Hypertension Phenotypes in Relation to Coronary Angiography and Intervention Outcomes

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Abstract:
Coronary artery disease is a major cause of death and disability in developed countries. Detection the predictors of CAD severity and PCI outcomes are important to improve health and longevity. Blood pressure (BP) changes were investigated and were found to be correlated with the major adverse outcome post PCI. BP phenotype recognitionز is simple and can be easily done. So using it for PCI outcome prediction is crucial and promising**.**

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Introduction

Coronary artery disease (CAD) is one of the most common cardiovascular diseases, characterized by high morbidity, disability, and death, (Hozumi & Yoshikawa, 2022)

Hypertension is not only a major risk factor for stroke and heart failure (HF), but more importantly for CAD because it can promote coronary atherosclerosis and lead to coronary lumen stenosis [2]. Furthermore, HTN and CAD often coexist, due to shared risk factors and pathophysiological mechanisms, as well as complex interactions. The patients with comorbid CAD and HTN have worse outcomes and prognosis than those with single disease [3].

In a population of men of Japanese ancestry, hypertension had a similar effect on both early and delayed CAD. In a selective population of Canadian patients, the relative risk of high blood pressure for CAD, declined with advancing age [3].

Prevalence of patients with comorbid CAD and HTN

Despite increasingly emerging studies in the field, the prevalence of patients with comorbid CAD and HTN in the entire population still remains unclear. The age-adjusted prevalence of patients with comorbid CAD and HTN increased from 4.22% in the 1999–2000 to 5.40% in the 2017–2018 [4].

Prognosis

Lubsen *et al*. explored the 6-year cardiovascular death rate in stable CAD patients with HTN and found that it was 1.68-fold higher than that with normotensive [5]. Granger *et al*. revealed that the in-hospital mortality rate of acute coronary syndrome (ACS) patients with HTN was significantly higher than that without HTN [6].

Previous studies showed that 50–60% CAD patients had comorbid HTN, and 13% HTN patients had comorbid CAD, implying a high prevalence of comorbid CAD and HTN in the general population [7]. The high prevalence and worse outcomes of comorbid CAD and HTN could cause a tremendous threat and burden to public health and should be paid more attention by patients, physicians and healthcare provider [8].

To optimize the antihypertensive treatment plan of HTN combined with CAD, and reduce the occurrence and death of cardiovascular events, American Heart Association (AHA)/American College of Cardiology (ACC)/American Society of Hypertension (ASH) and Chinese Society of Cardiology (CSC) issued related scientific statements in succession [9].

Link between Hypertension and Coronary Heart Disease

The pathophysiological link between hypertension and CAD can be described under two major pathways as described below in Figure (1).

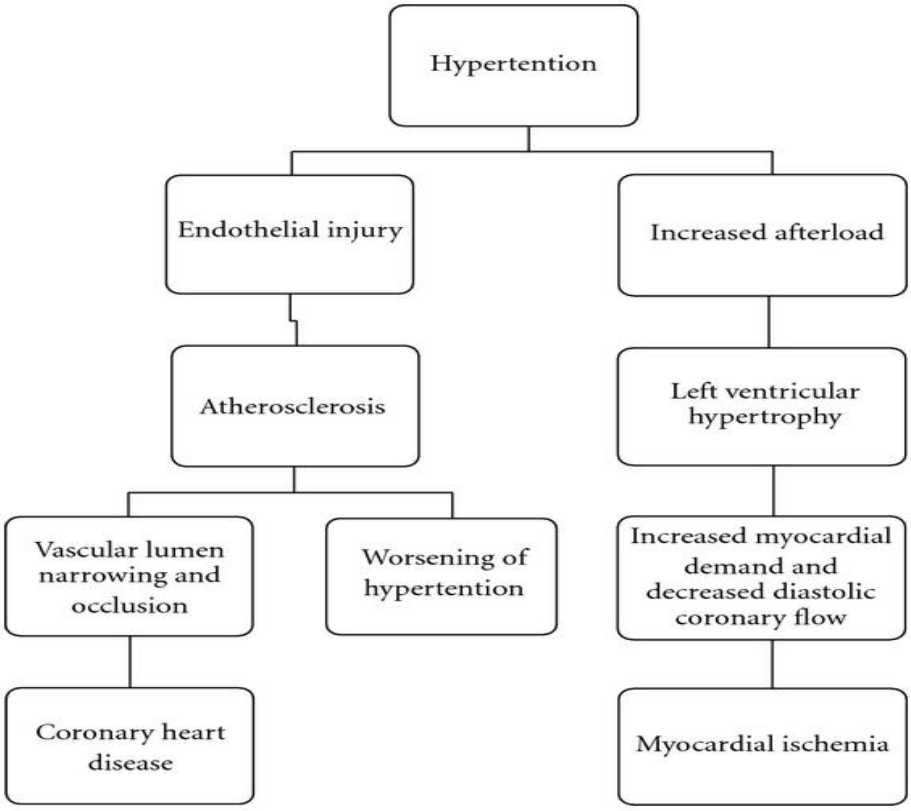

Figure 1: The pathophysiological link between hypertension and CHD [9].

