	subjects with SBP ranging from 125 to 170 mmHg	Taking 1.5 and 3 g of PPH for 3 wk (randomized double-blind, cross-over, placebo-controlled trial)	[64]

A list of human clinical trials. We reviewed mainly clinical trials involving hypertensive patients. BMI: Body mass index; GABA: G-aminobutyric acid; EGCG: Epigallocatechin-3-O-(3-O-methyl) gallate.

subjects with a high-normal blood pressure were given 100 mL of fermented milk containing 12.3 mg of GABA. They showed significant decreases of SBP after 8 wk and DBP after 12 wk. A reincrease in the blood pressure was observed after 4 wk following the discontinuation of ingestion[17]. The same hypotensive effect was observed in a trial of hypertensive patients, and no adverse reactions were observed[18,19]. From these results, the benefits and safety for hypertensive patients of GABA-containing fermentation foods are expected.

STEVIOSIDE

Stevioside, contained in Stevia which is a perennial plant of the Asteraceae, is a natural sweetener used widely in Japan and South America. It has been traditionally used as a herbal medicine in South America. A variety of physiological activities have been reported, such as improving insulin resistance in type 2 diabetes, an antihypertensive action, a diuretic action, and an antioxidant action[20,21]. Antihypertensive action has been indicated by several experiments using different hypertensive rat models[22]. The hypotensive effect of stevioside may be mediated by inhibiting Ca^{2+} influx into blood vessels and vasodilation[23,24]. In a human clinical trial, patients with mild to moderate essential hypertension given 250 mg of stevioside showed significantly decreased both SBP and DBP after 3 mo, and the effect persisted for one year[25]. Patients with mild essential hypertension taking 500 mg of stevioside 3 times daily for 2 years showed significantly decreased SBP and DBP. These hypotensive effects were noted to begin about 1 wk after the start of treatment and persisted throughout the study and no significant adverse effects were noted[26]. In a involving the administration of crude stevioside at 15.0 mg/kg per day for 6 wk to patients with essential hypertension, SBP and DBP decreased during the treatment, but a similar effect was observed in a placebo group. Therefore, crude stevioside did not show a significant antihypertensive effect compared to the placebo group[27]. These results indicate that stevioside contained in food

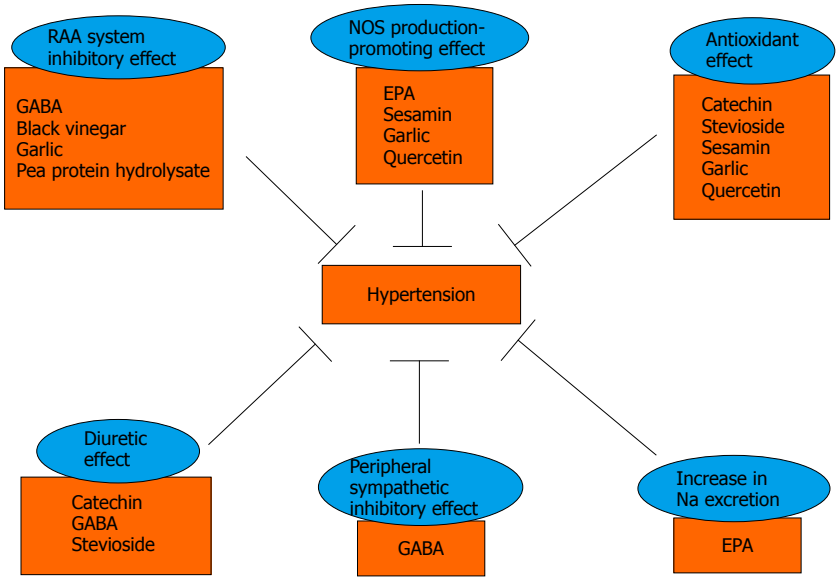

Figure 1 Antihypertensive mechanism of functional foods. Anti-hypertensive mechanism of functional foods in this paper. There are also some foods with multiple mechanisms. These suggest that they synergistically promote the hypotensive action. GABA: G-aminobutyric acid; RAA: Rennin-angiotensin-aldosterone.

has an insufficient antihypertensive effect, and so there is a need to take it as a supplement.

BLACK VINEGAR

Black vinegar is made from rice and produced by fermentation and aging. Since it contains an abundance of amino acids, various physiological activities, including antioxidant activity, have been reported. It has been reported that the activities are due to amino acids, acetic acid, and low-molecular-weight peptides[28]. When subjects were given a drink containing 15% black vinegar or 15% apple vinegar (each contains acetic acid at 750 mg/100 mL) for 8 wk, SBP was significantly reduced both at 2 and 10 wk after the intake, and no side effects were observed[29]. In another trial involving subjects given a drink containing tomato vinegar (750 mg/100 g per day) for 12 wk, SBP was significantly reduced at 10 and 12 wk after intake compared to a placebo group, and DBP was also reduced at 10 and 12 wk compared to the value before ingestion[30]. Moreover, subject given a drink containing apple vinegar (acetic acid 0.75 g/100 mL) or acetic acid (acetic acid 1.5 g/100 mL) for 8 wk, SBP was decreased from 6 wk after intake of apple vinegar drink, SBP and DBP were decreased from 4 wk after intake of acetic acid drink[31]. By experiment using spontaneously hypertensive rats (SHR) rats, the mechanism of this hypotensive action has been suggested to be the inhibitory effect of the renin-angiotensin system, such as the inhibitions of renin activity and ACE activity by peptides present in black vinegar[28,32]. Also, it has been reported that acetate has effects on lipid metabolism[33], and that drinking vinegar routinely improves lifestyle-related diseases as well as decreases blood pressures.

SESAMIN

Sesamin is a kind of lignan compound contained in a small amount of sesame. In recent years, a variety of bioactivities has been reported, such as antioxidant, cholesterol-lowering, lipid metabolism-enhancing, and liver-protective effects. Sesamin is also known for a hypotensive effect. However, there are many unclear points regarding the mechanism of action. Several animal experiments suggest that the hypotensive action of sesamin is involved in the vasodilating effect caused by NOS production enhancement and oxidative stress reduction in blood vessels due to the antioxidant effect[34-36]. In human clinical trials, mildly hypertensive subjects taking 60 mg/d of sesamin for 4 wk, showed significantly decreased SBP and DBP. No significant side effects were observed[37]. Since sesamin is often used in small amounts in cooking and its calorie content is high, the ingestion of a large amount at one time is difficult. Therefore, it is desirable for the active ingredient of sesamin to be taken as a supplement.

EPA, DHA

The results of epidemiological studies in the 1970s showed that people who lived on mainly a diet of fish in Greenland and Canada suffered less from coronary artery disease than Danes eating mainly meat. Human trials have indicated that diet supplementation with fish oil, generally more than 3 g/d, can lead to clinically relevant BP reductions in individuals with untreated hypertension[38,39]. Components exhibiting this anti-hypertensive effect of fish oil have been reported to be EPA and DHA, n = 3 fatty acids abundant in fish, and researches on them is progressing. Many animal experiments indicate that daily administration of EPA significantly decreased the development of hypertension in SHR dose dependently, although it did not affect to BP in normotensive rats[40]. Patients with uncomplicated mild to moderate essential hypertension treated with EPA (2.7 g/d) for 4 wk showed decreases in SBP and the

intraerythrocyte sodium content (R-Na), accompanied by an increase in the erythrocyte membrane EPA content. The decrease in R-Na was correlated positively with the decrease in SBP, and correlated negatively with the change in Na^+-K^+ ATPase activity. EPA may lower the blood pressure by altering the activities of the membrane sodium transport systems[41]. Antihypertensive mechanisms of fish oil, such as EPA and DHA, are considered to explain the decrease in the intercellular sodium concentration[41], increase in eNOS expression, decrease in oxidative stress[42], and altered biosynthesis of eicosanoids[43]. In human trials, patients with hyperlipidemia were assigned to receive 1800 mg/d of EPA or 10 mg/d of pravastatin for 3 mo. In the EPA group, the radial augmentation index (AI, a parameter for vascular aging), SBP, DBP, and C-SBP (the systolic pressure at the ascending aortic root, representing the vascular load of the left ventricle afterload), were decreased, respectively. In the pravastatin group, there were no significant changes in brachial BP, AI, or C-SBP. These results suggest that EPA but not pravastatin reduces cardiac afterload by reducing vascular reflected waves and lowering C-SBP[44]. On the other hand, subjects with hypertension and/or hypercholesterolemia supplemented with 2 g of DHA for 5 wk showed significantly decreased SBP, DBP, and heart rate[45].

GARLIC

Garlic preparations contain a wide variety of organosulfur compounds, of which allicin is the most notable, and it is responsible for the characteristic garlic odor[46]. Antihypertensive effects of garlic were reported in many studies using hypertensive rat models. The antihypertensive mechanism of garlic is assumed to involve ACE inhibitory effect[46], antioxidant effect[47], activation of NO formation[48], and reduction in the synthesis of vasoconstrictor prostanoids[49]. Although SHR fed diets containing either aged garlic extract (AGE) or raw garlic (RG) powder for 10 wk showed a reduction of SBP from 4 wk, Harmful effects were observed in the RG group, including a decrease in erythrocytes, an increase in reticulocytes, and the generation of a papilloma in the forestomach. These findings suggest that the long-term intake of raw garlic can be harmful to health[50]. Patients with uncontrolled systolic hypertension were allocated aged garlic extract (240, 480, and 960 mg containing 0.6, 1.2, and 2.4 mg of S-allylcysteine, respectively). SBP was significantly reduced in the 480 mg/d group over 12 wk, and reached borderline significant reduction in the 960 mg/d group at 8 wk, although blood pressure in the 240 mg/d group was not significantly different compared to the placebo group[51]. The efficacy of some clinical trials have been reported in addition to these[52-54]. Some trials suggested that garlic is associated with blood pressure reductions in patients with elevated SBP, but not in those without SBP elevation[55,56]. These reports suggest that the risk of excessive decreases in blood pressure is low when a healthy person ingests garlic.

QUERCETIN

Onion is a vegetable which is used in a variety of dishes in the world and has excellent storage stability. Onion is rich in phenolic compounds such as quercetin, which have an antioxidant effect[57]. It is expected to provide considerable health benefits. There are several reports that quercetin shows an antihypertensive effect through the antioxidant activity[58], inhibition of ACE activity[59] and Ca^{2+} influx[60]. It has been considered that these results show synergistic antihypertensive effect. Animal experiment using abdominal aortic constriction rat indicated that quercetin is also useful for preventing cardiovascular disease[61]. In human studies, apparently healthy subjects showed decreased arterial blood pressure 5 h after the administration of an onion-olive-oil maceration capsule formulation. In addition to this, a significant reduction in the plasma viscosity and hematocrit were observed[62]. Subjects with prehypertension and stage 1 hypertension ingested 730 mg quercetin per day for 28 d, and the blood pressure was not altered in prehypertensive patients after quercetin supplementation. In contrast, reductions in SBP, DBP, and mean arterial pressures were observed in the stage 1 hypertensive patients after quercetin treatment. However, indices of oxidant stress measured in the plasma and urine were not affected by quercetin[63], and so it is considered that components other than quercetin are also involved in the hypotensive effect of onion.

PEA PROTEIN HYDROLYSATE

Pea protein has been a focus of attention as an important and cheap vegetable protein with high nutritional and functional values and marked potency as an ingredient for the production of bioactive peptides[64]. Pea protein hydrolysate (PPH) showed high-level inhibition of ACE and renin activities[65]. PPH shows antihypertensive effects by influencing the renin-angiotensin system in rat model[64]. In clinical trials, subjects with SBP ranging from 125 to 170 mmHg took 3 g/d of PPH showed significant reductions in SBP of 5 and 6 mmHg in 2 and 3 wk, respectively. None of the participants reported any adverse side effects[64]. Beans such as peas, rich in vegetable protein with low lipids and low calories, are very important in health promotion. However, a complex process of protein purification, as described above, is necessary to obtain PPH with a hypotensive action. So, an abundant consumption of peas is not recommended. We expect that it will become possible to control the blood pressure based on these results and further research on bean proteins and the development of PPH supplements.

MANAGEMENT OF HYPERTENSION BY FUNCTIONAL FOODS

Besides the foods introduced in this paper, grains,

vegetables, fruits, milk, cheese, meat, chicken, wine, mushrooms, lactic acid bacteria, nicotianamine and egg are various food sources with potential antihypertensive effects. Their main bioactive constituents include ACE inhibitory peptides, vitamins C and E, flavonoids, flavanols, catechins, anthocyanins, phenolic acids, polyphenols, tannins, resveratrol, polysaccharides, fiber, saponin, sterols, as well as K, Ca, and P. These functional foods may provide new therapeutic applications for hypertension prevention and treatment, and contribute to a cardiovascularly healthy population[66]. In recent years, the DASH (Dietary Approaches to Stop Hypertension) diet has caught attention as a dietary therapy for blood pressure control. The DASH diet is a composite diet that cuts down fat, based on fruits and vegetables, beans, fish, low-fat dairy products, and cereals. It has been frequently reported as useful for lowering the blood pressure[5,67-72]. The mechanism of the the hypotensive action of the DASH diet has been considered mainly through the Na diuretic effect. In addition to this, as it is rich in K, its hypotensive action is particularly effective for blood pressure elevation due to salt overdose. Since Na is added and K is lost during food processing, actively taking K should be recommended in developed countries where processed foods are commonly consumed. It has also been reported that the intake of Mg reduces the onset risk of metabolic syndrome[73]. A DASH diet rich in Mg may reduce the risk of obesity.

We have reviewed the functions of foods, but such foods should be taken with care to complement human physiology. For example, there is a risk of causing high K hyperlipidemia in some patients with marked renal failure or who are taking anti-aldosterone drugs, ACE inhibitors, or angiotensin Ⅱ receptor blocker (ARB). For this reason, such people are not recommended to abundantly consume vegetables and fruits rich in K. Patients with obesity and diabetes who have restricted energy intake should not abundantly consume nuts and fruits containing much sugar. It is necessary for them to avoid excess calorie intake[74]. On the other hand, the intake of food with a diuretic effect is suitable for patients with renal failure because it has the action of body fluid volume control and lowering the blood pressure. However, overconsuming certain functional foods with a hypotensive effect may lead to unbalanced nutrition and adverse interaction with antihypertensive agents. Therefore, recommendations of a balanced diet based on functional foods and dietary advice tailored to an individual's physiology are recommended.

We summarize the functional foods with antihypertensive effects from the evidences in clinical studies. In contradiction to these studies, there are several reports indicating opposite results and many interventional studies with no statistical significance. For example, Green tea consumption was inversely associated with mortality due to all causes and cardiovascular disease[75], and there are a few reports described no effect of EPA on the blood pressure[76,77]. So, the potential of clinical applications of functional foods remains undetermined. Randomized controlled trials are needed to establish the clinical applications of functional foods.

CONCLUSION

In addition to drug therapy, the management of high blood pressure is essential for the improvement of lifestyle habits. Simply taking medicine for health is not enough. It is necessary to adopt a balanced diet and regular life with drug therapy. The first dietary step is to take a low-salt diet (optimal value: less than 6 g/d) in order to reduce the load on the kidneys and blood vessels. We hope that you will enjoy a richer dietary life by positively taking functional foods when presented. Also, we expect people to utilize them effectively as a means to practice "self-medication".

We are confident that in the future, further studies will expand the field of functional foods, and identify more useful functions of other foods, not only functional fruits and vegetables, for preventing hypertension-related and other diseases.

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REVIEW

Progress in neuregulin/ErbB signaling and chronic heart failure

Hong-Kun Yin, Xin-Yan Li, Zheng-Gang Jiang, Ming-Dong Zhou

Hong-Kun Yin, Xin-Yan Li, Zheng-Gang Jiang, Ming-Dong Zhou, Zensun (Shanghai) Sci and Tech Co., Ltd., Zhangjiang Hi-tech Park, Shanghai 201203, China
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Correspondence to: Ming-Dong Zhou, PhD, Zensun (Shanghai) Sci and Tech Co., Ltd., Zhangjiang Hi-tech Park, No. 68 Ju Li Road, Shanghai 201203, China. mdzhou@zensun.com
Telephone: +86-21-50802627
Fax: +86-21-50802621
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Abstract

Heart failure is one of the leading causes of death today. It is a complex clinical syndrome in which the heart has a reduced contraction ability and decreased viable myocytes. Novel approaches to the clinical management of heart failure have been achieved through an understanding of the molecular pathways necessary for normal heart development. Neuregulin-1 (NRG-1) has emerged as a potential therapeutic target based on the fact that mice null for NRG-1 or receptors mediating its activity, ErbB2 and ErbB4, are embryonic lethal and exhibit severe cardiac defects. Preclinical studies performed with animal models of heart failure demonstrate that treatment with NRG-1 significantly improves heart function and survival. Clinical data further support NRG-1 as a promising drug candidate for the treatment of cardiac dysfunction in patients. Recent studies have revealed the mechanism underlying the therapeutic effects of NRG-1/ErbB signaling in the treatment of heart failure. Through activation of upstream signaling molecules such as phosphoinositide 3-kinase, mitogen-activated protein kinase, and focal adhesion kinase, NRG-1/ErbB pathway activation results in increased cMLCK expression and enhanced intracellular calcium cycling. The former is a regulator of the contractile machinery, and the latter triggers cell contraction and relaxation. In addition, NRG-1/ErbB signaling also influences energy metabolism and induces epigenetic modification in cardiac myocytes in a way that more closely resembles healthy heart. These observations reveal potentially new treatment options for heart failure.

