

Clinical Paper

Endovascular cooling catheter related thrombosis in patients undergoing therapeutic hypothermia for out of hospital cardiac arrest^{☆,☆☆}



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ARTICLE INFO

Article history:

Received 24 December 2013

Received in revised form 20 May 2014

Accepted 23 May 2014

Keywords:

Therapeutic hypothermia

Cardiac arrest

Catheter related thrombosis

ABSTRACT

Background: Therapeutic hypothermia improves neurologic outcome and survival in patients following out-of-hospital cardiac arrest (OHCA). Endovascular cooling devices are commonly used to rapidly achieve and maintain hypothermia. The use of these devices may be associated with catheter related thrombosis. The objective of this study was to determine the risk of catheter related thrombosis associated with the use of an endovascular cooling catheter in patients referred for therapeutic hypothermia following OHCA.

Methods and results: We conducted a retrospective cohort study on consecutive patients, referred for therapeutic hypothermia following OHCA, between February 2012 and May 2013. Of 80 patients initially treated with therapeutic hypothermia, 61 completed the cooling protocol using an endovascular cooling device. The primary outcome was catheter related thrombosis defined as evidence of thrombus in the inferior vena cava, deep vein thrombosis or pulmonary embolism during the index hospitalization. We further evaluated the incidence of the primary outcome between patients on dose adjusted intravenous unfractionated heparin compared to those on a subcutaneous prophylactic regimen alone. Catheter related thrombosis was observed in 9/61 (14.7%), with nine events in the prophylaxis group compared to none in the full dose unfractionated heparin group (22.0% vs. 0.0%, $p=0.02$).

Conclusions: The use of endovascular catheters for induction of therapeutic hypothermia is associated with a high rate of catheter related thrombosis. This risk appears to be abrogated with dose adjusted unfractionated heparin infusion.

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1. Introduction

Therapeutic hypothermia (TH) is associated with improved neurologic outcomes and mortality in comatose survivors of out-of-hospital cardiac arrest (OHCA).^{1,2} Accordingly, TH is currently recommended as standard of care for OHCA survivors and

regionalized programs are being developed to optimize outcomes.¹ In Europe, the incidence of sudden cardiac arrest is estimated at between 0.4 and 1 per 1000 persons annually, thereby affecting between 350,000 and 700,000 people.² Previous reports suggest that 23% of patients suffering OHCA survive to hospital admission.³ A large proportion of these patients are eligible for TH, many of whom will accrue significant benefits from this therapy. Several cooling modalities are available including the use of ice packs, infusion of refrigerated crystalloid, external cooling blankets, bladder irrigation, and endovascular cooling devices.

Endovascular cooling catheters result in more rapid hypothermia, a greater proportion of time at target temperature and improved temperature regulation during the re-warming phase of

[☆] A Spanish translated version of the summary of this article appears as Appendix in the final online version at <http://dx.doi.org/10.1016/j.resuscitation.2014.05.029>.

^{☆☆} There are no relationships with industry to disclose.

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the TH protocol.⁴ Rapidly cooling patients to target temperature can decrease the risks of hypovolemia and electrolyte disturbances associated with the induction phase of TH.⁵ The device also functions as a central venous access line, thereby eliminating the need for additional central venous catheters and their inherent complications. Endovascular cooling is estimated to be used in more than half of patients referred for TH following OHCA.⁶

Current evidence suggests that TH may be associated with an increased risk of bleeding at temperatures $\leq 33^\circ\text{C}$ due to reduced synthesis and altered kinetics of clotting factors.⁵ Conversely, cardiac arrest and resuscitation is associated with an increased in blood coagulation and fibrin deposition.^{7,8} This delicate balance between the hemostatic deficit associated with hypothermia and the pro-thrombotic state of cardiac arrest can place patients undergoing TH at risk for both bleeding and clotting. Confirmation of the net clinical effects of these processes is integral in improving care for patients with OHCA receiving TH.

Catheter-related thrombosis (CRT) is an under recognized clinical complication with a variably reported incidence (2–67%) depending on surveillance, modality of imaging and patient or catheter characteristics.⁹

The use of endovascular catheters for TH may increase the risk of CRT further due to both local and systemic effects of hypothermia on coagulation profiles.^{10,11} Though widely utilized, the incidence of CRT remains unclear among patients with OHCA undergoing TH with endovascular cooling catheters. Accordingly, we evaluated the incidence CRT in patients undergoing TH using endovascular cooling catheters in a high volume regional cardiac center.

