

Physiopathology of unstable angina in hypertensive patients and clinical risk assessment

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Received: July 6, 2020, Accepted: August 21, 2020

Abstract

Unstable angina in patients exhibiting acute coronary syndromes without persistent ST-segment elevation is one of the major diagnostic and prognostic challenges that cardiologists worldwide are faced with, due to its multiple definitions and the difficulty related to a standardized evaluation. Long-term arterial hypertension represents a major risk factor for atherosclerotic disease, thus being an important risk factor and prognostic marker in acute coronary syndromes. In this article, we shall describe the physiopathological relationship between acute coronary syndromes and arterial hypertension and review the efficacy of Braunwald’s classification of unstable angina as a reliable prognostic tool in these patients.

Keywords: Unstable angina, arterial hypertension, Braunwald’s classification, acute coronary syndrome, atherosclerosis.

Introduction

Unstable angina is defined as myocardial ischemia at rest or minimal exertion in the absence of cardiomyocyte necrosis [1]. The name of unstable angina was introduced in 1971 by Fowler [2] and Conti et al. [3], including under its umbrella a wide range of

diseases, with multiple definitions such as: “preinfarction angina”, “crescendo angina”, “status anginosus”, “accelerated angina”, “acute coronary insufficiency”, “intermediate coronary syndrome” [4-7] and others. In 1989, Professor Braunwald noticed the need for uniformity in defining unstable angina, so he introduced a simple and accessible classification in order to facilitate the diagnosis, establish the prognosis, and also to conduct the proper treatment [8]. Three decades later, the classification which bears his name still remains valid, having been confirmed by multiple prospective studies over time [9, 10]. However, desiring to improve this classification further, professor Braunwald published another article in 2000, which added more prognostic power to his algorithm [11].

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Arterial hypertension is a highly prevalent disease, which many healthcare systems worldwide are confronted with. The overall prevalence of hypertension in adults living in both high-income and middle-income countries is about 42%, without major differences between the two subgroups [12], and it is estimated that the number of people with hypertension will increase by 15-20% by 2025 [13]. Moreover, the prevalence of hypertension becomes progressively higher with increasing age, being >60% in people aged >60 years [14]. It is well known that hypertension is a major risk factor for atherosclerosis, thereby having a crucial role in the development of coronary artery disease, including unstable angina [15]. Observational data indicate that for patients aged between 40 and 70, the risk of cardiovascular disease doubles for each increment of 20 mmHg in systolic blood pressure or 10 mmHg in diastolic blood pressure across a blood pressure range of 115/75 to 185/115 mmHg, leading to an increased risk of death from coronary artery disease and stroke [15].

Pathogenesis of unstable angina and the relationship with arterial hypertension

Since 1989, when professor Braunwald first published his classification of unstable angina [8], many studies have been conducted to establish the physiopathological changes in acute coronary syndromes, and today we have data incriminating four processes operating either on their own or in various combinations: 1) disruption of an unstable atheromatous plaque, which may be triggered at least in part by inflammation [16]; 2) coronary arterial vasoconstriction; 3) gradual intraluminal narrowing of an epicardial coronary artery caused by progressive atherosclerosis or restenosis after stenting; 4) oxygen supply-demand mismatch [17]. Plaque disruption with subsequent thrombosis is considered the main initiating mechanism in acute coronary syndromes [18]. Platelet activation and aggregation at the site of a plaque which underwent rupture or erosion is an important early process, leading to vascular obstruction [19, 20]. Vasoconstriction, as a dynamic obstruction mechanism, can involve epicardial coronary arteries (Prinzmetal angina) or small, intramural muscular coronary arteries. The latter may result from vasoconstrictors released by platelets, endothelial dysfunction, adrenergic stimuli, cold, and drugs [17].

After plaque disruption, activation of platelets and coagulation cascade play the central role in thrombotic obstruction. First, vascular injury exposes subendothelial collagen, which is responsible

for platelet activation, binding them at the level of glycoprotein Ib through the von Willebrand factor. Also, circulating thrombin has the capacity of activating circulating platelets. These two mechanisms lead to platelet degranulation with the release of adenosine and thromboxane A₂, causing further platelet activation and expression of platelet glycoprotein IIb/IIIa. In parallel, tissue factor exposed from the lipid-rich core of atherosclerotic plaque activates the coagulation cascade, which leads to the conversion of fibrinogen into fibrin by activated factor IIa. Glycoprotein IIb/IIIa expressed on the platelet membrane is now binding the circulating fibrinogen, causing platelet aggregation and producing a platelet-fibrin thrombus [17].

