JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 80, NO. 15, 2022

PUBLISHED BY ELSEVIER

THE PRESENT AND FUTURE

JACC STATE-OF-THE-ART REVIEW

Cardiac Phenotypes in Secondary Hypertension

JACC State-of-the-Art Review

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ABSTRACT

Several forms of secondary hypertension carry a high risk of cardiac morbidity and mortality. Evaluation of cardiac phenotypes in secondary hypertension provides a unique opportunity to study underlying hormonal and biochemical mechanisms affecting the heart. We review the characteristics of cardiac dysfunction in different forms of secondary hypertension and clarify the mechanisms behind the higher prevalence of heart damage in these patients than in those with primary hypertension. Attention to the specific clinical/biochemical phenotypes of these conditions may assist clinicians to screen for and confirm secondary forms of hypertension. Thereby, early signs of heart damage can be recognized and monitored, allowing individualized treatment to delay or prevent evolution toward more advanced disease. (J Am Coll Cardiol 2022;80:1480–1497) © 2022 by the American College of Cardiology Foundation.

Several forms of secondary hypertension carry a high risk of morbidity and mortality. Complications include hypertensive "crisis," stroke, aortic dissection, and cardiac events comprising myocardial infarction, arrhythmia, and congestive heart failure (HF).[1-6] Excessive amounts of catecholamines, aldosterone, angiotensin II, or cortisol exert deleterious effects on the myocardium[7-14] in

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received June 15, 2022; revised manuscript received August 3, 2022, accepted August 4, 2022.

Listen to this manuscript's audio summary by Editor-in-Chief Dr Valentin Fuster on www.jacc.org/journal/jacc.

ISSN 0735-1097/$36.00 https://doi.org/10.1016/j.jacc.2022.08.714

HIGHLIGHTS

- Secondary forms of hypertension, when untreated, cause more cardiac damage than primary hypertension and are associated with greater CV risk.
- Cardiac damage includes not only myocardial hypertrophy but also inflammation, fibrosis, apoptosis, and necrosis.
- Specific and timely treatment of secondary hypertension is needed to prevent cardiac damage.

secondary hypertension, including cardiac hypertrophy, systolic and diastolic dysfunction, stress-induced cardiomyopathy, myocarditis, and dilated cardiomyopathy (**Central Illustration**).[9,15-21]

Evaluation of cardiac phenotypes in secondary hypertension provides a unique opportunity to study underlying hormonal and biochemical mechanisms that contribute to cardiac dysfunction. To this end, we review involvement of these mechanisms in different forms of secondary hypertension, with a focus on the most common forms.

COARCTATION OF AORTA

Coarctation of the aorta (CoA) is a rare congenital heart disease that occurs in approximately 4 in 10,000 live births, accounting for up to 10% of all congenital heart defects, and with a male to female ratio between 1.27:1 and 1.75:1.[22] CoA is a common cause of hypertension in prepubertal children.[23]

PATHOPHYSIOLOGY. Anatomopathological studies demonstrate that the vascular area of CoA is characterized by abnormal composition of the arterial wall, including less smooth muscle mass, more collagen, intimal thickening, and impaired elastic fiber formation.[24] Interestingly, normotensive patients with repaired coarctation of the aorta (r-CoA) present with signs of premature arterial aging of the entire arterial tree, including endothelial dysfunction,[25] increased intima-media thickness, and increased arterial stiffness. Altogether, these vascular changes, as well as reduced baroreceptor sensitivity and chronically increased sympathetic activity, are thought to be the main mechanisms involved in the pathophysiology of hypertension in patients with CoA.[26] In other words, hypertension may be caused by a generalized vasculopathy from birth rather than by simple isolated aortic narrowing (**Figure 1**).

In a hypertensive rabbit model of CoA, alterations of smooth muscle cells were irreversible even after CoA correction, which may account for persistent morbidity observed in r-CoA patients.[27] Proliferation of undifferentiated smooth muscle cells into the subendothelial tissue was found to be the first cause of restenosis after CoA repair with balloon angioplasty.[28] Animal models of CoA have shown that left ventricular (LV) pressure overload related to the severity of aortic constriction and increased blood pressure (BP) leads to left ventricular hypertrophy (LVH), and LV dysfunction,[29] abnormalities also observed in humans. In the Dutch CONCOR (Congenital Corvitia) registry, which included 920 patients after r-CoA, there remained several commonly associated congenital defects: bicuspid aortic valve (56%), patent ductus arteriosus (15%), ventricular septal defect (23%) and atrial septal defect (6%), and patent foramen ovale (2%).[30]

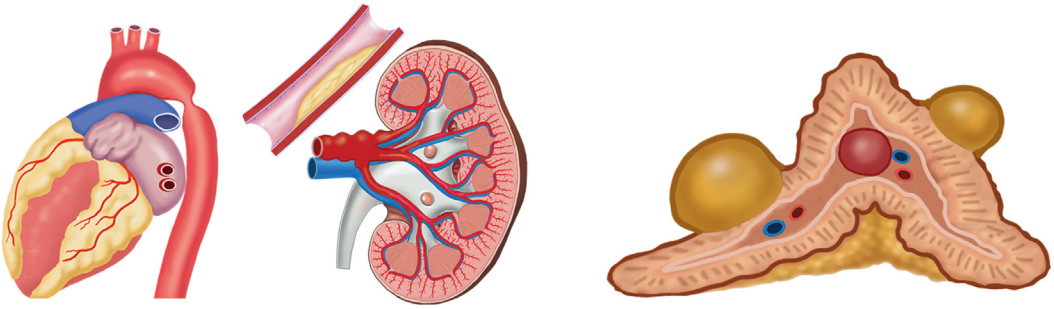
IMAGING STUDIES. The cardiac long-term imaging findings in adults with CoA may reveal adverse concentric cardiac remodeling and hypertrophy, diastolic dysfunction, left atrial dilation, and—in more advanced stages—systolic LV dysfunction.[17-20] In young patients with hypertension, especially in the presence of a bicuspid aortic valve, active search of CoA with an echocardiographic suprasternal view should be performed.

In r-CoA patients, the long-term local vascular complications include restenosis, aortic dilation, or aortic aneurysm. In a cardiac magnetic resonance (CMR) study that included 247 patients after r-CoA (mean age 33 years), Chen et al[31] showed that restenosis was present in 31% of patients, aortic dilation or aneurysms in 13% and 9% of patients, and systemic hypertension in 69% of patients. In an older long-term follow-up study after r-CoA, ~40% of patients developed hypertension within 30 years after surgery and >46% had LVH.[6] Even after successful early repair of CoA, central aortic stiffness remained markedly increased and associated with increased left ventricular mass (LVM) in normotensive young subjects.[32] Adults with r-CoA and concomitant aortic stenosis, when compared with patients with a similar degree of aortic stenosis without CoA, have higher LV global pressure load and cardiac remodeling.[33] The most common aortic arch geometries are the gothic and crenel types. The gothic has a triangular shape where the distance between the ascending and descending aorta becomes too narrow and the height of the arch is not maintained. The crenel type is

ABBREVIATIONS AND ACRONYMS

BP = blood pressure
CKD = chronic kidney disease
CMR = cardiac magnetic resonance
CoA = coarctation of the aorta
CS = Cushing syndrome
CV = cardiovascular
FMD = fibromuscular dysplasia
GLS = global longitudinal strain
HF = heart failure
LV = left ventricular
LVEF = left ventricular ejection fraction
LVH = left ventricular hypertrophy
LVM = left ventricular mass
LVMI = left ventricular mass index
MACS = mild autonomous cortisol secretion
OSA = obstructive sleep apnea
r-CoA = repaired coarctation of the aorta
RAS = renal artery stenosis
TTS = takotsubo syndrome

CENTRAL ILLUSTRATION **Cardiac Phenotypes in Secondary Hypertension**



	Coartation of Aorta	Renovascular Hypertension	Primary Aldosteronism	Pheochromocytoma /Paraganglioma	Cushing Syndrome
	• Vasculopathy • Sympathetic activity	• Angiotensin II • Aldosterone • Sodium/volume retention	• Aldosterone • Sodium retention	• Catecholamines	• Cortisol
LVH	↑↑	↑ARAS ↔FMD	↑↑	↑	↑
Diastolic Function	↓	↓ARAS ↔FMD	↓↓	↔	↓
Systolic Function	↓(advanced)	-	↓↓ strain	↓↓ strain	↓
In CMR	LVH, aortic dilatation	-	LVH, fibrosis, edema	fibrosis, edema	↔ fibrosis
Cardiac Events	CAD, HF	ARAS: CAD, AHF FMD: SCAD	CAD, HF, AF	TTS, hypertrophic/dilated cardiomyopathy, arrhythmias, ACS, AHF	CAD

Januszewicz A, et al. J Am Coll Cardiol. 2022;80(15):1480–1497.

