Verapamil and vasospastic angina: underuse in the elderly population

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1 Introduction

The first case of Prinzmetal angina was described in 1959 by Prinzmetal, et al. Since this description, several triggering factors have been associated with vasospastic angina (VA) and included: illicit drugs such as cocaine, amphetamine or marijuana, but also bitter-orange, alcohol, butane, chemotherapy drugs, over-the-counter medication and different antibiotics. Smoking is also a major risk factor for developing VA. Thus, except for smoking, many of conventional atherosclerosis risk factors do not appear to be applicable to VA. However, vasospastic angina can also occur without any triggering factor.

It is established that coronary spasm plays an important role not only in the pathogenesis of variant angina but also in ischemic disease in general, including resting and effort angina, acute myocardial infarction (AMI) and sudden death. In approximately one in ten patients with AMI, angiography does not reveal any obstructive coronary artery disease.

The classical symptoms are represented by recurrent resting angina with spontaneous remission. A circadian pattern has been noted and VA preferentially occurs in the morning hours. Complications of VA included AMI, malignant ventricular arrhythmia and even sudden cardiac arrest or death.

Conflicting results exist on the VA pathophysiology. In fact, proposed mechanisms responsible for this disease entity are the hyperactivity of sympathetic nervous system associated with a vagal withdrawal or a reduced nitric oxide synthase and endothelial dysfunction. A genetic predisposition has also been evoked.

Calcium channel blockers (CCBs) are the first-line therapy for VA. These agents have been shown to reduce symptomatic angina episodes, suppress inducible coronary spasm and most important, independently prevent major complications related to VA. Focusing on elderly patients, we review the results of clinical trials evaluated the use of CCBs in VA and try to provide some answers regarding the underuse of these drugs in these patients.

2 Definition, epidemiology and therapeutic strategy of VA

The term ‘variant angina’ or ‘Prinzmetal variant angina’ and ‘VA’ are often used interchangeably, but variant angina represents a specific form of VA that is diagnosed during a documented spontaneous vasospastic episode defined by a nitrate-responsive rest angina, associated with a transient ST-elevation. These concepts heralds from the original work by Prinzmetal, et al.

The VA hallmark feature is rest angina, especially at night or in the early morning, that promptly responds to short-acting nitrates. Several studies have evaluated the clinical risk factors associated with VA. Some recognized triggers for developing VA were previously described and included: illicit drugs such as cocaine, amphetamine or marijuana, but also bitter-orange, butane, chemotherapy drugs, over-the-counter medication and different antibiotics. Histamine, ergonovine or acetylcholine can provoke coronary spasm and are therefore used for diagnostic purposes. However, these tests are rarely performed in clinical routine. Unlike structural atherosclerosis coronary artery diseases, hypertension or diabetes do not dispose to VA. In contrast, smoking seems to represent an important VA risk factor; and smoking during coronary angiography has been shown to acutely induce spasm in susceptible individuals.

VA occurs more frequently in young patients. In teenagers and young adults, the use of illicit substances, particu-
larly cocaine, is an important cause of drug-induced AMI secondary to coronary spasm, with important therapeutic and prognostic implications.\cite{4} The racial differences in the VA incidence between ethnic groups have been evoked by Sasayama.\cite{13} In the study by Ong, et al.,\cite{14} in white population with acute coronary syndrome without any culprit lesion, 49% had a positive acetylcholine test, while 16% of French\cite{15} and 79% of similar Japanese patients developed VA after intracoronary acetylcholine.\cite{16}

