Successful Treatment of Refractory Angina Pectoris due to Multivessel Coronary Spasm with Valsartan

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Abstract

This case report describes a 78-year-old man with recurrent angina attacks due to coronary spasm. He was treated with maximum daily doses of antianginal and antioxidative medications, including isosorbide mononitrate (40 mg), diltiazem (200 mg), and tocopherol nicotinate (300 mg). Despite the use of these medications, rest angina occurred 2 or 3 times during sleep. Although his symptoms disappeared promptly with the use of sublingual glycerine trinitrate (GTN), an angiotensin II receptor blocker, valsartan (80 mg), was added on a daily basis with the intent of improving endothelial function and controlling his angina. After beginning 80 mg/day of valsartan, the number of the anginal attacks decreased by about 66%. The anginal attacks totally disappeared after the dose of valsartan was increased to 160 mg/day. To confirm the effect of valsartan on his angina, valsartan was stopped temporarily with his consent. His anginal attacks increased to the same frequency that was observed before valsartan; therefore, valsartan therapy was resumed. The data indicate that the addition of valsartan to maximum antianginal medications may be effective in helping to control angina attacks at rest due to coronary spasm.

Key words: coronary spasm, refractory angina, angiotensin II type 1 receptor blocker, valsartan

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Coronary spastic angina (CSA) is well treated with calcium antagonists and/or nitrates in most cases. However, despite the use of maximum doses of antianginal drugs, there are cases of refractory angina pectoris; some have been reported to be cured by mechanical interventions with coronary stents (1, 2) or pharmacological interventions other than ordinary antianginal medications, including β1-adrenoceptor agonists (3) and corticosteroids (4). The vascular endothelium is a multifunctional organ that plays an essential role in normal vascular physiology, and endothelial dysfunction may be a critical factor in the pathogenesis of CSA (5, 6). In patients with CSA, antioxidant administration, in addition to conventional treatments, has beneficial effects for endothelial function (7), the coronary vasomotor response to acetylcholine (8) and suppression of variant angina attacks (9). It has been reported that angiotensin II stimulates the generation of vascular reactive oxygen species via NADH/NADPH oxidase activation (10) and that an angiotensin II type 1 receptor blocker (ARB), valsartan, improves endothelial vasomotor dysfunction through suppression of free radical production in a rabbit infarction model (11). In addition, we previously reported that an ARB, candesartan, attenuates nitrate tolerance in patients with CSA (12). Therefore, we hypothesized that ARBs may have beneficial effects in the treatment of drug-refractory CSA.

Case Report

A 78-year-old Japanese man was admitted to the Cardiovascular Medicine Department of Kumamoto University Hospital due to angina occurring from midnight to early morning. CSA was suspected because the chest pain was not induced by effort during daytime. He was an ex-smoker (20 cigarettes per day for 43 years) who quit smoking 8 years previously. He did not have any coronary risk factors other than smoking. On the 2nd hospital day, he underwent coronary angiogram to elucidate the causes of his chest symptom. The control coronary angiogram revealed that his coronary arteries had no apparent organic lesions, therefore sub-
sequent coronary spasm provocation test by intracoronary injection of acetylcholine (ACh) was done as reported before (13, 14). The provocation test revealed that he had multivessel coronary spasm which led to the total occlusion of the right and left circumflex coronary arteries as well as severe narrowing of the left descending coronary artery. No organic lesions were observed after intracoronary injection of 0.5 mg isosorbide dinitrate into the right and 1.0 mg into the left coronary artery. These findings indicate that this patient had multivessel coronary spasm (Fig. 1), the most severe form of coronary spasm. During the provocation test, he complained of the same chest symptoms as he experienced before admission. The ECG during the examination revealed ST-segment elevation in leads I and aVL after ACh injection into the left coronary artery and in II, III and aVF after ACh injection into the right coronary artery (Fig. 2). These findings suggested that his angina was variant angina (15) although the ECG findings were obtained during just a
Figure 3. The upper bar graph shows the number of angina attacks based on symptoms collected from the patient’s diary during the observation period in this case report. Consumption of glycerine trinitrate fluctuated in accordance with the number of angina attacks and varied inversely with the dose of valsartan.

provocation test. Immediately after the coronary angiogram, treatment with long acting diltiazem (200 mg b.i.d.) and isosorbide mononitrate (40 mg b.i.d) was started. Because the treatment proved to be effective in reducing his angina, he was discharged from the hospital on the 7th hospital day. About 4 weeks after his discharge, on his first visit to the outpatient clinic, he complained of angina recurrence. He was treated with additional use of tocopherol nicotinate (300 mg t.i.d.) as reported previously (7) and was instructed to take the medication as late in the day as possible or just prior to sleep because his angina occurred from midnight to early morning. Despite the use of these medications lasting 4 weeks, he sometimes suffered from resting chest pain which occurred 2 or 3 times during sleep. He took glycerine trinitrate (GTN) at night as needed to relieve his angina. Because his symptoms disappeared promptly with the use of GTN, his chest symptoms were thought to be refractory angina pectoris due to coronary spasm. He was requested to keep a diary to record the number of angina attacks and the amount of GTN consumed until his next visit 4 weeks later. According to his diary, he had 18 angina attacks and took 19 tablets of sublingual GTN over a period of the 4 weeks (Fig. 3). With the expectation of suppression of anginal attacks through improving endothelial function, oral administration of valsartan (80 mg/day) was given on a trial basis. After the use of 80 mg valsartan, the number of angina attacks and GTN use during next 4 weeks was decreased by 66%. Furthermore, angina attacks completely disappeared after increasing the dose of valsartan to 160 mg and he did not consume any GTN tablets during the 4-week period (Fig. 3). Valsartan was administered twice a day at the same time as diltiazem and isosorbide mononitrate. To confirm the effect of valsartan on his angina attacks, valsartan was discontinued during the next 4 weeks with his consent. During this period, angina attacks recurred at about 50% of the number in the first 4 weeks in the absence of valsartan (Fig. 3). Because his blood pressure response to 160 mg of valsartan was acceptable and the drug was believed to effectively control his angina, valsartan was added to his regular prescription list. During the 4 weeks after valsartan was used on a regular basis, he had 1 angina attack and consumed 2 GTN tablets.