Key words: ErbB; Epigenetic modification; Heart failure; Metabolism; Neuregulin-1

Core tip: Neuregulin (NRG)-1/ErbB signaling plays a critical role in the development of the heart and the maintenance of cardiac function. In both pre-clinical and clinical studies, NRG-1 has demonstrated efficacy as a therapeutic agent for the treatment of heart failure. In model animals and clinical trials, short-term treatment with recombinant NRG-1 protein results in a long-term beneficial effect. Here, the mechanisms underlying the therapeutic effects of NRG-1 during heart failure are reviewed. The results indicate that NRG-1 induces a cardiac reverse remodeling process through the initiation of changes in both cell metabolism and epigenetic modification.

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INTRODUCTION

The neuregulins (NRGs) are a group of growth factors that regulate multiple cellular processes, including proliferation, apoptosis, adhesion, differentiation, metabolism, and epigenetic modification, through the activation of ErbB receptors and downstream signaling pathways. Increasing evidence demonstrates that NRG-1/ErbB signaling plays a critical role in the development of the heart and the maintenance of cardiac function. In both pre-clinical and clinical studies, NRG-1 has demonstrated efficacy as a therapeutic agent for the treatment of heart failure. This review will focus on the underlying mechanisms and recent achievements in the treatment of heart failure with NRG therapy.

NRG FAMILY AND THEIR RECEPTORS

NRGs are ligands for receptor tyrosine kinases of the ErbB family. In mammals, NRGs are a family of homologous proteins encoded by four genes, *NRG1*, *NRG2*, *NRG3*, and *NRG4*. NRG-1 is the most abundant family member expressed in the cardiovascular system and the only NRG currently known to play a role in the development and function of the heart[1-4].

Six NRG-1 isoforms generated by alternative splicing have been identified. All NRG-1 isoforms contain an epidermal growth factor (EGF)-like domain, which is critical for function. Proteolytic cleavage at the C-terminal end of the domain results in the release of a secreted, bioactive form of NRG-1[5,6]. Due to alternative splicing, the EGF-like domain of NRG-1 differs at the C-terminal end. An α- or β-variant is generated, and *in vitro* studies have demonstrated that NRG-1β isoforms are 10-100-fold more biologically active than NRG-1α isoforms[3,7-9].

NRG-1 is a growth factor that elicits function through interaction with the ErbB family of tyrosine kinase receptors and is regulated by stress[10,11]. The ErbB family contains four members: ErbB1, ErbB2, ErbB3, and ErbB4. ErbB1, also known as EGF receptor, does not bind NRG-1[2]. ErbB2 does not directly bind any ligands, but functions as the heterodimeric partner of the other three ErbB family members[12]. NRG-1 binds to ErbB3 and ErbB4, which results in the formation of ErbB2/ErbB3 and ErbB2/ErbB4 heterodimers and leads to the phosphorylation of cytoplasmic receptor tyrosine residues. Multiple intracellular signal transduction cascades, such as phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt), mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (Erk) 1/2, and focal adhesion kinase (FAK), are induced and stimulate cell proliferation, differentiation, and survival in many tissues including the heart[13-15].

NRG-1/ERBB SIGNALING IN CARDIAC DEVELOPMENT AND HEART FAILURE

The importance of NRG-1 in heart development was demonstrated in *Nrg1*-knockout mice. The *Nrg1* knockout was embryonic lethal, with the animals exhibiting cardiac developmental defects, such as the absence of ventricular trabeculation and insufficient myocyte differentiation[16,17]. Such results indicate that NRG-1 activity during cardiac development is not functionally redundant among family members[18-20]. The fact that NRG-2 and NRG-3 are expressed in the central nervous system and NRG-4 is expressed in pancreas and skeletal muscle further underscores the essential role for NRG-1 in cardiac development. Proteolytic cleavage is critical for the function of NRG-1, *Adam17*-knockout mice died at birth[21]. Interestingly, a deletion mutation in the cytoplasmic tail of NRG-1 is resistant to proteolysis and cannot activate ErbB receptors, suggesting that the intracellular domain is essential for the proteolytic processing of NRG-1 proteins[22]. Mice with disrupted *ErbB2* or *ErbB4* were also embryonic lethal before day 11, mirroring the phenotype of the *Nrg1*-knockout mice[23,24]. These findings implicate an essential role in cardiac development for NRG-1/ErbB2/ErbB4 signaling. *ErbB3*, however, is only expressed in mesenchymal cells of the endocardial cushion of the fetal heart. *ErbB3*-knockout mice were embryonic lethal at day 13.5 with defects in the endocardial cushion; however, the trabeculae had developed normally[24-26].

A function for NRG-1/ErbB2/ErbB4 signaling has also been confirmed in the adult heart[27]. Expression of *NRG-1* is found in the microvascular endothelial cells in the adult heart, but not in the large coronary arteries or in the aorta[10]. *ErbB2* and *ErbB4* are expressed in adult cardiomyocytes, while *ErbB3* is only expressed in fetal myocytes[27]. However, in one recent study, ErbB3 expression was detected in the adult myocardium, although its function in adult heart still remains to be determined[28]. Mice with a cardiac-specific knockout of *ErbB2* were phenotypically normal at birth, but spontaneously developed dilated cardiomyopathy at eight weeks of life. These animals were furthermore unable to survive pressure overload induced by aortic binding, and cardiac hypertrophy markers, skeletal α-actin and atrial natriuretic peptide, also significantly increased during the progression of heart failure[29]. The same result was observed in transgenic mice with a cardiomyocyte-specific null mutation in *ErbB2*[30]. In addition, the *ErbB4* conditional-knockout mice developed dilated cardiomyopathy with delayed conduction and impaired contractility by the third month after birth[31]. Based on these results, ErbB2/ErbB4 appears to be critical also for the maintenance of normal

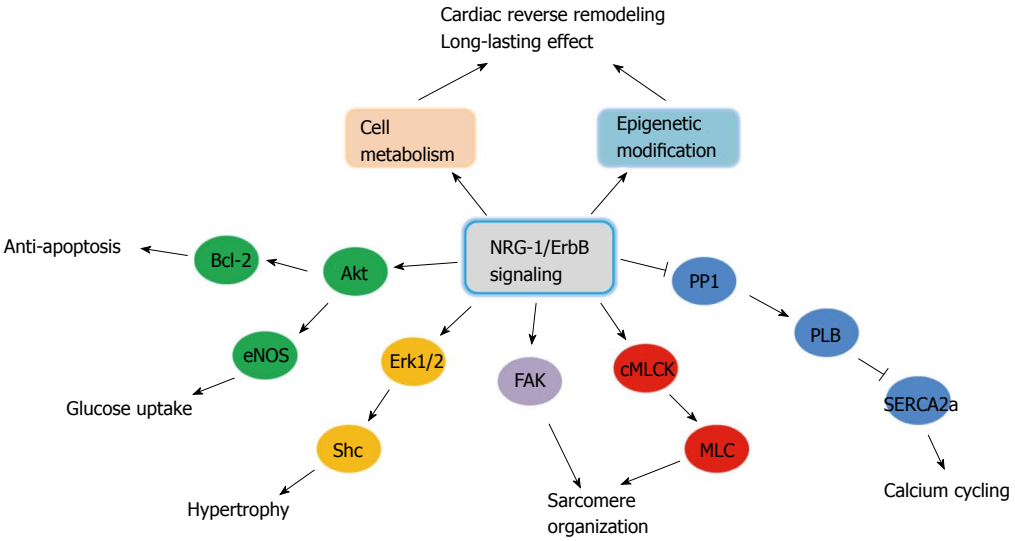

Figure 1 Role of neuregulin-1/ErbB signaling in heart. Neuregulin (NRG)-1 treatment affects various signaling pathways as well as leads to changes in cell metabolism and epigenetic modification that more closely resemble normal heart function. Akt: Protein kinase B; cMLK: Cardiac myosin light-chain kinase; eNOS: Endothelial nitric oxide synthase; Erk: Extracellular signal-regulated kinase; FAK: Focal adhesion kinase; MLC: Myosin light chain; PLB: Phospholamban; PP1: Protein phosphatase 1; SERCA2a: Sarcoplasmic reticulum Ca^{2+}-ATPase 2a.

function of the adult heart.

In clinical trials, breast cancer patients treated with trastuzumab (a humanized monoclonal ErbB2-targeted antibody) were found to have an increased risk for symptomatic heart failure and cardiac dysfunction[32,33]. This finding provided strong evidence for the critical role of ErbB2 in the adult human heart. In adult rat ventricular myocytes, treatment with NRG-1β resulted in activation of Erk1/2 and Akt, and significantly inhibited anthracycline-induced myofilament disarray. In contrast, simultaneous treatment of myocytes with anti-ErbB2 and doxorubicin led to more severe myofibrillar disarray than doxorubicin alone[34]. In the stress-induced rat model, administration of NRG-1β also led to significant improvement in the prevention of cardiac dilatation[35]. These results implicate a role for NRG-1/ErbB signaling in the maintenance of adult cardiac myocyte function and structure. Interestingly, *NRG1* mRNA levels were found to be increased in chronic heart failure patients, while the expression of *ERBB2* and *ERBB4* was reduced in a potential feedback mechanism[6,36], indicating a possible role for NRG-1/ErbB signaling during heart failure.

POSSIBLE MECHANISMS MEDIATING NRG-1/ERBB SIGNALING IN ADULT HEART

Based on *in vitro* and *in vivo* studies of cardiac myocytes, NRG-1/ErbB signaling regulates a number of cellular processes by activating signaling pathways such as PI3K/Akt, MAPK-Erk1/2, and FAK[15,27,34,37]. These canonical signaling cascades have been extensively reviewed elsewhere and will be addressed very briefly in this review[1,38,39]. In addition, recent studies indicate that NRG-1 functions as an effector molecule regulating energy metabolism[7] and epigenetic modification in cardiomyocytes[40]. A working model for NRG-1/ErbB signaling in heart is summarized in Figure 1.

CANONICAL SIGNALING PATHWAYS MEDIATING NRG-1/ERBB ACTIVITY

The PI3K/Akt pathway has been well studied in cell proliferation, growth, and apoptosis. In cardiac myocytes, activated Akt signaling inhibits apoptosis[41,42] and protects cardiomyocytes from apoptosis induced by serum starvation[27], cardiotoxic anthracycline[43], as well as β-adrenergic receptor activation[44,45]. This protective effect is dependent on the downstream activation of members of the Bcl-2 family, which typically block apoptosis[45,46]. Interestingly, NRG-1 shows a biphasic dose effect on p70S6K (a downstream protein kinase in the Akt/mTOR pathway) phosphorylation, as higher NRG-1 concentration leads to a decreased response[13]. In addition, Akt also promotes glucose uptake as well as activates endothelial nitric oxide synthase, which may contribute to cell survival under metabolic stress[7,47].

In adult cardiac myocytes, NRG-1 stimulates the Erk1/2 pathway, which leads to expression of genes associated with cardiac hypertrophy[13] as well as myofilament organization[34,37]. Erk1/2 activation is mediated by Grb2, Grb7, and Shc, which are downstream targets of ErbB2 and thus, also play a role in cardiac hypertrophy[48-51].

FAK signaling is involved in the formation of focal adhesion complexes as well as the restoration of sarcomeres in cardiac myocytes[52,53], and contributes to the growth and survival of myocytes[54,55]. In addition, cardiomyocyte FAK conditional knockout in mice was embryonic lethal,

and embryos exhibited a phenotype similar to the ErbB2 or ErbB4 cardiac-specific knockout mice[56,57]. These results provide evidence for a role of FAK in cardiac development.

Recent studies have identified cardiac myosin light chain kinase (cMLCK) as a downstream target of NRG-1/ErbB signaling in cardiomyocytes[58]. As a cardiac specific kinase[59], cMLCK is capable of activating myosin light chain[60], resulting in sarcomere organization[61]. Ventricular myocyte hypertrophy was found in cMLCK-deficient mice with histologic evidence of necrosis and fibrosis[62]. In our previous study, adenovirus-mediated gene delivery of cMLCK significantly improved cardiac function of post-myocardial infarction (MI) rats, and RNA interference of cMLCK reduced the beneficial effect of recombinant human NRG-1, rhNRG-1β (Ser177-Glu237 of the EGF-like domain of human NRG-1β2a developed by scientists at Zensun Company; Shanghai, China), on sarcomere organization[58]. Interestingly, although the cMLCK-knockout mice had attenuated MLC phosphorylation and decreased fraction shortening, NRG-1 infusion still improved cardiac performance, indicating that the beneficial effect of NRG-1 on heart function is not completely mediated by cMLCK[63].

Disruption of calcium homeostasis also occurs during the development of heart failure[64,65]. Sarcoplasmic reticulum Ca^{2+}-ATPase 2a (SERCA2a) is a Ca^{2+}-ATPase that regulates calcium uptake and contributes to cardiomyocyte relaxation[66,67]. SERCA2a activity is negatively regulated by phospholamban, a target of protein phosphatase 1[68,69]. It has been reported that rhNRG-1β enhances the intracellular calcium cycle in post-MI rats through the suppression of protein phosphatase 1 expression, which results in the improved SERCA2a activity[58]. The first clinical trial of gene therapy using adeno-associated virus (AAV) in the treatment of heart failure was performed in the United States. Both the safety and efficacy of SERCA2a delivery by gene transfer through a recombinant AAV1/SERCA2a were evaluated in patients with advanced heart failure[70,71]. A further 250 patients are currently being enrolled in a phase 2b trial for intracoronary administration of AAV1/SERCA2a[72].

EPIGENETIC MODIFICATION

Chronic heart failure is considered to be a remodeling process affected by multiple environmental factors, and too complex to be addressed by single pathway interventions[73]. NRG-1 treatment results in long-lasting benefits in animal models and human studies, indicating that NRG-1 at least partially stimulates cardiac reverse remodeling, as evidenced by a switch to fetal gene expression, rather than merely preventing cardiac dysfunction[35]. DNA methylation is one epigenetic mechanism known to directly regulate the expression of genes by altering the binding of transcription factors to DNA recognition elements[74], and dynamic DNA methylation/demethylation has been observed *in vivo*[75].

Epigenetic modification has been linked to cardiac hypertrophy and heart failure[76]. For example, class Ⅱ histone deacetylases (HDACs) suppress cardiac hypertrophy, partially through inhibition of the activity of myocyte enhancer factor 2[77]. In contrast, inhibition of HDAC activity results in increased cell size[78] and sarcomere disorganization in cultured cardiac myocytes[79]. Furthermore, the activity of histone acetyltransferase cofactors, such as cyclic AMP response element-binding protein (CREB)-binding protein and p300, is required in phenylephrine-induced cardiomyocyte hypertrophy[80]. In a model for congestive heart failure, the Dahl salt-sensitive rat[81], H3K4 and H3K9 were identified as two primary histone modification sites that were markedly altered in cardiac myocytes during the development of the disease. High-throughput analysis performed by chromatin immunoprecipitation of H3K4 or H3K9 on DNA prepared from human heart also revealed global epigenetic changes in cardiac myocytes, and changes occurred in multiple signaling pathways previously associated with the progression of heart failure[82].

In cultured rat Schwann cells, NRG-1β dose-dependently activated the transcription factor CREB, a protein with endogenous histone acetyltransferase activity[83]. In cultured muscle cells, NRG-1 activated mitogen and stress-activated kinase 1 and 2 and phosphorylated histone H3 in an Erk-dependent manner, resulting in chromatin remodeling[40]. Such results implicate a role for NRG-1 in epigenetic modification as well as provide a possible molecular mechanism.

Expression profiles of mRNA from NRG-1 treated and untreated cardiomyocytes have also been compared[58,84,85]. In our previous study, post-MI rats were infused with rhNRG-1β, and the total RNA extracted from the non-infarcted area of the left ventricle was analyzed on GeneChip arrays (Affymetrix, Santa Clara, CA, United States). The results demonstrated that improvement in cardiac function was accompanied by an increase in expression of several epigenetic-related genes[58] (Table 1).

The global epigenetic changes observed in our study reveal epigenetic modification as an important molecular mechanism underlying changes in cardiac myocytes induced by rhNRG-1β treatment. How these epigenetic changes are triggered by rhNRG-1β requires further investigation. Epigenetic modification also plays an important role in the development of cardiac dysfunction as well as hypertrophy, so that characterization of the epigenetic changes that occur will also help to improve our understanding of the molecular basis of heart failure.

CELL METABOLISM

Normal cardiac function relies on the maintenance of energetic homeostasis to a large degree. The cardiac myocyte is a highly oxidative cell type that utilizes mitochondrial respiration to generate most of its energy. In newborn heart, about half of the ATP production is derived from glycolysis[86]. After birth, fatty acid oxidation is significantly increased and accompanied

Table 1 Changes in mRNA levels of chromosome remodeling and histone modification genes in rat cardiomyocytes treated with rhneuregulin-1β

Gene	Fold increase (rhNRG-1β/vehicle)	Biologic process	Ref.
Embryonic ectoderm development (*Eed*)	1.56	Genetic imprinting, histone methylation	[114]
SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily a, member 4 (*Smarca4*)	1.48	Nucleosome disassembly, methylation-dependent chromatin silencing, ATP-dependent chromatin remodeling	[115]
Jumonji domain containing 6 (*Jmjd6*)	1.61	Histone H3-R2 demethylation, histone H4-R3 demethylation, histone lysyl 5-hydroxylation	[116,117]
Histone cluster 1, H4b (*Hist1h4b*)	1.49	Nucleosome assembly	[118]
CSRP2 binding protein (*Csrp2bp*)	2	Histone acetylation	[119]
H2A histone family, member Z (*H2afz*)	1.63	Nucleosome assembly	[120]
MYST histone acetyltransferase (monocytic leukemia) 3 (*Myst3*)	1.48	Chromatin modification, histone acetylation	[121]
Nuclear receptor coactivator 3 (*Ncoa3*)	2.33	Chromatin modification, histone acetylation	[122]
Nucleophosmin (nucleolar phosphoprotein B23, numatrin) (*Nmp1*)	1.8	Nucleosome assembly	[123]

NRG: Neuregulin.

by a parallel decrease in glycolytic rates[87]. The energy generated by mitochondrial oxidation is primarily derived from the fatty acid β-oxidation pathway, and in healthy heart, β-oxidation of fatty acids provides more than two thirds of cardiac energy[88].

