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Research Correspondence

Is Therapeutic Hypothermia a Risk Factor for Stent Thrombosis?

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To the Editor: Pre-clinical and clinical hypothermia trials cooling subjects between 18°C and 33°C have suggested potential deleterious prothrombotic effects (1). These data have raised major clinical concerns when considering that a large proportion of cardiac arrest survivors will undergo primary percutaneous coronary interventions (PPCIs). Moreover, in previous small clinical series analyzing the effect of therapeutic hypothermia (TH) in patients who undergo PPCI, it was observed that there was an increased rate of stent thrombosis (ST) in TH- compared with non–TH-treated patients (2). The aim of the present study was to determine whether there is a relationship between TH and ST.

We retrospectively reviewed the prospective database of the Hospital Universitario La Paz, Madrid, Spain. All patients were admitted consecutively between January 2008 and December 2012 after a PPCI with stent implantation for an ST-segment elevation acute coronary syndrome (STE-ACS), and we divided them into groups based on their exposure to TH. The hospital protocol standardized the use of double antiplatelet therapy before PPCI,

administered orally in the PPCI-only group, and a combination of intravenous aspirin plus crushed $P2Y_{12}$ inhibitor through the nasogastric tube in the PPCI-TH group. The choice of antithrombotic regimen was made at the discretion of the treating physician. In the PPCI-TH group, cooling started as soon as possible before the procedure, first with intravenous cold saline followed by the use of an automated cooling device. The target temperature (32°C to 34°C) was selected by the treating physician and maintained for 24 h, after which a controlled rewarming was set to reach 37°C in 12 to 24 h.

The incidence of ST was compared between the PPCI-TH and PPCI-only groups. Our analysis comprised both definitive/probable as well as acute/subacute ST. The classification followed the definition of the Academic Research Consortium (3). The institutional ethics review committee approved the present analysis.

Continuous variables are presented as mean ± SD and were compared with the use of the Student t test; variables that were not normally distributed were described as medians and interquartile

Table 1	Baseline Features and In-Hospital Management		
	PPCI-Only (n = 1,337)	**PPCI-TH (n = 77)**	**p Value**
Age, yrs	63.9 ± 14.1	61.2 ± 14.7	0.1
Male	1,043 (78.2)	66 (88.0)	0.03
Previous cardiovascular disease			
Previous heart failure	23 (1.7)	0 (0.0)	0.1
Previous ischemic heart disease	225 (16.9)	9 (12.0)	0.3
Previous atrial fibrillation	49 (3.7)	9 (12.0)	0.003
Coronary risk factors			
Diabetes mellitus	283 (21.2)	11 (14.7)	0.2
Hypertension	683 (51.2)	31 (41.3)	0.1
Dyslipidemia	537 (40.3)	20 (26.7)	0.02
Current or ex-smoker	836 (62.7)	36 (48.0)	0.01
Chronic renal failure	39 (2.9)	1 (1.3)	0.4
Peripheral artery disease	51 (3.8)	1 (1.3)	0.2
In-hospital management			
Mean of implanted stents	2 ± 1.2	2 ± 1.2	0.8
Aspirin	1,300 (97.5)	74 (98.7)	0.5
Clopidogrel	1,028 (77.1)	41 (54.7)	<0.0001
Prasugrel	375 (28.1)	37 (49.3)	0.0002
Clopidogrel and prasugrel	69 (5.2%)	3 (4.0%)	0.6
Unfractionated heparin	737 (55.3)	45 (60.0)	0.4
Bivalirudin	597 (44.8)	30 (40.0)	0.4
GP inhibitors IIb/IIIa	372 (27.9)	10 (13.3)	0.003
Intra-aortic balloon pump	80 (6.0)	23 (30.7)	<0.0001
Inotropes	219 (16.4)	59 (78.7)	<0.0001
Killip Kimbal II–IV	294 (22.0)	42 (56.0)	<0.0001
Mechanical ventilation	94 (7.1)	77 (100)	<0.0001
CVVHF	12 (0.9)	2 (2.7)	0.1

Values are mean ± SD or n (%).