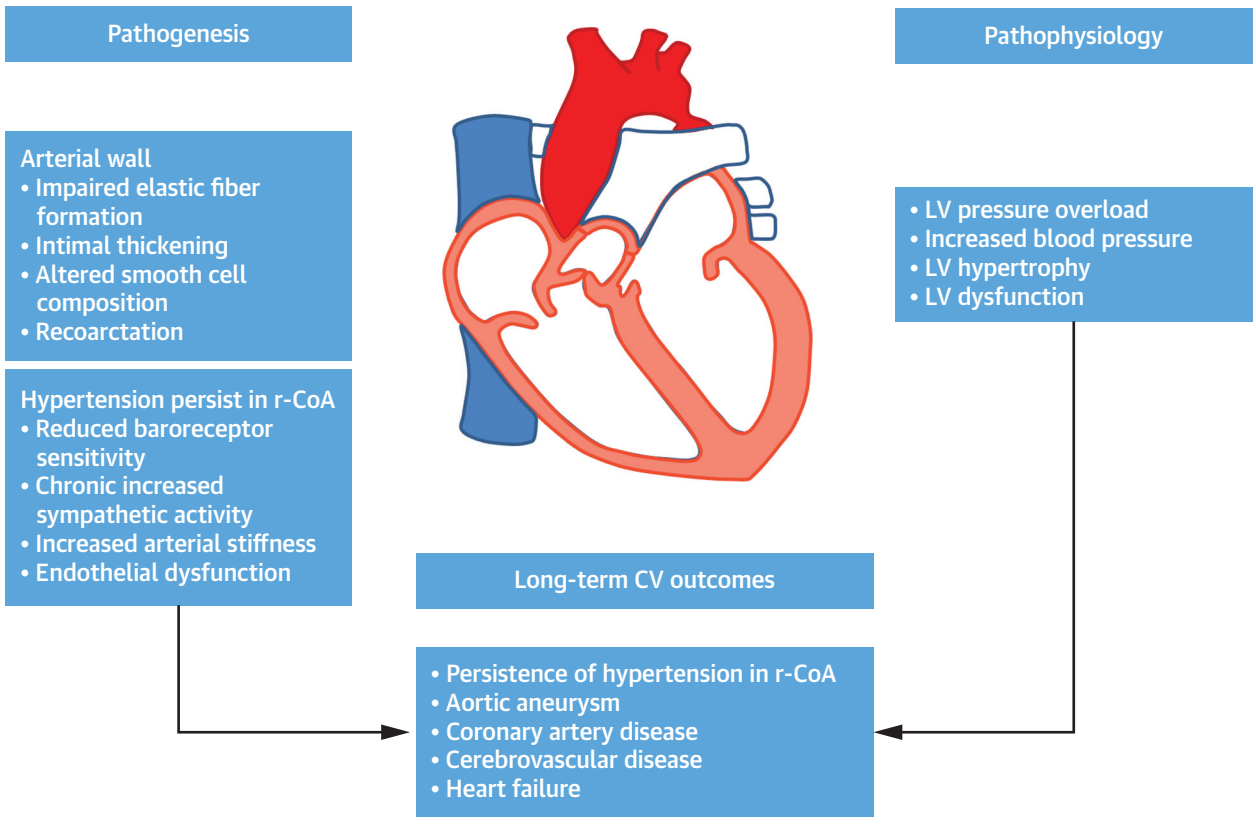
For any given blood pressure elevation, patients with secondary forms of hypertension such as primary aldosteronism (PA), renovascular hypertension, pheochromocytoma/paraganglioma (PPGL), Cushing syndrome (CS), and coarctation of the aorta (CoA) display a higher prevalence of structural and functional heart damage than patients with primary hypertension. Structural changes are not limited to an increase in left ventricular mass alone, but may include inflammation, fibrosis, and necrosis/apoptosis. Interestingly, these effects are largely independent of blood pressure (BP) levels and most likely represent the direct actions of biochemical substances excessively produced in each condition. ACS = acute coronary syndrome; AF = atrial fibrillation; AHF = acute heart failure; ARAS = atherosclerotic renal artery stenosis; CAD = coronary artery disease; CMR = cardiac magnetic resonance; FMD = fibromuscular dysplasia; HF = heart failure; LVH = left ventricular hypertrophy; SCAD = spontaneous coronary artery dissection; TTS = takotsubo syndrome.

characterized by a rectangular form where the distance between the ascending and descending aorta is not sufficiently reduced but the height is maintained.

In a CMR study of 105 patients (mean age 15 years) who underwent coarctation repair, the resting systolic BP and left ventricular mass index (LVMI) were significantly higher in those with a gothic shape compared with those with a crenel and normal shape.[34] Finally, in patients with r-CoA, residual aortic isthmus ratio was the strongest predictor of suboptimal reverse LV remodeling.[35]

CARDIOVASCULAR OUTCOMES. Although childhood survival of patients with r-CoA is now excellent, cardiovascular (CV) morbidity and mortality steeply increase in the fifth to sixth decades. Recoarctation, aneurysm formation, hypertension, and premature

FIGURE 1 **Impact of the Coarctation of Aorta on the CV System**



Long-term left ventricular (LV) pressure overload and remodeling as a consequence of persistent or de novo diagnosed hypertension as well as restenosis of aortic isthmus are common in adult patients with repaired coarctation of the aorta (r-CoA) and account for the increased cardiovascular (CV) morbidity and mortality. The cardiac long-term complications of the coarctation of aorta include concentric cardiac remodeling and hypertrophy, diastolic dysfunction, left atrial dilation, and—in more advanced stages—systolic LV dysfunction.

CV disease are mainly responsible for the adverse prognosis at later ages.[36] Even in the presence of a successful and early repair, no significant reduction in the prevalence of hypertension was found.[18] Indeed, hypertension is present in >50% of survivors of anatomically successful repair of CoA,[31] and has been shown to be an independent risk factor for suboptimal LVMI regression and CV events (arrhythmia, hospitalization for HF and death).[18] In the CONCOR registry, LVH was found in 27% of patients and was an independent risk factor for the occurrence of CV events.[30] In the same registry, after a mean follow-up of 9 years, 21% of patients experienced at least 1 CV event, mostly aortic complications and arrhythmia. Mortality in r-CoA patients was 3.3-fold higher than in the general population.[30] Early mortality has been attributed to complications of hypertension including aortic dissection and premature coronary artery disease.[6] Additionally, it has been shown that left atrial dysfunction and elevated pulmonary pressure are significant predictors of death in r-CoA.[37,38] In a long-term follow-up study, including 571 patients with r-CoA, survival analysis revealed that 30 years later only 72% of patients were alive.[39]

Taken together, the above-mentioned studies show that long-term LV pressure overload and remodeling as a consequence of persistent or de novo diagnosed hypertension, as well as restenosis of aortic isthmus, are common in adult patients with r-CoA and account for the increased CV morbidity and mortality.

