

Arterial hypertension in patients with coronary artery disease treated with coronary artery bypass surgery

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Abstract

Arterial hypertension is one of the leading modifiable risk factors in patients with coronary artery disease (CAD) who undergo coronary artery bypass graft (CABG) that has a major impact on clinical outcome. The incidence of hypertension in patients with CAD who undergo CABG ranges from 40 to 60%; of those, 29% have isolated systolic hypertension. Hypertension is indirectly associated with mortality through peripheral vascular disease, cerebrovascular disease, and renal dysfunction, which are all conditions highly predictable for cardiac death. Considering the prevalence of chronic hypertension, managing the treatment of patients with that disorder who undergo surgery is of major clinical importance, because these patients are at an increased risk of morbidity and mortality after surgery. The elevation of blood pressure secondary to discontinuation of long-term antihypertensive medication may occur postoperatively. Because hypertension does not manifest in the first few days after the operation, it is easy to overlook this important part of secondary prevention. The cardiovascular risk is principally focused on steady components of blood pressure [systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean blood pressure (BP)]; however, isolated systolic hypertension, the pulsatile nature of the beating heart, and ventricular-vascular coupling also provide important information about cardiovascular risk. Hypertension is a frequent complication of cardiac surgery. The introduction of antihypertensive drugs leads to concern that patients receiving such drugs might be at increased risk of perioperative cardiac liability. The approach to the treatment of perioperative hypertension is considerably different from the treatment of chronic hypertension. The ideal agent for treatment of hypertensive emergencies should act rapidly and predictably and be easily titrated, safe, inexpensive, and convenient – for example, clevidipine.

Key words: hypertension, arterial pressure; complications, perioperative risk.

Introduction

Coronary artery disease (CAD) is multifactorial, with multiple risk actors, and results in atherosclerosis of the coronary arteries. Coronary artery bypass surgery (CABG) and percutaneous coronary interventions are the

treatments of choice. Arterial hypertension is one of the leading modifiable risk factors in patients with CAD who undergo CABG that has a major impact on clinical outcome [1]. Arterial hypertension is thought to be associated with reduced coronary vasodilator reserve in the coronary microcirculation. Increased ventricular mass and coronary arteriolar abnormalities are the dominant features in patients with severe hypertension, whereas large-vessel coronary disease is the predominant feature in those with mild hypertension. In the United States, it is estimated that approximately 72 million people have hypertension [2]. Affecting approximately 30% of the U.S. population more than 20 years of age, hypertension is one of the most common chronic medical conditions [3, 4]. Moreover, the incidence of hypertension increases with age [5, 6] and affects men at a slightly higher rate than it does women. Worldwide, hypertension may affect as many as 1 billion people and be responsible for approximately 7.1 million deaths per year [7].

Sprague [8] first identified an association between hypertension and perioperative cardiac risk in 1929. He described a series of 75 hypertensive patients, one-third of whom died in the perioperative period; 12 of those had cardiovascular complications. The introduction of antihypertensive drugs has led to concern that patients receiving such drugs might be at increased risk of perioperative cardiac liability. The incidence of hypertension arterialis in patients with CAD who undergo CABG ranges from 40 to 60%; of those, 29% have isolated systolic hypertension. Several studies have shown that hypertension (including isolated systolic hypertension) is associated with a 40% increase in the likelihood of perioperative morbidity [9].

Hypertension is indirectly associated with mortality through peripheral vascular disease, cerebrovascular disease, and renal dysfunction, which are conditions that are highly predictable for cardiac death. During the first 30 days after the operation, hypertension is especially responsible for neurologic complications, which are divided equally between type 1 and type 2 events [10]. Considering the prevalence of chronic hypertension, the management of chronic hypertension in patients undergoing surgery is of major clinical importance, because these patients are at an increased risk of morbidity and mortality after surgery.

The classification of hypertension

The Seventh Report of the Joint National Committee (JNC 7) in 2003 on the prevention, detection, evaluation, and treatment of high arterial pressure recognizes that the risk of cardiovascular disease begins with a pressure of 115/75 mm Hg and doubles with each increment of 20/10 mm Hg. Individuals with a systolic arterial pressure of 120 to

139 mm Hg or a diastolic arterial pressure of 80 to 89 mm Hg should be considered as pre-hypertensive. The JNC 7 classifies arterial pressure in adults as: normal, systolic arterial pressure greater than 120 mm Hg and diastolic arterial pressure less than 80 mm Hg; pre-hypertension, systolic arterial pressure 120 to 139 mm Hg or diastolic arterial pressure 80 to 89 mm Hg; stage I hypertension, systolic arterial pressure 140 to 159 mm Hg or diastolic arterial pressure 90 to 99 mm Hg; stage II hypertension, systolic arterial pressure greater than 160 mm Hg or diastolic arterial pressure greater than 100 mm Hg. In JNC 7, isolated arterial hypertension (IA) was not noticed opposite to European Society of Hypertension/European Society of Cardiology (ESH/ESC) 2003 guidelines [11]. As in previous publications from the JNC, there are no recommendations or guidelines for the perioperative care of the hypertensive patient [12].

It is important to remember the ultimate goals in the treatment of hypertension, which are the reduction of the risk of cardiovascular events in the individual patient and in the population as a whole. Hypertension is only one of a number of risk factors for cardiovascular disease, and a number of guidelines, including those issued by The Writing Group of the American Society of Hypertension (WG-ASH), advocate treatment, not on the basis of arterial pressure alone, but according to the overall estimate of cardiovascular risk [13].