In original description, spontaneous episodes of rest angina were associated with transient ST elevation that promptly resolved with short-acting nitrates. ECG changes are usually present but in some cases symptomatic crisis may appear without any ECG change.\cite{17,18} The baseline ECG is usually normal or can depict nonspecific ST changes, or flat or negative T wave, whereas ECG highlight ST-elevation during the spasm. The most frequent and typical ECG changes affect cardiac repolarization related to the progressive ischemia which occurs very abruptly during coronary spasm. In more than 50% of cases, the first ECG change is a tall, symmetrical and usually peaked T wave that is associated with a mild increase in the QT interval.\cite{9,17,19} The presence of ST-segment elevation coincides with the spasm and the presence of angina. Reciprocal ST-segment depression can be seen. During the resolution period of ST-elevation, which occurs when the crisis vanishes, a negative T wave often appears. Concomitant changes in depolarization (transient intraventricular disorders, right bundle branch block in particular, Q clinical ECG wave) are very rare.\cite{9} The presence of ventricular arrhythmias is very frequent during VA. In Bayes series, short episodes of ventricular arrhythmias occur in 66% of the patients studied by Holter monitoring. The prevalence and importance of ventricular arrhythmia were related to the duration of episodes, the degree of ST-elevation, the presence of ST-T wave alternation and the presence of > 25% increase of the R wave.\cite{17} More infrequently, supraventricular tachycardia, second degree AV block, AV dissociation and sinus node dysfunction can occur.\cite{9} Ventricular fibrillation and sudden death may also occur.\cite{19}

In the majority of cases, patients are not hospitalized but present with pain suggestive of angina, not related to exercise.\cite{17,18,20} The diagnosis may be difficult, especially because the ECG usually normalizes in few minutes after symptoms resolution. Moreover, the median time period for diagnosis to be made following the initial presentation to a physician is two months.\cite{21} Symptoms appear at rest in contrast to classical angina pectoris. Finally, ventricular arrhythmia occurred at the end of an episode when ST-segment was turning to baseline reperfusion period.\cite{17,19}

Before international standardization of VA diagnosis criteria in 2015, there was no universal definition of VA, which has impeded the progress in understanding and diagnosis of this disorder.\cite{11} The diagnosis criteria of VA included the documentation of transient ischemic ECG changes (ST-elevation or ST-depression, new negative U waves), and a nitrate responsive angina (which usually occurs at rest, typically in the early morning hours, and is non reproducible during exercise). Typically, nitroglycerin is particularly effective to relieve the spasm.\cite{11} The ST-segment elevation implies in transmural focal ischemia, correlated to complete or near-complete coronary occlusion of an epicardial coronary artery in the absence of collateral occlusion. In variant angina, the dynamic obstruction can be superimposed on severe or non-severe coronary stenosis or occurs on an angiographically normal coronary artery segment. Hence, coronary angiography is usually part of the workup of these patients and can help to guide the treatment.\cite{22-24}

The crises of VA are now easily controlled. In only one of 20 patients in Bayes series, crises have continued after treatment.\cite{9,17} Mortality in patients with VA is relatively low. In one study, with a five year follow-up period, the mortality rate was estimated to 10%.\cite{17} Persistent smoking and history of first wind angina were the strongest predictors of mortality. It was shown that recurrences are possible in patients with alternans of the ST segment and T wave which may herald the occurrence of ventricular fibrillation associated with VA.\cite{19,25}

CCBs seem to be the established first line therapy for VA, and the decrease in frequency of VA is attributed to the widespread use of these drugs in the field of hypertension. Long-acting nitrates were also found to be efficient, and their vasodilatory effect may be additive to CCBs.\cite{4} Patient treated with CCBs, included verapamil, had better outcome than patients who received other medical therapy (P = 0.002). These CCBs exerted their beneficial effects within the first three months after diagnosis, presumably during the most active phase of disease.\cite{23}

### 3 Elderly patients and vasospastic angina

No study have especially addressed VA in elderly patients in terms of incidence, therapeutic strategy or gravity. Indeed, VA occurs more frequently in young patients whereas atherosclerosis provokes more frequently coronary heart diseases in elderly patients. In their study, Koshiba, et al.,\cite{26} have shown that perioperative VA is prevalent in elderly patients with coronary risk factors (hypertension, cigarette smoking and diabetes). One reason for the preva-
lence of VA in elderly patients undergoing abdominal or thoracic surgery under inhalational anesthesia combined with epidural anesthesia may be the instability of the automatic nervous system and hemodynamic changes, which may enhance inadequate anesthesia and the use of vasoressors. Moreover, instability of autonomic nervous system and vascular hyperactivity in these patients are supposed to be the underlying autogenic mechanism of the spasm.\[4,26\]