RENOVASCULAR HYPERTENSION

Renovascular hypertension caused by renal artery stenosis (RAS) represents one of the most common forms of secondary hypertension, with a reported

prevalence of 2% to 5% of all hypertensive individuals.[40] The most common causes of RAS are atherosclerosis and fibromuscular dysplasia (FMD) and account for 90% and 10% of cases respectively.[41]

PATHOPHYSIOLOGY. RAS causes a reduction of blood flow and perfusion pressure to the affected nephrons; hypoperfusion of the juxtaglomerular apparatus will activate the release of renin, thereby increasing the production of angiotensin II and aldosterone. Apart from intrarenal changes, this compensatory hormonal increase to restore renal perfusion has systemic effects (increased sympathetic nerve activity, arterial remodeling and vasoconstriction, activation of inflammatory pathways, and sodium/water retention)[41-43]; all may adversely affect the myocardium. It was suggested that modest changes in renal arterial diameter have minimal hemodynamic effects, and activation of these systems occurs when significant translesional pressure gradients across the artery develop with luminal obstruction >70% to 80%.[41-43] However, ischemia of even a small number of nephrons can cause the full syndrome of renovascular hypertension, as supported by numerous cases of segmental RAS with excess unilateral renin release, striking hyperplasia of the juxtaglomerular apparatus, and reversal of hypertension by partial nephrectomy or use of angiotensin-converting enzyme inhibitors.[44] In unilateral RAS, the healthy kidney is expected to, at least partly, compensate for the adverse effects of renin-dependent hypertension through normal pressure-natriuresis. However, in bilateral RAS, this compensation cannot be achieved, precipitating sodium/volume retention and leading to a volume-dependent hypertension phenotype and higher risk of "flash" pulmonary edema, ie, Pickering syndrome.[40]

Several lines of evidence suggest that both angiotensin II and aldosterone excess play important roles in the pathogenesis of LV remodeling and LVH.[8] Studies in animal models of renovascular hypertension showed that RAS is associated with atheromatous plaque formation in the aorta and carotid arteries,[45] increased cardiac inflammation and cellular senescence following increased renal release of cytokines,[46] and increased macrophage influx.[47] Cardiac mitochondrial injury and impaired mitophagy, resulting in greater cardiac remodeling, fibrosis, and diastolic dysfunction,[48] have been also reported; all were partially reversed after renal revascularization.[49]

IMAGING STUDIES. LVH has not only been attributed to pressure overload, but also to direct humoral effects mediated by angiotensin II and aldosterone. In patients with renovascular hypertension, LVMI is significantly higher compared with patients with primary hypertension, even after adjustment for age, sex, BP, body mass index, and duration of hypertension.[50]

Several small studies reported a high prevalence of LVH in patients with RAS. A meta-analysis of 16 studies by Cuspidi et al[51] showed that patients with RAS (atherosclerotic RAS and FMD) had an increased likelihood of LVH and a significantly higher LVMI compared with primary hypertensive counterparts.

In patients with atherosclerotic renovascular chronic kidney disease (CKD), RAS is associated with higher morbidity and mortality rates than other causes of CKD. This may reflect differential myocardial changes.[42] Patients with CKD and atherosclerotic RAS are characterized by a significantly higher prevalence of LVH, increased LVMI, and decreased LV diastolic function compared with CKD patients without atherosclerotic RAS[52] even after matching for age, glomerular filtration rate, and 24-hour ambulatory BP levels. Compared with patients with unilateral RAS, patients with bilateral RAS had a significantly higher LVMI and LV end-diastolic diameter, greater LV wall motion asymmetry index, and a greater proportion of dysfunctional LV wall segments. Despite a similar prevalence of diastolic dysfunction, a significantly higher prevalence of symptomatic HF in bilateral compared with unilateral disease was observed.[52]

Compared with patients with primary hypertension, marked cardiac structural and functional (both systolic and diastolic) abnormalities were observed in patients with renovascular hypertension with and without significant renal dysfunction.[21] Normal LV geometry was observed in 40% of patients with primary hypertension, 13% of patients with renovascular hypertension with serum creatinine levels <2 mg/dL, and no patients with renovascular hypertension with serum creatinine levels >2 mg/dL. Concentric LV remodeling and LVH was seen in 40% of patients with primary hypertension and in 73% of patients with serum creatinine levels <2 mg/dL, whereas the 9 patients with serum creatinine levels >2 mg/dL had predominantly (67%) eccentric LVH. The latter is probably caused by more pronounced volume overload in patients with severe renal dysfunction, which is known to be associated with systolic dysfunction.[21]

In contrast to studies performed in atherosclerotic RAS, no differences in LV morphology and function between patients with renal FMD and carefully matched control subjects with primary hypertension were noted.[53] Notably, BP was well-controlled, and the majority of patients did not have significant RAS.

LVH appears to be highly prevalent in FMD patients that are considered for renal angioplasty.[53] Another echocardiographic study included 144 hypertensive patients with significant RAS (≥70% stenosis on angiography), among them 32 patients with FMD. The prevalence of LVH was high but did not differ between patients with atherosclerotic RAS and patients with FMD-associated RAS.[54]

CV OUTCOMES. A meta-analysis by Cuspidi et al,[55] including 726 patients enrolled in 13 studies, suggested that renal artery revascularization added to antihypertensive therapy has a beneficial effect on LV structure, as reflected by significant decrease in LVMI. Larger LVMI decreases were observed in patients with FMD-associated RAS.[55] This meta-analysis also suggested that renal artery revascularization decreased the likelihood of LVH by 40%. Finally, a meta-regression analysis showed that lower post-intervention systolic BP was associated with larger regression of LVH.

The overall prognosis of atherosclerotic RAS is unfavorable.[4,5] In an analysis of a 5% random sample of the U.S. Medicare population, CV and renal morbidity and mortality after incident atherosclerotic RAS diagnosis greatly exceeded that of the general population.[4] Concerning the effects of revascularization vs medical therapy in patients with atherosclerotic RAS, previous randomized trials suggested no benefit of renal artery stenting on BP, renal function, and survival.[56,57] However, these trials met severe criticism because of numerous limitations, such as non-standardized inclusion criteria, inclusion of patients with mild/asymptomatic RAS, mild hypertension or advanced chronic kidney disease, poor assessment of stenosis severity, enrollment delays, protocol revisions during the trial, high crossover rates, low event rates, and most importantly, exclusion of patients with clinical presentation highly suggestive of functional RAS.[41,58] To this end, observational evidence suggests that in patients presenting with flash pulmonary edema, refractory hypertension, or rapidly declining kidney function, revascularization compared with medical therapy is associated with major reductions in risk for death and CV events. A prospective, longitudinal observational study at a single center suggests that revascularization of atherosclerotic RAS in HF is associated with a substantial reduction in all-cause mortality and hospitalization.[59]

In conclusion, cardiac morphology and function—particularly diastolic function—are worse in patients with atherosclerotic RAS compared with patients with primary hypertension, even after adjustment for multiple covariates, including BP level, age, sex, and renal function. These studies underscore atherosclerotic RAS as a significant CV risk factor and support the concept that other factors than hemodynamic overload (ie, neurohumoral and growth factors) may aggravate the cardiac abnormalities. By contrast, FMD-associated RAS does not appear to be associated with cardiac damage beyond the effects of BP increase per se, but data are limited and heterogeneous.

