Coronary Artery Spasm Induced by Injection of an Atropine-neostigmine Mixture. A Case Report.

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ABSTRACT. We report a case of coronary artery spasm which occurred after injection of neostigmine 3.5 mg mixed with atropine 1.5 mg to antagonize residual muscle relaxation after thyroid surgery in a 40 year-old woman with no history of heart disease. We hypothesized that increased acetylcholine levels induced by neostigmine may have elicited coronary artery spasm via mechanisms of endothelial modulation of vascular tone or activation of the autonomic nervous system. This case illustrates a rare, but serious, complication of reversal of neuromuscular blockade.

Key words: heart — coronary spasm — complications — neostigmine

Reversal of neuromuscular blockade with neostigmine and atropine is associated with no serious problems in the vast majority of patients, although it has been reported that it may cause dysrhythmias or even cardiac arrest especially in aged patients or patients taking tricyclic antidepressants.[1-3] We report a case of coronary artery spasm which occurred after reversal of neuromuscular blockade with atropine and neostigmine in a 40-year-old woman. To our knowledge, this is the first report of coronary artery spasm elicited by reversal agents.

CASE REPORT

A 40-year-old woman was scheduled for subtotal resection of the thyroid with bilateral neck lymph resection because of left thyroid cancer. Pre-anesthetic examination revealed no abnormal findings except for a 1 cm nodule palpated on the left anterior neck. Laboratory data including thyroid function were also within normal limits. There was no history suggestive of coronary artery disease. She had not taken any drugs habitually. ECG showed a sinus rhythm with a normal axis. (Fig 1A)

Preoperative medication consisted of atropine 0.5 mg and hydroxyzine 50 mg im. one hour before induction of anesthesia. Anesthesia was induced with thiopental 4 $mg \cdot Kg^{-1}$. The trachea was intubated after muscle relaxation with vecuronium 8 mg. Anesthesia was maintained with sevoflurane in 60% N_2O and 40% O_2 supplemented with pentazocine 30 mg and diazepam 10 mg iv. Muscle paralysis was maintained with pancuronium. ECG (lead II) and arterial oxygen hemoglobin saturation (SpO_2) were continuously monitored. Arterial blood pressure was measured by radial artery cannulation.

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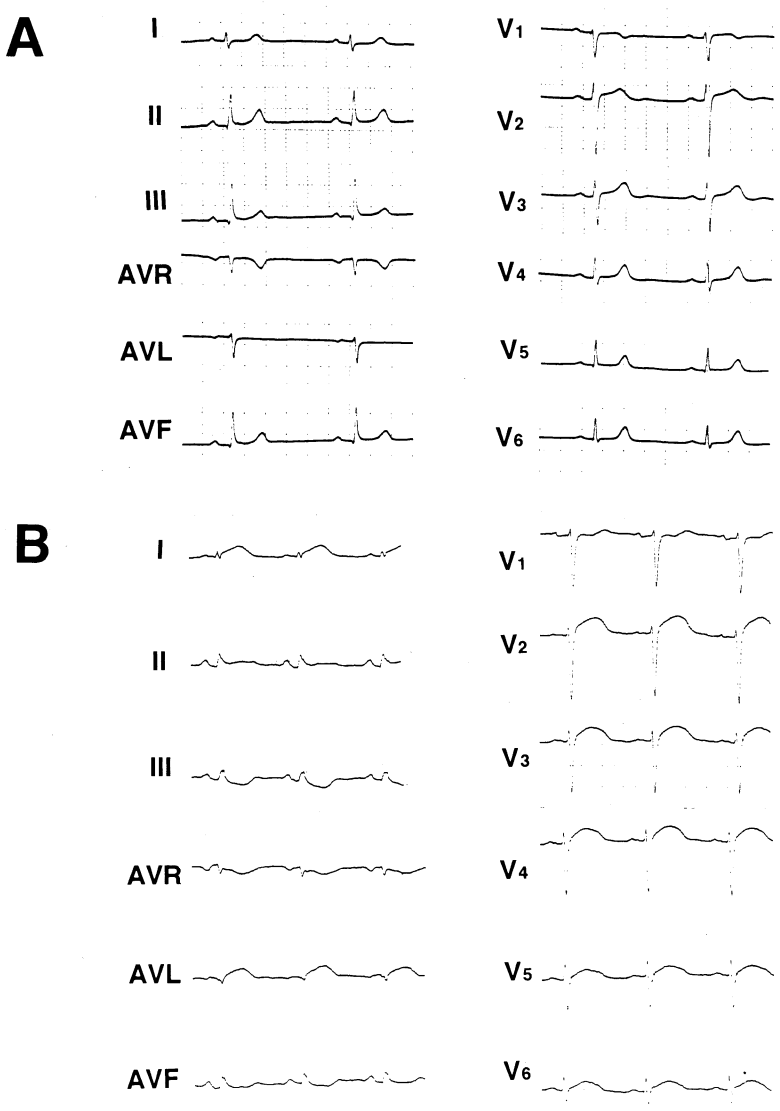

Fig 1. Electrocardiograms of a 40-year old patient before surgery (A) and during an episode of coronary artery spasm taken at the ICU (B). Note ST segment elevation in leads V2-5 and aVL.