According to the definition of WG-ASH (May 2005), hypertension is a progressive cardiovascular syndrome arising from complex and interrelated causes (Table I). Early markers of the syndrome often are present before elevated blood pressure is observed (Table II). Therefore, hypertension cannot be classified solely by discrete blood-pressure thresholds. Progression is strongly associated with functional and structural cardiac and vascular abnormalities that damage the heart, kidney, brain vasculature, and other organs and lead to premature morbidity and death. Normal individuals have normal blood pressure, loosely defined as a systolic pressure of 115 mm Hg and a diastolic pressure of 75 mm Hg; no identifiable cardiovascular disease; few, if any, risk factors for cardiovascular disease; no early-disease markers; and no apparent end-organ damage. Stage 1 hypertension includes occasional or intermittent blood-pressure elevations or early cardiovascular disease, several risk factors, and the presence of early markers of disease, but no target-organ damage. Stage 2 hypertension includes sustained blood pressure elevations or progressive cardiovascular disease, many risk factors, overtly present markers of disease, and early signs of target-organ disease. Stage 3 hypertension includes marked and sustained blood-pressure

Table I. Definition and classification of hypertension according to the Writing Group of the American Society of Hypertension

Classification	Blood pressure elevations		Cardiovascular disease	Cardiovascular risk factors	Early disease markers	Target organ disease
Normal	Normal or rare	or	None	None or few	None	None
Hypertension: Stage 1	Occasional or intermittent	or	Early	Several	Usually present	None
Stage 2	Sustained	or	Progressive	Many	Overtly present	Early signs present
Stage 3	Marked and sustained	or	Advanced	Many with progression	Overtly present with progression	Overtly present with or without cardiovascular disease events

Table II. Early markers for hypertensive vascular disease

Blood pressure:	
• exaggerated response to exercise	
• widened pulse pressure	
Vascular:	
• reduced small-artery elasticity	
• reduced large-artery elasticity	
• endothelial dysfunction	
• increased pulse-wave velocity	
• increased carotid intima-medial thickness	
• retinal vascular changes	
• microalbuminuria	
Cardiac:	
• increased LV wall thickness	• increased LV volume
• increased LV mass	• abnormal electrocardiogram
• B-type natriuretic peptide	

LV – left ventricular

elevations or advanced cardiovascular disease, many risk factors, overtly present and progressive disease markers, and overtly present end-organ disease.

The new WG-ASH Stage 2 blood pressure category corresponds to JNC 7 Stage 1, and WG-ASH Stage 3 to JNC 7 Stage 2, with the blood-pressure threshold “cut points” basically remaining the same (Table III).

In both sets of guidelines, the presence of target-organ damage and other cardiovascular risk factors lead to lower treatment thresholds for raised arterial pressure.

The WG-ASH definition appears to have moved toward the definition and classification published by the European Society of Hypertension (ESH) in 2003 [11]. The ESH version emphasizes the continuous relationship between blood-pressure level and cardiovascular risk and includes a classification based on total cardiovascular risk.

Table III. Comparison of classifications of the Seventh Report of the Joint National Committee (JNC 7) and the Writing Group of the American Society of Hypertension (WG-ASH)

JNC 7	WG-ASH	SBP [mm Hg]	DBP [mm Hg]
Normal	Normal	<120	and <80
Prehypertension	or	120-139	or 80-89
	Stage 1	<130	and <85
		130-139	or 85-89
Hypertension			
Stage 1	Stage 1 or	140-159	or 90-99
Stage 2	Stage 2	≥160	or ≥100
	Stage 3	160-179	or 100-109
		≥180	or ≥110

SBP – systolic blood pressure, DBP – diastolic blood pressure

White-coat hypertension

So-called “white-coat” hypertension is directly relevant to anaesthesiology. It is formally defined as a persistently elevated arterial pressure in combination with a normal ambulatory arterial pressure [14]. Currently white-coat hypertension is defined as an arterial pressure of 140/90 mm Hg or greater measured in the doctor’s office in the presence of an average daytime reading of less than 135/85 mm Hg [15]. All the guidelines for the management of hypertension indicate that the arterial pressure should be measured on a number of occasions over a period of weeks before the diagnosis of hypertension is confirmed. It is rare for the anesthesiologist to have this luxury of diagnostic confirmation, and often a decision has to be made about perioperative management on the basis of two or three readings taken over a period of hours. An initial elevation in a patient’s arterial pressure may result from a visit with a doctor or nurse, but the effect is greater for doctors than for nurses. This is impressively

illustrated by data from Mancia et al. [16]. They studied 30 subjects who underwent a 24-h intra-arterial recording after 5 to 7 days in hospital. During the period of intra-arterial recording, the arterial pressure was also measured at different times with a sphygmomanometer by a male doctor and a female nurse; half of the subjects were randomized to see the doctor first, and the other half the nurse. When the doctor took the first reading, the arterial pressure rose by an average of 22/14 mm Hg. The rises when the first arterial pressure was taken by a nurse were only half as great. When the reading was taken by a nurse, the arterial pressure usually returned to near baseline after 10 min, but this was not the finding when the pressure was taken by a doctor. In many surgical patients, the admission arterial pressure will not be equal to the patient's usual arterial pressure. If a member of the medical staff finds the patient's arterial pressure to be elevated, this should be confirmed by a nurse with appropriate training.

Prognostic power of arterial hypertension in patients with coronary artery disease treated with surgical myocardial revascularization

Van Brussel et al. [17] found that the presence of major risk factors like hypertension, diabetes, and smoking are predictive of cardiac mortality, as well as overall mortality, myocardial infarction, recoronarography, and percutaneous coronary intervention.

According to Karimi et al. [18], prognostic factors for in-hospital mortality after surgery that included all the pre-, intra-, and postoperative variables include a history of diabetes or hypertension; the presence of angina; Canadian Cardiovascular Society (CCS) grades III or IV; an ejection fraction $< 30\%$; absence of use of the internal mammary artery; prolonged length of cardiopulmonary bypass; and a prolonged stay in an intensive care unit. A small series of studies [18] showed that hypertension was a better predictor of vein-graft potency than arterial ones. Aggressive risk-factor reduction results in angina reduction, improvement in cardiovascular capacity, and a decrease in the average degree of coronary artery stenosis [19].