Even though the latest European Guidelines do not define hypertensive patients as a special population among those patients presenting acute coronary syndrome without ST-segment elevation [1], the relationship between the two is known, and many studies were conducted to assess the role of blood pressure in the prognosis of patients with acute coronary syndromes [21]. Hypertension and ischemic heart disease are some of the most prevalent dyads, and together with hyperlipidemia, the most prevalent triad in the United States [22]. Many physiopathological mechanisms leading to hypertension development also cause associated target organ damage, including ischemic heart disease. Such mechanisms include the sympathetic nervous system and renin-angiotensin-aldosterone system activation, increased vessel stiffness, endothelial dysfunction, increased inflammatory mediators, hemodynamic changes, and reduced vasodilator reserve or activity [23]. However, hypertension per se is also involved in the development of ischemic heart disease by several mechanisms. For example, elevated systolic blood pressure increases myocardial oxygen requirements by increased impedance to left ventricle ejection. The high afterload requires increased contractility, which is one of the three major determinants of myocardial energy consumption. Moreover, chronically elevated blood pressure promotes endothelial injury, resulting in impaired vasodilators release, and increases the release of inflammatory mediators, which promote the development of atherosclerosis and vascular occlusion. Moreover, chronic hypertension stimulates left ventricle hypertrophy, causing impaired myocardial blood flow and limited oxygen supply [23].

There are two major pathogenic mechanisms leading to ischemic heart disease in hypertensive patients: coronary microvascular dysfunction and epicardial coronary artery stenosis due to atherosclerosis.

The coronary arterial system is composed of three different compartments, with borders that cannot be clearly defined anatomically [24]: the

large epicardial coronary arteries, which offer little resistance to coronary blood flow, prearterioles, and intramural arterioles, with a significant pressure drop along their length. The latter are responsible for oxygen demand and supply matching, by metabolic regulation of coronary blood flow [25].

Abnormal coronary flow reserve, as a marker for coronary microvascular dysfunction, has been demonstrated in patients with essential hypertension, despite the presence of angiographically normal coronary arteries and the absence of left ventricular hypertrophy [26, 27]. The physiopathological basis of this phenomenon is represented by remodeling of both vascular and extravascular structures, and by changes in coronary hemodynamics [28]. The former includes remodeling of intramural arterioles and interstitial fibrosis, which leads to a decreased density of vessels in the coronary microvasculature, whereas hemodynamic changes refer to increased extravascular compressive forces with elevated systolic and diastolic wall stress and impaired relaxation [25]. Even if coronary microvascular dysfunction may be present in the absence of ventricular hypertrophy [29], their coexistence represents an additional risk factor for ischemic heart disease. It is worth mentioning that in patients without myocardial diseases, hypertension can promote coronary microvascular dysfunction that is at least partly reversible [25].

As mentioned above, epicardial coronary atherosclerosis is also an important consequence of chronic hypertension. The pathogenesis of hypertension is a multifactorial process, various abnormalities in ions transport being described in subsets of hypertensive individuals. These changes in electrolyte metabolism enhance contractile response, hypertrophy, and proliferation of vascular smooth muscle cells. Moreover, the dysfunctional endothelium of hypertensive patients fails to exhibit its inhibitory influence on vascular smooth muscle cell growth, amplifying the hypertrophy and stimulating the atherogenesis [30]. This medial thickening increases the distance required for diffusion of oxygen from the vascular lumen, leading to a decrease in oxygen pressure through the vascular wall, incomplete oxidative processes, and abnormalities in redox state [31, 32], causing lipid oxidation and tissue damage, which promote atherosclerosis. Other mechanisms, such as increased endothelial permeability for serum lipids, sympathetic overactivity, and endothelial microlesions caused by the blood flow turbulence, are also mentioned [21].

Arterial hypertension is involved in the pathogenesis of ischemic heart disease. However, it can also play the role of an aggravating factor in patients with established coronary artery disease, in whom it represents an adverse prognostic marker used in many risk scores, including the Global Registry of

Acute Coronary Events (GRACE) 2.0 risk calculator, which provides the most accurate stratification of risk both on admission and at discharge in patients with an acute coronary syndrome without ST-segment elevation [33, 34].