During 3.5 hour surgery anesthesia was completely uneventful. Histopathological diagnosis of the tumor was papillary carcinoma. Arterial blood pressure ranged 140-120/70-80 mmHg and her heart rate was 70-80 beats per minute. Five minutes after the end of surgery, the patient awoke and breathed spontaneously. A mixture of atropine 1.5 mg and neostigmine 3.5 mg was given intravenously to reverse residual muscle relaxation. The patient's arterial blood pressure suddenly increased to 180/110 mmHg and her heart rate to 100-110 beats/minute, with ST segment elevation on the monitor. The trachea was extubated and she was transferred to the postoperative ICU. On

arrival at the ICU after three minutes, a pulse oximeter indicated that SpO_2 ranged between 60-75%, and the PO_2 of the arterial blood was 49 mmHg despite oxygen administration (5 $l \cdot min^{-1}$) by a face mask. The trachea was reintubated and the lung was mechanically ventilated with 100% oxygen and 5 cm H_2O of PEEP. While SpO_2 improved to 95% with mechanical ventilation, arterial pressure decreased to 75/40 mmHg. A continuous infusion of dopamine at a rate of 5 $\mu \cdot kg^{-1} \cdot min^{-1}$ was began and dobutamine infusion was also combined to maintain systolic blood pressure above 100 mmHg. ECG showed ST-segment elevation in leads V_{2-5} and aVL. (Fig 1B) Infusion of nicardipine and nitroglycerin was started at a rate of 0.6 $\mu g \cdot min^{-1} \cdot kg^{-1}$ and maintained for the following two days. The ST segment elevation returned to the baseline after one hour. A chest X-ray film taken at the arrival in the ICU and on the next day revealed pulmonary congestion. An echocardiographic examination demonstrated impaired wall motion of the left anterior wall. On the third postoperative day the trachea was extubated and she was transferred to the ward. Creatinine phosphokinase and lactate dehydrogenase levels during the postoperative course were within normal limits. She was discharged home on the twelfth hospital day in stable condition.

DISCUSSION

Sudden ST-segment elevation in leads V_{2-5} and aVL, and hypokinesia of the left anterior wall demonstrated by echocardiographic examination are consistent with coronary artery spasm, probably at the left anterior descending coronary artery. Normal LDH and CPL levels in the postoperative days imply that myocardial ischemia was transient and myocardial infarction did not ensue in our patient.

Although coronary artery spasm has been well recognized as a serious complication of coronary bypass surgery with high mortality,[4,5] there have been only a few reports on coronary artery spasm occurring during other kinds of operations.[6-8] We have reported four cases of coronary artery spasms; two patients with non-coronary cardiac surgery, one patient with gastric surgery and one patient wth plastic surgery. Many stimuli, such as increased α-adrenergic activity, respiratory alkalosis, cold, local trauma and release of vasoactive substances from platelets, are known to elicit coronary artery spasm.[5] In one of the four cases, coronary artery vasospasm was triggered by extreme respiratory alkalosis. In the other cases, the factors which elicited coronary artery spasm were not identified. In the present case, reversal of muscle paralysis seems to have provoked coronary artery spasm.

Coronary artery spasm is produced by strong contraction of vascular smooth muscle due to disturbances of coronary vasomotion, and modulation of vascular smooth muscle tone is thought to play a critical role in triggering the event. Vascular smooth muscle tone is modulated by vasoactive substances such as prostacyclin, endothelium-derived relaxing factors (EDRFs), and endothelium-derived hyperpolarizing factor, which are synthesized and released by the endothelium under a basal condition and in response to stimulation.[9] Louder *et al*[10] demonstrated that coronary artery spasm is provoked in segments with atherosclerosis by intracoronary acetylcholine injection in humans, while normal coronary arteries are dilated. Acetylcholine has been

shown *in vitro* to stimulate EDRFs' synthesis and release in the endothelium, resulting in vasodilation, while it has a direct constricting effect on vascular smooth muscle.[9] Therefore, it is hypothesized that acetylcholine infusion induced coronary artery spasm, because the endothelial modulation mechanisms of vascular smooth muscle were impaired and the direct constricting effect on vascular smooth muscle was not opposed by EDRFs. Neostigmine as an anticholinesterase increases acetylcholine levels at all sites including neuromuscular junction and the myocardium. Therefore, the coronary artery spasm of our patient can be explained by an abrupt increase in acetylcholine levels due to the reversal of neuromuscular blockade in the myocardium. The reason for the absence of the endothelial dilator mechanism is unknown.