Discussion

This is the first report demonstrating that an ARB may be effective in suppressing angina attacks in a patient with severe, drug-refractory CSA. Of all ARBs, valsartan was used in this case because its AT1 selectivity is high enough (16) and indirect AT1 stimulation effect such as vasodilation and nitric oxide increasing by the drug was more highly anticipated (17). We speculate that angiotensin II type 1 blocking and antioxidative effects, and/or attenuation of nitrate tolerance were responsible for the beneficial effect of valsartan on CSA in this patient.

Drug-refractory coronary spastic angina

Coronary spasm plays an important role in the pathogene-
sisis of not only CSA but also ischemic heart disease in general (18). Multivessel coronary spasm is thought to be one of the most severe forms of CSA because simultaneous multivessel coronary spasm is associated with severe and extensive myocardial ischemia (14). Multivessel coronary spasm is often associated with refractory angina (19) and multiple medications are often used in this condition to try to relieve symptoms. In the present case, coronary angiography revealed severe multivessel coronary spasm with complete occlusion of the right and left circumflex coronary arteries. Aggressive medical treatment with a calcium channel blocker, a nitrate and vitamin E were not sufficient to control the anginal attacks. It has been reported that refractory CSA was successfully treated with a number of interventions including stenting (1, 2), β1-adrenoceptor agonists (3) and corticosteroids (4). In this case, the daily administration of 160 mg valsartan was effective in relieving angina that was refractory to conventional medications for coronary spasm.

**Manner of expression of valsartan effects on coronary spastic angina**

In the case, the effects of valsartan on coronary spasm could be dose dependent because 160 mg of valsartan was more effective to inhibit anginal attacks due to coronary spasm than 80 mg. However, 160 mg of valsartan after the temporary cessation of the drug failed to completely inhibit the attacks as observed with the previous administration of the same dose. This means that it takes some time to express the valsartan effects although acute effects were also observed to some extent. In this way, manner of valsartan effects on coronary spasm could be comprised of both acute and chronic effects.

**Mechanisms of acute effects of valsartan on coronary spastic angina**

The mechanisms of valsartan effect on coronary spasm are not clear from this study. It is not likely that valsartan acts solely to inhibit coronary spasm, although we did not demonstrate an effect of valsartan in the absence of other drugs. In general, large epicardial coronary arteries are mainly involved in coronary spasm (20), on the other hand, angiotensin II induces coronary contraction greater in small coronary arteries than in larger ones (21), therefore ARB seems to attenuate the contraction in small coronary arteries more. In this way, it is not likely that an ARB solo is effective enough like other ordinary antianginal drugs to suppress coronary spasm. However, it has been reported that coronary microvascular spasm also causes myocardial ischemia in patients with CSA (22). If the present case is one such case, there is a possibility that ARBs play a synergistic role to inhibit anginal attacks due to coronary spasm when they are given in combination with other agents such as calcium channel blockers and nitrates. This possibility gives an explanation for the acute effects of ARB in suppressing anginal attacks due to coronary spasm.

**Mechanisms of chronic effects of valsartan on coronary spastic angina**

It is well known that oxidative stress deteriorates vascular endothelial function, leading to decreased nitric oxide production and the precipitation of coronary spasm. We previously reported that plasma levels of thioredoxin, a sensitive biomarker of oxidative stress, are increased in patients with CSA (23). In fact, antioxidants like vitamin C and vitamin E have been reported to improve endothelial function (7, 8) and suppress anginal attacks (9) in patients with CSA. An antioxidant action of ARBs has also been recognized in recent years (10, 24-26). Thus, ARBs used in combination with other regular antianginal medications could be effective in preventing anginal attacks due to coronary spasm through an antioxidative effect. This possibility gives an explanation for chronic or long-term effects of ARB in suppressing anginal attacks due to coronary spasm.

**Another possible mechanism of valsartan on coronary spastic angina**

The effects of nitrates on anginal attacks are sometimes compromised by rapid development of tolerance during sustained therapy (27). In the present case, isosorbide mononitrate (40 mg b.i.d.) was used for a long time and it is possible that nitrate tolerance developed. We previously reported that candesartan attenuated nitrate tolerance through reducing oxidative stress induced by activation of angiotensin II (12). It is possible that the effect of ARBs on refractory angina due to coronary vasospasm could be mediated by the prevention of nitrate tolerance.

**Conclusion**

We report a drug-refractory case of CSA that was successfully treated with the ARB, valsartan as an add-on drug with regular antianginal medications. Multiple direct and/or indirect effects of the drug could be involved in reducing anginal attacks in this case. A randomized, prospective, controlled trial is needed to validate the widespread additive use of ARBs to treat refractory angina pectoris due to coronary spasm.

**References**


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