Artery Stenosis and Vasospastic Angina

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Vasospastic angina (VA) is caused by focal or diffuse spasm of an epicardial coronary artery, resulting in severe obstruction of the coronary artery lumen and myocardial ischemia. Vasospasm can occur in an angiographically normal coronary artery, but may also occur at the site of an existing organic atherosclerotic stenosis. Stable atherosclerotic plaques are rarely fatal, but can interfere with coronary blood flow and lead to stable angina. However, it has been suggested that vasospasm is associated with endothelial damage and subsequent atheroma rupture. Considering that acute coronary syndrome (ACS) is almost always caused by luminal thrombus or sudden plaque rupture applied to organic atherosclerotic plaques, coronary vasospasm can induce the rupture of a stable atheroma, which could lead to myocardial infarction and sudden cardiac death.

vasospastic angina coronary artery stenosis acute coronary syndrome

1. Overview

Vasospastic angina (VA) is a functional disease of the coronary artery and occurs in an angiographically normal coronary artery. However, it may also occur with coronary artery stenosis. We investigated the effect of coronary artery stenosis on clinical outcomes in VA patients. Study data were obtained from a prospective multicenter registry that included patients who had symptoms of VA. Patients were classified into two groups according to presence of significant coronary artery stenosis. Among 1920 patients with VA, 189 patients were classified in the “significant stenosis” group. The one-year composite clinical events rate was significantly higher in the significant stenosis group than in the “no significant stenosis” group (5.8% vs. 1.4%, respectively; $p < 0.001$). Additionally, the prevalence of ACS was significantly greater in the “significant stenosis” group (4.8% vs. 0.9%, respectively; $p < 0.001$). After propensity score matching, the adverse effects of significant stenosis remained. In addition, significant stenosis was independently associated with a 6.67-fold increased risk of ACS in VA patients. In conclusion, significant coronary artery stenosis can increase the adverse clinical outcomes in VA patients at long-term follow-up. Clinicians should manage traditional risk factors associated with atherosclerosis and control vasospasm as well as reduce the burden of atherosclerosis.

2. Vasospastic Angina

Vasospastic angina (VA) is caused by focal or diffuse spasm of an epicardial coronary artery, resulting in severe obstruction of the coronary artery lumen and myocardial ischemia [1]. Vasospasm can occur in an angiographically normal coronary artery, but may also occur at the site of an existing organic atherosclerotic stenosis [2]. Stable atherosclerotic plaques are rarely fatal, but can interfere with coronary blood flow and lead to stable angina [3].

However, it has been suggested that vasospasm is associated with endothelial damage and subsequent atheroma rupture [4]. Considering that acute coronary syndrome (ACS) is almost always caused by luminal thrombus or sudden plaque rupture applied to organic atherosclerotic plaques [5], coronary vasospasm can induce the rupture of a stable atheroma, which could lead to myocardial infarction and sudden cardiac death.

Overall, VA has a good long-term prognosis [6]. On the contrary, previous small studies have shown that significant coronary artery atherosclerotic stenosis is associated with a worse clinical outcome in patients with VA [7][8][9]. In other studies, there was no significant difference in prognosis of VA patients with or without significant stenosis [10]. Notably, most of the above studies showed the clinical outcome only in patients with VA, excluding patients with significant coronary artery stenosis [11][12][13]. Few studies have directly compared and evaluated in detail the clinical prognosis of vasospasm in patients with or without significant coronary stenosis with a long-term follow-up. Therefore, we investigated the effect of significant coronary artery stenosis on clinical outcomes in VA patients using a large-scale nationwide prospective registry.

3. Conclusions

According to results from this nationwide prospective large-scale registry, the incidence of 1-year composite clinical events including ACS was significantly higher in VA patients who had significant coronary artery stenosis at baseline CAG than those who had no significant stenosis; the adverse effects of significant stenosis were consistent after propensity score matching. However, there was no difference in clinical events between one-vessel coronary disease and multi-vessel disease. Especially, significant coronary artery stenosis was independently associated with a 6.67-fold increased risk of ACS in patients with VA at 1-year follow-up. Dyslipidemia, a traditional cardiovascular risk factor, was also independently associated with an increased risk of ACS.