2. Methods

2.1. Data source and patients

The University of Ottawa Heart Institute is the sole cardiac regional referral center for a population of approximately 1.3 million residents.^{12,13} In addition to providing STEMI care for all patients in the region, our institute provides comprehensive critical care for OHCA survivors requiring TH.¹⁴ All patients referred for TH are prospectively indexed in the University of Ottawa Heart Institute Cardiac Arrest Registry and demographic data, therapies, and clinical outcomes are recorded.

Patients were enrolled from February 2012 to May 2013 after referral to the UOHI following OHCA. To be included in the study, patients had to undergo TH utilizing an endovascular cooling device (Quattro ZOLL®, ZOLL Medical Corporation, Chelmsford, MA USA) inserted into the IVC via the femoral vein and have completed the full 72 h protocol, which comprised 24 h of cooling (comprising an induction and maintenance phase), followed by a 24 h active rewarming phase and a 24 h normothermia period. At the treating physician's discretion, patients received either full anticoagulation using dose adjusted intravenous unfractionated heparin (UFH), consisting of an initial heparin bolus followed by heparin infusion titrated to an Anti-Xa level of 0.35–0.67, or venous thromboembolism prophylaxis using subcutaneous heparin (5000 units every 8 h). Patients were classified into cohorts based on the presence or absence of full dose UFH during the period in which the endovascular catheter was in situ. Imaging studies were conducted at the discretion of treating physicians. All available echocardiogram, leg Doppler ultrasound and chest computed tomographic scan reports were reviewed for evidence of venous thrombosis. Patients were followed for the duration of their hospitalization. No follow-up was conducted after hospital discharge. The institutional ethics board approved the use of the data from the UOHI cardiac arrest registry for publication.

2.2. Outcome measures

The primary outcome of the study was occurrence of catheter related thrombosis (CRT) defined as thrombus in the inferior vena cava (IVC), deep vein thrombosis (DVT) or pulmonary embolism (PE) diagnosed on echocardiogram, leg Doppler ultrasound or chest computed tomography scanning during the index hospitalization. Secondary outcomes included individual components of the primary outcome, in-hospital death, overt bleeding and Thrombolysis In Myocardial Infarction (TIMI) major and minor bleeding.¹⁵

2.3. Statistical analysis

All continuous variables were described as mean (\pm standard deviation) or median (\pm inter-quartile range) and categorical variables as number (%), as appropriate. For the primary composite endpoint, all components are reported individually.¹⁶ Categorical variables were compared by Chi-square or Fisher's Exact Test, as appropriate. For continuous variables, comparisons were made using Student's *t*-test or Wilcoxon rank sum test, as appropriate. Analyses were performed using SAS (version 9.2, SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. Patients

From February 2012 to May 2013, 80 comatose patients (Glasgow coma scale <8) were referred for TH following OHCA. Of those referred, 5 underwent TH using a different modality and 5 patients were transferred to the medical intensive care unit for ongoing care. Nine patients, 4 of whom were on full dose intravenous UFH, were initiated on endovascular cooling but died prior to completing the full protocol. There was no documented CRT in any of these 9 patients. Autopsies were not performed on these patients.

In total, 61 patients underwent TH using endovascular cooling and completed the full protocol (Fig. 1A); 20 underwent cooling with dose adjusted intravenous UFH and 41 with subcutaneous prophylactic heparin. The indication for full dose anticoagulation was anterior STEMI in 12 patients and pre-existing atrial fibrillation in the remaining 8 patients. With regards to anticoagulation for anterior STEMI, it is our standard of practice to anti-coagulate patients until an echocardiogram has ruled out a left ventricular thrombus. Patients with pre-existing atrial fibrillation are maintained on therapeutic anticoagulation with intravenous heparin until resumption of Coumadin (with therapeutic international normalized ratio) or a novel oral anticoagulant.

Patient characteristics including baseline demographics, and hematologic parameters are shown in Table 1. The groups were well balanced, though patients with anterior wall infarcts were more likely to receive intravenous UFH as our practice is to anticoagulate patients with anterior wall myocardial infarctions prior to documentation an absence of left ventricular thrombus.

3.2. Primary outcome

The primary outcome, catheter related thrombosis, DVT or PE, occurred in 9 patients who received prophylactic dose heparin and in none of the patients who received full dose UFH (22.0% vs. 0%, $p=0.02$, Table 2). Of these patients, 7 had thrombus visualized on the catheter (17.1% of the total study) as identified by echocardiography; however, only 28 patients had imaging done with the catheter in situ, thereby making the incidence of CRT 25% among patients screened. Two patients developed symptomatic DVTs with one patient having near total occlusion of the distal IVC.

