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Nodal Tachycardia Induced By Neostigmine Administration During Off-Pump Coronary Artery Bypass Graft Surgery: What Makes the Difference? A Case Report

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ABSTRACT

Controlling the heart rate (HR) to a proper level is an important part during off-pump coronary artery bypass graft (CABG) surgery, particularly in two aspects. First, the oxygen consumption during cardiac work could be decreased, which is obviously beneficial for the myocardium suffering from inadequate blood supply. Second, slow heart action makes it easy for surgeons to perform. There are some treatments for lowering HR, where neostigmine is not commonly used but usually effective, which had been discussed more than 50 years ago. However, there are adverse responses that cannot be ignored and are even dangerous, for example, severe brady-arrhythmia and overload of secretion in the trachea. Here, we report a nodal tachycardia case after neostigmine infusion.

CASE DESCRIPTION

The patient was a 59-year-old woman (163cm, 70kg). She suffered hypertension for 30 years, and it was treated well by nifedipine of 30mg/qd and metoprolol of 12.5mg/bid. The patient also had a six-year history of diabetes with gliclazide modified release tablet of 30mg/qd for daily treatment. Both her blood pressure and glucose were within normal ranges. Four months before her admission for cardiac surgery, the patient felt a sudden headache with paroxysmal and pulsatile features, which progressed quickly and was accompanied by left hemiplegia. The massive cerebral infarctions were detected by routine head scans in both the right frontal lobe and right basal ganglia. Three days later, a secondary hemorrhage appeared during hospitalization. She finally recovered from the hospital after positive treatments without obvious sequela.

The patient started to feel chest tightness and shortness of breath after activities with a decreased exercise capacity of 500 meters walking since six months prior. No treatment was adapted until she was attacked by severe chest pain that could not be alleviated by bed rest. She then emergently was admitted into our hospital. Stenosis in the left main artery (LM), left anterior descending artery (LAD), left circumflex artery (LCX), and right coronary artery (RCA) were detected through computed tomography coronary angiography (CTCA), and off-pump CABG then was decided.

On admission to the operating room, the patient was gently sedated with observations of blood pressure 155/96 mmHg, pulse 70beats/min, and oxygen saturation 96% on FiO2 21%. The electro-cardiogram (ECG) revealed no signs of ischemia. FiO2 of 100% was supplied through facemask and saturation reached 100% within 5 minutes. A catheter was put into the left radial artery, and the invasive blood pressure continuously was measured from 160/98 mmHg. The blood gas indexes were within normal values (PH 7.48, PO2 280 mmHg, PCO2 35 mmHg, Na+ 139 mmol/L, K+ 3.5 mmol/L, Ca++ 1.13 mmol/L, Glu 8.2 mmol/L, Lac 1.1 mmol/L, Hct 32%, HCO3 27.1 mmol/L, Be 2.7 mmol/L, SO2C 100%, and Hb 11.2 g/dL). Sufentanyl of 1.5 ug/kg, etomidate of 0.3 mg/kg, and vecuronium of 0.6 mg/kg sequentially were infused for anesthesia induction and a 7.0ID tube was intubated into the trachea smoothly without obvious fluctuation of blood pressure or HR. The central venous catheter was put into the right subclavian vein and a swan-ganz catheter was floated through the right jugular vein, by which pressures of both central vein (CVP) and pulmonary artery (PA), cardiac output (CO), and oxygen saturation of mixed venous blood (SVO2) all were measured and continuously monitored.

Sufentanyl of 20 ug and midazolen of 2 mg were added to enhance anesthesia right before the operation began. Propofol of 4-6 mg/kg/h and vecuronium of 1 ug/kg/min intravenously were pumped to keep the anesthesia state. Noradrenaline of 0.01-0.1 ug/kg/min and isosorbide dinitrate of 30-50 ug/min also were used to stabilize blood pressure and coronary perfusion during the surgery. After dissection of the left internal mammary artery (LIMA), 20 mg esmolol was infused to decrease the heart rate from over 70 beats/min, according to the surgeon's requirement. Then additional bolus of it repeatedly was infused with a total of 200 mg for a period of over 10 minutes. However, the HR was almost unaffected, whereas both mean arterial pressure (MAP) and CO decreased. Remifentanyl of 8-15 ug/kg/h also was infused and similar outcomes with those induced by esmolol were obtained.

Neostigmine of 2 mg then intravenously was intravenously given by four infusions. The patient's HR dropped to 60 beats/min 10 minutes after the first infusion, with slight declines in MAP and CO whereas PA, CVP, and peak respiratory pressure remained unchanged. Thirty minutes later, however,

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the HR gradually increased to more than 90 beats/min when the LIMA-LAD bypass was built and the apex was lifted for further performance. At the same time, MAP declined from over 100 mmHg to 90-95 mmHg. Considering the effects of surgical performance, we added noradrenaline (NE) infusion to 0.1 ug/kg/min, which stabilized the blood pressure on this level but had no influence on HR. An additional infusion of 1 mg neostigmine was given then, without obvious effect on HR and MAP until 15 minutes later when Ao-SVG-PDA-LCX bypass was built and the heart was put back. The heart rate gradually increased again from 80-90 to over 100 beats/min and ST segments in II III leads of ECG were elevated. MAP also increased from 90-95 mmHg to 100-110 mmHg. CVP, PA, and blood gas indexes kept within normal limits. CO remained over 3.2 L, during this process. All these conditions continued until after the end of the surgery, and the patient was sent back to the intensive care unit (ICU).

