Impact of therapeutic hypothermia on coronary flow

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To the Editor:

Mild hypothermia therapy (HT) improves survival and neurologic outcome after sudden cardiac death (SCD) [1]. Despite the controversy between the relation of HT and stent thrombosis (ST) [2], our group reported an increased risk of ST in patients treated with HT [3]. Increased platelet activation and a potential inefficiency of antiplatelet therapy may explain the increased risk of ST in HT. Nonetheless, recent data suggest that other etiologic mechanisms may play a role in the occurrence of thrombotic events. Experimental models have demonstrated a relationship between HT and endothelial dysfunction [4]. Endothelial disorders have been associated with coronary-flow impairment and therefore thrombotic events [5,6]. The objective of our study was to analyze the impact of HT on coronary microcirculation by comparing the coronary flow measured by thrombolysis in Myocardial Infarction frame count (TFC) with and without HT.

From January 2010 to March 2013, 55 patients with out-of-hospital SCD were admitted in our institution and treated with HT (mean age 55.4 ± 15 years, 67% male). Of them, 39 (70.9%) patients had ST-segment elevation myocardial infarction (STEMI) and underwent primary PCI. The HT protocol was accomplished as previously described [2]. We selected those patients in whom two coronary angiographies (with and without HT) were performed (see Table 1). Five patients (12.9%) were included in the analysis. In every patient, a clear distal anatomic landmark was selected as the region of interest to quantify the TFC, and measurements were repeated in both normothermia and HT. In case of STEMI or ST, the coronary flow was always measured in a non-infarct related artery. Coronary angiography technique including catheter shape, catheter diameter, automatic contrast injection flow, and projection were the same for every paired angiography. An experienced reviewer blinded to the temperature condition assessed the TFC. TFC values were compared using *t*-test for repeated measures with SPSS ® v.18.0 (IBM Corp., Armonk, NY, USA).

Patient characteristics, clinical status and TFC are summarized in Table 1. Patients with cardiogenic shock were treated with IV norepinephrine and/or dobutamine infusion according to guidelines. Coronary angiography in normothermia was performed after SCD with a diagnosis of STEMI in 80% of patients. Coronary angiography in HT was indicated in 80% of patients because a suspicion of ST. Despite the small number of patients, a noteworthy trend towards a higher TFC was observed in hypothermia compared to normothermia (11.6 vs. 8.0; $p = 0.066$) (Fig. 1).

Van Genderen et al. [7] reported a significant microcirculatory disorder after HT as a result of changes in body temperature rather than changes in systemic hemodynamic variables. Accordingly, Ergenekon observed that newborn patients treated with hypothermia for hypoxic ischemic encephalopathy presented a sluggish peripheral flow when compared to controls [8]. Recently, Zoerner et al. [4] demonstrated that mild HT is associated with higher plasmatic levels of endothelin-1 (ET-1). ET-1, a potent vasoconstrictor isolated from endothelial cells, has a biological effect that includes platelet activation and vascular dysfunction and is associated with a lower endothelial progenitor cell mobilization after myocardial infarction [9]. High ET-1 levels have been linked to impaired coronary circulation including slow coronary flow and even no-reflow. Slow coronary flow is a recognized predictor of thrombotic events, although other factors may also play a role. The results of our study suggest that mild HT might slow down coronary flow and endothelial dysfunction seems to be the most plausible explanation considering the previous published data [4,7]. The identification of other potential pro-thrombotic mechanisms besides the coagulation and platelet disorders seems to be of pivotal importance when designing strategies for preventing thrombotic events. In this sense, the present manuscript should be considered as hypothesis generating and encourage future research. Although the small number of patients is the main limitation of the study, the strong trend towards a reduced TFC despite the limited sample and the difficulties finding patients with SCD with two coronary angiographies (with and without HT) should be taken into consideration.

Table 1
Patient characteristics, clinical status, and TIMI frame count during normothermia and hypothermia therapy.