Table 1
Baseline characteristics.

	Full dose UFH n = 20	Prophylactic dose UFH n = 41	p-Value
Age – years (SD)	58.6 (15.0)	55.6 (15.1)	0.47
Males – no. (%)	14 (70.0)	34 (82.9)	0.32
Hypertension – no. (%)	7 (36.8)	19 (51.4)	0.40
Diabetes – no. (%)	3 (15.8)	8 (21.0)	0.73
Dyslipidemia – no. (%)	9 (45.0)	14 (40.0)	0.78
Smoking – no. (%)	10 (52.6)	17 (44.7)	0.59
Cardiovascular history – no. (%)			
Myocardial Infarction	2 (10.0)	8 (21.6)	0.47
PCI	1 (5.6)	3 (8.8)	1.00
Bypass surgery	0 (0)	2 (5.1)	0.55
Stroke	2 (10)	2 (5.6)	0.55
Index rhythm – no. (%)			
VF/VT	19 (95.0)	36 (87.8)	0.56
Cause of arrest – no. (%)			
STEMI	12 (60.0)	14 (34.2)	0.10
Anterior	12 (100)	6 (54.5)	0.01
Other	8 (40.0)	27 (65.8)	
Systolic BP – mmHg (SD)	115.1 (25.1)	130.6 (33.0)	0.59
Heart rate – beats per minute (SD)	100.5 (32.0)	92.1 (19.8)	0.08
Hemoglobin – g L ⁻¹ (SD)			
Baseline	138.5 (19.9)	145.7 (14.5)	0.16
Nadir	93.3 (12.5)	97.9 (17.4)	0.30
Transfusions – no. (%)	6 (30.0)	7 (17.1)	0.32
Renal Function – GFR – MDRD median (IQR)	67.7 (29.0)	70.1 (27.6)	0.29
Nadir temperature – Celsius median (IQR)	33.2 (33.0–33.3)	33.2 (33.0–33.3)	0.39
Length of stay – days median (IQR)	17 (14–26)	19 (16–29)	0.41
Anti-platelet medication – no. (%)			
Aspirin	17 (85.0)	35 (85.4)	1.00
P2Y12 inhibitor	18 (90)	32 (90)	0.47
Glycoprotein IIb/IIIa Inhibitors	1 (5.0)	3 (8.1)	1.00
Anti-thrombotic medication – no. (%)			
Warfarin	1 (5.0)	1 (2.4)	0.55

UFH, unfractionated heparin; PCI, percutaneous coronary intervention; VF/VT, ventricular fibrillation/ventricular tachycardia; PEA, pulseless electrical activity; STEMI, ST elevation myocardial infarction; GFR, glomerular filtration rate; MDRD, modification of diet in renal disease; SD, standard deviation; IQR, interquartile range.

Two patients with a thrombus on the catheter developed a symptomatic PE confirmed on computed tomography, though only 3 of 9 (33%) patients were screened. In total, 10 patients in the study had imaging to rule out PE. Notably, the only 2 patients with a PE had documented clot on the cooling catheter. In total, symptomatic events occurred in 0/20 patients on full dose UFH and 3/41 patients on prophylactic dose heparin ($p=0.54$). The cooling catheter remained in situ for an average of 3.2 days and no difference in duration was seen between the patients with and without CRT (3.0 ± 0.0 vs. 3.1 ± 0.1 respectively, $p=0.19$).

3.3. Bleeding outcomes

Clinically overt bleeding occurred in 4/20 (20.0%) patients on full dose anticoagulation, and 4/41 (9.8%) patients in the prophylaxis group ($p=0.42$). In the full dose anticoagulation group, there

Table 2
Clinical outcomes.

	Full dose UFH (n = 20)	Prophylactic dose UFH (n = 41)	p-Value
Catheter-related thrombosis (primary) – no (%)	0 (0.0)	9 (22.0)	0.02
Thrombus in IVC	0 (0.0)	7 (17.1)	0.09
Deep venous thrombosis	0 (0.0)	2 (4.9)	1.00
Pulmonary embolism	0 (0.0)	1 (2.4)	1.00
TIMI major bleeding ^b – no (%)	1 (5.0)	3 (7.3)	1.00
TIMI minor bleeding	11 (55.0)	17 (41.5)	0.41
RBC transfusion ^a – no. (%)	6 (30.0)	7 (17.1)	0.32
In hospital mortality – no. (%)	1 (5.0)	5 (12.2)	0.65

^a Number of patients requiring at least one packed red blood cell transfusion.

