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CORRESPONDENCE

Research Correspondence

Hypothermia in Acute Coronary Syndrome

Brain Salvage Versus Stent Thrombosis?

To the Editor: Mild hypothermia therapy (HT), defined as body temperature between 33°C and 34°C, is associated with improvement in neurological outcome after cardiac arrest. HT reduces cerebral metabolism of glucose and oxygen consumption with ensuing neuroprotection. In 2002, randomized clinical trials in the setting of cardiac arrest validated the clinical applicability of HT in comatose patients who were survivors of an out-of-hospital cardiac arrest secondary to shockable rhythms (1). As a result, the European Resuscitation Council strongly recommends HT in these patients (2). Acute coronary syndrome (ACS) is the leading cause of cardiac arrest; a timely cardiac defibrillation and reperfusion therapy contribute to a better prognosis. The combination of early reperfusion and HT has been reported as safe and effective (3). However, complications of HT have been described and include infections or coagulation disorders, among others.

In this letter, we report our experience in patients with ACS and cardiac arrest treated with HT and its association with a high incidence of stent thrombosis (ST). From January 2010 through March 2012, a total of 28 comatose patients (20 men, mean age: 55 ± 18 years) were admitted to our hospital for out-of-hospital cardiac arrest and were treated with HT. In all cases, the first rhythm was ventricular fibrillation. HT was started in the emergency area by the administration of 4°C saline, 30 ml/kg (maximum: 2 l) infused in 30 min. Infusion was stopped if the temperature was < 33.5°C. In the intensive care unit, patients received standard treatment that included mechanical ventilation and correction of cardiovascular instability. All patients were sedated with an infusion of midazolam and morphine at doses that were adjusted for the management of mechanical ventilation. Neuromuscular relaxation was achieved with cisatracurium infusion to avoid muscular tremor. A urinary catheter with temperature sensor (Foley catheter, Rüsch sensor series 400 [silicon], Curity, Tyco, Athione, Ireland) was implanted. The extracorporeal HT system (Medivance Arctic Sun System, Louisville, Colorado) was used to control temperature. All patients reached 33°C fewer than 8 h from cardiac arrest, and this temperature was maintained for 24 h. Warming took place gradually in 24 to 30 h, with a rate of 0.10 to 0.15°C/h.

Coronary angiography was performed in 18 (65%) patients, of whom 15 had a final ACS diagnosis. Of them, 10 patients (66%) had ST-segment elevation myocardial infarction; percutaneous coronary intervention (PCI) was carried out in 11 patients. The mean interval from door to balloon was 78 ± 39 min. A total of 16 stents were implanted: 13 bare-metal stents and 3 drug-eluting stents. Antiplatelet therapy did not differ from the usual practice with dual antiplatelet therapy that included aspirin (maintenance: 100 mg/day), clopidogrel (maintenance: 75 mg/day) (loading dose in Table 1), and anticoagulation with Na heparin intravenously in all patients and glycoprotein IIb/IIIa receptor blockers if a large thrombus was seen in the catheterization laboratory (see Table 1). A total of 5 (31.2%) ST occurred during follow-up: 1 acute and 4 subacute. Four of them were bare-metal stents; all of them were in ST-segment elevation myocardial infarction patients. All were definite ST. In 4 patients, ST was diagnosed after coronary angiography, and in the last one, the diagnosis was made at

Table 1 Demographic and Procedure Characteristics of Patients With Mild HT Undergoing pPCI

Patient #	No. of Stents	Artery	BMS/DES	Size (mm)	Thrombectomy	AAS LD (mg)	Clopidogrel LD (mg)	Heparin (UI)	GP IIb/IIIa Inhibitor	Thrombotic Complication
1	1	RCA	BMS	3 × 18	Yes	500	600	7,000	Abciximab	Stent thrombosis
2	2	RCA	BMS	3 × 25/3 × 16	Yes	300	600	5,000	Abciximab	No
3	1	CXA	BMS	3.5 × 25	Yes	300	600	8,000	No	Pulmonary embolism
4	2	LAD*/CXA	DES	2.5 × 33/3 × 33	Yes	500	600	8,000	Abciximab	Stent thrombosis
5	1	LAD	BMS	3.5 × 18	No	300	600	5,000	No	Deep vein thrombosis
6	1	LAD	BMS	3.5 × 12	Yes	300	600	7,000	Abciximab	No
7	1	LAD	BMS	2.5 × 18	Yes	300	600	4,000	No	No
8	1	LAD	DES	3.5 × 20	No	500	600	6,000	No	No
9	1	LAD	BMS	2.5 × 14	Yes	300	600	8,000	Abciximab	Stent thrombosis
10	1	LAD	BMS	2.5 × 19	Yes	500	600	9,000	No	Stent thrombosis
11	4	RCA	BMS	3 × 18/3.5 × 8/2.5 × 13/2.25 × 13	Yes	500	600	8,000	Abciximab	Stent thrombosis