Vavlukis et al. [20] tried to evaluate the incidence and prognostic power of arterial hypertension in patients with coronary artery disease who were treated with surgical myocardial revascularization. Hypertension was found in 52.7% of patients before the operation, and it was the most frequent cardiovascular risk factor, without any difference between age groups, but it was present significantly more often in females ($P=0.0001$), diabetics ($P=0.0001$), and patients with preserved left ventricular (LV) function ($P=0.011$). The mean postoperative follow-up period was 5.97 ± 4.27 years.

Hypertension in this study was identified as a predictor of in-hospital morbidity ($r=0.085$ and $P=0.023$), especially associated with neurological (type 1) deficits, but it wasn't identified as independent risk factor. The most predictable was the occurrence of early neurological complications. The postoperative incidence of hypertension was low ($\sim 30\%$), with significant reduction of almost 20% in comparison with that in the pre-operative period, which is probably a result of postoperative treatment. Szyguta-Jurkiewicz et al. [21] studied 261 patients with acute coronary syndromes without ST-segment elevation who underwent early invasive strategy and coronary artery bypass grafting with the aim of comparing the 2-year health-related quality of life in patients with hypertension with the quality in those who had normal blood pressure. During the 2-year follow-up, patients with hypertension more often required hospitalization (23 vs. 10%, $P<0.01$). The rate of unstable angina during follow-up was similar in both groups (5 vs. 5%, NS). The health-related quality of life in hypertensive patients as measured by both the Physical (41.51 ± 10.61 vs. 42.58 ± 6.74 , $P<0.004$) and Mental (45.54 ± 12.35 vs. 48.95 ± 9.9 , $P<0.03$) Component Summaries of SF-36 and obtained on the basis of patients' subjective opinion 2 years after CABG was worse in patients with concomitant hypertension.

Christenson et al. [22] studied 77 consecutive patients who underwent CABG with a left ventricular ejection fraction (LVEF) less than or equal to 25% [hypertensive, $n=38$ (group I) and normotensive, $n=39$ (group II)]. They compared those patients with 2289 patients who underwent CABG with LVEF greater than 25% [hypertensive, $n=870$ (group III) and normotensive, $n=1419$ (group IV)]. Hospital mortality in group I was 5.3% and in group II 15.4% ($P<0.008$). In group III the mortality rate was 6.3%, and in group IV 2.2% ($P<0.001$). Postoperative low cardiac output occurred in 18% (group I) and 39% (group II) ($P<0.05$) and in only 5% in groups III and IV ($P<0.001$). Hypertensive patients with poor left ventricular function preoperatively ($\leq 25\%$) were found to have a lower hospital mortality rate and incidence of postoperative low cardiac output than those who were normotensive with LVEF less than or equal to 25%. Hypertensive patients also had more improvement in their left ventricular function and CCS class than did those who were normotensive. The results of this study, however, should be interpreted with caution, because of the small number of patients with low left ventricular ejection fraction analyzed.

The meaning of systolic blood pressure as a risk factor for cardiac adverse outcomes

Systolic blood pressure is affected by stroke volume, rate of systolic ejection, and the distensibility of the arterial tree [23]. Increases in pressure

decrease distensibility, which adversely affects circulation. Pulsatile energy (approximately 15% of cardiac work) accounts for up to 30% of left ventricular oxygen consumption [24]. Increased blood pressure occurs initially because of arterial stiffness or increased stroke volume. When stroke volume returns to normal, increased blood pressure is a consequence of systemic vascular resistance, and cardiovascular risk is related to mean arterial pressure or diastolic blood pressure. However, if arterial distensibility decreases while stroke volume and rate of systolic ejection remain constant, then the result is increased systolic blood pressure, decreased diastolic blood pressure, wider pulse pressure, and unchanged mean arterial pressure. Therefore, cardiac output, mean arterial pressure, and systemic vascular resistance alone do not adequately describe the contribution of arterial compliance to blood flow and cardiac work. The relationship of systolic blood pressure to left ventricular hypertrophy [25, 26] and the relationship of left ventricular hypertrophy to perioperative morbidity suggest that systolic blood pressure is a significant independent risk factor for adverse cardiac outcomes.

Left ventricular hypertrophy as a result of hypertension and its impact on outcome after coronary artery bypass graft

Hypertension is often connected with left ventricular hypertrophy (LVH). In research by Ioannidis et al. [27], patients with LVH (91% with arterial hypertension) showed a similar in-hospital mortality rate when compared with patients without LVH. However, LVH was a detrimental risk factor for late mortality, especially after the third postoperative year [27]. Several other studies have investigated the impact of LVH on in-hospital outcomes after CABG. Lin et al. [28] reported that LVH increased in-hospital mortality in patients who have had CABG. In addition, patients with severe LVH have an increased incidence of postoperative renal failure. Similarly, Christenson et al. [29] reported in a relatively large study that LVH was associated with worse in-hospital outcomes following CABG.

The meaning of the isolated systolic hypertension in patients treated with coronary artery bypass graft surgery

The data from the Framingham population by Franklin et al. [30] revealed a steady increase in systolic arterial pressure starting in childhood and continuing throughout adult life. In contrast, rises in diastolic pressure in early adult life stabilized or declined in the fifth and sixth decade of life. There was a steady rise in pulse pressure throughout adult life, and the rate of rise increased after the age of 50 years.

Isolated systolic hypertension, which is the presence of increased systolic blood pressure in the

absence of increased diastolic blood pressure, has emerged as an important predictor of cardiovascular morbidity in large epidemiological studies [31]. In the 6th report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure [32], isolated systolic hypertension was defined as SBP greater than 140 mm Hg with DBP less than 90 mm Hg.