^b With clinically overt bleed.

was one retroperitoneal bleed, one upper gastrointestinal bleed (GIB), one patient with hematuria and one with a liver laceration and hemoperitoneum secondary to cardio-pulmonary resuscitation requiring embolization of the superior mesenteric artery. None of these patients had thrombotic complications after anticoagulation was stopped. In the prophylaxis group, 2 patients had upper GIBs, 1 patient had a spontaneous hemorrhage into the psoas muscle and 1 had bleeding from the nasopharynx requiring nasal packing.

Of the bleeding events, only 1/20 (5.0%) met the definition of TIMI major bleeding (with clinically overt bleed) in the full anticoagulation cohort and 3/41 (7.3%) patients in the prophylaxis group ($p=NS$), while TIMI minor bleeding occurred in 11/20 (55.0%) patients on full anticoagulation and 17/41 (41.4%) in the prophylaxis group ($p=0.47$). In-hospital mortality was low, occurring in 5% of patients on full dose UFH and 12% of patients on prophylaxis ($p=0.65$). No deaths were directly attributable to either bleeding or thrombotic complications.

4. Discussion

In this study, we report a high incidence of venous thromboembolic complications associated with the use of endovascular cooling catheters when only prophylactic dose heparin was administered. This risk appeared to be abrogated with dose titrated intravenous heparin, with no apparent increase in rates of bleeding or transfusion. This observation is important given the increasing use of endovascular cooling catheters for induction and maintenance of TH in OHCA.

Patients undergoing TH for OHCA are at high risk of venous thrombotic complications given the highly inflammatory state, immobility, and presence of intravascular devices. Moreover,

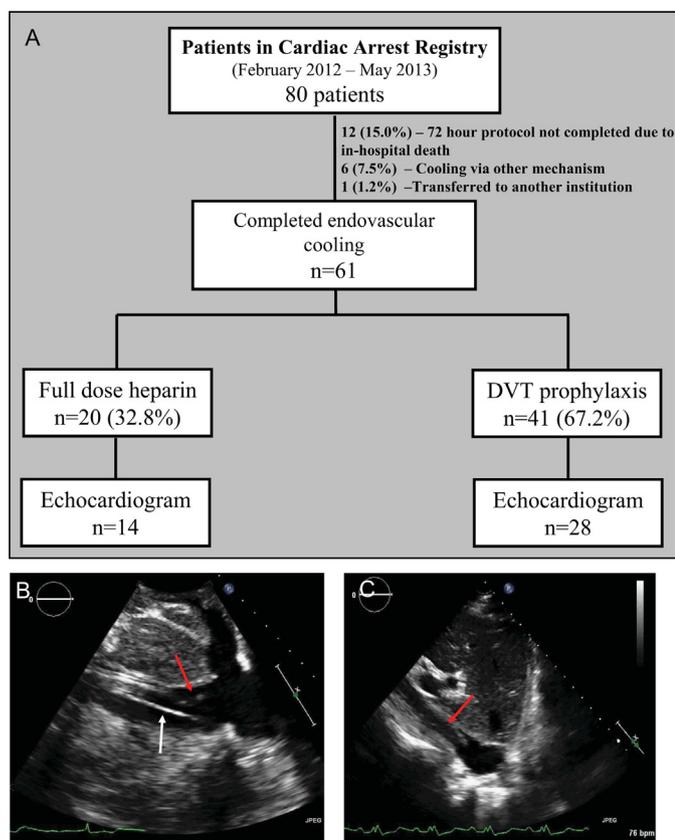


Fig. 1. (A) Selection of study population. Consecutive eligible patients referred for therapeutic hypothermia. (B) Subcostal view of the inferior vena cava with presence of endovascular cooling catheter (white arrow). A mobile thrombus is attached to the tip of the device (red arrow). (C) Large nearly occlusive thrombus (red arrow) in the inferior vena cava of a patient following endovascular cooling. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

patients undergoing endovascular cooling may be at even higher risk (as compared to patients undergoing TH by other means) given the need for an indwelling femoral venous catheter. Two previous studies have prospectively evaluated the incidence of DVT associated with femoral venous catheters.^{7,18} All patients in these studies underwent imaging of the lower extremity with either duplex ultrasonography¹⁷ or bilateral phlebography.¹⁸ Deep vein thrombosis was seen in 39/194 (20%) patients in the two studies. All but two events were sub-clinical and no documented pulmonary emboli were found. A randomized trial comparing subclavian and femoral venous catheters documented a thrombosis rate of 21.5% in the femoral catheter group.¹⁹ Current guidelines do not recommend prophylactic anticoagulation in hospitalized patients with indwelling central venous catheters.²⁰ The results of this study are consistent with previous studies that have showed a high rate of thrombotic complications associated with femoral venous catheters. Previous studies of indwelling venous catheters did not involve patients undergoing therapeutic hypothermia via the venous catheter. The notion that these catheters are associated with similar rates of thrombosis as other femoral catheters is an important consideration when weighing the risk and benefit of endovascular cooling following resuscitated cardiac arrest.