Endothelial Dysfunction

Endothelial dysfunction, characterized by an unfavorable balance between vasodilators, for example, nitric oxide and prostaglandin E_1, and vasoconstrictors, for example, endothelin and angiotensin II, is an important contributor to BP elevation in people with vascular disease. The injured endothelium loses its vasodilator capacity and contributes to thrombosis and vascular occlusion. Release of chemotactic cytokines and adhesion molecules at the luminal surface of the injured endothelium promotes adhesion of circulating mononuclear leukocytes to the vessel wall. This low-grade, self-perpetuating vascular inflammation underlies the atherosclerotic process. Inflammatory mediators activate medial smooth muscle cells, causing them to proliferate and migrate into the sub-intimal space [10].

Endothelial dysfunction and decreased nitric oxide availability related to mechanical and inflammatory injury of arteries are also associated with increased arterial stiffness and the development of isolated systolic hypertension. A decline in flow-mediated vasodilator capacity attributable to decreased endothelium-derived nitric oxide occurs in aging and subclinical vascular disease. Impaired endothelium-mediated vasodilation is responsible for the exaggerated exercise-induced increases in BP seen in these population groups [11].

Increased Afterload and Left Ventricular Hypertrophy

Hypertension by itself can cause myocardial ischemia in the absence of CHD. Increased afterload due to hypertension can result in significant left ventricular hypertrophy (LVH), which may impair ventricular relaxation and compromise coronary blood flow during diastole. Although genetic factors have been associated with LVH, chronic uncontrolled hypertension appears to be the major cause . Research has shown that LVH diminishes coronary flow reserve and independently predicts future CHD, HF, stroke, and sudden cardiac death [10].

Other Mechanisms of Hypertension and CAD

A variety of pathophysiological mechanisms contribute to the genesis of BP elevation and related target-organ damage, including CAD. These mechanisms include increased sympathetic nervous system and RAAS activity; deficiencies in the release or activity of vasodilators, for example, nitric oxide and prostacyclin, and changes in the natriuretic peptide concentration; increased expression of growth factors and inflammatory cytokines in the arterial tree; hemodynamic effects; and structural and functional abnormalities in conductance and resistance arteries [12].

Genetics

Genome-wide association studies have identified multiple genetic susceptibility variants, mostly single-nucleotide polymorphisms, for atherosclerotic disease. It has been suggested the polymorphisms of genes of the RAAS, particularly ACE, angiotensin II receptor type 1, and angiotensinogen, are implicated in the development of CAD and MI. The presence of hypertension further increases the risk of CAD and may explain why some individuals are more predisposed than others to developing coronary events. Some polymorphisms have also been implicated in the BP response to antihypertensive treatment. For example, genetic polymorphisms coding for the matrix metalloproteinases appear to modify CVD outcomes in hypertensive patients treated with chlorthalidone, amlodipine, or lisinopril [13].

Klotho, possibly an age-regulating protein, is located on human chromosome 13 (13q12), spanning about 50 kb in length and consisting of 5 exons and 4 introns [14]. Genetic studies have shown that Klotho is considered an important factor contributing to the lifespan and pathophysiology of hypertension and coronary artery disease (CAD) [15].

Physical Forces and Hemodynamics

Physical forces (pressure and flow) are the primary determinants of cardiac structure and function and influence coronary arterial remodeling and atherosclerosis. When SBP is elevated, both LV output impedance and intramyocardial wall tension increase, resulting in increased myocardial oxygen demand. The wide pulse pressure and systolic hypertension in older individuals are usually attributable to inappropriately high aortic impedance, which results from decreased aortic diameter or increased effective stiffness caused by aortic wall thickening and changes in wall composition. Aging is associated with thinning and fragmentation of vascular elastin and increased collagen deposition, a degenerative process that causes increased arterial

stiffness (reduction of elasticity) with an associated elevation in SBP and widening of the pulse pressure [15].