4 Use of calcium channel blockers in elderly VA patients

No specific trial studied CCBs use in elderly patient presenting VA. The only information available is provided by studies in young patients treated with CCBs or CCBs used in other context such as hypertension. CCBs may be classified according to their relative affinities for arterial smooth muscle and myocardium into the following group: dihydropyridines, which are relatively selective for arteries; benzoiazepines, which possess equally potent myocardial and arterial effects and phenylalkylamines, which predominantly affect the myocardium. These are further divided into subgroups (first, second, third generation). First generation include CCBs (nifedipine, nicardipine, diltiazem, verapamil) which have both a rapid onset and short duration of action. Adverse events are related to their rapid arterial vasodilatation. Second CCBs generation (felodipine, isradipine, nimodipine, nisoldipine, nitrendipine, gallopamil) were in response to these concerns. They are either slow release, longer acting formulations compared to first CCBs generation. Consequently, these drugs cause fewer vasodilatation-mediated adverse effects. The major advantage of third CCBs generation (amlodipine, lacidipine) is that they do not produce any clinically relevant increases in cardiac or peripheral sympathetic activity.

Verapamil is a phenylalkylamine (which predominantly affects the myocardium) of first generation. It is widely used for the management of atrial fibrillation, angina pectoris, VA, hypertension and cluster headaches. Verapamil is metabolized at the hepatic level, by cytochrome P450, thus its hypotensive effect could be increased by the following drugs, among others: rifampicin, macrolides, fluoxetine, proteases inhibitorsazole anti-nyctocics, valproid acid, cimetidine and cisapride. Regarding foods interactions, citrus fruits such as grapefruit juice, can inhibit cytochrome P450 activity and therefore could increase hypotensive effect. In contrary, there is a significant decrease in hypotensive effects with anti-convulsants such as phenytoin, carbamazepine and phenobarbital.\[27\] Studies have shown that verapamil can inhibit the efflux transporter P-glycoprotein (P-gp).\[28\] Coadministration of the P-gp inhibitor verapamil could significantly increase concomitants drug concentrations such as the non-vitamin K oral anticoagulant edoxaban causing an increasing bleeding risk.\[29\] Risk of hypotension following co-prescription of macrolides antibiotics and CCBs is important.\[30,31\] It exerts negative inotropic and chronotrophic effects. The second Danish Infarction Trial (DAVIT-II) demonstrated the ability of verapamil to reduce reinfarction rate after myocardial infarction.\[32\] This medication has a well-documented history as an effective antianginal treatment when directly compared with \( \beta \)-blockade.\[33\] Among the CCBs, verapamil is one of preferred therapies in the management of supraventricular arrhythmias. Verapamil slow cardiac conduction and reduce heart rate. It has more prominent effect on the AV node; thus PR interval and heart rate should be determined before commencing therapy.

Verapamil has been shown to be effective in the management of patients with VA.\[34\] In contrast during each period of verapamil treatment, a highly significant reduction in the number of episodes was observed (31 vs. 23). To assess the efficacy of verapamil in VA, Johnson, et al.\[35\] enrolled 16 patients in a double-blind randomized trial with nine months period of follow-up. During verapamil treatment, angina frequency decreased from 12.6 to 1.7 episodes of chest pain per week. During the study, the number of hospitalizations for clinical instability was also significantly lower with verapamil. As demonstrated in the previous study by Parodi, et al.,\[36\] the number of episodes of transient ST segment deviation during treatment with verapamil was also markedly reduced. In this patient population, no side effects implicating a reduction in dosage or a drug discontinuation were observed. The long-term benefit of chronic verapamil therapy in VA was reported by Freedman, et al.\[37\]. Among the 31 patients with sustained verapamil therapy, 21 were asymptomatic, nine were improved (1–4 attacks/month), and one had an average of eight angina attacks per month. Most patients in this study responded well to verapamil and if they did not, they responded to nifedipine (four patients), which emphases that when one CCB was ineffective at an appropriate dosage, the patient could respond to another.\[34\]

Parodi, et al.,\[38\] demonstrated the superiority of verapamil compared to propranolol in the reduction of the number of episodes of rest angina in 17 patients in whom VA was thought to be underlying mechanism of ischemia. The degree of improvement in symptoms was better with verapamil. In this study, verapamil was also superior to propranolol in preventing ergonovine-induced coronary spasm. As reported by Winniford et al.,\[39\] neither verapamil nor nifedipine adversely affect left ventricular performance in
patients with VA who showed good baseline left ventricular function.\[^{34}\]

