Med Discoveries
An open access journal of science and medicine

Article Type: Review Article
Volume: 2, Issue 11
Received: Oct 19, 2023
Accepted: Nov 17, 2023
Published Online: Nov 24, 2023

Bradycardia Concomitant with Hypertension

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Introduction

Bradycardia is defined as a Heart Rate (HR) <60 beats per minute (bpm) in adults, except for well-trained athletes (studies often use a lower cut-off of 50 bpm) [1]. Multiple potential causes of bradycardia include atrioventricular block, conduction tissue disease, sick node disease, Adams-Stokes syndrome, athlete's bradycardia, sleep apnea, nocturnal bradycardia, and perioperative reflex bradycardia. Even disorders like anorexia nervosa, which result in hypometabolism, can lead to sinus bradycardia [2]. If other causes are excluded, ageing is regarded as a significant risk factor for sinus bradycardia [1,3].

Hypertension is defined by a systolic BP (SBP) of ≥140 mmHg, diastolic (DBP) of ≥90 mmHg, or self-reported usage of antihypertensive drugs [4]. Globally, 3,5 bilion adults have non-optimal SBP (>110-115 mmHg) and 874 milion adults are hypertensive [5].

Hypertension has several causes, including primary (essential) hypertension, hypertension in pregnancy, and secondary hypertension. Secondary hypertension is characterized by elevated blood pressure, with an identifiable specific cause. The potential causes vary widely, with the most prevalent being renal parenchymal disease, renovascular disease, and drug-induced hypertension [6].

The range of possible differential diagnoses narrows when accompanied by bradycardia. It is common for patients with increased intracranial pressure to exhibit Cushing's reflex. This reflex is characterized by episodes of hypertension, apnea, and tachycardia, which may then transition into bradycardia. Its function is protective and allows for the maintenance of adequate cerebral perfusion pressure, which is necessary for blood flow through the cerebrovascular network [7]. This pressure is determined by the difference between mean arterial pressure and intracranial pressure.

Increased intacranial pressure is the most typical presentation of a patient with bradycardia with hypertension. However, it is possible for other etiologies to cause hypertension with a clinical picture of bradycardia. These etiologies are common but rarely mentioned in scientific literature [1,3]. The elevated blood pressure is there an adaptation of the organism to the unfavorable changes in the circulation. Chronic bradycardia is necessary for elevated blood pressure to occur. In the case of a sudden fall of HR, i.e. an acute heart block, it may result in a cardiogenic shock leading to death before the adaptation mechanisms can restore the equilibrium [8]. Bradycardia and hypertension are frequently co-presented and successful treatment of low heart rate often results in a reduction of observed blood pressure.

The correlation between bradycardia and hypertension can be partly explained by several mechanisms.

Impaired cerebral blood flow

It is well established that increased sympathetic nerve activity leads to the development of hypertension in most humans, but it has not been discovered what initiates this. Blood flow to the brain might have an important role in setting the level of sympathetic nerve activity, so narrowed vertebral arteries, that result in brain stem hypoperfusion might be primarily a cause of hypertension, subsequent arterial remodelling is a consequence, but there is only limited evidence to support causality. This has been named selfish brain hypothesis or Cushing's mechanism of hypertension [9]. Hypertensive rats display statistically significant reductions of brainstem parenchymal oxygen levels under physiological conditions compared to the control group. It is hypothesized that astrocytes release ATP in response to hypoxia, which in turn activates presympathetic rostral ventrolateral medulla neurons and drives sustained sympathetic excitation, resulting in a sustained increase in mean arterial BP [10]. Esther Warnert, et al. [9] proposed that congenital vascular differences of the posterior cerebral circulation (but not anterior, meaning that pressure controlling centre is in the posterior cerebrum), that lead to cerebral hypoperfusion could be partially the reason of the essential hypertension.

