

[Case Report]

**A case of refractory vasospastic angina pectoris
treated effectively with denopamine alone
– Pharmacological mechanism of its action –**

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(Received May 28, 2013, Accepted July 1, 2013)

SUMMARY

A 71-year old man suffered from chest pain on effort. He frequently experienced chest pain in the early morning while sleeping. During Holter monitor recording, he suffered from chest pain that ceased with sublingual administration of nitroglycerin. The recording showed horizontal type depression of the ST segment over 0.2 mV of channel CM5 during chest pain. Therefore, the patient was diagnosed with vasospastic angina pectoris.

Administration of isosorbide dinitrate and extended-released nifedipine per os was started, and for a while, chest pain ceased. However, after about 1 month, chest pains reappeared during sleep and bathing. Isosorbide dinitrate-tape was added, but it was not effective in treating the chest pain. The β 1 selective adrenergic receptor stimulant, denopamine, was then administered to prevent angina attacks. In the following month, there was no chest pain. The medicines were discontinued 1 at a time in the order isosorbide dinitrate-tape, nifedipine, and isosorbide dinitrate, at intervals of 1 month.

Although denopamine alone remained as a treatment, there were no angina attacks, and abnormal changes in the ST segment were not observed on Holter monitoring after 3 months of denopamine only. Denopamine alone was effective in the case of refractory vasospastic angina pectoris.

Key words: refractory vasospastic angina pectoris, adrenergic beta-1 receptor vasodilation, denopamine

I . Introduction

It has been shown that the incidence of vasospastic angina pectoris is more frequent in Japanese people than in Caucasians, and calcium channel blockers and/or nitrates were effective in these patients[1]. Conversely, it has been claimed that about 20% of cases are not treated effectively with combined administration of

calcium channel blocker and nitrate[2].

In refractory cases, it has been shown that nicorandil, sympathetic alpha-1 receptor blockade, steroids, vitamin E, magnesium, and bypass surgery were sometimes effective. A adrenergic beta receptor (β AR) stimulator-induced vasodilative response in the coronary arteries has been reported[3,4]. Other reports showed that combined administration of denopamine, a selective adrenergic beta-1 receptor (β 1AR) stimulant, was effective in cases of refractory vasospastic angina pectoris. However,

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Abbreviations: β AR, adrenergic beta receptor; β 1AR, adrenergic beta-1 receptor; β 2AR, adrenergic beta-2 receptor

there have been few reports that the administration of denopamine alone abolishes refractory angina attacks [5].

Here, I report on a refractory case whose symptoms were relieved by the administration of denopamine alone, and on the pharmacological role of β 1AR on coronary vasodilative action. Additionally, the problems of the guidelines for vasospastic angina pectoris edited by the Japanese Circulation Association are discussed.

II. Case report

A 71-year old man with no striking medical history, and who had given up smoking 50 years earlier, presented with episodes of angina. November 2010, he experienced left-sided precordial pain while cycling uphill. Soon after taking rest, the pain disappeared. Some days later, he woke with precordial pain at about 4 AM, that disappeared after about 15 min. He then suffered from frequent angina episodes during sleep at about 4 to 5 AM prior to visiting the outpatient clinic.

On visiting the clinic, his physical examination and laboratory tests were normal. Because he was suspected of having vasospastic angina pectoris, he was given sublingual nitroglycerin tablets to treat the angina attacks and put on a Holter monitor (Digital Walk FM-150, Fukuda Denshi, Chiba City, Japan). During the monitoring, he experienced an angina attack, and he promptly took a nitroglycerin tablet sublingually

with subsequent disappearance of precordial pain. The recording showed horizontal type depression of ST segments over 0.2 mV in channel CM5 during the attack of pain, and the ST segments returned to the isoelectrical level in accordance with the cessation of pain after taking nitroglycerin (Fig. 1) [6]. No other abnormal ST segment deviation was shown on the recording except during the angina attack. Coronary angiography was not performed because the patient's spouse had regular hemodialysis, and he needed to take care of her.

Immediately after Holter monitor recording, the patient was treated with extended-released nifedipine, 20 mg/day and isosorbide dinitrate (ISDN), 40 mg/day. There were no attacks during therapeutic trials with these agents. However, the attacks recurred 1 month later while asleep in the early morning and while taking a bath in spite of the administration of these agents. Additional treatment with ISDN- tape, 40 mg/day, was not effective in treating these attacks, but administration of sublingual nitroglycerin stopped the chest pain. An additional drug, denopamine, 20mg/day, a selective adrenergic beta-1 receptor (β 1AR) agonist, prevented these angina attacks.