				Normothermia coronary angiography							Hypothermia coronary angiography						
#	Age	CASS TFC	CASS IRA	Indication	Heart rate	MAP	IABP	Shock	Inotropes	TFC	Indication	Heart rate	MAP	IABP	Shock	Inotropes	TFC
1	56	13	2	STEMI SCD	80	83	No	Yes	DBT, NE	7	Stent thrombosis	70	80	No	Yes	DBT	8
2	57	3	13	STEMI SCD	80	54	No	No	No	7	Stent thrombosis	80	53	No	Yes	DBT, NE	7
3	67	19	13	STEMI SCD	110	50	Yes	Yes	DBT, NE	9	Stent thrombosis	110	73	Yes	Yes	DBT, NE	17
4	42	19	12	STEMI SCD	116	70	Yes	Yes	DBT, NE	7	Stent thrombosis	87	92	Yes	Yes	DBT, NE	11
5	72	19	19	Staged PCI	70	74	No	No	No	10	STEMI SCD	55	100	No	No	No	15

CASS: Coronary artery surgery study; DBT: Dobutamine; IABP: Intra-aortic balloon pump; IRA: Infarct related artery; MAP: Mean Arterial Blood Pressure; NA: Norepinephrine; PCI: Percutaneous coronary intervention; SCD: Sudden cardiac death; STEMI: ST-segment elevation myocardial infarction; TFC: TIMI Frame count.

In conclusion, mild HT appears to slow down coronary flow. Further studies with higher statistical power are needed to confirm this finding and clarify the association between hypothermia and endothelial dysfunction.

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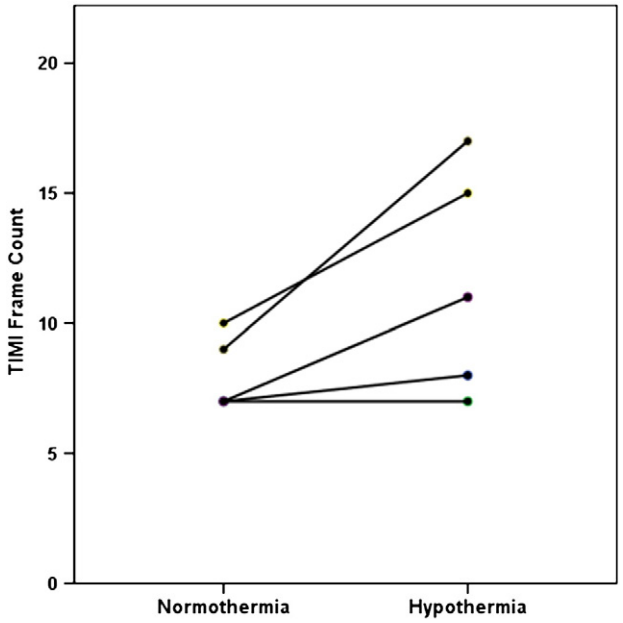

Fig. 1. TIMI frame count changes between normothermia and hypothermia treatment.

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Historical note on the attribution of the first description of aortic stenosis in the modern era ☆

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We humans as species have suffered degenerative cardiovascular disease since our very early history [1], and aortic stenosis has probably been present in many civilizations at different ages across the whole planet. Therefore it is of limited interest which was the first time that aortic stenosis was noticed as the origin of a particular clinical syndrome. It could have been noticed independently in several cultures with an accurate appraisal, but in this report we wish to focus on the early description of aortic stenosis that has endured in the tradition of our current historical frame.

The first description of aortic stenosis in the Modern Era of Western Civilization is usually adscribed [2] to Lazare Rivière, or Lazarus Riverus (1589–1655), who was a praised professor of Medicine at the University of Montpellier, in France. The book of Rivière entitled "*Observationes medicae & curationes insignes*" was first published in Paris in 1646. It consists of three hundred clinical reports of Rivière himself, followed by a section of observations provided by others ("*Observationes ab aliis communicatae*"). The book was a success, with other editions in London in 1646 and in Delft (The Netherlands) in 1651, with essentially the same content. In the editions published while Rivière was still alive there is no mention to aortic stenosis. However, in the preface to the reader of the chapter "Observations provided by others", Rivère announced the intention to publish this growing number of reports submitted freely by other physicians as a fourth hundred of *Observationes* "shall God allow me to live". But Rivère died in 1655 with his intentions unaccomplished.

The title page of the 1659 posthumous edition of Observationum Medicarum states: "*Necnon Centuria Quarta, post obitum Authoris in eius Musaeo reperta, et cura ac diligentia Simeonis Iacoz Doctoris Monspeliensis, in lucem nunc primum edita, cum Observatiorum morborum infrequentium, Anonymi cuiusdam, inter eius scripta repertis*" (And also a fourth hundred [of observations] collected from the archives of the author after his death, in the care and attentiveness of the Doctor of Montpellier Simeon Jacoz, never before edited, with observations of infrequent diseases, of

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