The complication of CRT – including thrombus in the IVC, DVT and PE – is likely under reported in clinical practice since only symptomatic patients will generally undergo surveillance imaging. While previous studies of endovascular cooling have reported on CRT, our study is the largest cohort specifically evaluating CRT

in survivors of OHCA undergoing TH. In patients with traumatic brain injury, endovascular TH was associated with a 50% rate of DVT,²¹ while in the Intravascular Cooling in the Treatment of Stroke study, 4 of 16 patients developed DVTs with all patients undergoing routine ultrasound assessment.²² Our findings confirm the high risk of thrombosis associated with endovascular cooling among patients with OHCA. The high incidence of CRT in patients undergoing TH with an endovascular cooling device following OHCA is an important finding. While cardiac arrest may be associated with a prothrombotic and hypercoagulable state,^{7,8} TH is conversely associated with a propensity to bleed.⁵ This high-risk patient group is therefore at increased risk of both bleeding and clotting, with the risk of thrombosis potentially further increased with an endovascular cooling device. This balance must be carefully weighed and heightened suspicion for thrombotic events is warranted in these patients.

Importantly, we observed no cases of CRT in patients placed on full dose UFH throughout the TH protocol. While previous studies²² precluded anticoagulation due to neurologic indications for TH, almost one third of patients in this study required full dose anticoagulation pending evaluation of their left ventricular cavity for thrombus formation. Our results suggest that full dose intravenous UFH may mitigate the risk of CRT in patients undergoing TH with endovascular cooling devices and should be considered in patients with acceptable bleeding risk profiles. Notably, we found no difference in bleeding rates between the two groups. Certainly, the use of relatively long, femorally inserted cooling catheters may predispose patients to a greater risk of thrombosis than catheters inserted in the internal jugular or subclavian veins. Moreover, shorter femoral catheters may also be less thrombogenic. Further research is needed to investigate this further. The use of antiplatelet agents had no effect on the rate of thrombosis. In the nine patients with a documented CRT, 4 (44%) were on dual anti-platelet therapy (DAPT) with aspirin and Ticagrelor, 2 (22%) on aspirin alone and 3 (33%) on no anti-platelets. In 56 patients without CRT, 36 (64%) were on DAPT with ASA and Ticagrelor, 7 (12%) on ASA monotherapy and 9 (16%) on no anti-platelet agents.

Our study has several limitations. Firstly, not all patients underwent screening for DVT/PE. Accordingly, the current report may underestimate the true incidence of this complication and the rate of subclinical thrombosis is likely higher than what we have reported. Regardless, symptomatic events were only observed in the prophylactic heparin group. Secondly, our study design does not permit definitive proof that the DVTs and PE observed are directly attributable to the endovascular cooling device. However, in the patient who developed PE, imaging clearly demonstrated mobile clot attached to catheter (Fig. 1B, Online video) while one of the two patients with DVT had near complete occlusion of the IVC with thrombus (Fig. 1C, Online video), suggesting this was a device related complication. Finally, while our analysis indicates that dose titrated UFH may be protective without any increased bleeding complications when administered during TH, the non-randomized nature of this study precludes definitive conclusions. As noted, these patients are at higher risk of bleeding and the use of full dose anti-coagulation should not be used without careful consideration of this risk.

Nonetheless, the current study raises an important safety concern in patients undergoing TH for OHCA and highlights important management issues in these critically ill patients. Firstly, routine surveillance with ultrasound imaging is warranted in patients while the device is in situ given the high incidence of this complication. Secondly, the catheter should be removed promptly once the cooling protocol is completed to decrease the risk period for thrombus development. Lastly, dose-adjusted intravenous UFH should be considered in patients with an acceptable bleeding risk

profile until prospective randomized study data becomes available.

Conflict of interest statement

The authors have no conflicts of interest to disclose.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.resuscitation.2014.05.029>.

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