Physiologically, bradycardia results in a reduction of cardiac output, that leads to brain stem hypoperfusion. To combat hy-

Citation: Zwoliński M, Zemsta K, Kulesza B, Tomasiuk R. Bradycardia Concomitant with Hypertension. Med Discoveries. 2023; 2(11): 1092.

poxia, the rostral ventrolateral medulla responds with sympathoexcitation and induces vasoconstriction, which results in a redistribution of cardiac output. Blood flow decreases to hypoxia-tolerant tissues while cerebral blood flow and blood flow towards vital organs either increase or remain constant [11,12]. Interesting is, that hypertensive patients treated with success have lower cerebral blood flow when compared to untreated patients. Therefore, although BP lowering results in a reduced risk of a cardiovascular event, it decreases cerebral perfusion [4]. Koide et al. [13] demonstrated an increase in regional cerebral blood flow after implantation of pacemaker and consequent improvement in cognitive function tests in the group of symptomatic bradycardia patients.

Baroreflex- the roles have been reversed

The baroreflex contributes importantly to regulation of the blood pressure and consequently is used to maintain the circulation to the brain and other organs. Baroreceptors measure systemic BP indirectly, by the degree of stretch of carotid arteries (carotid sinus) and aorta receptors. Increased pressure triggers parasympathetic activation and sympathetic inhibition, which in turn reduces heart rate, contractility, and vascular resistance, leading to decreased blood pressure. Conversely, a decrease in arterial pressure reduces the afferent discharge of baroreceptors, which then triggers reflex increases in heart rate, vascular resistance, cardiac contractility, and venous return [14].

Baroreflex activation may occur when vasoconstriction is induced by a factor that does not activate the sympathetic and parasympathetic systems (as their activation results in the activation of non-baroreflex mechanisms). The known state leading to this situation is hyperbaric hyperoxia, during which plasma oxygen concentration is increased up to 6%. It is characterized by vasoconstriction, hypertension and bradycardia. They are thought to be linked by a common mechanism-arterial baroreflex activation. The vasoconstriction is attributed to the direct effects of Reactive Oxygen Species (ROS) on vascular smooth muscle, with ROS leading to the creation of peroxynitrite (which is formed in a reaction of superoxide anion with nitric oxide). The bradycardia in this situation is caused by increase in parasympathetic activity. This can be explained by the activation of the baroreflex, which occurs after high arterial pressure caused by increased total peripheral resistance leads to increased stretch of walls of the carotid arteries and aorta. The baroreflex results in decreased HR and contractility, but cannot have a sufficient effect on the vessel walls and, hence, vascular resistance [15,16].

Overstimulation of cardiopulmonary receptors reduces BP, but also, if the stimulation is remarkably strong, it can cause a reflex bradycardic effect. Finally, this situation, where marked BP increase triggers a bradycardic effect by a carotid sinus activation cannot be excluded in the patient with marked and rapid BP increase followed by a delayed baroreflex resetting [17].

Frank-Starling law

According to the Frank-Starling mechanism, also known as heterometric autoregulation, the heart increases its contraction force when stretched, resulting in a direct relationship between end-diastolic volume and end-systolic pressure. This fundamental property regulates cardiac output intrinsically, enabling it to adjust to sudden changes in demand. It buffers the fall in cardiac output in the systolic heart failure to secure tolerable blood pressure to maintain perfusion of vital organs [18,19]. Furthermore, an increase in contraction force is generated by an increase in sarcomere length along the ascending limb of the force-length curve of the Frank-Starling law. The initial increase in force is thought to occur due to increased Ca^{2+} sensitivity, followed by another gradual increase in force after a few minutes. It is believed, this gradual increase in force is due to increased-Ca^{2+} release into cytoplasm (homeometric regulation).

The Frank-Starling mechanismregulates circulation by a fast and with relatively low-effort system of moving from one point of equilibrium to another [20,21].