In JNC 7, isolated HA had not been noticed in contrast to the United Nations Intergovernmental Negotiating Committee (INC) 6 and ESH/ESC 2003 guidelines [11]. As might be expected, isolated systolic hypertension accounts for the majority of cases of hypertension in patients more than 50 years old. In the National Health and Nutrition Examination Survey (NHANES) III data, Franklin et al. [33] found that 80% of the subjects aged more than 50 years who had hypertension had isolated systolic hypertension. That condition has not been sufficiently studied in the perioperative setting, and it may contribute to morbidity and mortality rates after CABG surgery. Understanding the relevance of isolated systolic hypertension as a perioperative cardiovascular risk factor is important [34, 35].

Aronson et al. [36] examined the association between isolated systolic hypertension and perioperative and postoperative in-hospital morbidity or mortality in patients undergoing cardiac surgery in a prospective study of 2417 patients in 24 centers who were undergoing elective cardiac surgery. Patients were classified as having normal preoperative arterial pressure, isolated systolic hypertension (systolic arterial pressure greater than 140 mm Hg) (approximately 30% of the patients who had CABG surgery also had isolated systolic hypertension), diastolic hypertension (diastolic arterial pressure greater than 90 mm Hg), or a combination of these. After adjusting for other risk factors, isolated systolic hypertension was associated with a statistically significant increase in the likelihood of perioperative morbidity [odds ratio (OR) 1.3, 95% confidence interval (CI) 1.1-1.6]. Although the mean systolic arterial pressure of the patients with isolated systolic hypertension was not given, since the average age of the patients was 65 years, it is tempting to speculate that it was considerably greater than 140 mm Hg. The authors concluded that isolated systolic hypertension was associated with a 40% increase in the likelihood of cardiovascular morbidity perioperatively in patients undergoing CABG. This increase remained present regardless of antihypertensive medications, anesthetic techniques, and other perioperative cardiovascular risk factors (e.g., age older than 60 years or history of congestive heart failure, myocardial infarction, or diabetes).

This common form of hypertension in the elderly may become the most common form of hypertension in the perioperative population, given the rapidly expanding elderly population referred for surgery.

The meaning of the pulse pressure in patients treated with coronary artery bypass graft surgery

Hypertension has been appreciated recently as a more complex marker for specific underlying cardiovascular disease [37]. Whereas previous investigations of cardiovascular risk principally focused on steady components of blood pressure (SBP, DBP, mean BP) [38], there is now clear evidence that the pulsatile nature of the beating heart and ventricular-vascular coupling provide important information about cardiovascular risk [39-41].

Pulse pressure (PP equals mean SBP minus mean DBP) is an index of conduit-vessel stiffness and the rate of pressure-wave propagation and reflection within the arterial tree [42].

When the buffering capacity of a compliant aorta is lost, the noncompliant aorta is less capable of compensating for low-pressure, low-flow periods throughout the cardiac cycle. These limitations may be amplified in patients with elevated pulse pressure in whom flow becomes highly pressure-dependent. Pulse pressure has been found to be strongly associated with cardiovascular risk [43]. Evidence suggests that increased vessel stiffness precedes development of atherosclerosis and exacerbates its consequences. The presence of a carotid bruit is independently associated with the development of acute renal failure after cardiac surgery [44]. In addition, pulsatile stress in central arteries may contribute to plaque rupture by a mechanical fatiguing effect [45]. Pulse pressure, which is necessarily increased in patients with isolated systolic hypertension, can be singled out as a greater predictor of risk for stroke, heart failure, coronary artery disease, and renal failure than diastolic blood pressure [46, 47].

In another study by Aronson et al. [48] of patients having coronary bypass graft surgery, a significant and progressive increase in the risk of renal composite was seen above a pulse pressure threshold of 40 mm Hg. The adjusted OR was 1.49 with a 95% CI of 1.17 to 1.89 for patients with a preoperative PP of 40 to 60 mm Hg vs. patients with PP \leq 40 mm Hg; the adjusted OR was 4.87 with a 95% CI of 1.86 to 12.75 for patients with preoperative PP $>$ 100 mm Hg vs. those with PP \leq 40 mm Hg. Patients with PP hypertension $>$ 80 mm Hg were three times more likely to die from renal-related events compared with those without PP hypertension (3.7 vs. 1.1%). Acute renal failure after coronary bypass graft surgery is associated with

pulse pressure hypertension and continues to be a devastating complication associated with multiorgan dysfunction, increased resource use, high cost, and increased mortality [49-51].

Secondary prevention of hypertension after coronary artery bypass graft

In past years, cardiac surgeons have focused considerable effort on optimizing the procedure of coronary artery bypass grafting. Technical developments ranging from cardioplegic arrest to beating-heart surgery have been shown to make the operation safer [52].

Grafting of the left internal mammary artery to the left anterior descending coronary artery has been documented to favorably impact survival as much or more than any other procedure or therapy in cardiovascular medicine [53].

These efforts to improve the technical aspects and perioperative care of patients undergoing CABG have been successful; during the past decade, the risk-adjusted mortality rate from CABG surgery has declined by 23%, despite a 30% increase in predicted preoperative risk [54]. However, despite this improvement in surgical mortality and morbidity outcomes, the long-term liabilities of intervention with CABG remain largely unsatisfactorily addressed—namely, progression of graft and native atherosclerotic disease. The long-term survival after CABG has not improved during the past 2 decades [55], underscoring the need for improvements in secondary-prevention strategies in these cases [56]. The recent recognition that patients with coronary artery disease have a higher incidence of traditional cardiovascular risk factors [57, 58] suggests that more aggressive preventive strategies will benefit a greater proportion of patients, and patients who have had CABG are no exception. Hypertension is a major modifiable risk factor for the development and progression of the underlying disease, atherosclerosis; hypertension has been shown to increase mortality 2 years after CABG surgery and significantly lower quality of life [59, 60].