Finally, although many patients with spontaneous coronary artery dissection harbor lesions of multifocal renal FMD, associated with hypertension or not, a small proportion of patients with renal FMD (<5%) may also develop spontaneous coronary artery dissection during follow-up.[60,61]

PRIMARY ALDOSTERONISM

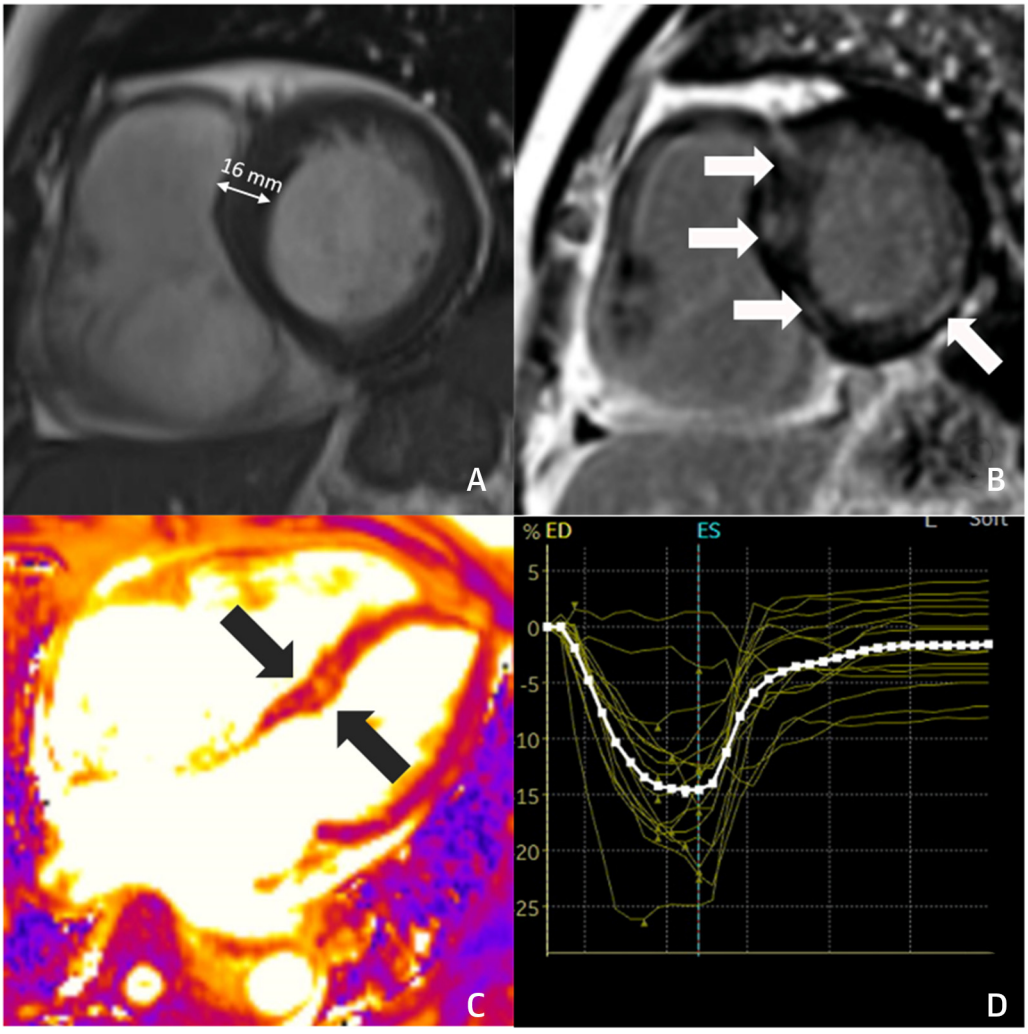
PATHOPHYSIOLOGY. The detrimental effects of aldosterone excess appear to occur independently of BP[62,63] and angiotensin II levels,[63,64] but are strictly dependent on the amount of concomitant sodium intake.[65] In the heart, the pathological cascade mediated by aldosterone excess is initiated by reactive oxygen species generation and vascular inflammation, followed by fibroblasts and myofibroblasts proliferation, collagen production, perivascular fibrosis, and finally, interstitial fibrosis.[7]

Experimental data document that aldosterone promotes inflammation by mechanisms stimulating reactive oxygen species generation. These include decreased expression of glucose-6-phosphate dehydrogenase at the vascular level,[66] stimulation of nicotinamide adenine dinucleotide phosphate oxidase expression,[67] and activity in macrophage[68] and heart muscle.[69] Mineralocorticoid receptor blockade has been shown to abrogate these effects. Interestingly, aldosterone-mediated oxidative activation of Ca2+/calmodulin-dependent protein kinase II promotes matrix metalloproteinase 9 expression in cardiomyocytes, which resulted in cardiac rupture in a murine model of myocardial infarction.[69]

In a setting of a high-salt diet, uninephrectomized rats treated with aldosterone displayed increased mRNA expression of several proinflammatory genes at the myocardial and aortic level.[67,70] In the heart, this resulted in coronary inflammatory lesions, characterized by medial fibrinoid necrosis and perivascular leukocyte infiltration at histopathological analysis. Eplerenone administration attenuated myocardial injury and blunted the aldosterone/salt effect on gene expression.[67,70]

The role of aldosterone in the induction of myocardial fibrosis is characterized by an imbalance

FIGURE 2 Cardiac Imaging in Primary Aldosteronism



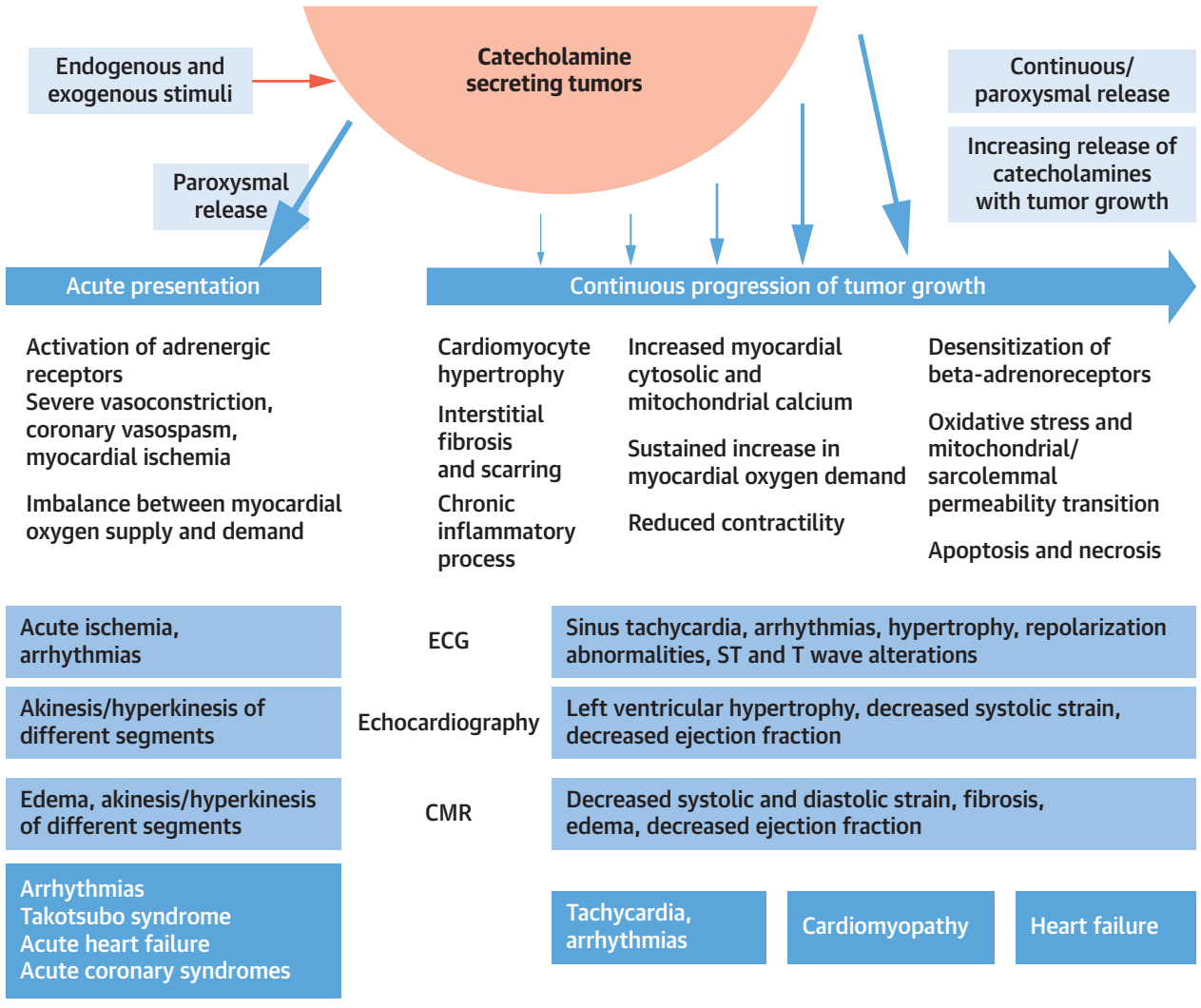
A 58-year-old patient with primary aldosteronism (right adrenal adenoma, right-side lateralization on adrenal vein sampling). The short-axis cardiac magnetic resonance image demonstrates moderate left ventricular hypertrophy (16 mm in the interventricular septum) **(A)**. Late gadolinium enhancement demonstrates fibrosis in the interventricular septum and inferolateral wall **(arrows) (B)**. T_2 mapping. The 4-chamber view demonstrates myocardial edema in the interventricular septum **(arrows) (C)**. Speckle tracking echocardiography images show decreased systolic function (longitudinal strain −15%) **(D)**.