During bradycardia (caused by a heart block) the pressures in the vena cava and jugular vein increase, which results in a sign of jugular vein dilatation [17], rise and that results in increased right ventricle filling. Similar situation can be observed within pulmonary veins and the left ventricle. As stated in the Frank-Starling law, increase in end-diastolic volume results in increase of the force and stroke volume. This result leads to a wide pulse pressure and also an increase in systolic BP. According to studies [22], hearts with chronic volume overload tend to utilize the Frank-Starling mechanism, while normal hearts balance an increased afterload by increasing contractility (Anrepp effect, homeometric autoregulation). This regulation is without a remarkable increase in the volume, observed and proposed as the main mechanism by Robert F. and Rushmer et al. [23] who devalue the role of the heterometric autoregulation on the control of the blood pressure. In animals with intact health, an intravenous infusion resulted in increased end diastolic pressure, but no change in stroke work was observed when the heart was at its maximum size. The researchers suggest that infusions while the heart is at less than maximum size (such as with the animal sitting or standing) would likely produce more consistent evidence with the observations made by Sarnoff and colleagues [24].

Heart block-clinical picture

Complete heart block is associated with a slow ventricular rate, usually 30 or 40 bpm. Occasionally, the HR may reach 50 or 60 bpm. Symptoms resulting from complete block itself are seldom seen; however, if sudden, it may cause an episode of syncope. A ventricular rate of 30 does not usually lead to pain, dyspnea, or severe prolonged weakness. The most frequent symptoms are palpitation, dizziness, and weakness. Occasionally, atrial contractions create visible, faint pulsations in the jugular pulse. A more distinctive observations that can be made are occasional, sudden and large pulsations in the jugular vein, produced by the concurrent contractions of the atria and ventricle, producing a reciprocal blood flow.

Important factor under consideration is that among patients with a heart block, hypertension was common in every aetiology group. Furthermore, in patients without hypertension with the HR getting slower, the BP tended to rise. Following the observation of an individual with transient complete heart block, it was discovered that slowing the HR resulted in an increase in systolic BP and a decrease in diastolic BP, leading to a broader pulse range [25]. Conversely, when patients were exiting the heart block and the HR increased, systolic BP decreased while diastolic BP increased. Majority of patients with a heart block have systolic hypertension and it responds to artificial cardiac pacing [26]. On the other side, according to studies [27,28] suggest that lowering the HR does not result in higher BP among patients with a pacemaker implanted. There was obseved an increase in pulse pressure (SBP-DBP) with HR lowering.

Complete heart block is the most prevalent in literature reason to hypertension due to bradycardia, but still there are only a few descriptions in literature, including only 5 case reports [17,29-32].

All participants exhibited bradycardia (HR 39-52) and presented with symptoms of resistant hypertension, including headache, paresthesia, dyspnea, and peripheral edema.

Various types of blocks were identified, including Atrioventricular (AV) dissociation, 2:1 AV block accompanied by right bundle branch block, and complete heart block.

Performed echocardiographies demonstrated an increase in left ventricle filling, indicated by a mitral E wave >1.5 m/s (reference range: 0.44-1 m/s), a left ventricular stroke volume of 116 ml, S` of 12 cm/s (>9.5 considered abnormal), mild left ventricular hypertrophy (maximum LV thickness of 18 mm), and a septal E/e` of 17 (>15 considered abnormal).

Heart block-treatment

Hinkle et al. [33] suggested that slow heart rates are associated with an increased risk of cardiac death in men with coronary heart disease, pulmonary disease or hypertension and those patients often had dysfunctions of their cardiac pacemakers or developed them soon. Therefore, these patients should receive appropriate attention.

For stable complete heart block, disorders that cause reversible heart block such as Lyme disease, myocardial ischemia, increased vagal tone, hypothyroidism, hyperkalemia, and drugs that depress Atrioventricular (AV) conduction should be identified and treated properly. Trans-thoracic echocardiography and 24-h Holter ECG should be applied to keep the patient monitored.

