

Original Article

Iatrogenic embolization following cardiac intervention: postmortem analysis of 110 cases[☆]

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ABSTRACT

Introduction: Iatrogenic embolization following cardiac investigative procedures may result from hydrophilic polymer emboli (HPE) from catheter valve and vessel wall calcifications, and air embolism from open heart surgery. This retrospective clinical pathologic analysis was undertaken to ascertain the frequency and extent of these potentially fatal complications.

Methods: This retrospective clinical pathologic autopsy analysis with premortem diagnostic imaging correlation identified 110 individuals who had undergone endovascular procedures between 2010 and 2016 within 90 days of death and followed by hospital autopsy. Clinical outcomes, radiologic studies, and autopsy materials were reviewed.

Results: Iatrogenic emboli were assessed as causing death in 9/110 autopsy cases (8.2%) and 9/34 (26.5%) cases with proven iatrogenic emboli. Iatrogenic emboli caused strokes in 10/110 (9.1%) autopsy cases including calcified emboli (CE, $n=6$), HPE ($n=2$), cardiac valvular tissue ($n=1$), and air embolism ($n=1$). Seven cases of calcified emboli complicating endovascular procedures were identified: four of the CE were thought to be the cause of death due to fatal strokes ($n=2$) and fatal myocardial ($n=1$) and colonic infarction ($n=1$). The CE likely originated from calcified aortic valves and atherosclerotic aortic plaques. Histologic evidence of HPE was found in 23% (25/110) of cases; 54% (26/48) showed evidence of infarction in postprocedural imaging, with radiologic evidence of infarction in 32% (8/25) of cases with HPE histology. Endovascular aortic repair was associated with the greatest density/distribution of HPE. HPE material showed degradation with time and was often associated with an inflammatory response. HPE directly contributed to death in three cases. One fatal air embolism followed open heart surgery, and one cardiac tissue embolus resulted in a major stroke.

Conclusions: We advocate for greater awareness of these underrecognized and occasionally fatal complications of endovascular procedures. Targeted postprocedural imaging has a role in the identification of iatrogenic embolic infarcts.

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1. Introduction

Patients undergoing endovascular procedures are at risk of iatrogenic emboli that can cause acute to subacute ischemic tissue injury, including organ infarction (e.g., stroke, myocardial infarction). For example, hydrophilic polymer embolization has recently been

described as a complication of the polymer used on many investigative and interventional endovascular devices. Hydrophilic polymer coating is commonly used to enhance lubrication of endovascular devices, including guidewires, sheaths, arterial catheters, central venous catheters, stents, and coils [1–4]. The consequences of this embolic foreign material may range from being asymptomatic to fatal, e.g., from stroke [3–5]. Other potential iatrogenic emboli include calcified material/debris [e.g., atherosclerosis-associated calcified emboli (CE)], displaced tissue, air embolism, or other foreign material introduced during the procedure. This retrospective clinicopathologic autopsy analysis with premortem diagnostic imaging correlation was undertaken to assess the incidence and severity of postendovascular iatrogenic emboli.

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2. Methods

2.1. Institutional and ethics approval

This research was approved by the Vancouver Coastal Health Authority (research study #V16-00019) and the University of British Columbia Clinical Research Ethics Board (certificate of approval #H16-00019). Informed consent for the autopsies had been granted by the legal next of kin. Medicolegal cases were excluded.

2.2. Selection of autopsy cases for review

An electronic pathology record database was searched for hospital (nonmedicolegal) autopsies from Vancouver General Hospital and St. Paul's Hospital (Vancouver) that included any of the following search terms within the final autopsy reports for the time period January 1, 2010, through Jan 30, 2016: angiogram, angiography, angioplasty, cardiac catheter, central line, emboli/embolus, embolization, "atheroemboli," calcific emboli/embolus," "calcium emboli/embolus," "calcified emboli/embolus," "atheromatous emboli/embolus," endovascular, polymer, and valvuloplasty. This initial search yielded 538 autopsy reports. These reports were then screened for identification of cases where the decedent underwent any type of endovascular procedure within 90 days of death. This secondary search yielded a total of 110 autopsy cases: 56 cases from St. Paul's Hospital and 54 cases from Vancouver General Hospital. The group of 110 decedents was anonymized for subsequent blinded assessments by assigning a unique case number for this study generated using a random number set from integers 0001 to 9999 using the Web site random.org.