The patient was extubated on the second day after surgery. Before that, her ECG returned to normal. During the first four days in the ICU, her HR kept over 100beats/min under the condition that both adrenaline of 0.01 ug/kg/min and NE of 0.05-0.1 ug/kg/min were infused. The patient stayed in the ICU for five days and 14 days after surgery, she was discharged from hospital without related complications. During her re-examination at two weeks, one month, and three months after she went back home, no obvious abnormalities were detected.

DISCUSSION

Neostigmine is well known to reversibly inhibit acetylcholinesterase. As a result, the acetylcholine at nicotinic (N) and muscarinic (M) receptors in especially the end of the parasympathetic nerve and motor end-plate is accumulated. It usually is used in operating rooms as a muscle relaxant antagonist to affiliate extubation after general anesthesia. Because of the adverse effects, such as severe bradycardia or even heart arrest [Maher 2011], neostigmine is not commonly used to lower HR unless it's a special situation. In this case, since general measures, including the applications of beta-blocker (esmolol) and the opioids showed little effects, neostigmine cautiously was used under intensive monitor. However, slow HR lasted for only a short period. Then, tachycardia unexpectedly appeared after the additional neostigmine of 1 mg was infused. Similar cases have not been reported before, and this tachycardia possibly induced by neostigmine is worth discussion.

The mechanism of lowering HR by neostigmine is well known. It is able to take the place of acetylcholine to combine with acetylcholinesterase, which reversibly inhibits the function of this cholinesterase and delays the breaking down of acetylcholine. As a result, acetylcholine accumulates at the ending of vagus, which activates the M receptors and then inhibits the atrionector, myocardium, and conducting system of heart. Although this effect is not as strong as that in the motor end-plate, neostigmine could significantly decrease HR even when methods routinely used have no effects as previously reported [Zhang 2018; Hesselvik 1997].

Acetylcholine also is the key transmitter in autonomic ganglia. By acting on the N1 receptor there, acetylcholine simultaneously activates sympathetic and parasympathetic nerves. Heart functions are controlled by both sympathetic and vagus nerves, where the latter is believed to play the major role [Laborde 2018]. Therefore, the acetylcholine accumulation induced by neostigmine generally results in inhibitory effects, such as lowering rather than increasing the HR, which is the main reason that neostigmine is sometimes used to treat paroxysmal supraventricular tachycardia (PST) [Schultheis 1997].

Why did the tachycardia happen in this case? First, we reviewed the physiopathology of autonomic function in the coronary-disease heart. It was reported that vagus dysfunction closely was related to myocardial ischemia. At the same time, circulating catecholamines was found up-regulated [Shanks 2013]. Both disrupted the original autonomic balance in the heart. That is, vagus might lose its superiority in heart controlling. In this opinion, acetylcholine accumulation at autonomic ganglia induced by neostigmine infusion does possibly increase rather than lower HR as a result of sympathetic enhancement. Second, vagus also was found to be sensitive to diabetes mellitus (DM). Autonomic nerve dysfunctions in DM have long been discussed. Many of the studies reported the decreased vagal tone and/or relatively increased sympathetic tone in cardiac complication of early DM [Fisher 2017]. Under such conditions as those in the present case, neostigmine may further enhance sympathetic action through inhibiting acetylcholine degradation at autonomic ganglia. Both indicate the importance of vagal-sympathetic-balance status in the effect of neostigmine on heart function, as well as explain the unexpected tachycardia in this case.

There still was significant decline in HR at first as described, which we think should be the result of direct M receptor activation at vagal ending like those of early reports. This effect quickly was covered, possibly by the further activation of sympathetic ganglia or other mechanisms. To the best of our knowledge, although no difference between the acetylcholinesterase at vagal ending and ganglia was reported, it is the nerve endings rather than ganglia that are vulnerable to injuries induced by DM or coronary artery disease (CAD), which at least partly explained the consequent increase of HR after neostigmine infusion.

According to the monitoring data, such as CVP, BP, airway pressure, and blood gas indexes, causes including inadequate anesthesia, hypovolemia, insufficiency in muscle relaxation, electrolyte disturbance and so on, that may increase HR, could be excluded. However, there still are other possibilities, for example, reduction in coronary blood infusion induced by vagal activation, further activation of adrenal medulla as a result of acetylcholine accumulation at sympathetic ending there on base of surgery and anesthesia stress.

Here, we report tachycardia possibly induced by neostigmine infusion, which provides additional evidence about the risk of this drug during CABG. Our review further suggests the potential contraindications for neostigmine, such as myocardial ischemia, DM, or other diseases with autonomic disturbance, for which the neostigmine administration should be more cautious.

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