After confirmation that there had not been any angina attacks the previous month, I initiated a trial of withdrawal of the other medicines one by one to verify the effectiveness of the administration of denopamine alone, with the patient's consent. The patient actively

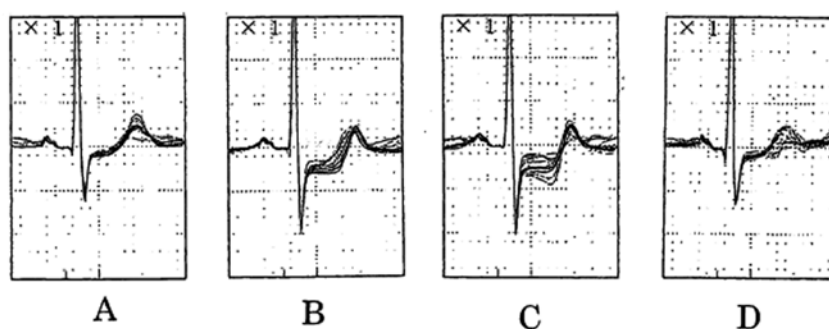


Fig. 1 Continuous electrocardiography in a patient with an anginal attack.

Electrocardiography is presented by means of superimposed electrocardiogram: 20 superimposed blocked waves per 5 min, comprising superimposed averaged electrocardiographic waves per 15 s block. Data were analyzed using SCM-6000 (Fukuda Denshi, Chiba City, Japan). A. Before angina attack (12 : 15-12 : 20 hours). B. Initiation of ST segments depression (12 : 20-12 : 25 hours). C. Experiencing angina attack and taking a nitrate sublingually (12 : 25-12 : 30 hours). D. Chest pain ceasing with ST segments returned to baseline (12 : 30-12 : 35 hours).

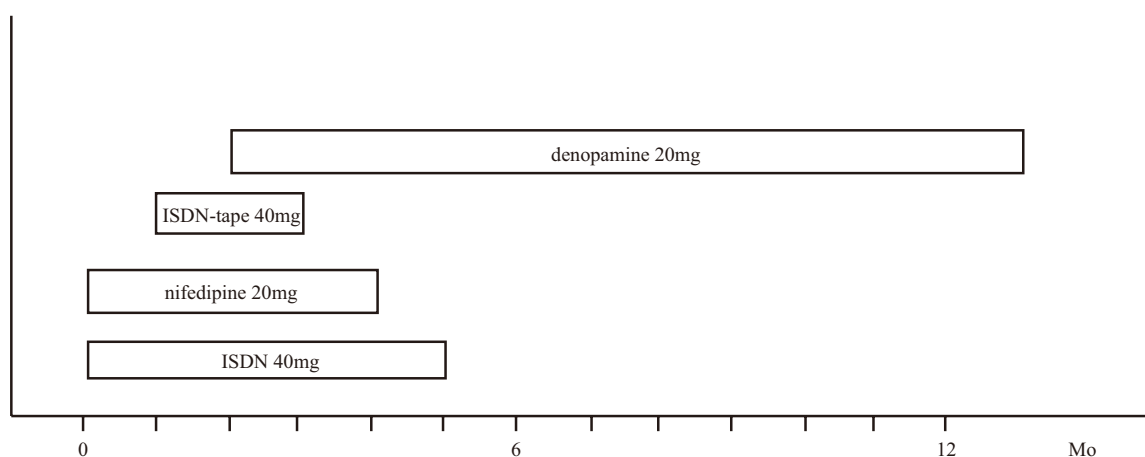


Fig. 2 Administration of medicines.

At first, ISDN, 40 mg/day, and extended-released nifedipine, 20 mg/day, were administered. Thereafter, denopamine, 20 mg/day, was added. After confirming that there were no further anginal attacks, ISDN-tape, nifedipine, and ISDN were discontinued in turn. Mo, month; ISDN, isosorbide dinitrate.

consented to this because some medicines would be stopped. First, the ISDN-tape was stopped while ISDN, nifedipine, and denopamine were continued orally on the same doses. The patient was advised that if an angina attack occurred, he should take a nitroglycerin tablet sublingually immediately and restart the previous treatment, namely the ISDN-tape.

Because there was no angina attack in the next month, nifedipine, and then ISDN in turn, were withdrawn at monthly intervals after confirmation that there had been no chest pain. After taking denopamine alone, the patient experienced light chest oppressiveness on getting up in the morning for 4 days continuously. These symptoms disappeared within 5 minutes after taking a nitroglycerin tablet sublingually. After that, the patient did not experience these symptoms. After 3 months of taking denopamine alone, the Holter monitor was put on. During monitoring, the patient did not have any symptoms and no abnormal ST segment deviation was recorded (Fig. 2). Over a 24-month period, no angina attack was observed. Thus, the administration of denopamine was fully effective in this case of refractory vasospastic angina pectoris.