*The thrombosed stent was the one placed in the LAD.

ASA = acetyl salycilic acid; BMS = bare-metal stent; CXA = circumflex coronary artery; DES = drug-eluting stent; GP = glycoprotein; HT = hypothermia therapy; LAD = left anterior descending artery; LD = loading dose; pPCI = primary percutaneous coronary intervention; RCA = right coronary artery.

autopsy. In all patients, ST caused myocardial infarction. One patient died of ischemic electric storm after ST and another died of pulmonary infection after a diagnosis of anoxic encephalopathy was made. The other 3 patients were discharged without brain damage. The mean time from primary PCI to thrombotic event was 174 ± 146 h (range 8 to 376 h). Furthermore, 2 patients had a thrombotic complication not related to PCI: 1 patient had a pulmonary embolism, and another patient had a deep vein thrombosis; both occurred before discharge. There were no bleeding complications.

During the same period, we performed 2,737 PCI (42.1% pPCI). Our rate of definite ST in this period in patients without HT was 0.44% (0.7% among patient undergoing pPCI). We are concerned about the higher than expected rate of ST in patients with pPCI treated with HT. Recently, Ibrahim et al. (4) described a 14.8% rate of ST among 27 patients treated with HT and PCI. In this series, the vasodilator stimulated phosphoprotein index was significantly higher in patients with HT compared with a control group without HT. There are recent experimental data that correlate HT with an increase in platelet activation, with platelet adenosine diphosphate receptor P2Y12 playing a central role (5). Because platelet adenosine diphosphate receptor P2Y12 is a pivotal target for antiplatelet treatment in ACS, particularly in patients with an implanted stent, we hypothesize that the dual antiplatelet therapy used may be inefficient in hypothermic conditions. Moreover, metabolic conversion of clopidogrel in the liver may be reduced in hypothermia conditions. Besides, patients with HT are mechanically ventilated and require nasogastric intubation for the administration of dual antiplatelet therapy and often need correction for cardiovascular instability. Under these conditions, absorption of antiplatelet drugs may be reduced, and prothrombotic status resulting from a critical state after cardiac arrest can not be ruled out. Further studies are needed to determine why hypothermia is associated with increased rate of ST.

In conclusion, in our practice, HT treatment is associated with a disturbingly high number of cases of ST, despite guideline-indicated antithrombotic therapy. New research is needed to determine the cause of these episodes, as well as the optimal antithrombotic therapy in these patients.

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Heyde's Syndrome Incidence and Outcome in Patients Undergoing Transcatheter Aortic Valve Implantation

To the Editor: Heyde's syndrome is the association between calcific aortic stenosis and gastrointestinal bleeding (GIB) due to angiodysplasia. This rare relationship is observed in approximately 3% of patients with aortic stenosis, and it was first suggested by Edward J. Heyde in 1958 (1). The pathogenesis of Heyde's syndrome involves an acquired von Willebrand factor (vWF) deficiency secondary to aortic stenosis and other degenerative disease in elderly patients with concomitant GIB (Fig. 1) (2). Surgical aortic valve replacement (SAVR) is considered the "gold standard" therapy in patients with severe aortic stenosis (3). Therefore, we hypothesized that transcatheter aortic valve implantation (TAVI) may also be effective to treat Heyde's syndrome patients at high risk for SAVR. To test this hypothesis, we retrospectively analyzed all patients treated for TAVI between November 2007 and February 2012. Heyde's syndrome was diagnosed in the presence of both severe aortic stenosis and a history of recurrent GIB with an instrumental diagnosis of angiodysplasia (documented by colonoscopy and esophagogastroduodenoscopy). Upper and lower GIB of unknown origin and/or related to other causes was defined as bleeding not related