In addition to the endothelial mechanism, it is also possible that neostigmine triggered coronary artery spasm through the autonomic nervous system. Yasue and his group[11,12] have shown that administration of methacholine or acetylcholine provokes coronary artery spasm in patients with vasospastic angina. They postulated that increased parasympathetic activity is involved in the initiation of coronary artery spasm and that the increase in parasympathetic nerve activity stimulates the sympathetic nervous system which then, in turn, causes coronary vasoconstriction via activation of α-receptors in large coronary arteries. Therefore, parasympathetic stimulation caused by neostigmine can be therefore attributed to the initiation of coronary artery spasm in our patient, although atropine was simultaneously given as a mixture.

The effects of thyroid surgery on the sympathetic nervous system must be considered. Surgical manipulation of the neck was necessarily accompanied by stimulation and/or damage to sympathetic nerve fibres, although we observed no significant changes in blood pressure and heart rate during surgery. It is therefore possible that surgical manipulations may also have contributed to the production of coronary artery spasm by autonomic nerve dysfunction induced by neostigmine administration.

Theoretically, the possibility also that atropine may have been related to provocation of coronary artery spasm, since we injected a mixture of neostigmine with atropine for reversal of muscle paralysis. We think, however, that atropine is unlikely to elicit coronary vasospasm, because it has been shown to suppress attacks of variant angina and was used as treatment for coronary artery spasm until calcium antagonists became available.[11]

Pulmonary congestion and the need for pharmacological support with dopamine and dobutamine infusions for a period of two postoperative days indicate that left ventricular dysfunction continued after the event. This may be explained by the concept of "stunned myocardium"; *i.e.*, prolonged myocardial dysfunction following transient myocardial ischemia.[13] It has been demonstrated that halothane and isoflurane attenuate post-ischemic left ventricular dysfunction.[14] The effects of sevoflurane, however, remain to be clarified.

In summary, we reported a case of coronary artery spasm in a 40-year-old woman with no history of coronary artery disease, which occurred subsequent to injection of a neostigmine and atropine mixture after thyroid surgery.

REFERENCES

1) Owens WD, Waldbaum LS, Stephen CR : Cardiac dysrhythmia following reversal of neuromuscular blocking agents in geriatric patients. Anesth Analg **57** : 186-190, 1978
2) Glisson SN, Fajardo L, El-Etr AA : Amitriptyline therapy increases electrocardiographic changes during reversal of neuromuscular blockade. Anesth Analg **57** : 77-83, 1978
3) Pooler HE : Atropine, neostigmine and sudden death. Anaesthesia **12** : 198-202, 1957
4) Buxton AE, Goldberg S, Harken A, Hirshfeld JR. J, Kastor JA : Coronary artery spasm immediately after myocardial revascularization. Recognition and management. N Engl J Med **304** : 1249-1253, 1981
5) Skarvan K, Graede E, Hasse J, Stulz P, Pfisterer M : Coronary artery spasms after coronary artery bypass surgery. Anesthesiology **61** : 323-327, 1984
6) Fujita Y, Sasaki Y, Endoh E, Kimura K, Fukui A, Ohsumi A, Takaori M : Intraoperative coronary artery spasm during noncoronary artery surgery. Journal of Cardiothorac Anesth **4** : 740-743, 1990
7) Briard C, Coriat P, Commin P, Chollet A, Menasche P, Echter E : Coronary artery spasm during non-cardiac surgical procedure. Anaesthesia **38** : 467-470, 1983
8) Whitten CW, Latson TW, Cochran RP, Elmore JC, Griffin JD : ST-segment elevation during cardiac electrophysiologic surgery. Anesthesiology **75** : 161-163, 1991
9) Vanhoutte PM, Shimokawa H : Endothelium-derived relaxing factor and coronary vasospasm. Circulation **80** : 1-9, 1989
10) Ludmer PL, Selwyn AP, Shook TL, Wayne RR, Mudge GH, Alexander RW, Ganz P : Paradoxical vasoconstriction induced by acetylcholine in atherosclerotic coronary arteries. N Engl Med **315** : 1046-1051, 1986
11) Yasue H : Pathophysiology and treatment of coronary arterial spasm. Chest **78S** : 216-223, 1980
12) Okumura K, Yasue H, Horio Y, Takaoka K, Matuyama K, Kugiyama K, Fujii H, Morikami Y : Multivessel coronary spasm in patients with variant angina : a study with intracoronary injection of acetylcholine. Circulation **77** : 535-542, 1988
13) Braunwald E, Korner RA : The stunned myocardium : Prolonged, postischemic ventricular dysfunction. Circulation **66** : 1146-1149, 1982
14) Warltier DC, Al-Wathiqui MH, Kampine JP, Schmeling WT : Recovery of contractile function of stunned myocardium in chronically instrumented dogs is enhanced by halothane or isoflurane. Anesthesiology **69** : 552-565, 1988