The adequate treatment of hypertension is associated with increased well-being [61] and reduction in stroke [62], myocardial infarction [63], and left ventricular hypertrophy [64].

Medications to prevent secondary hypertension are beneficial after acute coronary syndromes, but these benefits are less clear after coronary artery bypass graft surgery.

To assess the use of cardiovascular medical therapy among patients discharged after CABG surgery, 320 patients enrolled in the Routine vs. Selective Exercise Treadmill Testing After Coronary Artery Bypass Graft Surgery (ROSETTA-CABG) Registry [65] were controls. Most of the patients

were male and hyperlipidemic and underwent CABG surgery for relief of symptoms of angina. At admission, discharge, and at 12 months after discharge, acetylsalicylic acid was used in 71, 92 and 87% of cases, respectively, and some form of antiplatelet agent was used in 74, 94, and 89% of cases, respectively. The use of anti-lipid agents remained constant, from 55% at admission to 57% at discharge. However, 24% of patients were not receiving anti-lipid agents at 12 months. The use of β -blockers was 57% at admission, 71% at discharge, and 64% at 12 months. The use of calcium-channel blockers and nitrates decreased modestly from admission to discharge and remained stable at approximately 20 and 22%, respectively, at 12 months. Use of angiotensin-converting enzyme (ACE) inhibitors remained stable, from 33% at admission to 38% at 12 months. Hyperlipidemia, hypertension, obesity, and left ventricular ejection fraction less than 40% before CABG surgery were all found to be important determinants of medication use during the 12 months after discharge. However, the use of anti-lipid agents, β -blockers, and ACE inhibitors was found to be low among patients who had CABG surgery, despite their known therapeutic benefits. The EUROPA (European Trial on Reduction of Cardiac Events with Perindopril in Stable Coronary Artery Disease) study [66] confirmed that adding perindopril (8 mg once daily) to standard preventive therapy in the subgroup of patients with previous revascularization and without previous myocardial infarction (MI) resulted in the relative-risk reduction of 17.3% (95% CI 1.3-30.8%, $P=0.035$) for the composite primary end point of cardiovascular death, nonfatal MI, and resuscitated cardiac arrest; the reduction was 23% (95% CI 4.9-37.6%, $P=0.015$) in cases of fatal and nonfatal MI. In the 3047 revascularized patients without a history of MI, perindopril was associated with a relative-risk reduction of 31.7% in cases of fatal and nonfatal MI (95% CI 4.4-51.2%, $P=0.026$). Belcher [67] also found that poor medical management for secondary prevention was associated with less widespread and less effective therapy in patients after CABG, which resulted in unfavorable post-operative outcomes. In Polish research, Jankowski et al. [68] assessed factors influencing the management of hypertension in 1051 consecutive patients with hypertension and coronary artery disease (255 after CABG). Overall, 7.1% of hypertensives were not treated with any agent to lower blood pressure. High blood pressure ($\geq 140/90$ mm Hg) was found in 68.9% of hypertensives. Older age (OR 1.3, 95% CI 1.0-1.6) and hypertension awareness in patients (OR 0.6, 95% CI 0.3-1.0) were the only significant predictors of uncontrolled hypertension. Management of hypertension in the secondary

prevention of coronary artery disease was not satisfactory.

In research by Nie et al. [69] risk-factor modification after coronary revascularization was also far below optimal. In cases complicated by hypertension, 33.1% (469/1419) and 31.9% (453/1419) of patients had higher average systolic or diastolic pressures than were measured in hospital. Prompt and effective measures should be taken to enhance the secondary prevention and patient education to minimize the gap between clinical practice and evidence-based guidelines.

The postoperative incidence of hypertension was low (30%), with a significant reduction of almost 20% in comparison with the incidence during the preoperative period in the Republic of Macedonia, which is probably a result of postoperative treatment. ACE inhibitors, Ca-antagonists, and β -blockers were applied in 39.44, 30.1, and 33.6% of cases, respectively, with significant positive correlations found for all of them ($r=0.221$, $P=0.0001$, $r=0.316$, $P=0.0001$ and $r=0.093$, $P=0.031$) [20].

The population of Australian patients who had undergone CABG 6 to 20 years previously and who reported hypertension or heart failure, in addition to high cholesterol, was less likely to use statins. ACE inhibitors were the most commonly prescribed agents for management of hypertension either in combination with β -blockers, calcium-channel blockers, and diuretics (59%) or as the sole therapy (44%), followed by β -blockers (45%) and calcium-channel blockers (38%), either alone or in combination with other agents, and were more frequently used among patients with diabetes and those with symptoms of heart failure. Approximately 5.5% of patients having hypertension were not treated with antihypertensive medication, although some were taking long-acting nitrate therapy or antiarrhythmic agents such as sotalol [70]. The present management of secondary prevention in patients with hypertension after coronary artery bypass is poor. The elevation of blood pressure secondary to discontinuation of long-term antihypertensive medication may occur postoperatively. Because hypertension does not manifest itself in this circumstance in the first few days after the operation, it is easy to overlook this important part of secondary prevention. More consideration of replacement of anti-anginal drugs with concomitant antihypertensive effects is mandated.

Hypertension during coronary artery bypass graft operation

Hypertension is a frequent complication of cardiac surgery [71]. Perioperative hypertension occurs in 25% of hypertensive patients who undergo surgery [72]. During surgery, elevations in

blood pressure and tachycardia during the induction of anesthesia are likely to develop in patients with and without preexisting hypertension [73]. Common predictors of perioperative hypertension are previous history of hypertension, especially a diastolic blood pressure greater than 110 mm Hg, and the type of surgery [9, 48].