between collagen deposition and degradation by matrix metalloproteinases, whereas spironolactone has been shown to exert a protective role.[65,71] Aldosterone elicits profibrotic effects,[7] as well as indirect reparative responses to inflammation and cell death.[72] Additionally, aldosterone can directly stimulate hypertrophy in neonatal rat ventricular myocytes[73] and promote myocyte apoptosis.[74]

Besides its negative impact on myocardial structure and function, aldosterone induces electrophysiological rearrangement of cardiomyocytes[75] and conduction disturbances despite normal atrial pressure,[76] thus favoring the development and perpetuation of cardiac arrhythmias, including atrial fibrillation.

IMAGING STUDIES. Long-term excessive aldosterone exposure in patients with primary aldosteronism (PA) (also known as Conn's syndrome) results in an increased prevalence of cardiac organ damage, which is at least partly independent of BP elevation.[77] Echocardiographic LVH is one of the most prevalent hypertension-mediated causes of organ damage[16] and is a predictor of mortality in both patients with

FIGURE 3 Effects of Catecholamines on the Heart in Pheochromocytoma/Paraganglioma Patients



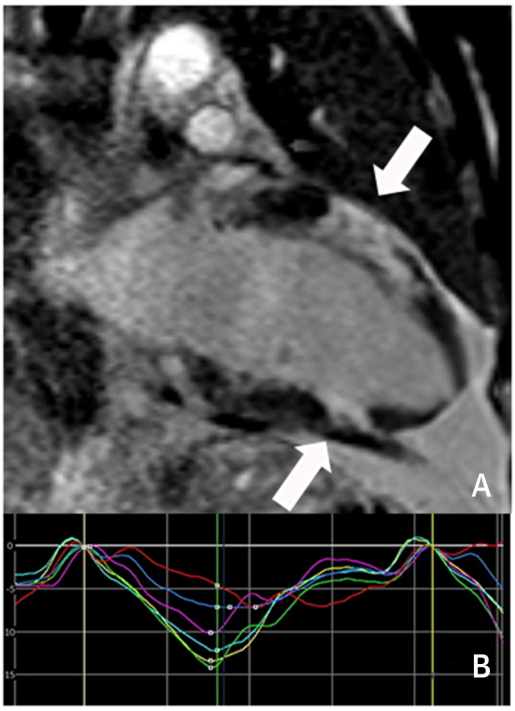
Pheochromocytomas and paragangliomas may have severe and even fatal cardiac consequences. Acute and chronic adverse effects of catecholamines on cardiac structure and function were proposed. Various acute and chronic pathophysiological mechanisms translate into diverse cardiac presentations. In addition, individual patients may be characterized by the presence of coexisting different cardiac alterations. CMR = cardiac magnetic resonance; ECG = electrocardiography.

hypertension and the general population.[78] Several studies have demonstrated that patients affected by PA have higher[79,80] and inappropriate[81] LV mass, together with increased relative wall thickness[82] compared with patients with primary hypertension (**Figure 2**). Echocardiographic evaluation following specific treatment of PA showed reduction of LVM.[79,83]

Aldosterone-mediated cardiac damage is not limited to LVH, but also includes impaired diastolic function and subclinical systolic dysfunction as evaluated by tissue Doppler imaging and speckle-tracking echocardiography[84] (**Figure 2**). Patients affected by PA display a significantly lower magnitude of global longitudinal strain (GLS),[85] longitudinal and circumferential layer-specific strains,[86] and left atrial strain,[87] reflective of subclinical myocardial dysfunction, compared with patients with primary hypertension. In a recent study, renin-independent aldosterone production was associated with alterations of cardiac structure and diastolic function.[88]

Nonischemic fibrosis, assessed with the presence of late gadolinium enhancement on CMR, was nearly 5 times more frequent in PA patients compared with control subjects[89]; this finding was confirmed by

FIGURE 4 Cardiac Imaging in Pheochromocytoma/Paraganglioma



A 34-year-old patient with pheochromocytoma (8 × 6 × 6-cm tumor of right adrenal gland, increased secretion of both metanephrine 3,651 ng/dL [URL 88 ng/dL]) and normetanephrine 2,215 ng/dL [URL 114 ng/dL]). Cardiac magnetic resonance, 2-chamber view. Late gadolinium enhancement demonstrating fibrosis in the anterior and inferior wall **(arrows) (A).** Speckle tracking echocardiography images show decreased systolic function (longitudinal strain) **(B).**

others.[90] Using T_1 mapping, a validated CMR technique,[91] extracellular mass (which correlates with interstitial fibrosis in myocardial biopsies) was shown to be higher in patients with PA compared with patients with secondary hyperaldosteronism, patients with primary hypertension, and healthy individuals, irrespective of BP. Myocardial sodium accumulation in PA patients was found to be increased compared with normotensive control subjects.[92] Additionally, both T_1 and T_2 mapping suggested an increased myocardial water content consistent with the presence of edema in the myocardial wall (**Figure 2**).[93]

CV OUTCOMES. Several studies[94,95] and a large meta-analysis including nearly 4,000 patients showed that patients with PA are exposed to an increased risk of cardiovascular and cerebrovascular events (stroke, coronary artery disease, HF, and atrial fibrillation) compared with patients affected by primary hypertension,[3] resulting in an increased CV mortality.

Unilateral adrenalectomy and life-long medical treatment with a mineralocorticoid receptor antagonist are the therapies of choice for unilateral and bilateral PA, respectively.[96] Whether medical and surgical treatments are equally effective in reducing CV risk in patients affected by PA has been extensively evaluated.[95] A large longitudinal study showed that mortality was 1.3-fold higher and the incidence of CV events (myocardial infarction or coronary revascularization, hospitalization for HF, or stroke) was nearly 2-fold higher in medically treated patients with PA than in patients with primary hypertension and comparable risk profile.[97] However, the risk excess was limited to those patients with persistently suppressed plasma renin activity on mineralocorticoid receptor antagonists, whereas in patients with unsuppressed plasma renin activity, the risk did not differ between those with PA and those with primary hypertension.[97] Conversely, in patients who underwent unilateral adrenalectomy, the risk of CV events was lower than in patients with primary hypertension.[97] Medically treated patients with PA are exposed to an increased risk of incident atrial fibrillation compared with patients with primary hypertension,[98,99] but again only when plasma renin activity remained suppressed. In contrast, patients with unsuppressed plasma renin activity who underwent unilateral adrenalectomy or were treated with mineralocorticoid receptor antagonists did not display a significantly increased risk. These results highlight the importance of periodic evaluation of the renin angiotensin aldosterone axis to guide therapy with mineralocorticoid receptor antagonist and dose titration to adequately block the mineralocorticoid receptor activity in patients with PA.