2.3. Pathology case review

Hematoxylin and eosin (H&E) glass slides were processed from 5- μ m sections of formalin-fixed paraffin-embedded tissue blocks taken at the time of autopsy as per standard local autopsy procedures. Three anatomical pathologists and one anatomical pathology resident, now certified pathologist, reviewed all of the extracranial H&E slides for the 110 autopsy cases. Histologic slides of the brain were reviewed by a neuropathologist (J.M.) with familiarity with hydrophilic polymer emboli (HPE) appearance(s). Glass slides from brain sections were also variably stained with Luxol Fast Blue/H&E and other special stains such as Bielschowsky at the discretion of the original autopsy neuropathologist. As HPE remains a relatively recent phenomenon, each of the pathology slide reviewers was provided a document that included all published images of hydrophilic polymer material (up until March 2016). After reviewing the varied appearances of hydrophilic polymer material, the pathology reviewers blindly assessed an average of 32 cases (min 10, max 60) without knowledge of the initial pathology report or clinical details of the case at the time of slide review. Cases identified as having histologic findings of emboli (e.g., HPE, CE) were confirmed with at least one of the other reviewers. Where disagreements occurred, the opinion of a third reviewer was sought.

2.4. Radiology case review

The diagnostic imaging review was completed by one staff radiologist and one radiology fellow, both with subspecialty expertise in neuroradiology. The anonymized list of 110 decedents was provided to the radiologists who then undertook an independent review of any relevant available imaging studies for each patient. Any pertinent findings found in the post endovascular procedure imaging (e.g., evidence of infarction) were correlated with preendovascular imaging, where available, to determine if the radiologic changes could represent a complication of the endovascular procedure. A total of 48 cases had relevant postprocedural imaging that was reviewed.

2.5. Clinicopathologic and radiologic data review

The histology and radiology reviews were completed independently, and the findings of each group were not revealed until both groups had completed their assessments. The two data sets were then compared to determine what level of agreement existed between the findings. We also undertook additional analysis of patient electronic medical records in cases where procedure-associated emboli were identified to better understand their course in hospital and events leading up to death.

3. Results

3.1. Overall autopsy profiles

The average age of the 110 individuals that met our case criteria was 65 years (range 19–95), comprising 65% males and 35% females. A total of 3520 H&E glass slides were examined (average 35 slides/autopsy). Documented endovascular procedures included cardiac angiography (48%), extracorporeal membrane oxygenation (ECMO) (22%), coronary stenting (14%), transcatheter aortic valve implantation/replacement (TAVI/TAVR) (13%), endovascular (aortic) aneurysm repair (EVAR) (9%), venous central line catheterization (7%), continuous venovenous hemodialysis (CVVHD) (7%), abdominopelvic angiography (6%), intracranial angiography (6%), pacemaker/implantable cardioverter defibrillator (ICD) (5%), myocardial biopsy (3%), coil embolization (2%), inferior vena cava (IVC) filter placement (2%), cardiac ablation (2%), and cardiac septal wall defect repair (1%). We identified 34 cases with embolic phenomenon (average age: 65 years): 25 cases with HPE, 7 cases with CCE, and single cases of both tissue embolism and air embolism. The identified emboli were associated with death in 9 cases (average age: 66 years).

3.2. Hydrophilic polymer emboli

Histologic evidence of HPE was found in 23% (25/110) of the cases reviewed. The average age was 65 years (range 19–84), with 57% males and 43% females. The interval from final endovascular procedure to death was <1 to 41 days. Endovascular procedures included cardiac/coronary angiography ($n=12$), coronary stenting ($n=4$), EVAR ($n=3$), ECMO ($n=3$), TAVI ($n=2$), CVVHD ($n=2$), and single cases of cerebral angiography, abdominal angiography, coil embolization, chemoembolization, central line, myocardial biopsy, and IVC filter placement (Table 1). Notably, reference to any type of foreign intravascular material was initially made in 16% (4/25) of the original autopsy reports.