There is evidence from many studies that conditions that may represent target-organ damage as a result of hypertension contribute to perioperative cardiac risk. A study by Lee et al. [74] identified ischaemic heart disease, heart failure, and renal failure as risk factors for perioperative cardiac complications. It would seem sensible to suggest that anesthesiologists pay more heed to the presence of significant target-organ damage than to a diagnosis of hypertension. The American Heart Association/American College of Cardiology (ACC/AHA) guidelines note that hypertension (stages 1 and 2) is not an independent risk factor for perioperative cardiovascular complications [75]. However, they suggest that stage 3 hypertension (systolic arterial pressure ≥ 180 mm Hg and/or diastolic arterial pressure ≥ 110 mm Hg) should be controlled before surgery. High arterial pressures are associated with high levels of afterload and cardiac work. This may predispose to myocardial ischemia and infarction, especially in the presence of coronary artery disease and left ventricular hypertrophy. However, there is evidence that very rapid control of arterial pressure with drugs such as sublingual nifedipine is associated with increased morbidity and mortality [76]. Invasive arterial-pressure monitoring is indicated for major procedures, and the arterial pressure should be actively managed to prevent elevations of the mean arterial pressure of greater than 20% from baseline. Monitoring should continue into the postoperative period until it is clear that the patient is cardiovascularly stable.

Perioperative liability of blood pressure and its etiology

It has been noted that patients diagnosed as 'hypertensive' display increased cardiovascular liability during receipt of anaesthesia. There is certainly a pathophysiological basis for such a belief. Established hypertension is associated with an increased systemic vascular resistance. Increased arterial resistance has been associated with low partial pressure of oxygen in skeletal muscle and secondary metabolic acidosis despite adequate cardiac output and oxygen content of arterial blood [77]. The microcirculatory changes that produce inadequate tissue perfusion appear to resolve after a period of 6 to 8 h, but this interval does not correlate with re-warming following moderately hypothermic cardiopulmonary bypass [78]. Humoral

factors may have a role, since a number of circulating mediators are present and produce the whole-body inflammatory response to cardiopulmonary bypass [79]. The systemic vasodilatation associated with anaesthesia might well be expected to have profound effects on arterial pressure in such patients. Prys-Roberts et al. [80] and Goldman and Caldera [72] have demonstrated that induction of anaesthesia is associated with a decrease in arterial pressure to a similar nadir in both hypertensive and normotensive patients. Christakis et al. [81] reported that the incidence of low systemic vascular resistance (SVR) is more common in patients undergoing normothermic perfusion and in those with longer cardiopulmonary-bypass times [82]. Diabetics, patients with peripheral vascular disease, and those with an LVEF of less than 40% are less likely to have low SVR and associated hypotension. The findings of Chung and colleagues [83] and those from the Multicenter Study of General Anesthesia [84] indicate that patients with pre-existing hypertension frequently have high arterial pressures during the intraoperative period.

Hypertension following coronary artery bypass graft surgery – predisposing factors

Systemic hypertension occurs in more than one third of patients having coronary artery bypass graft operations.

Roberts et al. [85] found that certain preoperative clinical, angiographic, and biochemical factors predispose to the development of perioperative hypertension. These included a well documented history of hypertension, an elevated blood pressure the day prior to operation, an obstruction of the left main coronary artery greater than 50%, and increased levels of dopamine β hydroxylase. The hemodynamic pattern of perioperative hypertension was that of an increased systemic vascular resistance, which was associated with increased levels of plasma catecholamines and plasma renin activity.

An elevation in the concentration of plasma epinephrine and norepinephrine, suggesting enhanced sympathoadrenal responsiveness to the challenge of cardiopulmonary bypass, was characteristic of the hypertensive group in the study of Wallach et al. [86], which may be a useful predictor of the development of postoperative hypertension.

Perioperative hypertensive emergencies and urgencies

Hypertensive emergencies [severe elevations in blood pressure ($>180/110$ mm Hg) complicated by evidence of impending or progressive target-organ dysfunction] require immediate treatment to

prevent or limit end-organ damage. Examples of hypertensive emergencies include hypertensive encephalopathy; intracerebral hemorrhage; subarachnoid hemorrhage; acute stroke; hypertension-induced acute renal dysfunction; and hypertension associated with unstable angina, acute myocardial infarction, acute coronary heart failure, and acute aortic dissection. The blood pressure should be reduced by 10 to 15% (maximum of 20%) in a controlled fashion within the first hour, with a continued decrease towards 160/100 mm Hg during the next 2 to 6 h, as tolerated by the patient. This goal decreases the likelihood of too aggressive control, which may result in target-organ hypoperfusion. Patients with chronic hypertension have cerebral and renal perfusion autoregulation that is shifted to a higher range. The brain and kidneys are particularly prone to hypoperfusion if blood pressure is lowered too rapidly. With the threat of organ injury diminished, attempts should be made to control blood pressure to baseline levels during a period of 24 to 48 h. A more rapid reduction is indicated in patients with aortic dissection. Hypertensive urgency is associated with severe elevations in blood pressure without progressive target-organ dysfunction. Since end-organ dysfunction is not present, these situations require less rapid reductions in pressure (hours to days) [87, 88].

When emergent surgery is necessary, excessive preoperative blood-pressure elevations should be lowered to limit or prevent possible aggravation of bleeding and damage to vital organs. Assuming there is no immediate threat to vital-organ function, as may occur in patients with end-organ disease secondary to chronic hypertension, such perioperative elevations in blood pressure can generally be considered hypertensive urgencies [89].