Permanent pacemaker implantation due to heart block is indicated in third-degree or second-degree type 2 or 2:1 block. An indication is also atrial arrhythmia, irrespective of symptoms, with third- or high-degree AV block, especially with high-risk conditions [34]. In the situation of hypertension secondary to bradycardia artificial pacing contributes to BP lowering by decreasing time of diastolic filling and restoring atrioventricular synchrony.

The effect of ivabradine

Ivabradine is a selective f-channel inhibitor. The f-channels play a major role in the generation and modulation of cardiac activity. These channels gradually depolarize the cellular membrane until it reaches a threshold for an action potential. Their function is under cAMP-mediated control of sympathetic and parasympathetic stimulation and underlies the modulation of HR by the autonomous nervous system. The recent development of “heart rate reducing” drugs, which act as selective f-channel inhibitors has made possible to selectively slow down HR without alternating other aspects of cardiac function [35].

Emerging evidence suggests that pharmacological heart rate lowering is not beneficial in patients with preserved ejection fraction. Its effect is uncertain in patients with cardiovascular disease and a high baseline HR. In those patients β blockers are the most optimal [36]. The primary effect of ivabradine is to reduce HR and the poor outcomes of its function suggest that an elevated HR is only a marker of cardiovascular risk (a well established one), but it is not a determinant of outcomes [37]. Lowered HR over a long time period results in no benefit in outcomes and may lead to more prevalent symptoms of bradycardia.

Ivabradine provides an opportunity to research effects of lowering HR without directly changing other aspects of cardiac function, enabling examination of the pathophysiology of diseases such as sinoatrial node dysfunction or sinus bradycardia.

Rimoldi et al. [27] examined haemodynamic changes following administration of ivabradine compared to placebo. The mean HR decreased from 73 to 64 (p-value 0,003), brachial systolic BP increased insignificantly from 136 to 142, and diastolic from 71 to 74. The most concerning changes were in central BP, with a significant increase of 11 mmHg in systolic and 4 mmHg in diastolic pressure. The stroke volume change from 86 to 107.2 ml was also statistically significant. Of note, bradycardia can increase the diastolic filling time of the ventricle, ultimately increasing stroke volume. Conceivably, the observed increase in central pressure could also be related at least in part to an increased stroke volume pumped into an aorta.

It should be noted that comparable findings have been observed among patients with heart block. For instance, echocardiography has revealed increased LV filling and LV stroke volume, observations characteristic to the Frank-Starling mechanism [17]. The increased stroke volume and lowered HR result in increased pulse pressure, as observed, which tends to increase systolic BP, and decrease diastolic. In patients with impaired windkessel function resulting from increased arterial stiffness, the effects of worse adaptation of the aorta to additional blood flow during systole will be magnified [38].

Multiple studies have shown, that ivabradine mostly leads to lowered BP, despite possible regulatory mechanisms that should increase the pressure to maintain cardiac output [39]. It is proposed and researched that the ivabradine has pleiotropic effects, including improvement of endothelium dependent vascular relaxation, lowering rennin-angiotensin-aldosterone axis activation, antioxidant, anti-inflammatory, anti-atherosclerotic effects [40].

Conclusion

The hypertension secondary to bradycardia is a common, but under-reported clinical problem. In this instance, the increased blood pressure is a reaction of the body to the decreased cardiac output caused by the bradycardia. The bradycardia must be chronic to permit the occurrence of hypertension. While the underlying mechanism remains undetermined, several hypotheses exist. The two most plausible mechanisms are the selfish brain hypothesis and the effects of Frank-Starling mechanism. The selfish brain hypothesis is based on the regulatory reaction of central nervous system to maintain perfusion of the brain in the setting of reduced cardiac output. The Frank-Starling mechanism hypothesis is based on the direct relation between ventricle filling (preload) and stroke volume to preserve the cardiac output. It results in higher central and pulse pressure, possibly also in increased systolic BP. However, these theories are currently challenged by insufficient clinical evidence. That is why further research on the mechanisms underlying the relationship between slow heart rate and increased blood pressure is still needed.

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