Metabolic abnormalities are clearly involved in the development of heart failure; however, controversy remains concerning the specific alterations in cardiac metabolism and the underlying mechanisms. In late-stage heart failure induced in dogs through pacing-overdrive, fatty acid oxidation-related enzymes were found to be downregulated, while the rate of glucose oxidation dramatically increased[89,90]. Analysis of ^{13}C nuclear magnetic resonance demonstrated that fatty acid oxidation was suppressed in hypertrophic, compensated heart, whereas lactate and glucose oxidation were unaffected[91]. In contrast, pressure overload-induced hypertrophy in a rat model exhibited a significant increase only in glucose oxidation[92]. This phenomenon was confirmed in a second rat model, in which supra-renal aortic constriction was used to induce hypertrophy; glycolytic capacity was modestly elevated but no significant decline in fatty acid oxidation occurred in the hypertrophic heart[93]. These conflicting observations highlight the complexity of energy metabolism in the failing heart.

Emerging evidence indicates that the shift in substrate preference from fatty acids towards glucose in cardiac myocytes can improve heart function and slow the progression of heart failure[94], possibly due to the fact that fatty acids waste more ATPs in cardiac metabolism[95,96]. Furthermore, in advanced or end-stage heart failure, the levels of long- and medium-chain acyl-CoA dehydrogenases were dramatically downregulated, resulting in the suppression of fatty acid oxidation[88]. Thus, a switch to carbohydrate metabolism appears to improve heart function in the short term, whereas fatty acid oxidation benefits long-term cardiac reverse remodeling.

In a different NRG-1 study, freshly isolated adult rat cardiomyocytes were treated with recombinant human NRG-1β (Neomarkers; P.H. Stehelin and Cie; Basel, Switzerland), and expression profiles were generated with cDNA arrays[84]. Expression reprogramming of several cellular processes was revealed, such as improved redox regulation, enhanced utilization of carbohydrates, and increased fatty acid β-oxidation[84]. In our experiments, rats with sustained MI were intravenously infused with rhNRG-1β, and microarray analysis was performed. Expression profiling revealed alterations in a number of genes, including carnitine palmitoyltransferase-1, a key enzyme responsible for the mitochondrial entry of fatty acids[97]. A series of fatty acid metabolism enzymes were also upregulated in myocardium[58] (Table 2). Our microarray data therefore support a model where cardiac fatty acid β-oxidation is increased during rhNRG-1β treatment, and this model is consistent with the observation that rhNRG-1β plays a role in reverse remodeling. However, the causality between energy metabolism and NRG-1-induced reverse remodeling is still an unanswered question, and thus whether a shift in metabolism is the cause or consequence of remodeling requires further investigation.

PRECLINICAL STUDIES WITH NRG-1 FOR THE TREATMENT OF HEART FAILURE

Multiple isoforms of NRG-1 in humans are generated as a result of alternative splicing. Preclinical *in vivo* studies have demonstrated that several of the isoforms are capable of improving heart function by reducing hypertension[47], improving cardiomyocyte proliferation[27], inhibiting apoptosis[43], and enhancing angiogenesis[98] and Ca^{2+} handling[99]. rhNRG-1β was used in a series of animal models to evaluate its effect on heart function[35]. Intravenous administration of rhNRG-1β significantly improved cardiac function and survival in

Table 2 Changes in mRNA levels of fatty acid metabolism enzyme genes in rat cardiomyocytes treated with rhneuregulin-1β

Gene	Fold increase (rhNRG-1β/vehicle)	Function	Ref.
Carnitine palmitoyltransferase Ib, muscle (*Cpt1b*)	1.83	Rate-limiting enzyme which imports fatty acid for mitochondrial oxidation	[124]
Acyl-CoA synthetase, long-chain family 4 (*Acsl4*)	2.31	Promotes fatty acid uptake	[125]
2,4-dienoyl CoA reductase, mitochondrial (*Decr1*)	2.04	Catalyzes the rate-limiting step that prepares polyunsaturated fatty acids to be utilized as substrates for β-oxidation	[126]
Hydroxyacyl-CoA dehydrogenase (*Hadhb*)	1.59	β-subunit of the mitochondrial trifunctional protein, catalyzes the last three steps of mitochondrial β-oxidation of long-chain fatty acids	[127,128]
Transketolase (*Tkt*)	1.97	Necessary for the production of NADPH, especially in tissues actively engaged in biosyntheses, such as fatty acid synthesis	[129]
Acetyl-CoA acetyltransferase 1 (*Acat1*)	1.89	Enzyme participates in ten metabolic pathways including fatty acid metabolism	[130]
Hydroxysteroid (17-beta) dehydrogenase 4 (*Hsd17b4*)	1.64	Enzyme involved in peroxisomal fatty acid β-oxidation	[131]
Dodecenoyl-coenzyme A delta isomerase (*Dci*)	1.66	Mitochondrial fatty acid oxidation enzyme	[132]
Protein kinase, AMP-activated, β1 non-catalytic subunit (*Prkab1*)	1.98	Regulatory subunit of the AMP-activated protein kinase, involved in regulating de novo biosynthesis of fatty acid and cholesterol	[133]

NRG: Neuregulin.

a rat model of heart failure induced by the ligation of left anterior descending coronary artery. In the heart failure model induced by chronic pacing, rhNRG-1β treatment improved the left ventricular end diastolic and systolic pressures, as well as cardiac contractility and relaxation. In addition, a second recombinant form of NRG-1 (recombinant human glial growth factor 2, rhGGF2) also prevented cardiac dysfunction and improved survival in doxorubicin-induced heart failure in the mouse[100].

An engineered bivalent human NRG-1β (generated through the synthetic linkage of two NRG-1β moieties) protected against acute doxorubicin-induced cardiomyopathy without proneoplastic effects[101]. In another study, administration of recombinant human NRG-1 (Novartis Pharmaceuticals, Basel, Switzerland) significantly improved heart function and reversed cardiac remodeling of diabetic cardiomyopathy in rats with chronic heart failure[102]. In addition, rhGGF2 treatment improved residual left ventricular function and normalized a number of myocardial genes altered by MI in rats[85].

CLINICAL STUDIES OF NRG-1/ERBB IN HEART FAILURE

During the past 30 years, many drugs have been developed for the treatment of heart failure, including β-blockers, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, and brain natriuretic peptide. Despite the fact that these therapies have improved clinical outcomes significantly, heart failure has become the major cause of cardiovascular death[103]. Therefore, the development of new treatments for heart failure continues to be necessary.

Multiple *in vitro* and *in vivo* studies have confirmed the beneficial effects of NRG-1 on cardiac function[27,98,99], thus rendering NRG-1 a promising drug candidate for the treatment of heart failure. To date, two different isoforms of NRG-1 have been tested in human clinical trials. Since 2004, phase 1 and phase 2 trials in China, Australia, and the United States have confirmed that rhNRG-1β is safe and well tolerated in both chronic heart failure patients and healthy controls. In a phase 2, randomized, double-blind, multicenter, placebo-controlled study, 44 patients with New York Heart Association functional class II or III stable chronic heart failure were randomly assigned to four groups and treated with placebo or rhNRG-1β (0.3 μg/kg per day, 0.6 μg/kg per day, or 1.2 μg/kg per day) through a ten-hour intravenous infusion per day for ten consecutive days. At day 30, patients treated with rhNRG-1β exhibited significantly increased left ventricular ejection fraction (LVEF%), as well as reduced end-diastolic and end-systolic volumes, which continued to decrease at day 90 and were accompanied by a sustained increase in LVEF%, indicating a long-term effect for rhNRG-1β in cardiac reverse remodeling[104]. In another clinical trial, 15 patients with stable chronic heart failure received a daily infusion of rhNRG-1β for 11 d. Improved hemodynamic effects were observed, and the increase in LVEF% was sustained for 12 wk[105]. A phase 3 trial designed to measure the safety and efficacy of rhNRG-1β in a larger cohort of chronic heart failure patients is currently ongoing in China.

Another NRG-1 isoform utilized in clinical trials is GGF2 (also known as NRG-1β3). In a phase 1, single-infusion, dose-escalation study, a single dose of rhGGF2 was well tolerated up to 0.75 mg/kg, whereas higher doses were associated with serious adverse events[106]. Patients with symptomatic heart failure receiving a single dose of rhGGF2 exhibited increased left

ventricular function over 28 d compared to placebo[107]. A phase 1b study designed to evaluate the effect of rhGGF2 single intravenous infusion on midazolam pharmacokinetics is ongoing (registration at www.clinicaltials.gov, NCT01944683).

A complicating issue is the fact that *ERBB2* has a well-described role as an oncogene, particularly in the development of breast cancers[108,109]. Although recent publications support the idea that *NRG1* functions instead as a tumor-suppressor gene[110], NRG-1 treatment for cardiac therapy raises a concern for a potential increased risk of cancer. However, ErbB2-associated cancer is often NRG-independent, and furthermore *NRG1* is often silenced by methylation in breast cancers[111]. In addition, chromosome translocation breakpoints targeting *NRG1* on 8p12 have been found in breast and pancreas cancer cell lines[112,113]. Finally, our previous clinical experience demonstrated that the incidence of cancer of any type in > 1000 subjects treated with rhNRG-1β was no different than in patients treated with placebo. Together, these findings indicate that there is a low risk for the development of cancer during NRG-1 treatment.

CONCLUSION

A number of experimental results from both clinical studies and animal models have demonstrated the importance of NRG-1/ErbB signaling in adult heart function. Expression profiling has firmly established that in addition to canonical ErbB2 downstream pathways, energy metabolism and epigenetic modification also play roles in NRG-1-mediated reverse remodeling of heart failure. Additional studies, however, are still necessary to elucidate the precise molecular mechanisms utilized. Finally, a recombinant human NRG-1 peptide has demonstrated significant potential as a novel drug candidate for chronic heart failure in preclinical and clinical studies. Further studies illuminating mechanisms mediating NRG-1/ErbB signaling will therefore help to facilitate the development of novel strategies for the treatment of chronic heart failure and to better understand the function of NRG-1 in cardiac physiology.

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Symplicity-3 hypertension trial: Basic and clinical insights

Benjamin J Scherlag, Sunny S Po

Benjamin J Scherlag, Sunny S Po, Heart Rhythm Institute, University of Oklahoma Health Sciences Center, Oklahoma City, OK 73104, United States
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Correspondence to: Benjamin J Scherlag, PhD, Heart Rhythm Institute, University of Oklahoma Health Sciences Center, 1200 Everett Drive (6E103), Oklahoma City, OK 73104, United States. benjamin-scherlag@ouhsc.edu
Telephone: +1-405-2054457
Fax: +1-405-2717455
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Abstract

Symplicity-3 hypertension (HTN) was a recently completed clinical trial that was assumed to be the basis for the approved use of renal artery denervation for the treatment of resistant hypertension in the United States. Dramatic reductions in blood pressure had been reported in two clinical trials (Symplicity-1HTN, -2HTN) carried out in Europe, however Symplicity-3HTN did not show a significant reduction of systolic blood pressure in patients with resistant hypertension 6 mo after renal artery denervation as compared with a sham control. (Denervation group, blood pressure reduction: -14 ± 24, Sham control: -12 ± 26 mmHg). In this review we discuss several potential explanations for the failure of efficacy of Symplicity-3HTN taking into account basic and clinical factors which could have played a role in the discrepancy between the European and American experience.

Key words: Hypertension; Renal artery denervation; Aorticorenal ganglia; Atrial fibrillation

Core tip: The failure of the Symplicity-3 trial which subjected patients to renal artery denervation to significantly reduce resistant hypertension has been ascribed to many factors. In this review, we focus on the lack of a "biomarker" as a major deficiency in achieving the expected efficacy. We also present experimental and clinical evidence to support the importance of a biomarker to acutely predict long term success of renal artery denervation for effective treatment for drug resistant hypertension.

Scherlag BJ, Po SS. Symplicity-3 hypertension trial: Basic and clinical insights. *World J Hypertens* 2015; 5(2): 74-78 Available from: URL: http://www.wjgnet.com/2220-3168/full/v5/i2/74.htm DOI: http://dx.doi.org/10.5494/wjh.v5.i2.74

INTRODUCTION

Renal artery denervation as a procedure for patients with resistant forms of hypertension burst onto the clinical scene in 2009[1] and quickly was followed by clinical trials, Symplicity-1 hypertension (HTN)[2] and Symplicity-2HTN[3]. What was predicted to be a reduction of 5 to 10 mmHg turned out to be a mean reduction of systolic pressure by as much as 32 mmHg even for follow-up periods of 2-3 years. When Medtronic sponsored Symplicity-3HTN as a multi-center trial, enrolling 530 patients, in the United States, it was expected that the European extensive experience would be confirmed. One important difference in Symplicity-3HTN was the inclusion of a sham controlled

group, which is common in pharmacological trials but unusual for a procedural study due to potential ethical reservations. In any event, the recently published report[4] concluded that the results did not show a significant reduction of systolic blood pressure 6 mo after renal artery denervation (-14 ± 24 mmHg) compared to the sham controls (-12 ± 26 mmHg). However, there was no issue with the safety of the procedure using the Symplicity renal-denervation catheter. In this review we consider the potential factors and their relative importance to explain the striking differences in the outcomes of these Symplicity trials.

HISTORICAL BACKGROUND

Experimental animal studies have shown that sympathetic nerve hyperactivity is a critical component in the initiation and maintenance of systemic hypertension. For example it has been shown that chronic HTN can be induced by chronic electrical stimulation of the left stellate ganglion[5]. In this regard, Smithwick and Thompson[6] reported on 1266 cases of surgical splanchnicetomies performed to treat malignant HTN. There was a successful lowering of blood pressure, however, these methods were associated with high perioperative morbidity and mortality and long-term complications, including bowel, bladder, and erectile dysfunction, in addition to severe postural hypotension. Although this clinical approach was generally abandoned, experimental studies progressed on the neurogenic basis for essential hypertension[7,8]. These ongoing studies were eclipsed by the general acceptance of the concept that hypertension was based on an abnormality of the rennin-angiotensin-aldosterone system[9].

The seminal study which brought the neurogenic basis of hypertension to the forefront was published in 2009 in which sympathetic nerves in the adventitia of the renal arteries were ablated by transvascular application of radiofrequency energy (8-10 watts) caused a marked reduction of blood pressure in patient with drug resistant hypertension. Specifically, Krum *et al*[1] using a monopolar electrode catheter (Symplicity) performed renal denervation in 45 patients, 5 untreated patients served as controls. Entry blood pressure (BP) averaged 177/101 ± 20/15 mmHg. At 6 mo, the treated patients showed an office-based BP reduction of -22/-11 ± 10/5 mmHg while the 5 controls had BP increases of +14/+9 mmHg. These startling results, that even surprised the initial investigators quickly morphed into 2 prospective randomized controlled trials, simplicity-HTN 1, HTN2 with as similar or greater dramatic results over follow-up periods as long as 3 years.

The mechanism proposed to explain these findings was suggested to be ablation of sympathetic afferents which after months modulate the vasomotor centers to decrease general sympathetic efferent outflow[10]. This hypothesis was supported by radiotracer dilution studies which showed a 47% spillover of nor-epinephrine within 1 mo of bilateral renal denervation.

POTENTIAL FACTORS TO EXPLAIN THE FAILURE OF SYMPLICITY-HTN3

The unexpected efficacy failure of Symplicity-3 as reported by Bhatt *et al*[4] has engendered a flurry of letters to the editor of the New England Journal of Medicine[11] raising multiple concerns regarding the findings reported in the Symplicity-3 trial. It is interesting to note that Dr Bhatt, the lead investigator in the Symplicity-3 trial, in reply to these letters stated: "We agree that various selection criteria and characteristics of our patient population-such as the exclusion of patients with white-coat hypertension, the inclusion of obese patients and a variety of baseline characteristics or medications could account for the null results of this trial, as compared with the findings of previous trials[11]". Thus, the lead investigator concedes that trial differences could have been the basis of the negative results for Symplicity-3. Many of the same caveats were detailed in a joint consensus statement[12] by respected investigators in the field indicating potential flaws in the Symplicity-3 trial. In a recent report Messerli and Bangalore[13] addressed the possible causes of the failure of the Symplicity-3 trial in light of the dramatic successes of Symplicity-1 and -2. "At first blush, the most likely explanation for the findings of the SYMPLICITY HTN-3 study is the inclusion of a sham-control group. In clinical trials testing interventional procedures and medical devices, sham procedures are seminal, analogous to the use of a placebo in pharmaceutical trials. However, for ethical reasons sham procedures are frowned upon; neither the SYMPLICITY HTN-1 study nor the HTN-2 study had a sham-control cohort. For this reason, placebo effects may well explain all or most of the blood-pressure differences noted in the first two trials. Lack of efficacy could also be caused by incomplete or ineffective denervation. No reliable markers of renal denervation are available, and questions remain as to what exactly the procedure accomplishes. Nevertheless, the ablation catheter used in the SYMPLICITY HTN-3 study was no different from that used in the SYMPLICITY HTN-1 and HTN-2 studies." In this regard, we suggest that the focus of each of the Simplicity trials on ablating the variable structure of the post-ganglionic axons on the renal artery adventitia provides an important impediment for achieving sympathetic denervation. Indeed, the percent of non-responders in a number of previously reported studies, using the Symplicity approach, ranges from 10%-43%[10,14].