3.2.1. Characteristics of HPE findings

We identified numerous amphiphilic-to-basophilic, nonrefractile, nonpolarizable intravascular emboli with a fibrillar/lamellar and variably granular appearance occluding small arterioles (Fig. 1). In cases where the decedent had undergone multiple and complex endovascular procedures (e.g., EVAR), we noted a large burden and varied appearances of the polymer material. We identified multiple cases of HPE in the brain ($n=4$) in addition to the following organs: kidneys ($n=13$), lungs ($n=8$), heart ($n=7$), spleen ($n=4$), liver ($n=2$), pancreas ($n=2$), and single organ findings in the colon, stomach, adrenal gland, and skeletal muscle. The varied inflammatory response to HPE included histiocytic, giant cell, lymphocytic, and polymorphonuclear infiltrates.

3.2.2. HPE implication in cause of death

We had hypothesized that for the majority of the HPE-positive cases, the polymer emboli would result in negligible/minimal effects within the identified tissues. However, we identified three cases where the location and density of HPE were associated with significant infarction, likely causing death (cases 8, 12, and 15; Table 1).

Table 1
Overview of clinical information for HPE-positive cases

*Infarction?	Organ(s) with HPE	Death interval (d)
No	Heart	0.5
-	Heart	1
No	Kidney, spleen	1
Yes (CT + MRI head)	Kidney	1
No	Kidney	1
No	Heart	2
No	Lung	2
Yes (CT head)	Stomach, rectum, liver, pancreas, lung, spleen, kidney, adrenal, skeletal muscle, brain	3
Yes (CT head)	Kidney	6
No	Kidney, lung	7
No	Spleen	7
No (✱)	Heart	9
No	Spleen, kidney	10
Yes (MR head)	Heart	10
Yes (CT head)	Heart, kidney, lung, brain	14
No	Lung	17
Yes (CT head)	Brain	19
Yes (CT abdomen)	Heart (myocardium + coronary vasa vasorum), kidney	20
Yes (CT head)	Pancreas	22
No	Kidney	23
No	Kidney	25
No	Kidney, liver	30
No	Kidney, lung	30
No	Lung	37
No	Lung	41

Included are patient demographics, endovascular procedures employed, postprocedural radiology-confirmed evidence of infarction, HPE-affected organs, and death interval after final endovascular procedure. "x" indicates cases where the presence of HPE was implicated in the final cause of death. CT, computed tomography; MRI, magnetic resonance imaging.

3.2.3. Correlation of radiologic and pathologic reviews

Postprocedural imaging studies were available for 44% (48/110) of cases; 16 of these also had recent preprocedural imaging (CT or MRI) available for comparison. We observed radiologic evidence of postprocedural infarction in 54% (26/48) of these cases. Infarction was predominantly identified in the brain owing to the fact that most postprocedural imaging was CT or MR of the head. Notably, postprocedural imaging was completed in 52% (13/25) of cases with HPE histology, and radiologic evidence of some type of infarction in these cases was 62% (8/13), representing 32% (8/25) of all the HPE-positive cases. However, except for a single case of bowel infarction, all of the radiologic findings of infarction in HPE-positive cases were in the brain.

3.3. Calcified emboli

Our electronic search identified 11 cases, of which 7 (4 males) were confirmed to have CE upon pathologic histologic review. One case (no. 2) had calcified material in his coronaries only (Table 2). The interval from final endovascular procedure to death ranged from <1 to 90 days. Stroke was diagnosed due to a sudden, hyperacute clinical presentation of large middle cerebral arterial occlusion following an endovascular procedure during which a catheter passed through the aortic valve in case 1 and immediately postprocedure in cases 5 and 6. Their noncontrast CTs of head revealed hyperdense vessel signs (Fig. 2A) and "salted pretzel" signs [6] (Fig. 2B). In two cases (numbers 3 and 7), head CT performed to investigate continued comatose state revealed new embolic strokes.