Postoperative hypertension (arbitrarily defined as SBP \geq 190 mm Hg and/or DBP \geq 100 mm Hg on two consecutive readings after surgery) [90] may have significant adverse sequelae and are typically considered hypertensive emergencies, as are acute elevations in blood pressure (>20%) in the intraoperative period [91]. Postoperative hypertension often begins approximately 10 to 20 min after surgery and may last up to 4 h. If left untreated, the patients are at increased risk for bleeding, cerebrovascular events, and myocardial infarctions [91]. Coronary artery bypass surgery is associated with high rates of postoperative hypertension [87]. The approach to the treatment of perioperative hypertension is considerably different than the treatment of chronic hypertension. In many patients, the development of postoperative hypertension is a result of withdrawal of their long-term antihypertensive regimen. One preventive approach is to substitute long-acting preparations

of the patient's long-term antihypertensive regimen starting, if possible, several days before surgery and continuing through the morning of the day of surgery. Hypertension that occurs in relation to tracheal intubation, surgical incision, and emergence from anaesthesia may be treated with short-acting β -blockers, ACE inhibitors, calcium-channel blockers, or vasodilators. Postoperative situations that may result in a hypertensive emergency include rebound hypertension after withdrawal of antihypertensive medications, hypertension resulting in bleeding from vascular surgery suture lines, and hypertension caused by acute catecholamine excess [92].

Pharmacotherapy of perioperative hypertension in patients treated with surgery revascularization

The ideal agent for treatment of hypertensive emergencies should be rapid-acting, predictable, easily titrated, safe, inexpensive, and convenient. Preferred agents in patients treated with CABG surgery include labetalol, nicardipine, fenoldopam, nitroglycerin, and sodium nitropruside clevidipine.

Labetalol

Labetalol is a combined selective α_1 -adrenergic receptor blocker and nonselective β -adrenergic blocker given by intravenous bolus or continuous infusion.

The hypotensive effect of labetalol begins within 2 to 5 min after its intravenous administration, reaching a peak at 5 to 15 min following administration and lasting for about 2 to 4 h [93]. Labetalol reduces the systemic vascular resistance without reducing total peripheral blood flow. In addition, the cerebral, renal, and coronary blood flows are maintained [94]. Due to its β -blocking effects, the heart rate is either maintained or slightly reduced. Unlike pure β -adrenergic blocking agents that decrease cardiac output, labetalol maintains cardiac output [94]. However, the use of labetalol after cardiac surgery has shown a significant reduction in heart rate and blood pressure along with reductions in cardiac index [95, 96]. Sladen et al. [97] found that after labetalol administration in hypertension following coronary artery bypass grafting, the cardiac index decreased by 18.5%, with a 12.5% decrease in stroke index and 8.1% decrease in heart rate. Because of these actions, labetalol should be avoided or used with caution in patients with preoperative and postoperative cardiac dysfunction. In patients with normal left ventricular function, intravenous labetalol appears to be a safe, effective agent in controlling post-CABG hypertension, with the added potential benefit of enhanced myocardial oxygen balance. Labetalol should be used with caution in patients with heart failure and avoided in patients

with severe sinus bradycardia, heart block greater than first degree, and asthma.

Calcium-channel blockers – nicardipine

Currently, nicardipine is the most widely used dihydropyridine. This is due to its potent afterload-reducing activity and relatively short duration of action, although its effect may increase the longer the drug is being infused. The onset of action of intravenous nicardipine is from 5 to 15 min, with a duration of action of 4 to 6 h [98]. A therapeutic benefit of nicardipine is that the agent has been demonstrated to increase both stroke volume and coronary blood flow, with a favorable effect on myocardial oxygen balance [99, 100]. This property is beneficial in patients with coronary artery disease and systolic heart failure. Another calcium-channel blocker used in hypertensive patients is diltiazem.

The efficacy of diltiazem in reducing the arterial pressure after coronary artery surgery within the first 30 min is comparable to nitroglycerin and sodium nitroprusside. However, after 30 min, diltiazem affords better myocardial performance and more effective control of hypertension than the other medications [101].

Fenoldopam

Fenoldopam is a peripheral dopamine-1 (DA-1) receptor agonist administered by intravenous infusion for the treatment of severe hypertension. Fenoldopam is unique among the parenteral blood pressure agents, because it mediates peripheral vasodilation by acting on peripheral dopamine-1 receptors. Fenoldopam is rapidly and extensively metabolized by conjugation in the liver, without participation of cytochrome P-450 enzymes.

The onset of action of fenoldopam is within 5 min, with the maximal response achieved within 15 min, and the blood pressure gradually returns to pretreatment values without rebound once the infusion is stopped [102]. Although fenoldopam provides rapid reduction in blood pressure, this change is often accompanied by reflex tachycardia. In one study, after administration of fenoldopam, a marked increase in heart rate, cardiac index, and stroke volume index could be observed, which was more pronounced due to the initially stronger decrease of systemic vascular resistance, with a stronger decrease of pulmonary vascular resistance [103].

Nitroglycerin

Nitroglycerin, an anti-anginal and antihypertensive drug, is a direct vasodilator of peripheral capacitance and resistance vessels. It is a greater venodilator than an arterial dilator. By decreasing preload, nitroglycerin

decreases left ventricular end diastolic volume and pressure and reduces myocardial-oxygen demand. Nitroglycerin also dilates coronary arteries, increasing the blood supply to ischemic regions of the heart. Intravenous nitroglycerin has an onset time of 2 to 5 min, a duration of action of approximately 10 to 20 min, and an elimination time of about 1 to 4 min by hepatic metabolism [104]. Nitroglycerin is not considered an acceptable primary therapy in the management of either hypertensive emergencies or urgencies [92], but it may be a suitable adjunct therapy since it may have little or no efficacy when used alone and its antihypertensive action is caused by venodilation. Low-dose administration (approximately 60 mg/min) may be used as an adjunct to antihypertensive therapy in patients with hypertensive emergencies associated with acute coronary syndromes or acute pulmonary oedema.