III. Discussion

Although in this case coronary angiography and a

drug-induced test for vasospasms were not performed, in accordance with the guidelines of the Japanese Circulation Association [7], the diagnosis of refractory vasospastic angina pectoris was made for these reasons; (1) angina attacks occurred at rest, mainly while asleep; (2) ST segment deviation with chest pain was observed during Holter monitor recording; (3) administration of combined nitrate and a calcium channel blockade did not prevent the angina attacks.

Addition of denopamine to nitrate and the calcium channel blocker prevented the angina attacks. After the cessation of angina attacks, administration of nitrate and the calcium channel blocker were stopped in turn. Although finally denopamine alone was given, the angina attack did not recur and the Holter monitor recording did not show abnormal ST segment changes. It was therefore concluded that the administration of denopamine alone was effective in this refractory vasospastic angina case. This has seldom been reported before [5].

It is widely accepted that stimulation of adrenergic β 1AR and/or β 2AR receptors causes dilatation of both large and small coronary arteries [8,9]. Although Parent et al. showed in dogs that resistant coronary arterial dilatation via β AR was caused by nitrogen oxide generated in the endothelium [10], Ghaleh et al. concluded that large coronary arterial dilatation by

stimulation of β AR was a direct reaction mainly caused by β 1AR, and was neither dependent on coronary blood flow nor on the endothelium of vessels in an in vivo experiment[11]. In their first report of vasospastic angina pectoris, Prinzmetal et al. described a case who was responsive to the administration of nylidrin hydrochloride, a sympathetic vasodilator of peripheral arteries[12].

Amenta et al. presented data on β AR values and the ratio of β 1AR and β 2AR in human large coronary arteries, using radioreceptor binding and autoradiographic techniques. Analysis of isoforms indicated that the binding capacity in the right coronary artery was greater than that in the left coronary artery and the anterior interventricular branch; in addition, the ratio of β 1AR to β 2AR was greater in the right coronary artery than in the left coronary artery and the interventricular branch. The result of autoradiographic analysis revealed a predominance of β 1AR in the medial layer (namely smooth muscle layer) and that β 2AR was localized primarily in the adventitia, the adventitia-media border, and the intimal layer[13]. It is thought that the action of the β 1AR stimulant is different in the region of large coronary arteries.

Focal spasm has been shown to be most common in the right coronary artery[14]. Fifteen cases that included data on 18 focal arteries were given denopamine[5,15-22]. Ten of these focal arteries were the right coronary arteries and 8 were the left. Three of 15 cases showed both left and right coronary artery spasms. Seven cases with sole right coronary artery spasms, 2 sole left, and all 3 cases of both right and left were treated effectively with denopamine. Ten of the focal arteries were right coronary arteries and 5 were left. Thus, denopamine was effective in all 10 right coronary arteries. Although there are only a few arteries describing lack of the treatment effect of denopamine, these reports were 3 patients all with sole left coronary artery spasms[16]. It seems that the right coronary artery cases were more responsive to denopamine than the left coronary cases. This might be because β 1AR was more concentrated in the right coronary artery than in the left.

Shimizu et al. described 2 cases that were not

responsive to denopamine but did respond to venous injection of norepinephrine for the treatment of left coronary artery vasospasm[16]. Although it is known that norepinephrine causes contraction of the coronary arteries via the adrenergic alpha-1 receptor, Miyashiro and Feigl showed that norepinephrine had a direct dilative action on the coronary artery via β 1AR and β 2AR[23]. Further, Sun et al. reported that norepinephrine directly dilated human coronary arterioles and small arteries isolated from the left ventricle via β 2AR in an in vivo experiment[24]. In patients in whom administration of denopamine is not fully effective, consideration should be given to the combined administration of denopamine and β 2AR selective stimulants, reflecting the present-case report and the fact that there is a greater concentration of β 2AR in the left coronary arteries than in the right coronary arteries.

It has been reported that a transplanted heart developed vasospastic angina pectoris and a surgical denervated heart had vasospasms[25,26]. In these studies, the authors referred to the possibility of other factors besides the autonomic nervous system as the cause. Almost all medicines to induce diagnostic vasospasms and treat angina in patients do not work directly on the autonomic nervous system but work on vascular receptors. The abnormal function of vascular receptors might also be considered as the cause of vasospasms.

The guidelines of the Japanese Circulation Association for the treatment of vasospastic angina pectoris do not recommend treatment with β 1AR stimulants[7]. Because the acetylcholine test to induce vasospasm is recommended, it seems preferable to actively treat with denopamine.

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