In all cases, the histology of the sampled brain sections was striking for the abundance of CCE within multiple vessels of different sizes and

locations. The embolic material was composed of calcified particles of varying size that generally resulted in complete vessel occlusion (Fig. 2C and D). Adjacent acute cerebral infarcts in multiple vascular territories were also seen. Patient 5 had scattered CCE causing ischemia. However, the embolic material occluding the left middle cerebral artery (MCA) M1 branch was found to be cardiac tissue with sutures within it (see tissue embolus description below). Case number 2 had extensive myocardial infarction due to calcified material causing complete occlusion of two coronary arteries. Cases 1, 3, and 5 had undergone procedures that involved manipulation of a heavily calcified, sclerotic aortic stenosis (AS) valve, and cases 2, 3, and 6 had calcified and ulcerated aortas.

3.3.1. CE implication in cause of death

Four cases (patients) were adjudicated as dying from the effects of iatrogenic CE (Table 2: 1, 2, 4, and 5). Case 1 died from extensive brain stem and right cerebral hemispheric infarction. Case 2 died from sudden massive myocardial infarction. Case 4 died from extensive colonic infarction leading to sepsis. Case 5 died from extensive left hemispheric infarction.

3.4. Tissue embolism

This case (no. 5) involved a 75-year-old woman with a past history of ST-segment elevation myocardial infarction, resultant third-degree heart block, permanent pacemaker insertion, and two drug-eluting stents for complete occlusion of the right coronary artery 5 years previously. Due to worsening heart failure, she underwent repair of a left ventricular aneurysm and aortic valve. During the surgery, the left brachiocephalic vein was injured by in situ pacemaker wires and was repaired intraoperatively. A left MCA territory infarct was identified day 1 postoperatively. Concurrently, she developed right-sided weakness, and a head CT scan confirmed a recent left MCA territory infarct involving the basal ganglia, insula, and left temporal lobe (Fig. 3A). At autopsy, the left MCA contained a tissue embolus confirmed by microscopic analysis (Fig. 3B). The embolic tissue displayed focal granulomatous inflammation to foreign suture-like material (Fig. 3C) that had two appearances: eosinophilic and pale to white. These were suggestive of two different types of sutures. Fragments of eosinophilic material consistent with BioGlue surgical adhesive were also identified. Detailed examination of the heart showed a left ventricle aneurysm repair site mural thrombus admixed with BioGlue and suture material, the likely source of the left MCA embolus. Extensive acute cerebral infarction was confirmed in the vascular territory of the left MCA.

3.5. Cerebral air embolism

A 32-year-old woman was admitted for elective repair of an atrial septal defect and patent foramen ovale. At the end of the procedure, some air was noted in the left side of the heart on transesophageal echocardiography. Emergent measures to perform retrograde cerebral perfusion for the treatment of possible cerebral air embolism (CAE) were performed. This included Trendelenburg positioning and gas evacuation via the aorta. However, as sedation was withdrawn, she remained unresponsive with decerebrate posturing. A non-contrast CT head showed global ischemia in multiple territories, generalized edema, and multiple air bubbles (Fig. 4A). Accordingly, there was no role for hyperbaric medicine intervention, and the patient died from massive CAE. Neuropathologic examination showed marked cerebral swelling with uncal and cerebellar tonsillar herniations and pronounced leptomeningeal congestion with multiple petechial hemorrhages. There were multiple areas of recent infarction, including the left frontal lobe, both occipital lobes, and thalamus (Fig. 4A). Microscopic examination confirmed the presence of extensive acute cortical infarction with perivascular vacuolation, indicative of severe cortical injury with edema (Fig. 4B and C).