Sodium nitroprusside

Sodium nitroprusside is an arterial and venous vasodilator that decreases afterload and preload [105], resulting in a decrease in peripheral resistance without causing an increase in venous return. Sodium nitroprusside is often considered a drug of choice for hypertensive emergencies, since it has an immediate onset of action and a duration of effect of only 2 min. In patients with coronary artery disease a significant reduction in coronary perfusion pressure (coronary steal) may occur [106]. In addition, the drug's vasodilatory adverse effects are frequently not predictable or preventable, and they may involve organs other than the heart. Another disadvantage of sodium nitroprusside involves accumulation of cyanide and thiocyanate. Thiocyanate is mainly eliminated through the kidneys. Cyanide removal requires adequate hepatic function and renal function and bioavailability of thiosulfate. Thus, nitroprusside may cause cytotoxicity due to the release of cyanide, with interference of cellular respiration. Cyanide will also interfere with the vasodilator activity of sodium nitroprusside and lead to tachyphylaxis. Considering the potential for severe toxicity with nitroprusside, this drug should only be used when other intravenous antihypertensive agents are not available and only in specific clinical circumstances in which patients have normal renal and hepatic function [105].

Clevidipine

Acute hypertension during cardiac surgery can be difficult to manage and may adversely affect patient outcomes. Clevidipine is a novel, rapid-acting, third-generation dihydropyridine L-type calcium-channel blocker with an ultrashort half-life that decreases arterial blood pressure with a fast

termination of effect due to metabolism by blood and tissue esterases. As an arterial selective vasodilator, clevidipine reduces peripheral vascular resistance directly, without dilating the venous capacitance bed to decrease arterial blood pressure without negatively impacting cardiac function. Stroke volume and cardiac output usually increase. In addition to maintaining renal function and splanchnic blood flow, clevidipine has been shown to protect against ischemia/reperfusion injury in an animal model of myocardial ischemia [107]. Several trials have shown clevidipine to be very effective in the control of preoperative and postoperative hypertension [108].

In the randomized, double-blind, placebo-controlled multicenter Efficacy Study of Clevidipine Assessing Its Preoperative Antihypertensive Effect in Cardiac Surgery (ESCAPE – 1) [109], the efficacy and tolerability of clevidipine in treating preoperative hypertension were evaluated. Patients treated with clevidipine demonstrated a rate of treatment success of 92.5% and a significantly lower rate of treatment failure (7.5%, 4 out of 53) than patients receiving placebo (82.7%, 43 of 52; $P < 0.0001$). Clevidipine achieved target blood pressures (SBP reduced by $\geq 15\%$) at a median of 6.0 min (95% CI 6-8 min). A modest increase in heart rate from baseline occurred during administration of clevidipine. Adverse events for each treatment group were similar.

The effectiveness of this drug in treating acute postoperative hypertension was assessed in the ESCAPE – 2 study [110]. In this research, clevidipine-treated patients had a significantly lower incidence of treatment failure than patients receiving placebo [8.2% (5 of 61) vs. 79.6% (39 of 49), $P < 0.0001$]. Treatment was successful in 91.8% of patients receiving clevidipine. Median time to target systolic blood pressure with clevidipine was 5.3 min (95% CI 4-7 min). No clinically significant increase in heart rate from baseline was observed, and adverse event rates were similar for both treatment groups.

The ECLIPSE (Evaluation of Clevidipine in the Perioperative Treatment of Hypertension Assessing Safety Events) trial [111] was performed to compare the safety and efficacy of clevidipine with nitroglycerin, sodium nitroprusside, and nicardipine in the treatment of perioperative acute hypertension in patients undergoing cardiac surgery.

There was no difference in the incidence of myocardial infarction, stroke, or renal dysfunction for clevidipine-treated patients compared with the other treatment groups, as well as no difference in mortality rates between the clevidipine, nitroglycerin or nicardipine groups. Mortality was significantly higher, though, for nitroprusside-treated patients compared with clevidipine-treated patients ($P = 0.04$). Clevidipine was more effective than

nitroglycerin ($P = 0.0006$) or nitroprusside ($P = 0.003$) and was equivalent to nicardipine in maintaining blood pressure within a pre-specified range. However, when the blood-pressure range was narrowed, clevidipine was associated with fewer excursions beyond these limits than nicardipine.

This research confirms the safety and effectiveness of clevidipine in treating perioperative hypertension in comparisons with both placebo and currently used drugs such as nitroprusside, nicardipine, or nitroglycerin.

Conclusions

Hypertension is a complex disease with multiple components deserving a critical re-evaluation in the perioperative period. It is a major modifiable risk factor for the development and progression of the underlying disease, atherosclerosis, and it has been shown to increase mortality 2 years after CABG surgery and to significantly lower the quality of life. Hypertension is indirectly associated with mortality through peripheral vascular disease, cerebrovascular disease, and renal dysfunction, which are all conditions that are highly predictable for cardiac death.

The adequate treatment of hypertension is associated with increased well-being and reduction in stroke, myocardial infarction, and left ventricular hypertrophy.

Considering the prevalence of chronic hypertension, the management of patients with chronic hypertension undergoing surgery is of major clinical importance, since these patients are at an increased risk of morbidity and mortality after surgery. The long-term survival rate after CABG has not improved during the past 2 decades, underscoring the need for improvements in strategies for secondary prevention in these patients.

Hypertensive urgencies and emergencies occur in approximately 50% of patients during and immediately after cardiac surgery. The goal of controlling perioperative hypertension is to protect organ function. When considering a potential course of treatment, it is most important to balance the risks associated with hypertension against the risk of end-organ hypoperfusion that may accompany antihypertensive therapy. When treatment is necessary, therapy should be individualized. The ideal antihypertensive agent should provide immediate onset of action, a short-to-intermediate duration of action, ease of precise titration, and demonstrated safety and efficacy in the treatment of perioperative hypertension. New agents like clevidipine may be a valuable option for patients with perioperative hypertension during CABG [112-115].

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