In regard to the lack of biomarkers there is a striking analogy between catheter ablation for atrial fibrillation and catheter ablation for refractory hypertension. Besides the fact that both groups of patients who are candidates for these procedures have failed drug therapy: (1) Both

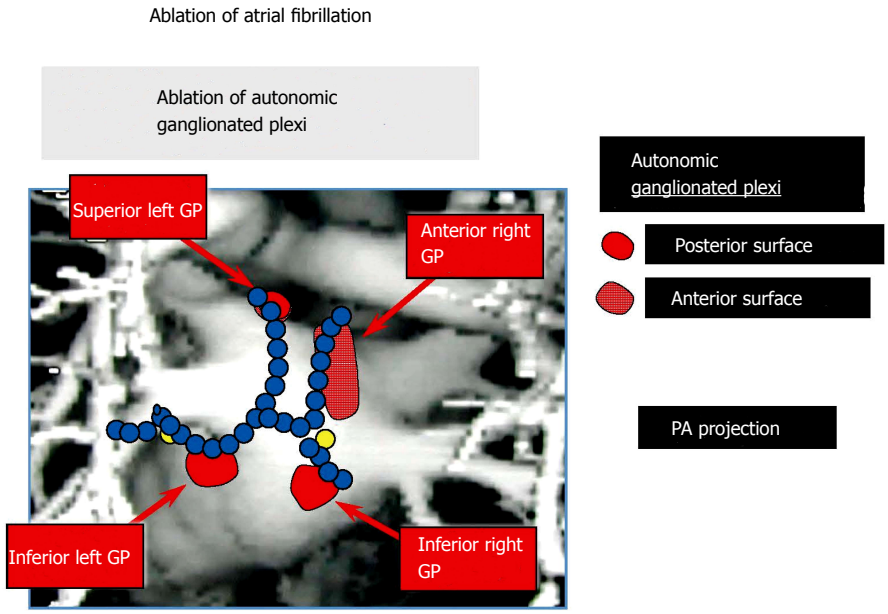

Figure 1 An anatomic figure of the left atrium depicting the lines of radiofrequency applications used to isolate the pulmonary veins in patients undergoing catheter ablation for atrial fibrillation. Note that the lesion lines may, in part, also ablate the ganglionated plexi (GP), albeit incompletely. These nerve clusters are situated at the pulmonary vein - atrial junctions and contribute to the neural basis of atrial fibrillation[12].

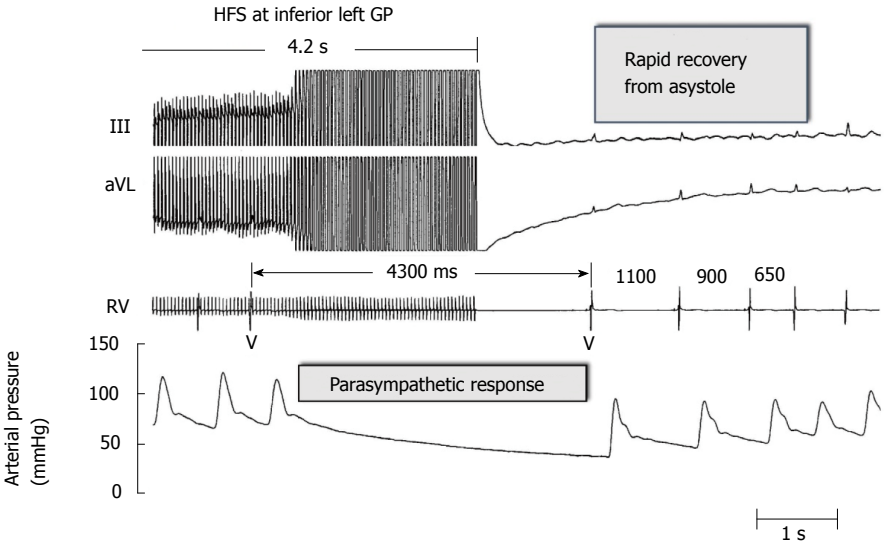

Figure 2 The use of high frequency electrical stimulation applied to the left ganglionated plexi in a patient with atrial fibrillation induced a marked slowing of the ventricular rate by a parasympathetic response at the A-V node. The ensuing heart block manifested an asystolic pause of 4300 milliseconds (ms) which showed a rapid recovery with the cessation of electrical stimulation. The traces from above are: Leads III and aVL of the electrocardiogram; an electrogram recorded from the right ventricle (RV); and arterial blood pressure. GP: Ganglionated plexi; HFS: High-frequency stimulation.

invasive procedures use radiofrequency applications to achieve pulmonary vein isolation (PVI) or renal artery denervation (RAD); (2) It is common that after the procedure AF or high BP is not any different than prior to the procedure. A "blanking" period of various durations ensues before a salutary effect is determined; (3) There is no "biomarker" at the time of the procedure to gauge the success or failure of the intervention; and (4) In both cases neural factors appear to play a critical role in the outcomes.

INFLUENCE OF A BIOMARKER IN ATRIAL FIBRILLATION AND RENAL NERVE DENERVATION

Since 2004[15], in our clinical electrophysiological procedures for AF catheter ablation, we have used additional ablation of clusters of nerves called ganglionated plexi (GP) located at the pulmonary vein-atrial junctions as adjunctive to pulmonary vein isolation (PVI) (Figure 1). High frequency electrical stimulation of these GP invariably leads to marked A-V block induced bradycardia *via* a parasympathetic effect on the AV node (Figure 2). Destructive radiofrequency current application to the GP causes inability of the same high frequency stimulation to slow the heart rate (Figure 3). A recent study by Katritsis *et al*[16] consisting of 242 patients who were candidates for catheter ablation were randomized to PVI alone, GP ablation alone or a combination of PVI + GP and followed for 2 years after a single procedure. The success rates were: 44 (56%), 39 (48%), and 61 (74%), respectively.

Could an analogous scenario be in play with renal sympathetic denervation? The articorenal ganglion was studied by Doelzel[17] in the dog and Norvell in the human[18]. In the latter study, a detailed dissection of the renal plexus and the aorticorenal area was carried out in 57 adult cadavers of both sexes. Figure 4 shows that the aorticorenal ganglia was found localized in

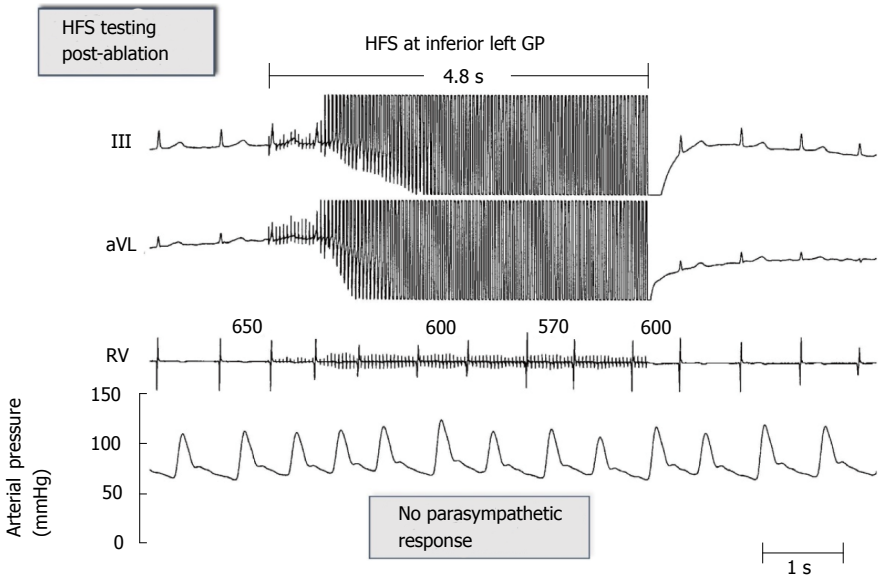

Figure 3 After ablation of the ganglionated plexi at the pulmonary vein-atrial junctions the same level of high frequency stimulation failed to elicit any parasympathetic response and no slowing of the ventricular rate. Traces are the same as in figure 2. See text for further discussion. GP: Ganglionated plexi; HFS: High-frequency stimulation.

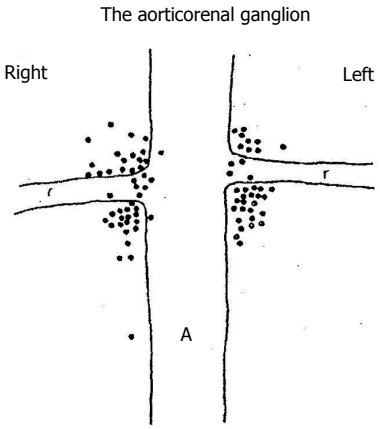

Figure 4 Diagrammatic representation of the junction of the aorta (A) and the renal arteries (R). The dots indicate the localization of the aorticorenal ganglia determined by detailed dissection in 57 cadavers[15].

the area of the real artery at the ostium and junction of the aorta. To test the hypothesis that this bilateral ganglion could have a similar biomarker role in renal denervation as the GP contribute to catheter ablation of AF, in the anesthetized dog, we compared the effects of electrical stimulation of sympathetic nerves on the adventitial surface of the renal arteries to similar frequency and intensity applied to the aorticorenal ganglia on heart rate and blood pressure.

Electrical stimulation applied to the renal artery adventitia did not affect the heart rate but significantly increased systolic and diastolic blood pressure (Baseline: 134 ± 24/96 ± 18 mmHg, RAs stimulation: 157 ± 26/114 ± 18 mmHg. Electrical stimulation applied to the aorticorenal ganglia did not affect heart rate but significantly increased systolic and diastolic blood pressure: 207 ± 44/147 ± 26 mmHg, $P < 0.05$ compared to baseline. In summary, there was a significantly greater effect on both systolic and diastolic BP caused by the same level of electrical stimulation applied to the aorticorenal ganglia than to the adventitial nerves of the renal arteries[18].

Could a similar biomarker be shown in the clinical setting of hypertension? A recent report by Pokushalov *et al*[19] involved 27 patients (14 randomized to PVI only, and 13 randomized to PVI and renal artery denervation), all of whom were followed for 12 mo after ablation. All had a history of paroxysmal atrial fibrillation and hypertension. "To confirm renal denervation, we used high-frequency stimulation (HFS) before the initial and after each RF delivery within the renal artery. Rectangular electrical stimuli were delivered at the ostium of the targeted renal artery at a frequency of 20 Hz, with an amplitude of 15 V and pulse duration of 10 ms… for 10 s…Renal sympathetic denervation was considered to have been achieved when the sudden increase of blood pressure …was eliminated in the presence of HFS."

Nine of the 13 patients (69%) treated with PVI with renal denervation were AF-free at the 12-mo post-ablation follow-up examination *vs* 4 (29%) of the 14 patients in the PVI-only group ($P = 0.033$). At the end of the follow-up, significant reductions in systolic (from 181 ± 7 to 156 ± 5, $P < 0.001$) and diastolic blood pressure (from 97 ± 6 to 87 ± 4, $P < 0.001$) were observed in patients treated with PVI with renal denervation without significant change in the PVI only group.

CONCLUSION

Although many explanations have been put forward to try to explain the lack of efficacy of the Symplicity-3 trial for renal artery denervation to treat resistant forms of hypertension, it appears that one major reservation has been the lack of a biomarker for the induction of an increase in blood pressure and then after ablation the inability to show the same hypertensive response. A clinical trial to test this acute effect as a predictor of success would negate the reliance on a blanking period (weeks) for central

autonomic remodeling to occur in order to determine whether the reduction of blood pressure has been achieved.

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MINIREVIEWS

Diagnosis and management of thoracic aortic dissection: An update

Ruth A Benson, Ben O Patterson, Ian M Loftus

Ruth A Benson, Ben O Patterson, Ian M Loftus, St George's Vascular Institute, St George's Healthcare NHS Trust, London SW170 QT, United Kingdom
Author contributions: Benson RA, Patterson BO and Loftus IM contributed to this paper.
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Correspondence to: Ruth A Benson, BSc, MBChB, MRCS, Vascular Research Fellow, St George's Vascular Institute, St George's Healthcare NHS Trust, Blackshaw Road, London SW170 QT, United Kingdom. ruth.benson@gmail.com
Telephone: +44-20-87253205
Fax: +44-20-87253495
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Abstract

Acute thoracic aortic dissection is part of the acute aortic syndrome triad. Caused by an intimal tear in the lumen of the aorta, it leads to the creation and propagation of a false lumen. In the acute setting this can lead to malignant hypertension, pain and end organ malperfusion. In the chronic setting it can lead to aneurysm formation and rupture. It remains the most common aortic emergency, affecting up to 4 per 100000 people per year in the United Kingdom and United States. Despite advances in treatment and centralisation of vascular services, it continues to be associated with a high pre-admission and in-hospital mortality. Dissection is classified in several ways according to anatomical extent, timing and underlying pathology, all of which guides clinical management. Traditionally, medical management has been the mainstay of treatment in patients with uncomplicated disease. Surgery has been used in symptomatic patients. With published information now available from several prospective international registries, we are beginning to see the advantages of newer surgical treatment options such as endovascular repair, in the acute setting. This review provides an update on diagnosis and management of aortic dissection, including new information that has become available in recent years.

Key words: Aortic dissection; Endovascular; Acute aortic syndrome; Aneurysm; Dissecting; Endovascular procedures; Hypertension, Malignant; Registries

Core tip: Aortic dissection remains the most common aortic emergency, affecting up to 4 per 100000 people per year in the United Kingdom and United States. Surgical management is indicated in dissection complicated by uncontrolled pain and hypertension, end-organ malperfusion and aneurysmal dilatation with risk of rupture. This update discusses results of thoracic stenting from more recently published prospective international registries, including risks and benefits to treated patients affected by this incredibly high risk condition.

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INTRODUCTION

Aortic dissection is one of the conditions included in the term "acute aortic syndrome". This collection includes true dissection, intramural haematoma and penetrating aortic ulcer[1]. Of these acute dissection is the most common, affecting up to 4 people in 100000 annually[2]. Despite advances in therapies, pre-hospital mortality remains high at 20%. Thirty percent of all dissections surviving to a vascular centre will die before discharge[2]. Mortality depends on dissection type, cause and treatment options. New information on the management of type B acute dissection has been published in recent years. This review will discuss all forms of thoracic aortic dissection, with a focus on the recent shifts towards use of surgical management of acute type B dissection using thoracic endovascular repair (TEVAR) rather than best medical therapy alone.

DEFINITION

Dissection refers to the separation of the intima/inner media and outer media/adventitia of any artery, due to the tracking of blood into this potential space *via* a tear in the intima. The false passage can track both antegrade and retrograde[3]. Traditionally they are considered acute if within 14 d of onset and chronic after 14 d. However, publication of survival curves in patient presenting with dissection has shown that survival drops sharply around 30 d post-presentation[4,5]. Therefore the terms acute (< 2 wk), subacute (2-6 wk) and chronic (> 6 wk) have been suggested by a recent European panel[6].

CLASSIFICATION

Three classification systems are in common use. The Stanford and DeBakey classification systems use anatomical markers to differentiate dissection type (Figure 1). Stanford type A dissections involve the ascending aorta, while type B originate anywhere distal to the origin of the left subclavian artery[7]. The DeBakey system has three groups. Type 1 involves ascending and descending aorta, type 2 ascending aorta only and type 3 descending aorta only[8]. The European Society of Cardiologists categorise dissection by aetiology using 5 classifications based on pathogenesis of the intimal injury. The advantage of this system, is that it can be used to guide clinical management toward medical or surgical therapy[1]. During this review, the authors will use the Stanford classification due to its wide use within the literature.

RISK FACTORS

As with other aortic pathologies such as aneurysmal disease, those at greatest risk overall are white, male and over 60[8,9]. Type B dissection accounts for 25%-40% of all dissections[10] although recent literature suggests type B dissection is more common than type A amongst African American patients[11]. A study by the international Registry of Acute Aortic Dissection (IRAD) using data from 12 international centres showed that men accounted for 68% of acute presentation[9]. Hypertension, increasing age and pre-existing arterial disease were also common factors.

Systemic hypertension is present in up to 75% of patients at presentation. Physical exertion or a period of emotional stress may be identified as a trigger, likely due to it leading to an acute episode of hypertension[12]. Familial aneurysmal syndromes and connective tissue disease is an important factor in younger patients, more specifically Marfan's syndrome with fibrillin-1 deficiency, Ehler-Dahnlos type Ⅳ (abnormal type Ⅲ procollagen) and any other cause of cystic medial necrosis[13-15]. Other congenital defects related to younger presentation are a bicuspid aortic valve (likely due to associated aortic root abnormalities) and coarctation of the aorta (and its associated hypertension)[16]. Other causes of disease in the younger patient include pre-existing vasculitic disease, pregnancy and cocaine abuse[9,17]. Vascular interventions may also act as a trigger, for example following percutaneous cardiac catheterisation, coronary artery bypass grafting, or thoracic stenting procedures for aneurysmal disease.