PHEOCHROMOCYTOMA AND PARAGANGLIOMA

PATHOPHYSIOLOGY. There are several possible acute and chronic adverse effects of catecholamines on cardiac structure and function that may explain the distinct features of pheochromocytoma/paraganglioma (PPGL)-related cardiac alterations (**Figure 3**). Acute release of catecholamines by PPGL increases heart rate and myocardial contractility. Further effects include vasoconstriction, coronary vasospasm, and myocardial ischemia. Imbalance between myocardial oxygen supply and demand leads to myocardial stunning, damage, and necrosis.[9-13] Chronic effects of catecholamine overproduction include stimulation of cell growth and cardiomyocyte hypertrophy, induction of interstitial fibrosis, and

chronic inflammatory processes.[9-14] Catecholamines can also exert direct toxic effects on the myocardium through enhanced lipid mobility, calcium overload, free radical production, oxidative stress, or increased sarcolemmal permeability.[9-13,100]

In animal models, catecholamine excess induces myocardial dysfunction associated with cellular lipotoxicity and is associated with metabolic and electrophysiological stunning.[101] Furthermore, catecholamines promote cardiac myocyte apoptosis through stimulation of beta1-adrenoreceptor.[102]

IMAGING STUDIES. Experimental findings suggest that catecholamines play a role in LVH through stimulation of protein synthesis.[9] In a total of 21 echocardiographic studies in patients with PPGLs, the frequency of LVH in PPGL has ranged from 19% to 75%.[14,103-113] In only 4 studies, patients with PPGL were compared with BP-matched control subjects, based on ambulatory BP measurements.[103-106] In the 2 largest studies, patients with PPGLs were characterized by higher LVMI than control subjects[105,106]; in 2 smaller studies, no differences in LVMI were found.[103,104] At 1 to 5 years after curative surgery, 4 of 6 prospective studies showed significant decreases in LVMI and 1 in the posterior wall thickness.[105-108] These data support a causal, BP-independent relationship between catecholamine overproduction and LVH.

In most studies, the only parameter used to evaluate systolic LV function in patients with PPGL has been left ventricular ejection fraction (LVEF). Three studies reported an increase of LVEF after surgery.[14,109,110] Only 4 studies evaluated GLS in patients with PPGL.[105-107,111-113] In 3 studies, all with well-matched control groups based on ambulatory BP monitoring, patients with PPGLs were characterized by decreased GLS at baseline compared with control subjects, followed by improvement in GLS on post-surgical follow-up (**Figure 4**).[105-107] Of note, Dobrowolski et al[105] reported that at baseline, GLS was inversely related to plasma metanephrine concentrations independently of age and LVH. This suggests that catecholamine excess may cause myocardial fibrosis, resulting in systolic dysfunction independently of LVH.[105]

Impaired baseline values in several parameters of diastolic function (eg, E/A ratio, e' velocity, and E/e' ratio) and improvements after curative resection of PPGLs have been observed in some but not in all studies.[105-107,109,113] In a meta-analysis of echocardiographic studies in secondary hypertension by Tadic et al,[111] LV diastolic function appeared to not be impaired in patients with PPGLs.

So far, only 2 studies in patients with PPGLs evaluated cardiac alterations by means of CMR. Ferreira et al[14] showed that 29 patients with newly diagnosed PPGL were characterized by impaired LVEF, impaired peak systolic circumferential strain and diastolic strain rate, and higher focal fibrosis compared with healthy and hypertensive control subjects. Postoperatively, impaired LVEF had normalized and LVMI had decreased, whereas impairments in systolic and diastolic strain persisted.[14] Higuchi et al[114] showed in a retrospective study that there was no difference in LVMI and global systolic and diastolic strain between 16 patients with PPGL and hypertensive control subjects. Of note, the authors found higher basal, but not apical, circumferential strain in patients with PPGLs.[114]

In rare instances, high levels of catecholamines released from tumors may cause myocarditis as indicated by endomyocardial biopsies or at autopsy.[9-12,115] Although often undiagnosed and self-limited, such episodes of myocarditis may sometimes be fulminant and lead to severe HF, or even persist as subtle chronic myocarditis.[116] Two recent studies have utilized CMR to document the presence of myocardial fibrosis and edema related to PPGL.[14,114] In the study by Ferreira et al,[14] patients with PPGL compared with hypertensive control subjects presented more frequently with focal fibrosis (59% vs 14%) (**Figure 4**) and high T_1 mapping values suggestive of myocardial edema (22% vs 2%). In the same study, myocardial T_1 abnormalities persisted in PPGL patients after surgery suggesting subtle (median 12% of LV) but long-lasting interstitial fibrosis.[14]

CARDIOMYOPATHY AND TAKOTSUBO SYNDROME. Beyond myocardial inflammation, a phenotype of hypertrophic or dilated cardiomyopathy has also been identified in patients with PPGL.[117] In a thorough literature review, Zhang et al[118] studied 163 patients with PPGLs and cardiomyopathy, including dilated cardiomyopathy (39%), typical takotsubo syndrome (TTS) (23%), inverted TTS (18%), hypertrophic cardiomyopathy (6%), myocarditis (5%), and unspecified cardiomyopathy (9%). Although surgical treatment was associated with increase in the LVEF in 96% of cases, lack of surgery (18 patients) was associated with adverse events (44%), cardiac transplantation (2 cases), and death (33%).[118]

Although PPGL was previously excluded as a specific cause of TTS, a better understanding of the acute effects of the catecholamine storm unleashed by the PPGL and the high rates of TTS observed in these patients have more recently reinstated PPGL as a

significant physical trigger of TTS.[119-121] It has been postulated that in the acute phase of TTS, catecholamines induce direct myocardial injury and/or coronary microvascular vasoconstriction together with an increased cardiac workload. These may contribute to an acute "supply-demand mismatch" followed by postischemic stunning.[122-124] Critical analysis of cardiac imaging of some PPGL cases with initial diagnosis of myocarditis revealed subsequently features of TTS.[115]

Rates were higher in PPGL-related TTS complications compared with TTS not related to PPGL, including cardiogenic shock (34.2% vs 4.2%; $P < 0.01$) and HF (46.7% vs 17.7%; $P < 0.01$). Antecedent stressors are less common in PPGL-related TTS.[123] Of interest, basal forms of TTS (also called inverted TTS), where only basal segments are involved, are rare overall but appear to be commonly reported in patients with PPGL-induced TTS.[120] However, it has been suggested that there is no one distinctive ventricular dysfunction pattern in PPGL-induced TTS. This is supported by a recent review, which showed the following frequencies of localization patterns in PPGL-induced TTS: apical (ballooning) 44%, midventricular 6%, basal (inverted) 26%, global 21%, and focal 1%.[125] The authors also showed that PPGL-induced TTS, compared with TTS of all types (cohort of 1,750 patients), is characterized by extensive LV dysfunction (ejection fraction 26% vs 41%) and high complication rates (in-hospital complications 72% vs 22%; cardiogenic shock 40% vs 10%). However, no differences in death rates were found (3.7% vs 4.1%).[125]

Cardiac metabolic, morphological, and functional abnormalities in TTS not associated with PPGL might be persistent. In the area of edema, fibrosis develops and increased T_1 mapping values suggest persistent alterations.[126] As described in the previous text, a similar pattern of subtle focal and diffuse myocardial fibrosis and inflammation has been shown in patients with PPGLs after surgery, in the absence of TTS.[14] This might suggest that acute catecholaminergic storms in TTS and longstanding catecholamine secretion by PPGL may lead to similar myocardial alterations.[126]