Braunwald unstable angina classification and its prognosis and diagnosis utility

Professor Braunwald's first classification of unstable angina was designed to facilitate communication about these patients, to guide decision-making regarding diagnostic and therapeutic measures and to provide a more precise basis for enrolling patients in clinical trials and for evaluating their outcome [8].

Braunwald's classification is focused on four major aspects of unstable angina: 1) the severity of the clinical manifestations; 2) the clinical circumstances in which unstable angina occurs; 3) the presence or absence of transient electrocardiographic changes; 4) the intensity of antianginal treatment [8].

According to the severity of clinical manifestations, unstable angina is divided into three classes, as follows.

- Class I: New-onset severe or accelerated angina. Patients with new-onset, less than two months in duration, exertional angina pectoris that is severe or frequent (>2 episodes/day), or patients with chronic stable angina who develop accelerated angina (angina is more frequent, severe, longer in duration or precipitated by distinctly less exertion than previously), but who have not experienced pain at rest during the preceding 2 months;
- Class II: Angina at rest, subacute. Patients with one or more episodes of angina at rest during the preceding month but not within the preceding 48 hours;
- Class III: Angina at rest, acute. Patients with one or more episodes of angina at rest within the preceding 48 hours [8].

According to the clinical circumstances in which unstable angina occurs, it can also be divided into three classes.

- Class A: Secondary unstable angina. Patients in whom unstable angina develops secondary to a clearly identified condition extrinsic to the coronary vascular bed, which aggravates myocardial ischemia. Such conditions reduce myocardial oxygen supply, increase myocardial oxygen demand and include anemia, fever, tachyarrhythmias, and others. It is easy to understand how a sudden rise

in blood pressure, by mechanisms described earlier, can be a precipitating factor for myocardial ischemia;

- Class B: Primary unstable angina. Patients who develop unstable angina pectoris in the absence of an extracardiac condition that has intensified ischemia, as in class A;
- Class C: Postinfarction unstable angina. Patients who develop unstable angina within the first 2 weeks after a documented acute myocardial infarction [8].

Electrocardiographic changes refer to the presence or the absence of ST-T segment abnormalities seen on an electrocardiogram recorded during an episode of chest pain [8].

In terms of treatment, unstable angina is classified as follows: 1) unstable angina occurring in the absence of or with minimal antianginal therapy; 2) unstable angina occurring in the presence of appropriate therapy for chronic stable angina; 3) unstable angina occurring in the presence of maximally tolerated doses of all three categories of antiischemic drugs (beta-adrenergic blockers, long-acting nitrates, and calcium antagonists) [8].

In time, this classification has been validated by many studies. For example, Calvin et al. [9] reported that acute myocardial infarction within 14 days (class C) and ST-segment depression in the presenting electrocardiogram were both markers of increased risk. Other studies reported that myocardial infarction occurred more frequently in those with recent pain (class III) and in postinfarction patients (class C). ECG changes were also independent risk factors [10]. Moreover, a high unstable angina class (IIIB or IIIC) led to a high rate of coronary revascularization [35]. De Servi et al. also reported a correlation between clinical class and coronary anatomy,

showing that patients with recent worsening angina without rest pain (class IB) presented calcified lesions more frequently than patients with angina at rest (classes IIB and IIIB) did, as the latter showed thrombus or intraplaque hemorrhage on angiography more frequently [36].

After troponin assays were introduced in clinical practice in the late 1990s, it was found that some patients diagnosed with unstable angina, having undetectable levels of serum creatine kinase or creatine kinase-MB, had detectable levels of serum cardiac troponin I or troponin T. At that moment, this entity was named “minor myocardial injury” [37]. Pathological studies have demonstrated that the underlying mechanism is represented by focal myocardial necrosis, not large enough to be detected by serum creatine kinases measurement and caused by repetitive embolization of thrombi from an unstable atheroma [38, 39]. Elevated troponins have been found in approximately one-third of patients with unstable angina at rest (class IIIB) [40] [41], but in only 10% of patients in class I [42]. Moreover, the risk for myocardial infarction and death increases with increasing serum troponin concentration and may be 20% in 30 days and 25% within 6 months in patients with the highest troponin levels [43, 44].