Increased arterial stiffness elevates SBP by increasing pulse-wave velocity and altering wave reflection from the periphery. With each ejection of blood from the LV, a pressure (pulse) wave is generated and travels from the heart to the periphery at a pulse-wave velocity that depends on the elastic properties of the conduit arteries. The pulse wave is reflected at any point of discontinuity in the arterial tree and returns to the aorta and LV. The elastic properties and length of the conduit arteries determine the timing of the wave reflection. In younger people, the pulse-wave velocity is sufficiently slow (≈5 m/s) that the reflected wave reaches the aortic valve after closure, leading to a higher DBP and enhancing coronary perfusion by providing a "boosting" effect. In older people, particularly those who are hypertensive, pulse-wave velocity is greatly increased (≈20 m/s) because of central arterial stiffening. Thus, the reflective wave reaches the aortic valve before closure, leading to the higher SBP, pulse pressure, and afterload and a lower DBP [16].

Oxidative Stress

Oxidative stress is a critical feature of both hypertension and atherogenesis. In vascular tissue, the principal effectors of oxidative injury are the NAD(P)H oxidases, which are activated by mechanical forces (eg, hypertension), hormones (particularly angiotensin II), oxidized cholesterol, and cytokines. Several NAD(P)H oxidase isoforms expressed in endothelial and vascular smooth muscle cells are upregulated in the setting of atherosclerosis and arterial injury. Angiotensin II receptor–dependent activation of NAD(P)H oxidase stimulates formation of oxidant superoxide anion (O_2^-), which reacts with nitric oxide to form the powerful oxidant peroxynitrite ($ONOO^-$). The resultant reduction in nitric oxide bioactivity contributes to the vasoconstrictor response to angiotensin II and elevates BP. Angiotensin II–induced activation of NAD(P)H oxidase also stimulates oxidation of low-density lipoprotein cholesterol and increases the expression of monocyte chemoattractant protein-1 and vascular cell adhesion molecule-1, thus linking activation of the RAAS to the atherosclerotic process [17].

Humoral and Metabolic Factors

Angiotensin II elevates BP and promotes target-organ damage, including atherosclerosis, by mechanisms that include direct effects on constriction and remodeling of resistance vessels, stimulation of aldosterone synthesis and release, enhancement of sympathetic outflow from the brain, and facilitation of catecholamine release from the adrenals and peripheral sympathetic nerve terminals. Aldosterone can mimic or potentiate the vasotoxic properties of angiotensin II and norepinephrine. Angiotensin II promotes cardiac and vascular smooth muscle cell hypertrophy directly via activation of the angiotensin II type 1 (AT1) receptor and indirectly by stimulating expression of a number of growth factors, cytokines, and adhesion molecules. AT1 receptor activation also contributes to endothelial damage and atherogenesis by inhibiting the mobilization of endothelial progenitor cells from the bone marrow, thus impairing endothelial regeneration and vascular repair processes [18].

ACE inhibitors and ARBs limit oxidative reactions in the vasculature by blocking the activation of NAD(P)H oxidase, supporting the concept that these RAAS blockers may have important vasoprotective effects beyond BP lowering. Furthermore, there is evidence of interaction between the RAAS and dyslipidemia: Hypercholesterolemia upregulates the RAAS, particularly vascular AT1 receptor density and functional responsiveness, and systemic angiotensin II peptide synthesis, whereas the RAAS stimulates the accumulation of low-density lipoprotein cholesterol in the arterial wall. These findings suggest that these antihypertensive drug classes may have clinically important vasoprotective effects beyond BP lowering. This hypothesis has yet to be supported by the results of randomized, controlled trials [19].

Recent evidence suggests that a second angiotensin II receptor subtype (AT2), which is not expressed in the normal vasculature but appears to be induced in the setting of vascular inflammation/hypertension/atherosclerosis, may oppose the vasoconstrictor, antinatriuretic, and proinflammatory effects of the AT1 receptor. Because of the apparent vasoprotective effects of AT2 receptor activation, AT2 receptor agonists have been considered for the treatment of hypertension, but there is no evidence that they are effective in treating hypertension in humans [20].