CV OUTCOMES. It is estimated that arrhythmias are found in up to 20% of patients with PPGL. Sinus tachycardia is the most common finding, followed by atrial fibrillation/flutter, bradyarrhythmia, and ventricular tachycardia.[11,127] ECG findings in patients with PPGLs include generalized low voltage, ventricular repolarization abnormalities (prolonged QT), ST-segment alterations, abnormal T waves, ventricular tachycardia, and supraventricular and ventricular arrhythmias.[12,115] The pathophysiology and management of PPGL-related arrhythmias has been recently extensively reviewed by Nazari et al.[11]

Available data indicate a relatively a high incidence (19%) of CV complications in a large group of 145 patients with pheochromocytoma.[127] In another retrospective analysis of 189 consecutive patients with PPGLs, acute cardiac complications were diagnosed in 7.4% of patients, the most common being TTS.[2] However, there are no sound data that compare this prevalence with a matched population of patients with primary hypertension. A study from the Netherlands showed that CV mortality does not reduce life expectancy following surgical resection of apparently benign PPGL as compared to the general population.[128] Another review of case reports showed that after tumor resection, complete recovery of LV function is observed in 97.7% of patients with PPGL-related TTS and in 73.3% cases of other PPGL-related cardiomyopathies.[129] Given the beneficial effect of causal treatment, it seems reasonable that, in a patient with an unexplained acute or chronic heart failure or other cardiac disease, including but not limited to myocarditis, TTS, and cardiomyopathy, screening for PPGL should be performed.

CUSHING SYNDROME

PATHOPHYSIOLOGY. Cushing syndrome (CS) is associated with a plethora of metabolic and CV comorbidities, which in synergy cause increased CV morbidity and mortality.[1] Excessive glucocorticoids induce hyperglycemia, insulin resistance, and diabetes mellitus (35%-50% of patients), complex dyslipidemia (40%-70%), hypertension (80%-85%), a hypercoagulable state, visceral obesity, and low-grade inflammation.

Mild autonomous cortisol secretion (MACS), characterized by biochemical evidence of increased cortisol secretion in the absence of overt clinical features of CS,[130] is found in around 30% of patients with adrenal tumors.[131] In a recent European multicentric study of 1,305 patients with benign adrenal tumors, 35% had possible MACS and 11% had definitive MACS.[132] The prevalence and severity of hypertension were higher in MACS than in nonfunctional tumors (adjusted prevalence ratios for hypertension 1.15, for use of ≥3 antihypertensive drugs 1.31), similar to overt CS. Patients with MACS have increased risk of CV events and higher mortality than those with nonfunctional tumors.[133,134]

Hypercortisolism-induced hypertension is a multifactorial disease characterized by activation of

mineralocorticoid and glucocorticoid receptors, the renin-angiotensin system, the sympathetic nervous system, and an impaired balance between vasodilators and vasoconstrictors.[131] Because cardiac myocytes express both the mineralocorticoid receptor and the glucocorticoid receptor but lack 11ß-HSD2, supraphysiological cortisol concentrations will activate both cardiac receptors.[135]

IMAGING STUDIES. A wide array of abnormalities has been observed in patients with CS; these include subclinical or overt systolic and diastolic dysfunction, LV concentric remodeling and hypertrophy, and less frequently, dilated cardiomyopathy and HF.[136-138] An echocardiographic study of 42 patients with CS documented greater prevalence of LVH with concentric remodeling and lower midwall fractional shortening.[136] Similar findings were observed with CMR, and in 18 patients with CS, a lower biventricular systolic function and greater LV wall thickness was observed compared with age-, sex-, and body-matched control subjects.[139] In another CMR study of 38 ACTH-dependent CS patients, those with active disease had higher BP levels and LV mass, greater LV mass to end-diastolic volume ratio (an equivalent of relative wall thickness), but similar LVEF to control subjects.[140] Speckle tracking echocardiography may identify even mild subclinical changes in longitudinal strain among patients with CS and well-controlled BP.[141]

Conceivably, the observed cardiac remodeling is at least partially independent of BP elevations and caused by the direct effect of cortisol on the myocardium, and the term of CS cardiomyopathy has been used.[142] There appears to be no strong connection between LVH and BP.[143] Indeed, hypercortisolism-associated cardiomyopathy with typical structural changes was also observed in CS without hypertension.[138] LVH seems to be predominantly dependent on the duration of the hypercortisolism, rather than on cortisol excess.[136] The direct effects of prolonged hypercortisolism on the myocardium are, however, poorly understood.[144] Myocardial biopsies from patients with Cushing's syndrome indicate myocardial hypertrophy, fibrosis, and myofibrillolysis,[117] and increased expression of atrogen-1, a marker for muscle atrophy.[142]

By utilizing integrated backscatter, an echocardiographic study identified increased fibrosis in patients with active untreated CS compared with hypertensive patients and control subjects.[15] Fibrosis also correlated with GLS and the E/E' ratio. In contrast, in a CMR study, there was no late gadolinium enhancement noted in this patient cohort.[139]

Treatment of hypercortisolism was accompanied by a 15% reduction of LVM and similar increase in LVEF in young patients with CS, as assessed by CMR.[139] In an echocardiographic study of 71 patients with CS, two-thirds presented with concentric remodeling or hypertrophy; a subset of 22 patients were also evaluated after remission, and all cardiac mass parameters were improved but normalized in about only one-fourth of participants.[138] Although the observed improvements may be unrelated to BP changes,[137,139] a persistence of the cardiac dysfunction despite successful treatment is likely.[145] Still, improvements in systolic LV shortening parameters assessed with strain imaging have also been observed following normalization of corticosteroid excess.[137]