CLINICAL PRESENTATION

Ninety percent of patients present with sudden onset pain in the chest. In type A dissection it may radiate to the neck, and in type B to the interscapular area[18]. Diabetes is thought to account for the remaining, asymptomatic dissections[19]. New aortic regurgitation is picked up in 31% of patients, and a radio-radio/radio-femoral delay in 15%[8]. Type A presents with hypotension in up to 25% of patients, whereas type B dissections tend to present with hypertension[8]. If both true and false lumens are perfused the aortic branches, and therefore end organs, will remain perfused. If this is not the case, dissection can present with neurological symptoms such as stroke, renal failure, bowel ischaemia or limb ischaemia[20]. These are considered high-risk features, and their effect on management is discussed below. On occasion, an asymptomatic dissection can lead to aortic dilatation and rupture, either acutely, or up to three years after the initial event[10].

DIAGNOSIS AND INVESTIGATION

Differential diagnoses include myocardial infarction, pulmonary embolus, perforated viscus, stroke or other neurological insult and embolic disease[21]. ECG and X-ray are not sensitive enough to diagnose dissection, but will identify concomitant acute coronary syndromes or act as indicators of alternative diagnoses[22]. CT angiography remains the recommended first line investigation in those suspected of having dissection[1]. It is also useful for planning surgical intervention. Other first

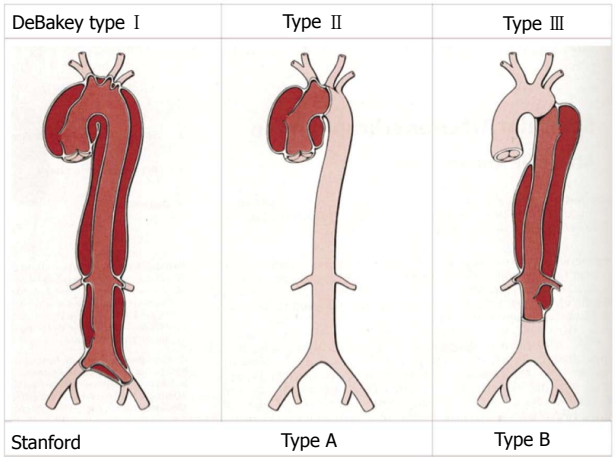

Figure 1 Illustration of the DeBakey and Stanford classifications for aortic dissection. The DeBakey system takes into account tear entry site and propagation within ascending or descending aorta. The Stanford system is more blunt. Type A is one with any involvement of the ascending aorta, type B any involvement of the descending aorta[43].

line modalities include transoesophageal ECHO, which has the advantage of identifying new aortic regurgitation or pericardial effusion. However it cannot image the entire aorta, and is heavily operator dependent[1]. Magnetic resonance angiography lacks radiation exposure, and uses less nephrotoxic agent, which benefits patients with evidence of renal hypoperfusion. However availability is more limited and imaging takes longer, making it more suitable in the chronic setting or for patient follow-up. All three of these modalities have sensitivity and specificity of over 95% for diagnosis[23].

INITIAL MANAGEMENT

The mainstay of initial management is resuscitation and stabilisation, to allow transfer for diagnostic imaging and subsequent treatment. Large bore venous access and invasive monitoring including arterial line, cardiac monitoring and urinary catheterisation should be instigated. Close monitoring of end organ function will help identify any deterioration quickly. This includes cardiac monitoring as a proxy for coronary perfusion, cerebral perfusion, limb perfusion and urine output. Wherever possible, this should be in a high dependency setting.

In those patients presenting with hypertension, a target systolic blood pressure of between 100-120 mmHg and heart rate of 60-80 beats per minute should be sought[1,24]. The aim of this is to decrease shear force on the aortic wall and prevent further propagation of the dissection flap[25]. Systolic pressure control in the emergency setting is commonly in the form of a short acting intravenous beta-blocker such as Labetalol. This should be balanced against any deterioration of end organ perfusion. Once haemodynamically stable, the patient should be imaged without delay.

MANAGEMENT OF CONFIRMED DISSECTION

Acute type A dissection

The mainstay of treatment for type A dissection is surgical. Left untreated, it carries a 50%-91% mortality at 7 d, due to rupture, stroke, visceral malperfusion, cardiac tamponade and heart failure[8]. Surgery involves open replacement of the aortic root and affected arch with a prosthetic graft. In extensive dissection involving the ascending and descending aorta, a portion of the graft can be sutured in a way that leaves a free section within native aorta. This provides a landing zone for the stent graft required to treat the rest of the diseased aorta and is known as a hybrid repair. The time lag between first and second stages of repair remains controversial[26]. In hospital mortality following a procedure such as this remains 24%[27]. Further surgical intervention in the form of aortic valve replacement or coronary artery bypass may also be indicated. Three and five year survival rates are 75% and 73% respectively[28].

Acute type B dissection

Uncomplicated: Despite earlier trends towards stenting all acute type B dissection, international consensus is yet to publish recommendations for its use over medical management in uncomplicated disease. The VIRTUE registry's intermediate findings indicate support for use of stenting in this setting, following favourable results for all-cause mortality (18%), dissection related mortality (12%) aortic rupture (2%), retrograde type A dissection (5%), and aortic reintervention rates (20%) at a follow up of three years[29]. One year results from the ADSORB trial have shown similar results to this. However the main advantage of stenting over medical management appears to be improved rates of false lumen thrombosis alone[10].

Medical management involves careful blood pressure control, to prevent further tearing or aortic dilatation. Beta blockers remain first line therapy, with follow-up shared between cardiology and the vascular surgeon[1,20]. Alternatives such as calcium channel blockers can be used in patients unable to tolerate first line therapy for any reason, *e.g.*, chronic obstructive pulmonary disease. Survival rates of up to 78% at three years are reported[30] (Table 1).

Complicated

This group includes patients presenting with evidence of end-organ ischaemia, aortic rupture, pain or refractory hypertension, as well as those patients initially described as uncomplicated in whom disease has progressed despite optimal medical treatment[22,24]. These patients have a much poorer prognosis, with mortality approaching 50% in the untreated group[31]. Endovascular repair is the mainstay of treatment, with a 30 d mortality of

Table 1 Trials looking at outcomes of type B dissection according to management strategy

Registry	Authors	Design	Indication	Duration	Conclusion
Instead trial	Nienaber *et al*[37]	Prospective randomised trial	Comparison of TEVAR *vs* medical therapy in chronic type B dissection	2 yr	TEVAR failed to improve survival or adverse events despite favourable aortic remodeling
Instead-XL	Nienaber *et al*[39]	Prospective randomised trial	Long-term outcomes of cohorts recruited to INSTEAD trial	5 yr	TEVAR plus best medical therapy improved 5-yr aorta-specific survival
Mother registry	Patterson *et al*[36]	Collation of data from 5 clinical trials including VIRTUE and INSTEAD	Mid-term outcomes following endovascular repair using TEVAR for acute type B dissection	5 yr	TEVAR provides good midterm protection from aortic-specific pathology High rates of re-intervention
Virtue registry	The Virtue registry investigators[29]	Prospective Multicentre Clinical trial	Safety, performance and health economic data in patients receiving the Valiant endograft	3 yr (2006-2012)	TEVAR provides protection from aortic related death in midterm High rates of re-intervention
Adsorb trial	Hughes[10]	Multicentre randomised clinical trial	Comparison of best medical therapy *vs* medical therapy and TEVAR for acute type B dissection	1 yr	TEVAR leads to improved aortic remodeling compared to medical therapy alone

TEVAR: Thoracic endovascular repair.

9.8%[32]. Even following surgery, 56% of cases will have ongoing false lumen perfusion, which can progress towards aortic expansion and rupture in 20%[33]. False lumen re-perfusion occurs in up to 16%, and this may require further surgery[34]. Over a 34 mo follow-up period data indicated 26% of patients required re-intervention for endoleak, distal fenestrations and concomitant pathology[35]. Retrograde type A dissection following TEVAR is a rare complication. Pooled data including the MOTHER registry found an incidence of 1.7% after TEVAR for all causes, with a mortality rate of 33.6%. Treatment for dissection was a significant risk factor, with an odds ratio of 10.0 (CI: 4.7-21.9) in acute disease and 3.4 (CI: 1.3-8.8) in chronic disease[36].

CHRONIC TYPE B DISSECTION

Medical management in chronic dissection has remained the mainstay of treatment. This follows results from randomised trials comparing optimal medical management alone to that in combination with thoracic stenting, the most significant being the INSTEAD trial[37]. This trial recruited patients with uncomplicated type B dissection in the sub-acute phase, and randomised 140 into one of the two groups described above. Follow up was 2 years, during which time endovascular repair failed to demonstrate a survival advantage for all cause mortality (88.9% ± 3.7% *vs* 95.6% ± 2.5% with optimal medical therapy) or aortic related mortality[38]. As with acute dissection, it did lead to higher rates of false lumen thrombosis (91.3% *vs* 19.4%).

A recently published analysis of the data from the same cohort, analysing outcomes from years 2 to 5 post randomisation (INSTEAD-XL) found a reduction in aorta-specific mortality in patients who underwent surgery (0% *vs* 3.6%, $P = 0.001$)[39]. By 5 years, there were significant differences in maximum aortic diameter (56.4 ± 6.8 mm *vs* 44.5 ± 11.5 mm medical management *vs* stenting respectively), false lumen diameter (37.1 ± 9.1 mm *vs* 10.4 ± 13.2 mm) and complete false lumen thrombosis (22% *vs* 90.6%). This appears to indicate that although there is little difference in survival between the two management strategies before two years, the advantages of stenting become apparent between 2 and five years post presentation. Despite this, two patients suffered from spinal cord ischaemia post TEVAR, and three patients required conversion to an open procedure following TEVAR within two years of randomisation.

Up to 15% of chronic dissection will be complicated by aneurysm formation; a survival analysis from the IRAD registry identified aortic growth and aneurysm formation to be the most common complication during follow-up[5]. Despite this, accurate prediction of the timing and course of progression remain elusive[6]. Once progression occurs, intervention should be planned. As with most surgery, TEVAR has an appreciable reduction in short-term morbidity and mortality in these patients, compared to an open operation (93% *vs* 79% respectively)[24,31]. At 10 years, survival following open surgery has been reported at 35%, while equivalent data for endovascular management is still unknown[31].

FOLLOW-UP

It is clear that dissection carries significant risk of disease progression despite optimal treatment and irrespective of aetiology. In those with hereditary aortic wall structure defects, mortality from rupture in an aorta measuring greater than 6 cm is 12%, with women at higher risk than men[40]. Therefore lifelong surveillance is mandatory, with axial imaging in the very least being used for routine imaging. MRA reduces the contrast and radiation exposure over a patient's lifetime compared to CTA[41]. Imaging at 1, 3, 6 and 12 mo followed by annual review is recommended by the European Society of Cardiology[1]. Intervals should be altered depending on aortic size. All patients should receive

life-long blood pressure management, and treatment should involve cardiology and vascular surgical input at all stages[42].

CONCLUSION

Optimal management of all type A dissections and uncomplicated or chronic type B dissections has changed little in recent years. However with the publication of results from multi-centre randomised controlled trials now becoming available, we are seeing the potential advantages in early use of endovascular repair on both short and longer-term mortality, progressive aortic dilatation and aortic remodeling. Throughout all of this, the message persists; aortic dissection remains a disease with a high mortality and need for life-long follow-up.

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MINIREVIEWS

From hypertension to heart failure

Klara Magyar, Roland Gal, Adam Riba, Tamas Habon, Robert Halmosi, Kalman Toth

Klara Magyar, Roland Gal, Adam Riba, Tamas Habon, Robert Halmosi, Kalman Toth, 1st Department of Medicine, University of Pecs, Medical School, 7624 Pecs, Hungary

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Correspondence to: Kalman Toth, MD, ScD, FESC, Professor, 1st Department of Medicine, University of Pecs, Medical School, H-7624 Ifjusag Str. 13., 7624 Pecs, Hungary. toth.kalman@pte.hu
Telephone: +36-72-536000

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Abstract

Hypertension is an increasing health problem worldwide especially among the elderly. Its therapeutical importance is indicated by the caused organ damages like hypertensive heart disease (HHD) and heart failure with the subsequent higher morbidity and mortality in the population. In HHD ventricular hypertrophy develops as a compensatory mechanism for pressure overload but as the left ventricular compliance decreases, the process can transform into heart failure with firstly preserved and then into reduced ejection fraction (HFpEF, HFrEF). The main characteristics of underlying mechanisms involve cardiomyocyte growth, vessel changes, increased collagen production in all of which several mechanical stress induced neurohumoral agents, signal transduction pathways are involved. According to the new ESC and AHA guidelines five main groups of antihypertensive agents can be applied for decreasing blood pressure and for the prevention of organ damages. Occasionally, patients are not able to tolerate antihypertensive medication because of side effects, drug intolerance or interactions thus it is more difficult to reach the target blood pressure values. Therefore there are several efforts to complete the existing therapeutical possibilities against the development of organ damages like inhibition of Rho/ROCK pathway (*e.g.*, statins), regulation of ROS formation, influence on mitochondrial biogenesis and enhancing recombinant adenovirus hepatocyte growth factor gene. Hypertension induced oxidative stress causes DNA breaks producing the activation of nuclear poly(ADP-ribose) polymerase-1 (PARP) enzyme that leads to energy depletion and unfavorable modulation of different kinase cascades. PARP activation promotes the development of HHD, and its transition to heart failure. Therefore inhibition of PARP-enzyme offers another new therapeutical approach among hypertensive patients. The purpose of this review is to give a comprehensive summary about the most significant mechanisms in HHD and an insight into new potential therapies.

Key words: Hypertension; Hypertensive heart disease; HfpEF; Organ damage; PARP-inhibition

Core tip: There is numerous literature dealing with hypertensive heart disease and its therapeutical opportunities. In our work we have tried to combine clinical aspects with experimental data, which represent the future scope of the therapeutical opportunities in the prevention of organ damages not only *via* antihypertensive effect.

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INTRODUCTION

Hypertension is a major public health problem associated with high cardiovascular morbidity and mortality. Generally the prevalence of high blood pressure appears to be around 30%-45% in the whole population, which shows a higher prevalence with ageing. In case of adults, hypertension is defined as a systolic blood pressure of at least 140 mmHg and a diastolic of 90 mmHg according to the various guidelines (*e.g.*, the new ESH/ESC guideline). However, there are some subgroups of patients in whom the goal blood pressure is different. For instance, the elderly can benefit from lowering systolic blood pressure only to between 140 and 150 mmHg. In diabetic patients, however, the target blood pressure is lower than in the general population. In these patients the diastolic blood pressure should be less than 85 mmHg. According to the concept of J-curve hypothesis, it can be harmful to reduce both systolic and diastolic blood pressure to markedly low values.

Hypertension is an important risk factor of cardiovascular diseases, stroke, renal disease and peripherial artery disease[1]. According to epidemiological data, hypertensive heart disease (HHD) is one of the most important hypertensive organ damage. The most common consequences of HHD are heart failure, ischemic heart disease and arrhythmias. The Framingham Heart Study showed that 20 mmHg elevation of systolic blood pressure is associated with 50% increased risk of heart failure[2]. Hypertension is of course not the sole factor contributing to the development of heart failure but multi-variate analysis using time-dependent modelling revealed that myocardial infarction conferred the greatest risk of developing heart failure. As a consequence of its high prevalence, hypertension carried the greatest population-attributable risk[3]. Thus blood pressure lowering (antihypertensive therapy) markedly reduces the incidence of major cardiovascular (CV) events like HHD and heart failure[4].

Registries proved that nearly half of the patients with heart failure have a preserved ejection fraction (HfpEF). HFpEF is most common among the elderly, women and patients with left ventricular hypertrophy[5].

DEVELOPMENT OF HHD

Hypertensive heart disease encompasses a wide spectrum including asymptomatic cardiac hypertrophy and clinical heart failure (with either preserved or reduced ejection fraction). Elevated blood pressure changes the structure and function of blood vessels and left ventricle. These alterations are also known as remodeling, which is an adaptive mechanism in response to long-term changes in hemodynamic conditions, but it may also subsequently contribute to the pathophysiology of circulatory disorders[6,7].

Alterations in left ventricle, for instance hypertrophy and ischemia, predispose to heart failure in hypertensive patients. Cardiac hypertrophy is an adaptive response, a compensatory mechanism to pressure or volume overload directing to the attenuation of wall tension and the maintenance of cardiac output. The left ventricle mass can increase either as a result of wall thickening or ventricular dilation. The relative wall thickness (the ratio of the left ventricular wall thickness to diastolic diameter) determines the type of hypertrophy (eccentric or concentric). It is influenced by the type of overload (pressure or volume), by the neurohormonal activation (plasma renin level), extracellular matrix changes, concomitant diseases (coronary artery disease, diabetes mellitus, obesity), demographic and genetic factors (*e.g.*, ACE gene polymorphism)[7,8].

Sustained hypertrophy is often the initial step towards the progression of congestive heart failure[7].

It is now well known that symptomatic heart failure can occur either in the setting of reduced (HFrEF) or preserved ejection fraction (HFpEF)[9]. The classic course of HHD progression is a so-called "burned-out" of left ventricle in which hypertension leads to concentric hypertrophy followed by diastolic and finally systolic insufficiency[10].

In an other group of hypertensive patients the development of myocardial infarction causes directly systolic heart failure (HFrEF) independently from hypertrophy[8] (Figure 1).

HISTOLOGY

High blood pressure caused alterations in cardiac structure and function, eventually resulting in impaired myocardial performance, coronary haemodynamics and apoptosis.

It has been well established that pathogenesis of HHD involves all components of the heart, including myocytes and non-myocytic cells, such as fibroblasts and endothelial cells, extracellular matrix proteins, fibrillar collagen, and coronary vessels[11].