CVVHF = continuous veno-venous hemofiltration; GP = glycoprotein; PPCI = primary percutaneous coronary intervention; TH = therapeutic hypothermia.

ranges, and differences were analyzed with the Kruskal-Wallis method. Categorical variables were compared by the chi-square test or Fisher exact test.

A total of 1,414 PPCI for STE-ACS were performed during the study period; in 77 patients, TH was used due to a comatose state after cardiac arrest. The access site for the PPCI was always femoral in the PPCI-TH group and was radial in 59% of the PPCI-only group. Baseline characteristics and in-hospital management are shown in Table 1. All patients received a P2Y$_{12}$ inhibitor. Clopidogrel was more commonly used in the PPCI-only group, whereas the PPCI-TH group received significantly more prasugrel. Aspirin was not administered to 33 (2.5%) patients in the PPCI-only group and 1 (1.3%) patient in the PPCI-TH group, mainly due to allergy or recent gastrointestinal bleeding. Both loading and maintenance doses of aspirin in all of the PPCI-TH–group patients were given intravenously. Glycoprotein IIb/IIIa inhibitors were more commonly used in the PPCI-only group.

A mean of 2 ± 1.2 stents were implanted in both groups, with an overall incidence of ST of 2.3% (n = 32). Among the patients experiencing ST, 30 (2.3%) were in the PPCI-only group: 17 (1.2%) were acute and 13 (1.0%) were subacute. In the PPCI-TH group, there were only 2 (2.7%) ST: 1 definitive acute and 1 probable subacute. Major bleeding, according to GRACE (Global Registry of Acute Coronary Events) definition (4), was observed in 6 (8.0%) patients in the PPCI-TH group as compared with 17 (1.3%) in the PPCI-only group (p < 0.001).

All-cause mortality at 30 days of follow-up was significantly higher in the PPCI-TH group than in the PPCI-only group (n = 33 [44%] vs. 65 [4.9%], p < 0.001). In the PPCI-TH group, 31 patients had a reliable cause of death. Eleven arrived at the hospital in cardiogenic shock that did not improve despite successful revascularization, and died early due to multiple organ failure (MOF) without any acute decompensation; 1 died due to liver rupture related to resuscitation maneuvers; 1 died of unexplained cause (suspected sepsis), and post-mortem examination revealed absence of ST; 1 died of brain death; and 17 died due to the withdrawal of life-sustaining treatment secondary to severe post-anoxic encephalopathy. The other 2 deaths were classified as ST: 1 definite acute ST in a clopidogrel-treated patient complicated with retroperitoneal bleeding after a new PPCI, and 1 subacute probable ST that died on the 25th day of evolution due to MOF.

It has been suggested that TH-treated patients may have an increased risk of ST (2), mainly due to MOF and lower liver metabolism of drugs that inhibit the ADP P2Y$_{12}$ receptors and thromboxane A$_2$ synthesis. In the present observational study, even under the prelude of greater hemodynamic support and a higher frequency of hemorrhagic complications in the PPCI-TH–treated patients, the incidence of ST was almost identical to that of patients not treated with TH. Therefore, and under the need of further prospective trials, we believe that adequate antithrombotic management could be achieved in this population with both the progressive introduction of third-generation P2Y$_{12}$ inhibitors and consideration that the route (intravenous aspirin and crushed nasogastric P2Y$_{12}$) (5) and time (before PPCI) of administration may influence the final result.

In our study, the incidence of ST under the effects of TH is less than that observed in previous series and similar to that expected in standard PPCI-treated patients. The described prothrombotic effects of TH are not clinically relevant in patients treated according to general recommendations.

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Letters to the Editor

Effects of Heparin on Temporal MicroRNA Profiles

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Liebetrau et al. (1) used serial sampling in patients undergoing transcoronary ablation of septal hypertrophy to determine the temporal release of microRNAs (miRNAs) after cardiac injury. This model offers the advantage that the time of onset of myocardial damage is precisely known. However, heparin is routinely administered during intra-arterial coronary interventions, including septal ablation (2). Others (3) and we (4) have recently shown that even a single heparin bolus is sufficient to significantly alter measurements of miRNA by quantitative polymerase chain reaction, in particular the spike-in *C. elegans* control, Cel-miR-39, that was also used for normalization in the study by Liebetrau et al. (1).