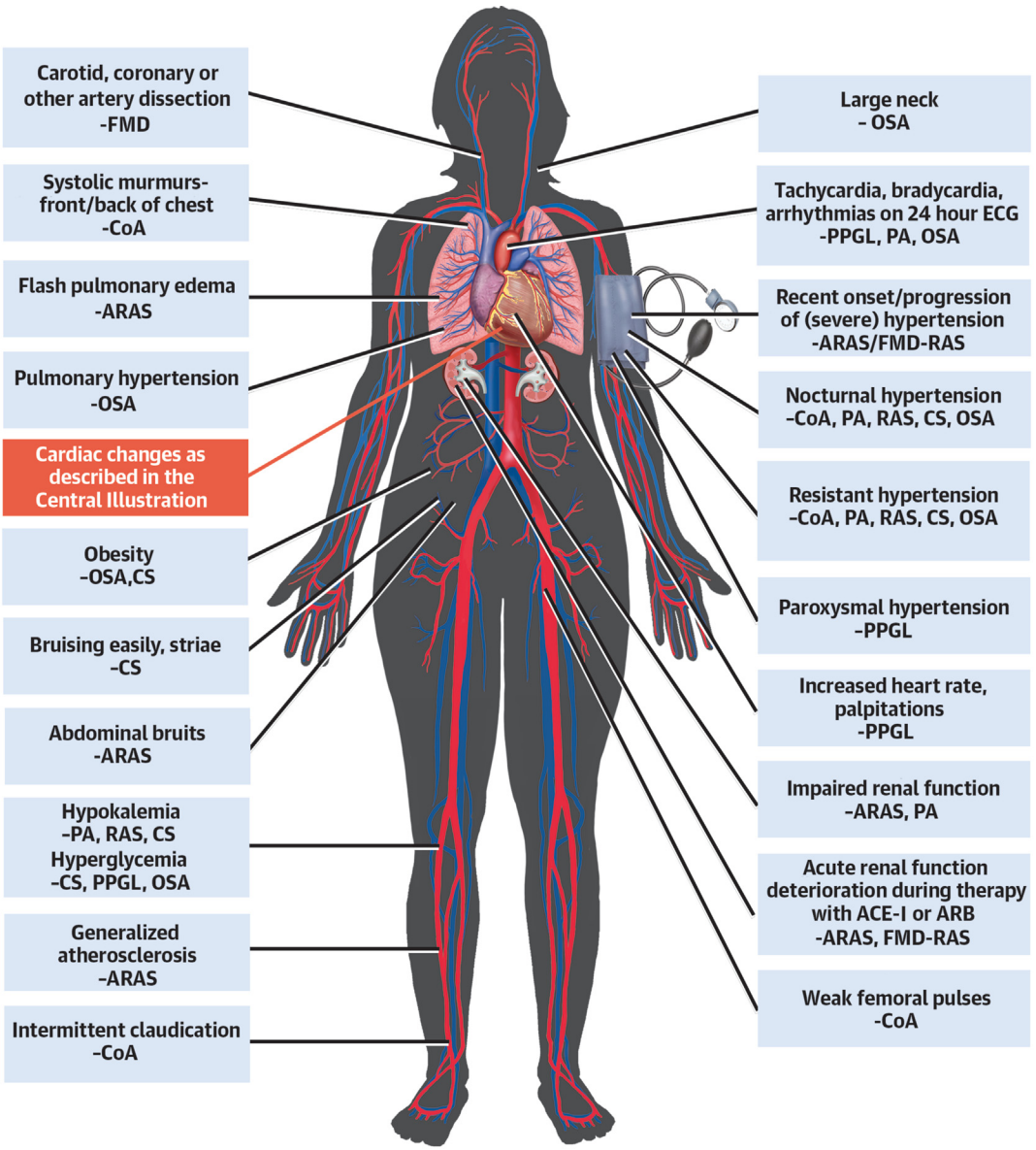
CV OUTCOMES. In CS, the risk for venous thromboembolism is significantly increased, especially during the 3 years preceding the diagnosis until one year following surgical remission.[1] Incidence rates amount to 9%,[146] corresponding to an OR of 18.[147] In the Danish National Registry, patients with active CS had a 7-fold increased risk of venous thromboembolism, a 6-fold increased risk of HF, and a 4.5-fold higher risk of stroke, compared with the control population in the 3 years preceding the diagnosis.[148] The OR for myocardial infarction was 2.1 and increased further to 3.5 and 2.8 up to 1 year, and >1 up to 30 years after diagnosis. Comparable data were reported by a Swedish nationwide study of 502 patients with CS and a median follow-up of 13 years. The standard incidence rates for myocardial infarction were 4.4 and 13.8 for deep vein thrombosis during the 3-year period before diagnosis.[149] Another acute complication of CS is hypertensive crisis, which will require hospital admission in 9% of patients with CS.[150]

Patients with CS have a >2-fold increased mortality compared with the general population.[151-153] The highest mortality rate (up to 7-fold) is observed in those patients who are not in remission following treatment. For patients in remission, mortality rates are lower but still increased during long-term follow-up (2-fold).[151,153] Hypertension and diabetes mellitus have been found in some but not all studies to be independent factors associated with increased mortality.[154] All-cause mortality is mainly related to CV disease: in a Swedish study, 63 of 133 deaths were related to CV diseases, including 32 deaths from ischemic heart disease and 9 from ischemic stroke.[153]

OTHER FORMS OF SECONDARY HYPERTENSION

Among other forms of secondary hypertension, data on cardiac complications have been collected mainly for acromegaly and obstructive sleep apnea (OSA).

FIGURE 5 Signs, Symptoms, and Screening of Secondary Hypertension



Screening of secondary forms of hypertension in patients at risk or with specific biochemical/clinical phenotypes of these conditions. Although in some cases the symptoms of secondary forms of hypertension may be mild, the coincidence of cardiac changes (Central Illustration) with the symptoms shown in the figure should make discerning clinicians suspect secondary forms of hypertension. ACE-I = angiotensin-converting enzyme inhibitor; AF = atrial fibrillation; ARB = angiotensin receptor blocker; ARAS = atherosclerotic renal artery stenosis; CAD = coronary artery disease; CoA = coarctation of the aorta; CMR = cardiac magnetic resonance; CS = Cushing syndrome; ECG = electrocardiography; FMD = fibromuscular dysplasia; OSA = obstructive sleep apnea; PA = primary aldosteronism; PPGL = pheochromocytoma/paraganglioma; RAS = renal artery stenosis.

OBSTRUCTIVE SLEEP APNEA. Whether OSA should be classified as a secondary form of hypertension is controversial. Unlike the "classic" forms, no single pathogenetic factor responsible for the development of hypertension and cardiac complications can be identified. On the contrary, many factors and comorbid conditions are responsible for the development of cardiac complications in patients with OSA, among which the most important are obesity, PA, hypoxia-induced catecholamine excess, activation of the renin-angiotensin system, concomitant cortisol excess, and primary hypertension.[155,156]

OSA is an independent factor associated with LVH both in patients without hypertension and in patients with resistant hypertension, obesity, as well as in the general population.[157,158] A continuous relationship between the probability of developing LVH and OSA severity has also been shown.[157] Some studies also suggest that OSA is related to left atrial enlargement, but the results of studies are equivocal.[156] Of interest, in a large meta-analysis, it has been proven that patients with OSA are characterized by right ventricular dilation, increased wall thickening, and altered right ventricular function.[159] Data on the effect of OSA on diastolic function are conflicting. However, it should be considered that OSA often coexists with obesity, metabolic abnormalities, and resistant hypertension, which are also strong factors in the development of diastolic dysfunction.[160,161] Most of the investigations performed so far have shown also that OSA is related to the decrease in GLS.[155,162] It should be noted that studies showed favorable effect on cardiac structure and function of continuous positive airway pressure and weight reduction in patients with OSA.[155]

ACROMEGALY. Acromegaly is a rare condition mainly caused by a growth hormone secreting pituitary adenoma that occurs in approximately 9 individuals per 100,000 inhabitants.[163] Chronic exposure to high levels of growth hormone promotes adverse somatic and metabolic effects through the action of its mediator, insulin-like growth factor I. Cardiac involvement is frequent in patients affected by acromegaly and comprises a series of pathological alterations known as "acromegalic cardiomyopathy," which can occur even in the absence of hypertension and other classical CV risk factors.[164] Biventricular concentric hypertrophy with increased contractility is an early feature of acromegalic cardiomyopathy,[165] followed by hypertrophy progression, fibrosis, and consequent diastolic dysfunction. In patients with long-lasting disease, severe systolic and diastolic dysfunction develop, and the patients experience symptoms of heart failure.[164] An increased prevalence of valvular heart disease[166] and arrhythmias[167] has also been reported.

CONCLUSIONS

Despite some heterogeneity in patient characteristics and between studies, for any given BP elevation, patients with secondary forms of hypertension such as PA, renovascular hypertension, PPGL, CS, and CoA display a higher prevalence of structural and functional heart damage than patients with primary hypertension. Structural changes are not limited to an increase in LVM alone but may include inflammation, fibrosis, and necrosis/apoptosis. Interestingly, these effects are largely independent of BP levels and most likely represent the direct actions of biochemical substances excessively produced in each condition (**Central Illustration**). Therefore, clinicians should screen and confirm diagnosis of these secondary forms of hypertension in patients at risk or with specific biochemical/clinical phenotypes of these conditions (**Figure 5**). In this way, the early signs of heart damage can be carefully recognized and monitored, thereby facilitating management and treatment of affected patients.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

Drs Januszewicz, Dobrowolski, Śpiewak, and Prejbisz are supported by the National Science Centre, Poland, grant number: 2019/35/B/NZ5/03424. Dr Reincke is supported by grants from the Else Kröner-Fresenius Stiftung (2012_A103 and 2015_A228) and by the Deutsche Forschungsgemeinschaft (German Research Foundation, Projektnummer: 314061271-TRR 205 and Projektnummer 440885333). All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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KEY WORDS cardiac damage, cardiac events, imaging, secondary hypertension