Structural remodeling of HHD is characterized by enlarged cardiac myocytes with altered energy metabolism, fibroblast proliferation and activation, fibroblast-myofibroblast transformation and excessive collagen deposition, which all lead to a more rigid myocardium[12,13]. Coronary resistance vessels are also affected, perivascular fibrosis of intramyocardial coronary arteries and arterioles produce intimal-medial thickening[14].

NEUROHUMORAL MECHANISMS

The remodeling and growth regulation of the heart involve several mechanisms including neurogenic, humoral, autocrine and paracrine factors.

The activation of renin-angiotensin-aldosterone

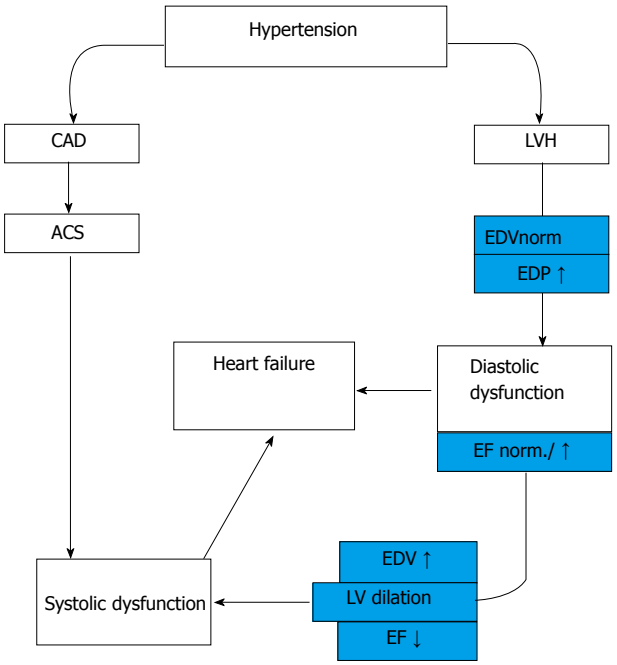

Figure 1 Development of hypertensive heart disease. HT: Hypertension; LVH: Left ventricle hypertrophy; EDV: End-diastolic volume; EDP: End-diastolic pressure; EF: Ejection fraction; CAD: Coronary artery disease; ACS: Acut coronary syndrome.

system (RAAS) is one of the most important processes, which contribute to the development of hypertension including vasoconstriction, generation of reactive oxygen species (ROS), vascular inflammation, vascular and cardiac remodeling (hypertrophy and fibrosis). Therefore the RAAS system plays a prominent part in accelerating hypertensive organ damages[15,16]. Moreover angiotensin converting enzyme (ACE) is responsible for the production of angiotensin Ⅱ (Ang Ⅱ), which correlates to left ventricle hypertrophy. Individuals have different plasma ACE concentrations due to the insertion/deletion polymorphism of ACE gene, which also shows a close relationship to ventricular hypertrophy[12].

Mineralocorticoids have a physiological role in volume regulation, but they also activate the sympathetic nervous system (SNS), which results in baroreceptor dysfunction, impaired arterial compliance and marked myocardial and vascular fibrosis[17].

The sympathetic hyperactivity rises blood pressure directly (even without RAAS activation), possesses metabolic effects (*e.g.*, insulin resistance) and facilitates the development of LVH.

It has been well established that pathogenesis of cardiac remodeling is also associated with insulin resistance, increased activity of insulin-like growth factor-1 and myocardial pro-fibrotic matricellular protein osteopontin, thyroid hormons and the elevated level of brain and atrial natriuretic peptides[12].

STRESS-INDUCED SIGNALING PATHWAYS

It is well known that hypertension induced oxidative stress plays an important role in the development of cardiac injury. Potential sources of ROS are the NADPH oxidases, nitric oxide synthase, lipoxygenases, cyclo-oxygenases, xanthine oxidase, cytochrome P450 enzymes, and the mitochondrial respiratory chain[18]. ROS mediated damages are implicated in endothelial dysfunction, inflammation, hypertrophy, apoptosis, cell migration, fibrosis and angiogenesis[19]. ROS impair the function of ion-channels and decrease the amount of high energy phosphates. These changes can result in alterations of myocyte and smooth muscle cell calcium homeostasis leading to increased cell proliferation[20]. Oxidative stress can lead to single stranded DNA breaks and changes in signaling pathways evolving alterations in LV structural and mechanical properties[21].

The single stranded DNA breaks provoke the activation of nuclear poly(ADP-ribose) polymerase-1 (PARP) enzyme, which can decrease the cellular NAD^+ and ATP pools leading to energy depletion with inadequate glycolysis and mitochondrial respiration, promoting apoptotic or necrotic cell death[21-25].

The activation of PARP-enzyme has a central role in the pathophysiology of several cardiovascular diseases including the development of HHD, transition of HHD to HF by influencing collagen production *via* modulation of different kinase cascades[21,22]. Cellular adaptations of the heart are typically initiated by stress responsive signaling pathways, which serve as central transducers of cardiac hypertrophic growth and/or ventricular dilation.

These signaling pathways include extracellular signal-regulated protein kinases (ERK), p38 mitogen-activated protein kinases (p38-MAPK), c-Jun NH2-terminal kinases (JNK), several protein kinase C (*e.g.*, PKC delta and epsilon) isoforms and Akt-1/glycogen synthase kinase-3b (GSK-3β) signaling cascade. These cascades have also been implicated in affecting the decision of myocytes to either survive (Akt-1/GSK-3β, ERK, PKCepsilon, JAK) or undergo programmed cell death (p38 MAPK, PKC delta, JNK)[20-22] (Figure 2).

It has been observed that RhoA/ROCK pathway is also involved in hypertension and in the development of consequent cardiac hypertrophy. It has a close relationship to Ang Ⅱ, which can increase ROCK activity and contributes to the maintenance of hypertension, to the increased medial thickness and perivascular fibrosis in coronary arteries[26]. This mechanism also affects stretch-induced ERK activation and vascular smooth muscle cell growth[27].

TREATMENT STRATEGIES IN HYPERTENSION

The main goal of antihypertensive therapy is the prevention of organ damages thus the prevention of life-threatening consequences such as stroke, myocardial infarction HHD or heart failure[1]. Although previous clinical trials focused mainly on improving mortality in HF, nowadays it is recognized that preventing heart failure is better for the patients and financially it is cost-

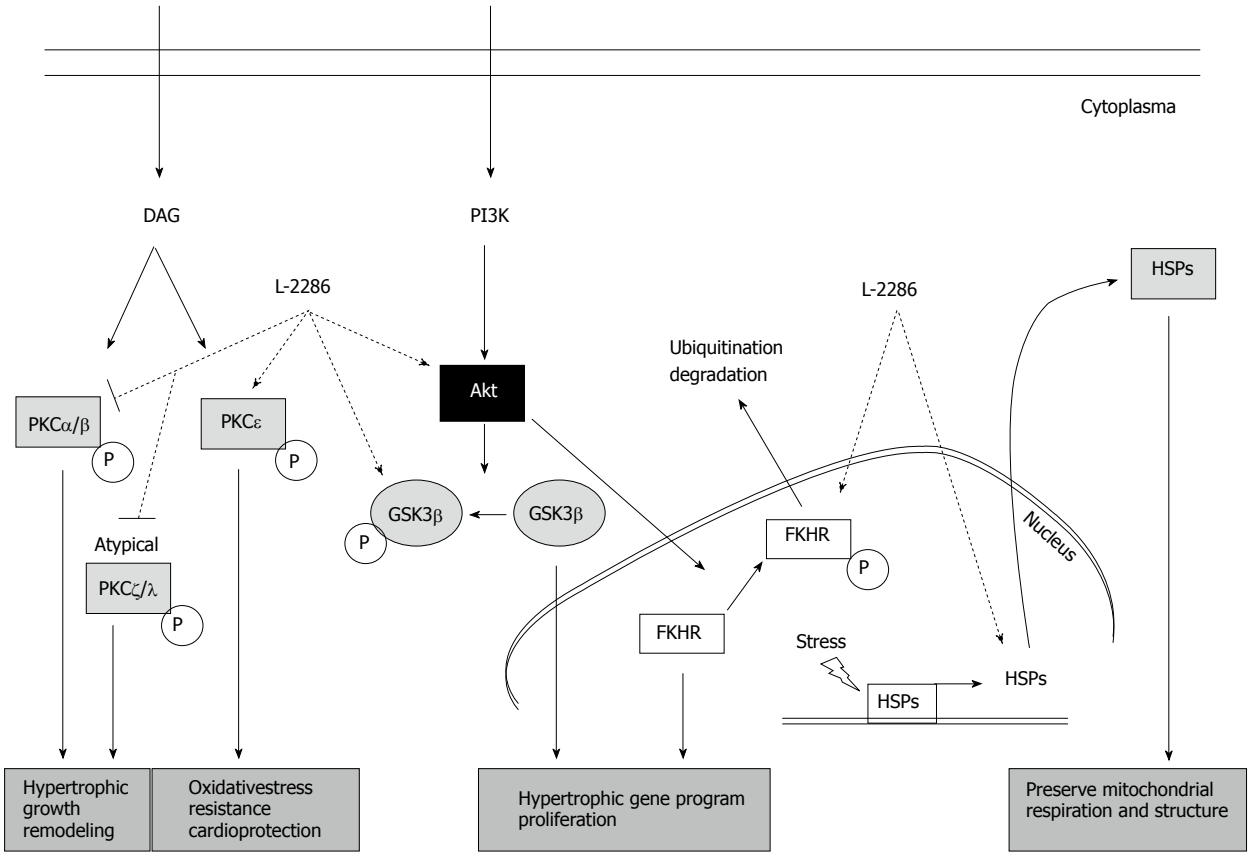

Figure 2 Summary of protein kinase C and Akt-1/GSK-3β signal pathway and the alterations due to poly(ADP-ribose) polymerase-1 inhibition (22 with permission of Deres L and the authors). DAG: Diacylglycerol; FKHR: Forkhead transcription factor; GSK-3β: Glycogen synthase kinase-3 β; HSP: Heat shock protein; PARP: Poly(ADP-ribose) polymerase-1; PI3K: Phosphatidylinositide 3-kinase; PKC: Protein kinase C.

effective for the health care system. It is well-known that effective antihypertensive therapy reduces the incidence of heart failure by more than fifty percent[28].

Based on current guidelines, the cornerstones of antihypertensive pharmacological therapy are diuretics, beta-blockers, angiotensin converting enzyme inhibitors (ACE-I), angiotensin receptor blockers (ARB) and calcium antagonists (CA)[29].

Blocking sympathetic hyperactivity is thought to be an essential tool in the treatment of CV diseases. Besides the blood pressure lowering effect of beta-blockers, they are able to reduce sympathetic overactivation. Moreover, they reverse left ventricular remodeling and can decrease the incidence of heart failure. Among diuretics, the thiazides mean the first line of choice because of efficacy and price. They are recommended in left ventricular hypertrophy, and can reduce cardiovascular morbidity and mortality.

ARBs and especially ACE-inhibitors significantly decrease all cause mortality in patients with hypertension. ACE-I can both prevent developing HF and decrease LV and vascular wall remodeling. A large body of evidence suggests that all of these are induced by the downregulation of enzymatic pathways involved in the interstitial collagen formation. CA effectively reduce blood pressure by dilating arteries with decreasing Ca(2+) influx into smooth muscle cells of the arterial wall. They can be used in combination therapy with most of the antihypertensive drugs. According to the statement of ESC and ESH, all above mentioned drugs are suitable for the initiation and maintenance of antihypertensive treatment because the main benefits of these drugs are due to the lowering of BP *per se* and are largely independent of the drugs employed[28].

NEW THERAPEUTIC POSSIBILITIES IN HYPERTENSION

Although there is an increasing number of effective antihypertensive drugs that can be used in the clinical practice, there are many patients who can not reach the goal blood pressure. In the United States, there are approximately 70 million hypertensive patients and about 40 million of them do not have their blood pressure under proper control. The main factors in the background of this phenomenon are side effects, drug intolerance or interactions and therefore poor adherence of patients to the prescribed medication[29]. Therefore in the last several years experimental researches tried to focus on treatments that alleviate end-organ damage itself without lowering blood pressure.

This approach is supported firstly by large trials with statin therapy. The main role of statins was the prevention

of coronary artery disease, myocardial infarction and other adverse cardiovascular events. Statins possess both lipid-dependent and lipid independent effects. They are able to lessen inflammation, improve endothelial function and decrease thrombogenicity[30].

In the background of the favorable pleiotropic effects of statins, we need to mention the modulation of intracellular pathways, involved in cell growth regulation/apoptosis and gene expression (Ras, Rac, Rab and Rho)[30,31]. It has already been demonstrated primarily in experimental but also in human studies that high dose atorvastatin inhibits the synthesis of isoprenoids, which are functionally important in the Rho/Rho-associated coiled-coil containing kinase (ROCK) pathway[30]. Moreover, the inhibition of Rho/ROCK pathway by statins may cause improvement in endothelial function and decrease vascular inflammation and atherosclerosis. The localization of these proteins has been shown in vascular smooth muscle cells but their role needs to be determined in the context of atherosclerosis. These findings open an option for specific ROCK1 or ROCK2 inhibitors, which could have greater therapeutic effect with less toxicity[30]. Furthermore, statins decrease the number of angiotensin-1 receptors through RhoA, Ras, Rac1 and the Rho/kinase system, which regulates the ROS formation through NADPH oxidase[32].

The ASCOT-LLA study revealed the role of statins in the prevention of CV events among hypertensive patients[33,34]. Large clinical trials demonstrated that statin therapy may provide clinical benefits to patients with heart failure. Analysis of the Daunia Heart Failure Registry in 2013 elucidated that treatments with atorvastatin are associated with fewer cardiac deaths and better left ventricular performance[35,36].

Mitochondrial dysfunction also seems to be an important factor in the development of HHD[29,37,38]. Another therapeutic strategy can be the stimulation of mitochondrial biogenesis through the AMPK or the eNOS/Nitric Oxide/Cyclic Guanosine Monophosphate pathway[37-43]. Resveratrol, which has a well-known positive effect in the prevention of cardiovascular diseases, is a potent stimulator of the mitochondrial biogenesis[44-49]. An other way is to augment the mitochondrium against oxidative stress. ACE-I and ATII receptor blockers, which are originally antihypertensive drugs, bear antioxidant properties beside blood pressure lowering effect. However, it is not clear whether they target mitochondrial reactive oxygen species (ROS) formation directly or indirectly[50,51]. Thirdly, regulating mitochondrial iron homeostasis and reducing mitochondrial iron content may also yield to cardioprotection because of inhibition of hydroxyl radical formation and mitigation of oxidative stress[36].

There is an expanding number of evidence that the previously mentioned resveratrol significantly attenuates the development of cardiac dysfunction[52]. This ability is already proved in spontaneously hypertensive rats (SHR), transverse aortic constricted rats (TAC), models of hypertension and pressure overload-induced heart failure. Although resveratrol alone does not have any systolic or diastolic blood pressure lowering effect, in TAC rats resveratrol markedly increased glutathione, sodium oxide dismutase 2 levels and decreased 4-hydroxy-2-nonenal - a marker of lipid peroxidation - and LV macrophage and mast cell infiltration. Furthermore, a combination of resveratrol with hydralazine treatment significantly reduced blood pressure, improved systolic and diastolic function, decreased fibrosis and improved vascular geometry. The low-dose resveratrol itself was unable to reach these favourable actions. However, resveratrol alone alleviated cardiac fibrosis and some of the functional abnormalities in SHRs[53].

The cardiomyocyte function enhancer ranolazine reduces myoplasmic free Ca(2+) during diastole at high-stimulus rates. Therefore ranolazine showed to be effective in reducing diastolic dysfunction with inhibition of the increased late sodium current in the SHR leading to reduced Ca(2+) overload[54].

Hu *et al*[55] found that HGF expression is attenuated in hypertrophic and fibrotic myocardium of spontaneolusly hypertensive rats (SHR) and injected recombinant adenovirus hepatocyte growth factor gene (Ad-HGF gene) in the left ventricular free wall. The upregulation of myocardial HGF expression in SHR animals significantly suppressed myocardial fibrosis, collagen I content, LVMI, LVEDP, and increased -dP/dt_{max} value[55].

In the last decade PARP inhibitors received growing attention. Although they do not have any antihypertensive effect, our workgroup demonstrated that an isoquinoline derivative PARP-inhibitor, *i.e.*, L-2286 has beneficial effects against oxidative cell damage, ischemia-reperfusion injury and the development of postinfarction, or long-term high blood pressure-induced heart failure in hypertensive animals (SHR)[21,22,25,56,57]. The PARP-inhibitor treatment significantly decreased the collagen deposition in the myocardium thus with echocardiography less prominent septal and posterior wall thickness could be measured. Moreover, in old SHR animals the transition of already developed HHD into manifest heart failure was also blocked by pharmacological PARP-inhibition. In an other long-term experiment, PARP-inhibitors decreased also the hypertensive remodeling of the great vessels in spontaneously hypertensive rats. Our experimental data also proved that the influence on the Akt-1/GSK-3β, MAPKs, MKP-1 and PKC pathways could be the underlying mechanism behind the PARP-inhibition[21,22,25,56,57].

The concept that it is possible to prevent organ damages without blood pressure lowering effect in hypertension is very promising since the goal blood pressure can not be reached in a high number of patients. This is why PARP-inhibitor co-administration could give us a potential new therapeutical approach beside the antihypertensive therapy to prevent hypertension induced

organ damages.