Considering these results, it was suggested that patients with class IIIB unstable angina should be divided into troponin-positive and troponin-negative subgroups (Figure 1). The risk for cardiovascular death or myocardial infarction at 1 month in class IIIB troponin-positive subgroup is estimated to be 15-20%, while the troponin-negative subgroup has a far better prognosis, with a risk of <2% [11]. These findings suggest that negative troponin measurement does not exclude ischemic heart disease,

CLASS	Class A Secondary unstable angina	Class B Primary unstable angina	Class C Postinfarction unstable angina
Class I New onset severe or accelerated angina	IA ^{+/-} _{1/2/3}	IB ^{+/-} _{1/2/3}	IC ^{+/-} _{1/2/3}
Class II Angina at rest, subacute	IIA ^{+/-} _{1/2/3}	IIIB ^{+/-} _{1/2/3}	IIIC ^{+/-} _{1/2/3}
Class III Angina at rest, acute	IIIA ^{+/-} _{1/2/3}	IIIB ^{+/-} _{1/2/3} Troponin +/-	IIIC ^{+/-} _{1/2/3}

Figure 1. Braunwald’s revised classification of unstable angina. The columns contain classes based on clinical circumstances, whereas the lines show classes based on clinical manifestation severity. For each class, the superscript represents the presence or the absence of electrocardiographic changes, where “+” means present and “-” absent. The subscript defines the three classes based on treatment, where “1” means absent or minimal antianginal therapy, “2” means appropriate therapy for chronic stable angina and “3” means maximally tolerated doses of all three categories of antiischemic drugs. For Class IIIB, the revised classification introduced a subclassification based on the presence (+) or absence (-) of abnormal cardiac specific troponin (I/T) levels [11].

but it rules out high-risk patients with unstable angina [11]. Even if those results were correct, today this second classification is not valid anymore, because according to the latest Guidelines for the management of acute coronary syndromes in patients showing no persistent ST-segment elevation [1], the presence of angina associated with myocardial necrosis, certified by serum necrosis markers measurement, is consistent with myocardial infarction, so the troponin-positive IIB class of unstable angina no longer meets the criteria for unstable angina, but myocardial infarction.

Even so, there is a big difference in prognosis between troponin-positive and troponin-negative acute coronary syndromes. Compared to non-ST-segment elevation myocardial infarction patients, those with unstable angina do not experience myocardial necrosis, have a substantially lower risk of death, and appear to derive less benefit from intensified antiplatelet therapy as well as early invasive strategy [45–47]. Moreover, the introduction of high-sensitivity cardiac troponin measurements in the last few years, instead of standard troponin assays, has resulted in increased detection of myocardial infarction (about 4% absolute and about 20% relative increase) and a reciprocal decrease in the diagnosis of unstable angina [48–51].

As the sensitivity of serum cardiac-specific troponin assays has been continuously improved, the non-ST-segment elevation acute coronary syndromes are turning again into a grey zone of ischemic heart diseases, due to increased variability in tests sensitivity, leading to significant heterogeneity in classification. It is unclear to what extent patients presenting with acute coronary syndromes without ST-segment elevation do or do not have elevated serum cardiac troponin levels, the only limit being the assay sensitivity, and to what extent those levels are still specific enough to keep their prognostic value. As professor Braunwald suggested in 2013, maybe it is the time to prepare a requiem for unstable angina [48].

Conclusions

Current European guidelines recommend the use of risk calculators, such as GRACE 2.0 and the Thrombolysis In Myocardial Infarction (TIMI) risk score for patients with non-ST-segment elevation acute coronary syndromes, highlighting the fact that quantitative assessment of ischemic risk by means of integrative scores is superior to clinical assessment alone [1]. However, the clinical assessment of patients with unstable angina based on Braunwald's classification has proven its efficacy over the years, and it should be used in addition to current risk calculators and

assisted by new serum cardiac markers, which have shown promising results as prognostic markers [52], in order to assess the risk and choose the right therapeutic strategy for these patients. In this context, a review of the latest Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation is necessary.

On the other hand, arterial hypertension, which is included as a risk factor in both the above-mentioned scores, is closely involved in the pathophysiology of acute coronary syndromes, both as a predisposing factor for coronary artery disease and also as an aggravating condition of myocardial ischemia. Therefore, optimal management of arterial hypertension is an important strategy for both reducing target-organ damage (ischemic heart disease) and for improving prognosis in acute coronary syndromes.

Conflict of Interests

The authors confirm that there are no conflicts of interests.

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