Vasospasm is common in patients with no or mild coronary artery stenosis [14]. Although the tendency of coronary artery spasm may be the only cause of functional coronary artery abnormalities, it also overlaps with significant coronary artery stenosis. However, the prevalence of co-existing significant coronary artery stenosis in VA patients was reported to be relatively low, within 10% in a previous Japanese study [8][15]. In our study, 9.8% of patients with VA also had a significant stenosis rate; this rate is comparable to the previous reports. Despite a low incidence of significant atherosclerotic coronary stenosis in VA patients, once an atherosclerotic plaque is present, it can contribute to the development of ACS by coronary vasospasm [16][17]. Ishii M. et al. [18] showed the clinical outcome of patients with coronary spasm combined with significant atherosclerotic stenosis. Among 1760 patients with typical or atypical angina-like chest pain who underwent provocation test, 358 (20.3%) patients had significant stenosis. Of the 358 patients with significant stenosis, 233 (65.1%) patients showed vasospasm after provocation test. Contrary to the design of our study, they demonstrated that provoked spasm at the site of significant stenosis was an independent risk factor for major adverse cardiac events. Those mechanisms have not been clearly demonstrated in human studies; an animal study showed that vasospasm might be one of the mechanisms triggering atherosclerotic plaque injury and subsequent acute ischemic myocardial injury [19]. Coronary artery stenosis and subsequent plaque rupture with thrombus formation after vasospasm in animal models have many obvious differences with the human and clinical situation. However, this mechanism could provide theoretical

support to the significantly greater incidence of clinical events, including ACS, in VA patients with significant stenosis compared to VA patients without significant stenosis in our study.

In the present study, the multivariate analysis also demonstrated that significant coronary artery stenosis was a strong and significantly correlated factor of 1-year ACS in patients with VA by 6.67-fold. Takagi et al. [8] also showed that significant coronary artery stenosis (≥50% luminal diameter narrowing) independently increased the risk of major adverse cardiac events by 2.04-fold in VA patients who survived out-of-hospital cardiac arrest during a 32-month follow-up period. Their study targeted higher acuity patients (who had cardiac arrest) compared with our study, and they included additional major adverse cardiac events such as cardiac death, nonfatal myocardial infarction, hospitalization for unstable angina and heart failure, and appropriate ICD shocks. Their findings are comparable with our study in that significant stenosis can increase cardiac events, but the more severe characteristics of the enrolled patients and diverse clinical outcomes differed from our study. In another study, Takatsu et al. [20] showed that mild coronary artery stenosis above 0% increased the risk of major adverse cardiac events including acute myocardial infarction, unstable angina, and development of severe coronary disease by 1.66-fold over an 11-year follow-up. While they enrolled patients excluding organic significant stenosis, which was different from our study, their findings highlight the importance of coronary artery stenosis at baseline CAG in patients with VA by demonstrating that even a small atherosclerotic burden can contribute to the increase in adverse cardiac events.

Dyslipidemia, as a traditional cardiovascular risk factor of atherosclerotic cardiovascular disease [21], was also an independent risk factor for 1-year ACS in patients with VA regardless of significant coronary artery stenosis at baseline CAG. Although VA is a functional disease [1], the traditional cardiovascular risk factors should be remedied through appropriate medical therapy.

There are few studies with direct comparisons between VA patients with or without significant coronary stenosis and detailed evaluations of the clinical prognosis over a long-term follow-up. We presented refined data results by adjusting the baseline characteristics of VA patients with or without significant coronary stenosis by performing propensity-score matching. Therefore, our study is novel and more rigorous compared with previous studies in that no previous studies have performed analysis on a matched population.

Several limitations of this study must be considered. First, this was a prospective multicenter cohort study and may have unavoidable methodological biases that could impact the results. However, to reduce bias as much as possible, we performed propensity score matching and multivariate logistic regression. Second, although stenosis and vasospasm of coronary artery were evaluated in this VA-Korea registry, it was not possible to determine whether vasospasm occurred in the presence of atherosclerotic stenosis. However, it yielded a meaningful finding that suggested VA patients with significant stenosis had worse clinical outcomes, whether the vasospasm occurred in the fixed atherosclerotic lesion or caused an atherosclerotic burden in another, non-spastic coronary artery. Third, there was no information on whether coronary intervention had been performed in the “significant stenosis” group after baseline CAG, which could affect the clinical outcome in VA patients. In addition, there was no information on drug therapy after vasospasm was demonstrated by EG provocative tests, which could also have

affected the clinical prognosis in VA patients. However, although drug information was limited and not presented here, there was no significant difference between the “significant stenosis” group and “no significant stenosis” group regarding whether drug therapy was maintained during the follow-up period.

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