CONCLUSION

Although several effective novel and modern anti-hypertensive therapies were introduced in the last decade, hypertension caused organ damages, especially HHD and heart failure, remain a leading cause of morbidity and mortality in hypertensive patients. That is the reason for the growing number of researches trying to focus on treatments that alleviate end-organ damage itself even without lowering blood pressure. Several drugs, like statins or PARP-inhibitors exert beneficial effect on intracellular signaling, and could be an important part of the treatment of hypertensive patients in the future.

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MINIREVIEWS

Clinical implication of hematological indices in the essential hypertension

Ahmet Karabulut, Aytac Karadag

Ahmet Karabulut, Department of Cardiology, Acibadem University School of Medicine, Acibadem Atakent Hospital, Istanbul 34303, Turkey
Aytac Karadag, Department of Internal Medicine, Acibadem Atakent Hospital, Istanbul 34303, Turkey
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Correspondence to: Ahmet Karabulut, MD, Associate Professor, Department of Cardiology, Acibadem Atakent Hospital, Turgut Ozal Bulvari No. 16, Istanbul 34303, Turkey. drkarabulut@yahoo.com
Telephone: +90-505-3577477
Fax: +90-212-4044445
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Abstract

Prognostic value of haematological indices, especially red cell distribution width, neutrophil lymphocyte ratio and mean platelet volume, was reported with numerous investigations in miscellaneous cardiovascular settings. Their major prognostic value was linked to oxidative stress and inflammation since their level was correlated with major inflammatory markers such as high sensitive C-reactive protein and interleukins. Oxidative stress and chronic inflammation are also postulated as the main pathophysiologic mechanism of essential hypertension (HT) and its vascular complication. Recently, correlation between HT and haematological parameters was searched in numerous studies, which has made the topic more popular. Herein, we reveal the correlation between haematological indices and HT and we also demonstrate the clinical implication of this correlation. Impaired haematological parameters may strongly indicate hypertensive end-organ damage.

Key words: Hypertension; Inflammation; End-organ damage; Haematological indice; Platelet activation

Core tip: We demonstrated the correlation between haematological indices, particularly red cell distribution width, neutrophil lymphocyte ratio and mean platelet volume, and hypertension and we also clarified the clinical implication of the haematological markers in hypertensive end-organ failure. Impaired haematological parameters may strongly indicate the hypertensive end-organ damage.

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INTRODUCTİON

Systemic arterial hypertension (HT) is a common health disorder with uncertain aetiology and pathophysiology.

It affects 20%-30% of the adult population and it can lead to severe end-organ damage and clinical manifestation, including coronary heart disease and stroke, which constitute the leading cause of mortality in the general population[1]. Beside genetic predisposition, several mechanisms were proposed to clarify the pathophysiology of essential HT[1-3]. Vascular reactivity and endothelial dysfunction, which result in increased peripheral vascular resistance, is one of the major hypotheses in the pathogenesis. Recently, it has become evident that the immune system and chronic inflammatory status may play a role in the pathogenesis of HT[2-5]. Many inflammatory markers, such as high sensitive c-reactive protein (hsCRP), cytokines, and adhesion molecules have been found elevated in HT, supporting the role of inflammation[2-6].

Haematological indices, particularly red cell distribution width (RDW), neutrophil lymphocyte ratio (NLR) and mean platelet volume (MPV), were established as markers of systemic inflammation and vascular pathology[7-15]. Their prognostic value was clearly demonstrated in coronary artery disease, stroke and several other vascular diseases. Correlation of such haematological indices and HT was also investigated and it was proposed that haematological indices may predict the severity of HT and end-organ damage[16-22]. With this review, we aimed to show the place of haematological indices in the essential HT and demonstrate its clinical implication.

MECHANISM OF ESSENTIAL HT

The aetiology of essential HT is not clear, however, it has been accepted as a multifactorial disease arising from the combined action of many genetic, environmental and behavioural factors. Renal sodium retention, vascular hypertrophy, endothelial cell dysfunction, sympathetic nervous system hyperactivity, upregulation of the renin-angiotensin-aldosterone system, altered T-cell function, insulin resistance and dietary and habitual factors were postulated as common mechanisms of HT[1-5]. However, oxidative stress and inflammation seem to play a major role in the pathophysiology of HT and also concomitant end-organ damage[4-6]. Excessive reactive oxygen species generation decreases nitric oxide level, which predisposes to endothelial cell dysfunction. Enhanced oxidative stress reduces antioxidant capacity in the cardiovascular, renal and nervous systems. In the cardiovascular system, reactive oxygen radicals play a pathophysiological role in inflammation, hypertrophy, proliferation, apoptosis, migration, fibrosis, angiogenesis and rarefaction, which are important processes contributing to endothelial dysfunction and cardiovascular remodelling in HT[4-6]. Recently, the synergy of haematological indices and HT was searched in many HT-associated clinical conditions after clear demonstration of the correlation between haematological indices and endothelial cell dysfunction[16-22]. Non-dipper HT had carried about three times the risk of atherosclerotic cardiovascular events compared to the dipper group. The majority of the investigations focused on this specific non-dipping group, since atherotrombosis and inflammation was more prominent in this group[23-29].

RED BLOOD CELL INDICES

Red cell distribution width

Red cell distribution width is a measure of the variability in the circulating erythrocytes' size, which is usually used for haematological disorders. It can be obtained easily from a routine complete blood count in a short period. Although the initial application of RDW was the differential diagnosis of anaemia, recent investigation revealed that RDW is also an important prognostic factor in cardiovascular diseases[7-8]. It was proposed that there is a linkage between RDW and inflammatory and neurohormonal activation and also accelerated atherosclerotic process which may enhance the impact of RDW in the was cardiovascular diseases. Several mechanisms were proposed to explain the exact role of RDW in the clinical setting[7-8]. Inflammatory and neurohormonal activation could be one of the mechanistic links between elevated RDW and increased mortality. The correlation between elevated RDW and inflammatory markers such as B-type natriuretic peptide, sedimentation and white blood cells was established. Higher RDW may result from ineffective erythropoiesis due to chronic inflammation. Inflammatory cytokines have been found to suppress the maturation of erythrocytes, which enable juvenile red cells to enter into the circulation and increases the heterogeneity in size[30-31]. Moreover, elevated RDW may reflect enhanced erythropoiesis resulting from the circulating levels of neurohormonal mediators, which lead to an increment in the heterogeneity of circulating red cells. Elevated RDW levels were also associated with carotis intima-media thickness, which reflects atherosclerotic process[32]. Finally, all these mechanisms, including chronic inflammatory state, neurohormonal activation and accelerated atherosclerotic process, may contribute to adverse clinical outcomes and bad prognosis in the variety of cardiovascular diseases. Oxidative stress was proposed as another mechanism of the prognostic value of RDW. Red blood cells have powerful antioxidant capacity and serve as a primary oxidative sink. They are prone to oxidative damage, which reduces cell survival, and enhance the release of juvenile erythrocytes into the circulation. Elevated RDW levels were associated with poorer pulmonary function and progression of pulmonary HT, which reflect oxidative stress conditions[7].

The correlation between RDW and HT was also well established. Higher RDW values are strongly correlated with higher systolic and diastolic blood pressure[19-21]. Elevated levels of RDW were also documented in non-dipping HT, which are closely related to adverse

cardiovascular outcomes and higher inflammatory status[21,23]. Elevated levels of RDW were linked to hypertensive end-organ damage. Kilicaslan *et al*[16] showed that an elevated RDW level was associated with concentric left ventricular hypertrophy. It was speculated that the development of target organ damage in HT is accompanied by the increasing impairment of erytropoiesis by the mechanism of inflammation[23]. In patients with HT, RDW levels showed a significant relationship with inflammatory markers such as hsCRP, interleukin-6 and fibrinogen[16,18,33]. Elevated RDW was also correlated with pulse wave velocity and carotid intima media thickness[32]. In the HT group, RDW levels and glomerular filtration rate seemed to be linked[30]. Erythrocyte deformability may serve as a marker of endothelial dysfunction in the kidney, which may trigger nephropathy.

Hematocrit

Haematocrit is a determinant of whole blood viscosity. Viscosity affects peripheral resistance to blood flow, and peripheral resistance affects blood pressure[34]. Most hypertensive patients exhibit increased blood viscosity compared with healthy controls[35]. Although, the details of this association is unclear, reduction of the red cell deformability and an increase in the size, numbers and aggregability of red blood cells may worsen the microcirculation and enhance the end-organ damage. Therefore, the diameter of a red cell is about 8.5 micron, and that of the smallest capillaries about 3 micron, the deformability of the red cells plays an important role in capillary flow[36]. Decreased red cell deformability could cause an increased microvascular flow resistance, which may result in target organ damage. Haematocrit in upper quartiles may indicate end-organ damage in HT.

Mean corpuscular volume

Epidemiological studies show no relation with higher mean corpuscular volume (MCV) in hypertensive, whereas, some studies suggest that hypertensive patients have lower MCV. Decreased MCV levels may reflect higher blood viscosity, since a high red cell level may lead to down-regulation of MCV as an adaptive mechanism[34].

WHITE BLOOD CELL INDICES

White blood cells play a major role in both the initiation and progression of atherosclerosis and have been implicated in acute rupture of atherosclerotic plaques[37]. In addition, neutrophils aggregate with platelets to exacerbate vascular plugging in the microcirculation. Neutrophils also prompt the secretion of inflammatory mediators[38].

Neutrophil-lymphocyte ratio

The neutrophil-lymphocyte ratio is associated with a worse outcome in various diseases and is defined as an emerging potent marker of inflammation[38]. It was reported that NLR is an independent factor of mortality and major adverse cardiac events in acute and chronic ischaemic heart diseases[13]. The NLR was also found to be significantly higher in non-dipping HT[27,28]. Increased NRL may indicate hypertensive end-organ damage. The neutrophil-lymphocyte ratio is not static, and varies with the of critical illness. Thus, NLR may give prognostic clues about the activity of disease and response to therapy. In addition, the protective effect of some anti-hypertensive drugs correlated with NLR decrement, which suggests the role of NLR in the severity of HT[39,40].

White blood cell count

White blood cell (WBC) count constitutes an inflammatory marker and it tends to increase in HT. The WBC count was higher in non-dipping HT and WBC counts in the highest quartile may reflect enhanced inflammatory response and end-organ damage[41]. Hypertensive men with a high Framingham 10-year cardiovascular risk score showed higher levels of WBC[42].

PLATELET INDICES

Mean platelet volume

Mean platelet volume has known to be an indicator of platelet activation and, its correlation with cardiovascular disease is well established[9,11-12]. Platelets play a pivotal role in the development of atherosclerotic lesions, plaque destabilization, and atherothrombosis. It has been clearly demonstrated that MPV is an unfavourable prognostic factor in ischaemic coronary heart disease[11,12]. A few studies have also proposed that MPV may predict microvascular injury in coronary vessels and diabetic microvascular complications, including nephropathy and hypertensive microvascular end-organ damage[17,43-45]. Gunebakmaz *et al*[17] reported that higher MPV quartile values were more common in left ventricular concentric hypertrophy compared to normal cases. High MPV levels were also linked to non-dipping HT[24-26]. Platelet activation and inflammatory response is the probable mechanism of MPV prognostic value. Hence, an increased MPV value usually accompanies high hsCRP value. Mean platelet volume levels were associated with severity of end end-organ damage, including carotid atherosclerosis, left ventricular hypertrophy and renal damage[43-45]. There is a stepwise increase between MPV and the severity of hypertensive disease. Mean platelet volume was also found higher in ophthalmologic complications[46]. Moreover, its level was increased in masked HT[47].

Platelet distribution width

Platelet distribution width reflects the platelets' reactivity. The platelet distribution width (PDW) is a more specific marker of platelet activation, since it does not increase during simple platelet swelling[10]. Spencer *et al*[48] reported that there is a strong correlation between PDW and the severity of hypertensive disease.

P-selectin (CD62P)

P-selectin also shows platelet activation. It is a direct mediator of vascular inflammation and injury[49]. Preston *et al*[49] showed that platelet activation and p-selectin may participate in the accelerated target organ injury in high-risk hypertensive patients[50].

Anti-hypertensive therapy results in a reversal of platelet morphology abnormalities and indices of platelet activation. This may contribute to a reduction in thrombosis-related complications seen in those whose blood pressure lowering is effective[51].

CONCLUSION

Haematological indices, predominantly RDW, NLR and MPV, reflect oxidative stress and inflammatory state, which also postulate as major mechanisms of HT and its vascular complication. There is a stepwise relation between the severity of HT, hypertensive end-organ damage and haematological indices. However, it is still not clear whether these parameters are responsible in the pathogenesis of HT or they increase as a result of the progression of hypertensive disease. There is a need of further investigations to clarify definitive pathophysiologic mechanism of HT regarding the role of hematological indices. Nevertheless, there is a clear consensus that these haematological parameters have a prognostic value in the essential HT and their abnormality may strongly suggest hypertensive end-organ damage.

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ORIGINAL ARTICLE

Retrospective Study

Catheter ablation for atrial fibrillation in a subset of patients with concomitant hypertension

Tushar Sharma, Benjamin J Scherlag, Hiroshi Nakagawa, Warren M Jackman, Ralph Lazzara, Sunny S Po

Tushar Sharma, Benjamin J Scherlag, Hiroshi Nakagawa, Warren M Jackman, Ralph Lazzara, Sunny S Po, Heart Rhythm Institute at the University of Oklahoma Health Sciences Center, Oklahoma City, OK 73104, United States

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Correspondence to: Benjamin J Scherlag, PhD, Heart Rhythm Institute at the University of Oklahoma Health Sciences Center, 1200 Everett Drive (6E103), Oklahoma City, OK 73104, United States. benjamin-scherlag@ouhsc.edu
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Abstract

AIM: To study patients with atrial fibrillation and hypertension who had successful catheter ablation for changes in blood pressure 1 year later.

METHODS: A retrospective study was performed on patients who had catheter ablation for atrial fibrillation (AF) and hypertension (HTN) which included local autonomic ganglionated plexi denervation and pulmonary veins isolation. Of the records of 119 patients, follow-up data was found in order to determine the presence of sinus rhythm and data on systolic (SBP) and diastolic blood pressure at 2 wk, 3 mo, 6 mo and 1 year after the ablation procedure. Transthoracic echocardiograms were taken at the time of the catheter procedure to determine left atrial dimensions (LADs) and left ventricular size.

RESULTS: There was no significant difference in the pre-ablation mean blood pressures between the two groups (P = 0.08). After 1 year 33 of the 60 with AF and HTN were in sinus rhythm, of whom 12 had normal LADs, $\leqslant$ 4 cm Group 1, and 21 had enlarged left atria (LADs > 4 cm, Group 2). For Group 1, at 1 year of follow up, there was a significant difference in the SBP (119.2 ± 13 mmHg) compared to pre-ablation (142.6 ± 13.7 mmHg, P = 0.001). For Group 2, there was no significant difference in the SBP, pre-ablation (130.3 ± 17.5 mmHg) and at 1 year of follow up (130.4 ± 13.4 mmHg, P = 0.75). All patients were on similar anti-hypertensive medications. There was a trend for a greater left ventricular size in Group 2 compared to Group 1.

CONCLUSION: We suggest that Group 1 had HTN due to sympathetic hyperactivity, neurogenic HTN; whereas HTN in Group 2 was based on arterial vasoconstriction.

Key words: Atrial fibrillation; Hypertension; Autonomic nervous system; Catheter ablation

Core tip: A retrospective study of 119 patient with atrial fibrillation (AF) and hypertension (HTN) underwent catheter ablation consisting of pulmonary vein isolation and local cardiac autonomic denervation. After 1 year 33 were in sinus rhythm and fell into 2 categories based on significant differences in left atrial dimensions (LADs). Although similarly medicated, Group I (LADs $\leqslant$ 4 cm) had a significant decrease in blood pressure compared to Group 2, LAD > 4 cm. We conclude that HTN in Group 1 was neurogenic and ameliorated by neural ablation; whereas HTN in Group 2, manifested arterial vasoconstriction as the mechanism for HTN.

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INTRODUCTION

Early studies seeking the mechanism for clinical hypertension (HTN) focused on the sympathetic nervous system as the underlying cause. It was well known that sympathetic stimulation of the heart led to increased contractility leading to high blood pressure. Indeed, a concept was put forth by several investigators suggesting that HTN was neurogenic in origin[1-5]. The seminal studies of Goldblatt *et al*[6], induced chronic HTN in animals who had a clip (stenosis) on the renal arteries which provided the basis for the discovery of the role of the renin/angiotensin/aldosterone syndrome as a cause of HTN[7]. This concept became the prevalent view and has become the mainstay of therapeutic strategies to control HTN, *i.e.*, use of angiotensin blocking agents and diuretics. The acceptance of a sympathetic contribution is evidenced by the addition of beta-blockers to the antihypertensive regimen. The Framingham study has provided evidence linking HTN and atrial fibrillation (AF). In a multivariate analysis it was found that HTN was an independent predictor for developing AF, with an odds ratio of 1.5 for men and 1.4 for women[1]. The sequence of pathological events in this association might start with increased vascular resistance followed by ventricular hypertrophy and atrial dilatation, the last providing the substrate for AF[8].

The recent dramatic effects of renal sympathetic denervation[9] has revived the neurogenic concept[10] particularly in regard to the treatment for resistant forms of hypertension. In this regard, Schlaich *et al*[11] cited experimental[12] and clinical[13] evidence that afferent nerve denervation may play a more significant role in "the sustained blood pressure-lowering (by) renal denervation … *via* the removal of renal afferent activity and the subsequent effects on central sympathetic outflow". It is interesting to note that renal sympathetic denervation has also been applied to patients with concomitant hypertension and atrial fibrillation. Scherlag *et al*[14] reported that renal artery denervation reduces systolic and diastolic blood pressure in patients with drug-resistant hypertension and reduces AF recurrences when combined with pulmonary vein isolation (PVI).