Hypertension and Stable Angina Management

Patients with hypertension and chronic stable angina pectoris should be treated with beta-blockers plus nitrates as antianginal drugs. In these patients, hypertension should be controlled with beta-blockers plus an ACE inhibitor or an ARB with the addition of a thiazide or thiazide-like diuretic if needed. If either angina pectoris or hypertension remains uncontrolled, a long-acting dihydropyridine calcium channel blocker (CCB) can be added to the therapeutic regimen. Nondihydropyridine CCBs, such as verapamil and diltiazem, cannot be used if LV systolic dysfunction is present. Combining a beta-blocker with either verapamil or diltiazem must be done with caution because of the increased risk for bradyarrhythmia and heart failure. Beta-blockers plus an ACE inhibitor or an ARB should be used initially in patients with hypertension and CAD who have chronic kidney disease. Patients with hypertension and vasospastic angina pectoris should be treated with nitrates plus CCBs [21].

Hypertension and Acute Coronary Syndrome Management

In patients with acute coronary syndrome (ACS), the initial treatment of hypertension should include a short-acting beta1 selective blocker without intrinsic sympathomimetic activity, such as metoprolol tartrate or bisoprolol. Treatment with beta-blockers should be given initially within 24 hours of experiencing the symptoms of ACS. In persons with severe hypertension or ongoing ischemia, intravenous esmolol may be considered. In hemodynamically unstable patients or in those with decompensated heart failure, treatment with beta-blockers should be delayed until the patient is stabilized [21].

In persons with ACS and hypertension, nitrates can be used to reduce BP, ongoing myocardial ischemia, or pulmonary congestion; however, nitrates should not be administered to patients with suspected right ventricular infarction or to those with hemodynamic instability. Intravenous or sublingual nitroglycerin is preferred initially [22].

Angiographic findings in HPN with CAD

Coronary artery disease (CAD) is relatively rare in subjects below 40 years of age, as it occurs in about 6–10% of them, but it has grave medical, social, psychological, and economic consequences in this age group. Sudden cardiac death, which is the most severe complication of CAD, occurs also in young subjects, and some authors believe it is one of the most common causes of mortality among young adults [23].

With rapid civilization changes and increasing prevalence of conventional risk factors for CAD, premature atherosclerosis is a growing problem, occurring in even younger age groups including those in the third and fourth decade of life. The PL-ACS registry data indicate that acute coronary syndromes (ACS) occur most commonly in patients in the sixth and seventh decade of life, with 1% of cases occurring in subjects below 40 years of age and 8.03% occurring in the age range of 40–49 years [24].

Although the aetiology of CAD in young subjects is related to coronary atherosclerosis in 80% of cases, a number of differences regarding both the risk factor profile and clinical and angiographic characteristics exist in comparison to older patients [25].

Coronary angiography (CAG) more often shows normal coronary arteries, prompting for a search for non-atherosclerotic aetiology such as coronary spasm, vasculitis, embolism, or hypercoagulability. In young and very young subjects, destructive lifestyle factors have also been highlighted, including exaggerated ambitions, competition, workaholism, poor diet, use of psychoactive substances including cocaine, marijuana, and anabolic steroids, and disregarding early disease symptoms [25]. In the recent years, we have been witnessing extremely rapid advances in modern invasive cardiology techniques, resulting in improved ACS treatment outcomes mostly in regard to in-hospital mortality. In contrast, views on long-term outcomes in this patient group vary. In general, few data on CAD in young adults are available in the literature, mostly from case reports and small series, often related to genetic aspects and familial occurrence of the disease [25].

Despite the increasing prevalence of hospitalizations for acute heart failure (HF), few data are currently available describing this clinical syndrome [26]. Acute exacerbation of HF is generally due to a critical increase in pulmonary capillary pressures irrespective of left ventricular (LV) ejection fraction. Although diastolic dysfunction appears to be the necessary condition for the occurrence of symptoms in HF without overt LV systolic dysfunction, underlying mechanisms that precipitate sizeable elevation in pulmonary capillary hydrostatic pressures are not completely understood in this setting [26].

Accordingly, the optimal management of acute diastolic HF remains widely based on an empirical approach, including cautious utilization of loop diuretics and nitrates, relief of precipitants, and determination of the underlying heart disease. Numerous studies have highlighted that coronary artery disease (CAD) is frequently associated with the occurrence of acute pulmonary edema [26].

Concurrent acute coronary syndrome is typically suggested by a history of myocardial infarction, angina, and significant ST shifts on the electrocardiogram at rest on admission. Conversely, the diagnosis generally turns toward other etiologic mechanisms, such as uncontrolled hypertension, when criteria for myocardial ischemia are lacking, although the prevalence of CAD has never been assessed in this setting. The aim of the present study was to investigate the prevalence of angiographic CAD in patients hospitalized for acute diastolic HF without clinical and electrocardiographic evidence of myocardial ischemia on admission [27].

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