There are very few studies that directly compared CCBs in the treatment of VA. Nifedipine, diltiazem and verapamil totally or partially blocked the ergonovine-induced angina ST elevation in most patients. Verapamil was not quite as effective in this regard as were the other CCBs.\[^{34}\]

Regarding CCBs use in elderly patients, in general, these drugs are well tolerated. However, patients are less likely to tolerate first generation (including verapamil) CCBs, which have a rapid onset of action, than the gentler second or third CCBs. Adverse effects including peripheral oedema, headache, flushing, and hypotension leading to dizziness are quite frequently because of abrupt peripheral arterial vasodilatation.\[^{40}\] This mismatch of dilatation favors fluid extravasation as capillary pressures rise.\[^{41,42}\] This side effect occurs less commonly with the non-dihydropyridine CCBs. The peripheral oedema associated with CCB use is not associated with weight gain and is not responsive to diuretic therapy.\[^{43}\] The cardiovascular side effects of verapamil include frequently junctional bradycardia and variable degrees of atrioventricular block. Moreover, verapamil may trigger heart failure decompensation in patients with left ventricular dysfunction.\[^{40}\] So, verapamil should be avoided in the presence of systolic heart failure; generally, all CCBs should be used cautiously in the heart failure patient (if at all), because use of this drug class can be associated with heart failure exacerbation.\[^{44,45}\] Clearly, negatively chronotropic CCBs, including verapamil, should not be used in patients with bradycardia, sinus node dysfunction or atrioventricular nodal block. Patients with Wolff-Parkinson-White syndrome with atrial fibrillation, however, should not receive verapamil. In this syndrome, anterograde conduction over that accessory pathway may increase with verapamil, with an ensuing increase in ventricular response rate, occasionally deteriorating into ventricular fibrillation.\[^{46}\]

The geriatric population is not exempt from adverse effects induced by verapamil. Among elderly patients who are taking verapamil during a hospital stay, approximately 1 person out of 40 experienced an adverse reaction that was causally attributable to the drug. Although verapamil-induced hypotensive effects increase with age, in older persons a PR interval prolongation caused by drug is less marked than in younger subjects.\[^{47-49}\] Profound sinus bradycardia and cardiac arrest due to co-administration of verapamil and beta-adrenergic blocking drugs have previously been described.\[^{50-52}\] In patients, without hepatic or kidney disease, verapamil serious effects are mainly mentioned with accidental overdose or with very high therapeutic doses (> 240 mg/day).\[^{43}\] Controversial links exist between verapamil and increased risk of cancer in the elderly. In their study, Beiderbeck-Noll, \textit{et al.},\[^{53}\] have shown that verapamil was significantly associated with cancer, whereas no associations were found with others CCBs. Braun \textit{et al.},\[^{54}\] showed a similar risk of cancer incidence in patients treated by CCBs and other drugs. Constipation is also a common dose-dependent side effect of verapamil and this drug was frequently stopped for this reason in the elderly patient.\[^{40,55}\] Pooled data from 1042 patients on the safety of controlled-onset, extended-release verapamil up to 540 mg compared with placebo or an active comparator drug found an overall incidence of 13% for constipation, which was slightly higher among patients older than 65. In these studies, placebo constipation rates were surprisingly low—1% to 2%.\[^{56}\] Rarely, transaminase values increase with verapamil and skin eruption can occur with this compound. Underuse of verapamil in VA in elderly patients can be explained by the absence of studies specifically addressed to them and by the fact that physicians may be afraid of using these drugs in view of their potential adverse side effects.

\section{5 Conclusions}

Even if VA incidence seems not to be so frequent in elderly patients due to the generalization of CCBs use for hypertension, the perioperative period appears to be a particularly risky situation promoting VA occurrence in these patients. Although no specific study addressed this issue in elderly patients, CCBs seem effective in treating and preventing VA. Verapamil is less used than other CCBs because of increased cardiac adverse effects incidence linked to this drug, especially in elderly patients.

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