Since 2004 the procedure for catheter ablation in patients with AF in our clinical electrophysiological practice has consisted of PVI plus ablation of hyperactive autonomic nerve clusters called ganglionated plexi (GP) at the PV-atrial junctions. This combined procedure has been shown to increase the success rates for maintaining sinus rhythm compared to PVI alone[15,16]. It was in this context that we hypothesized that a subset of our patients presenting with HTN and AF would manifest the neurogenic form of HTN based on hyperactivity of the intrinsic cardiac autonomic nervous system. Furthermore, based on the previous report[15] we surmised that the patients with the neurogenic and drug resistant form of HTN would respond with a significant blood pressure reduction due to the decrease of autonomic hyperactivity caused by PVI plus GP ablation.

MATERIALS AND METHODS

We performed a retrospective study of 119 patients who had undergone catheter ablation using an irrigated tip ablation catheter (Biosense/Webster, Navi-Star, Thermocool catheter, Diamond Bar, CA, United States) for mapping and ablation.

The procedure for catheter ablation has been previously described in detail[15]. Briefly, General anesthesia was administered in all patients. Localization of GP was obtained by application of high-frequency stimulation to each GP (HFS; 20 Hz, 10-150 V and pulse width 1-10 ms; S-88 stimulator, Grass Instruments Division, Astro Med Inc., Warwick, RI, United States). Within 5 s of HFS, a marked parasympathetic response is elicited, which is arbitrarily defined as a $\geqslant$ 50% increase in mean R-R interval during AF. Each parasympathetic response is verified by both hypotension and high grade AV block. For GP ablation, radiofrequency (RF) current is delivered at 25-35 W for 40-60 s during saline irrigation at each site of positive parasympathetic response to HFS. RF applications are repeated until the parasympathetic response to HFS is eliminated.

After the 4 left atrial GP are ablated, pulmonary vein antrum isolation is performed. The endpoint of PV antrum isolation is elimination of potentials within the isolated antral area. As antrum isolation typically transects the ARGP and SLGP areas, we use the ARGP and SLGP ablation sites as the starting points for right and left antrum isolation, respectively. Echocardiographic studies were accomplished transthoracically which provided an anterior-posterior measurement of the left atrial dimensions.

Inclusion criteria were: (1) Successful catheter ablation for AF involving both GP ablation and PV isolation

Table 1 Anti-hypertensive drugs taken by patients before and after catheter ablation procedures

No. of patients	Anti-hypertensive agents
7	ACE inhibitor
7	Calcium channel blockers
2	Beta blockers
1	Angiotensin 2 receptor blocker
6	ACE inhibitor, beta blocker
3	Calcium channel blocker, angiotensin 2 receptor blocker
2	ACE inhibitor blocker. Calcium channel blocker
2	ACE inhibitor, diuretic
1	Calcium channel blocker, beta blocker, diuretic
1	Calcium channel blocker, beta blocker
1	ACE inhibitor, calcium channel blocker, diuretic

(patient should have been in sinus rhythm after one year); (2) Co-existence of AF and HTN; (3) Knowledge of left atrial dimension (LAD) by echocardiographic measurement; and (4) All patients were on anti-hypertensive drug regimens.

The exclusion criteria included: (1) Recurrence of AF at the end of one year; (2) No GP ablation; and (3) No follow up blood pressure data.

Of the 119 patients reviewed, there were 60 patients with co-existing AF and HTN. Of these 60 patients, only 33 patients who had been contacted were in sinus rhythm at the end of one year of follow up. The purpose of the study was to determine the differences in the blood pressure levels before ablation and at different periods of follow-up. The pre-ablation systolic (SBP) and diastolic (DBP) blood pressures of the patients in the two groups were compared with the post-ablation SBP and DBP at two weeks, three months, six months and one year of follow-up.

Statistical analysis

Statistical analyses were done using the SAS software (V 9.1). All statistical tests were carried out at an alpha of 0.05. Data is expressed as mean ± SD. Repeated measures analysis of variance (ANOVA) was used to determine if the mean SBP and DBP changed over the follow up periods for the two groups. Post-hoc analysis was done to compare the mean blood pressures across the individual follow up periods.

RESULTS

Patient medications

All of the 33 patients included in the chart review were on single or multiple antihypertensive medications prior to the ablation procedure (Table 1). Although 8 patients were on a single medication all the others were taking multiple anti-hypertensive agents and all continued these same regimens during the follow-up period.

Echocardiographic analysis

There were 12 patients with normal sized left atria (LAD ⩽ 4.0 cm) and 21 patients with enlarged left atria (LAD > 4.0 cm). On the basis of the blood pressure responses during progressive periods of follow-up, the 33 patients could be divided into two groups based on their LAD, *viz*., < 4.0 or > 4.0. Table 2 compares the descriptive statistics for all 33 patients that met the inclusion criteria divided into the 2 groups. Although there was a greater absolute mean value in group 1 (142/83 mmHg) *vs* group 2 (130/80 mmHg) the difference was not statistically significant prior to ablation (P = 0.08) For patients with LA dimensions ⩽ 4.0 cm (Group 1), there was a significant difference in the mean SBP levels, at 2 wk after the ablation procedure (126.8 ± 19.4 mmHg) compared to SBP, pre-ablation (142 ± 13.7 mmHg, P = 0.008). This change persisted at three and six months of follow up. The mean SBP levels at one year of follow up (119.2 ± 13 mmHg) were significantly lower than the pre-ablation mean SBP levels (142 ± 13.7 mmHg), for patients with LADs ⩽ 4.0 cm, P = 0.001.

Table 2 Comparison of descriptive statistics between Study Groups

Variable	Group 1 (LAD ⩽ 4 cm), mean ± SD	Group 2 (LAD > 4 cm), mean ± SD
AGE (yr)	58.3 ± 9.2	60.4 ± 6.8
LAD (cm)	3.63 ± 0.34	4.54 ± 0.4
Pre-ablation SBP (mmHg)	142.6 ± 13.7	130.3 ± 17.5
Pre-ablation DBP (mmHg)	83.8 ± 11.6	80.6 ± 15.6
SBP - 2 wk (mmHg)	126.8 ± 19.4[a]	129.6 ± 16.9
DBP - 2 wk (mmHg)	76.2 ± 13.5	78.9 ± 11.5
SBP - 3 mo (mmHg)	129.1 ± 15.4[a]	132.1 ± 13.6
DBP - 3 mo (mmHg)	77.6 ± 12.8	79.1 ± 12.2
SBP - 6 mo (mmHg)	123.7 ± 16.8[a,b]	134.3 ± 14.4
DBP - 6 mo (mmHg)	76 ± 10.1	77.7 ± 9.5
SBP - 1 yr (mmHg)	119.2 ± 13[a,b]	130.4 ± 13.4
DBP - 1 yr (mmHg)	70.4 ± 12.2	78.7 ± 9.1

Group 1: LAD ⩽ 4.0 cm; Group 2: LAD > 4.0 cm; [a]P ⩽ 0.05 compared to SBP pre-ablation; [b]P = 0.008, P = 0.001, Group 1 SBP compared to Group 2 SBP at 6 mo and 1 year, respectively, after the GP and PVI ablation procedure. LAD: Left atrial dimension; SBP: Systolic blood pressure; DBP: Diastolic blood pressure.

For patients with LADs > 4.0 cm (Group 2), there was no significant difference in the mean SBP levels, pre-ablation (130 ± 17.5 mmHg) and at 2 wk of follow-up (129 ± 16.9 mmHg) (P = 0.92). For patients with LADs > 4.0 cm, there was no significant difference in the mean SBP levels, pre-ablation and at 1 year of follow up (130 ± 13.4 mmHg, P = 0.75). There was no significant difference in the mean DBP throughout the follow up periods for both groups.

Figure 1 compares the proportion of patients with left ventricular hypertrophy (LVH) in both groups. Although the number of patients with or without LVH were not significantly different, the trend showed a lower incidence of LVH in Group 1 (33%) *vs* Group 2 (56%) and a corresponding higher number lacking LVH in Group 1 (67%) *vs* Group 2 (44%). The small sample size and wide range of standard deviation may have precluded obtaining statistical significance (P =

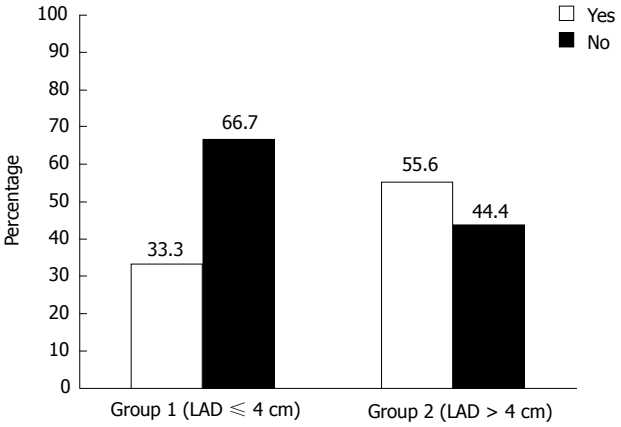

Figure 1 Distribution of the percent incidence of left ventricular hypertrophy in the two study groups. Although the number of patients with or without left ventricular hypertrophy (LVH) were not significantly different, the trend showed a lower incidence of LVH in Group 1 (33%) *vs* Group 2 (56%) and a corresponding higher number lacking LVH in Group 1 (67%) *vs* Group 2 (44%).

0.08).

DISCUSSION

Major findings

Although there was no significant difference between the initial blood pressures of the two groups, the response to GP ablation and PVI were dramatically different during the follow-up periods. Specifically, in Group 1 patients, there was a marked decrease in the mean SBP over the short term (from 142 ± 13.7 mmHg to 126.8 ± 19.4 mmHg within 2 wk) which was maintained after 3 and 6 mo. At 1 year the mean SBP was even more significantly decreased compared to the initial values (119 ± 13 mmHg, P = 0.001). In contrast, in Group 2, there was no change in SBP over the same time periods, even though the response to AF ablation was exactly the same as in Group 1. Since the anti-hypertensive drug history was heterogeneously distributed for both groups, these findings suggest that Group 1 patients with the putative "neurogenic" form of HTN, *i.e.*, due to increased ventricular contractility, represented a sub-population of HTN resistant to drugs prior to catheter ablation. It is of interest that recent studies of another group of patients with a resistant form of HTN have been shown to respond to renal artery denervation with an endovascular method for applying radiofrequency ablation to adventitial sympathetic nerves[10,11]. Experimental evidence has shown that the neurogenic form of HTN derives from an increase of sympathetic activity which increases the BP through enhanced ventricular contractility, so-called "cardiogenic hypertension". Sustained HTN has been shown to occur experimentally by chronic electrical stimulation of the left stellate ganglion[17].

In a recent study from our laboratory, we developed an acute model simulating inappropriate sinus tachycardia[18]. In 14 anesthetized dogs; 0.3 mg of 10^{-3} solution of epinephrine was injected into the anterior right ganglionated plexi (ARGP). In eight of the dogs there was a significant increase in the average heart rate of 57 beats/min but no change in systolic blood pressure. In six dogs both heart rate and systolic blood pressure were equally and significantly accentuated and remained elevated for at least 30 min. In addition ventricular arrhythmias were also observed which overwhelmed sinus rhythm. Other studies provided functional evidence of neural connections between ganglionated plexi in the atria which, when stimulated chemically, caused marked sympathetic effects on the ventricles, including ventricular arrhythmias[19].

It should be mentioned that sympathetic afferents may also play a critical role in the marked reduction of SBP in the Group 1 patients after GP ablation and PVI. Ardell[20] in a review of the cardiac neurons that inhabit the GP and the atrial neural network emphasized the afferent connections from these intrinsic cardiac elements to the brainstem. How does this scenario for reduction of BP by renal denervation translate to the present study? We hypothesize that the findings of the present studies suggest that multiple visceral sites, *e.g.*, the heart and renal arteries, which are autonomically innervated can be a source of abnormal sympathetic afferent conduction to central vasomotor centers leading to excessive efferent return to neuro-effector junctions to the same structures. Hyperactivity of GP has been shown to contribute to the propensity for AF by excessive release of cholinergic and adrenergic neurotransmitters *via* postganglionic axons innervating the PVs and atria[21-23]. Hyperactive GP may also send excessive afferent signals to central sympathetic centers which in turn would increase sympathetic outflow returning to the heart and vasculature. The results would be enhanced propensity for AF and increased ventricular contractility and vasoconstriction, *i.e.*, the neurogenic form of AF and HTN. Ablation of the GP would therefore, have a dual salutary effect by reducing both efferent and afferent activity leading to amelioration of HTN and suppression of AF. This scenario is what was found in the sub-population of patients in the present study with the appropriate biomarkers, *i.e.*, normal LAD dimensions and drug resistant HTN. In this regard a recent case report, described the application of renal artery denervation without PVI in a patient with drug resistant HTN and symptomatic, persistent AF. After a short follow-up of 5 mo the patient is in sinus rhythm with a reduction of blood pressure prior to renal sympathetic denervation (148/80 mmHg) to 111/60 mmHg. Of interest, echocardiography showed a left atrial diameter of 45 mm prior to ablation which was slightly reduced after ablation[24].

Study limitations

We do not know if eliminating anti-hypertensive drugs from those patients with the "neurogenic" form of HTN manifesting normal left atrial dimensions would have resulted in a reduction in SBP than we found. However, in those patients with the "arterial vasoconstrictor"

form of HTN manifesting LADs greater than 4 cm, there was no significant change in mean SBP over the same follow-up period, even though they had the same AF ablation procedure and the same salutary outcome, *i.e.*, restoration of sinus rhythm while still on antihypertensive agents. It has been noted by the authors of the Symplicity trials that the extension of renal artery denervation to patients who respond favorably to drugs is problematic. Indeed, Frohlich[25] in a recent editorial indicated that, "Only a small fraction of patients with hypertension have "drug resistant hypertension"…Consequently, the mass extrapolation to all patients with hypertension for…this specialized procedure does not seem appropriate at this time. Therefore, we do not know if patients in Group 2, off drugs, would have also responded with significant reductions of SBP after catheter ablation. A distinct limitation of this study is the small numbers of patients in groups 1 and 2 which requires that the findings be interpreted with caution. Further studies of the co-morbidity (AF and HTN) in a larger cohort of patients will help to corroborate the present findings, particularly if one group contains those having PVI alone or PVI plus GP ablation[14].

Significant differences were found in the mean SBP before ablation and at follow up intervals, with the SBP being lower post GP ablation in patients with AF and HTN with normal LADs. Based on previous experimental and clinical studies we conclude that HTN in Group 1 was sympathetically based, *i.e.,* neurogenic HTN, and drug resistant whereas HTN in Group 2, mainly drug responders, manifested arterial vasoconstriction as the mechanism for HTN. We hypothesize that GP ablation in Group 1 served to reduce afferent and efferent sympathetic enhanced ventricular contractility leading to HTN amelioration. Further studies in patients with hypertension and AF undergoing PVI and GP ablation, using a prospective protocol and a larger sample size, may be required to achieve more definitive results.

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COMMENTS

Background

Hypertension commonly occurs with atrial fibrillation. The authors studied patients who were successfully treated for atrial fibrillation over a period of 1 year. A sub-group of these patients also had a dramatic reduction of blood pressure into the normal range. The authors determined the mechanisms for the concomitant suppression of these two morbidities on the basis of the singular ablation procedure performed by our cardiologists.

Innovations and breakthroughs

Since 2004 the authors' clinical laboratories have used a singular hybrid procedure which combines the isolation of the muscle tissue of the pulmonary veins, the atrial fibrillation origin, from the rest of the atrium with ablation of the nerve clusters at the pulmonary vein-atrial junctions which induce the abnormal activity arising in the pulmonary veins. A retrospective study was performed in patients who underwent this procedure and collected follow-up data at 2 wk to 1 year after the procedure. Of the 33 patients who were in normal heart rhythm throughout the authors found that 21 had no change in blood pressure whereas in 12 their blood pressures were normal. All patients were on similar multiple anti-hypertensive drugs. The authors found that the non-responders had enlarged atria while the responders had normal sized atria before and after the procedure and follow-up. These finding suggested that there was a sub-population of patients whose hypertension was neurally based in the heart while the others had hypertension due to factors outside the heart, *i.e.*, abnormality of the renin-angiotensin-aldosterone system, which caused the arteries to constrict leading to enlargement of the heart chambers.

Applications

Only recently has it been shown that patients with forms of hypertension resistant to multiple drug regimens had a neurogenic basis for their condition which could be dramatically reduced by neural ablation procedures. Just as in small population the resistant forms of hypertension represent a small proportion of the general population with high blood pressure which does not respond to multiple drug therapy. The authors suggest that non-invasive methods for determining heart size by ultrasound, particularly the atrial dimensions can be used to categorize patients with drug resistant and drug responsive hypertension thereby foregoing weeks or months of drug trial for the former group.

Terminology

Hypertension: Abnormally high blood pressure; Atrial Fibrillation: A very rapid and irregular heart rate which can become persistent and can lead to heart failure and strokes; Ablation: A procedure in which an electrode catheter is introduced into the heart which allows the application of radiofrequency energy to create lesion to destroy abnormal heart or nerve tissues.

Peer-review

The authors performed a retrospective study to discuss the significant differences in the mean systolic blood pressure before ablation and at follow up intervals, with the systolic blood pressure being lower post ganglionated plexi ablation in patients with atrial fibrillation and hypertension with normal left atrial dimensions. These observations are interesting, and could be helpful in further clinical studies.

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