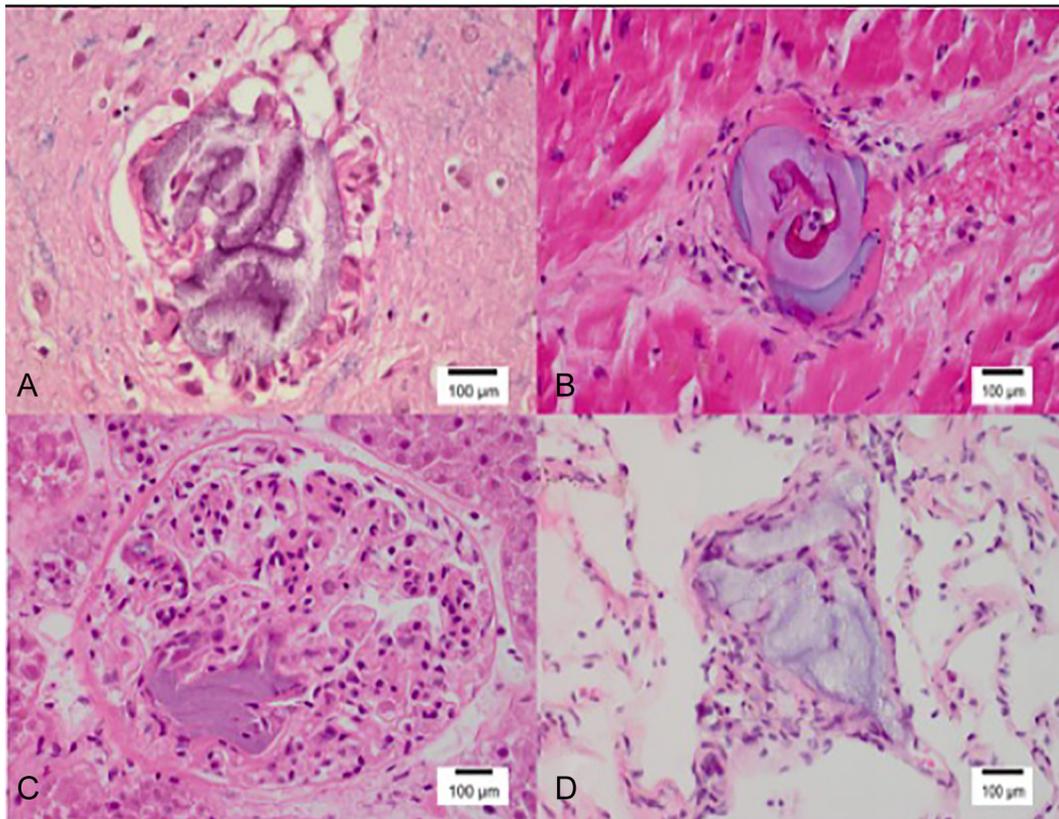


Fig. 1. Representative photomicrographs (400 \times) of HPE from 4 of the 25 HPE-positive autopsy cases. Each example shows an amphiphilic-to-basophilic, nonrefractile, nonpolarizable intravascular embolus with a fibrillar/lamellar and variably granular appearance. (A) Brain HPE showing histiocytic foreign body response (case 17). (B) Myocardial HPE showing complete arteriolar occlusion (case 6). (C) Renal HPE showing HPE lodged within the afferent arteriole of a glomerulus (case 8). (D) Lung HPE occluding a pulmonary arteriole with histiocytic cell response (case 16).

4. Discussion

Iatrogenic infarction, including stroke, following cardiac procedures is a recognized risk factor, especially when left-sided heart procedures are undertaken. Stroke may result from watershed infarcts of the brain in vulnerable border zones between vascular territories of the brain supplied by the anterior, middle, and posterior cerebral arteries, usually due to procedure-related hypotension [7], prolonged procedural vascular occlusion, or embolic phenomena. A review of stroke and encephalopathy following cardiac procedures by McKhann et al. [8] found that patients with preexisting cerebrovascular disease are at increased risk for poor neurological outcomes. Also, it is recognized that new surgical innovations and techniques (e.g., endovascular instruments) have allowed for treatment opportunities for patients at the extremes of age and infirmity, a patient group that also has the greatest

risk for neurological injury [9]. Although much clinical literature exists in the field of iatrogenic stroke study, including a recent review on the topic [10], to our knowledge, this is the first autopsy-based retrospective clinicopathologic analysis of iatrogenic embolism complicating cardiovascular procedures, including pre-mortem diagnostic imaging correlation.

4.1. Polymer emboli (HPE)

Hydrophilic polymer coating is commonly used to enhance lubrication of endovascular devices, including guidewires, sheaths, arterial catheters, central venous catheters, stents, and coils [1–4]. There is increasing recognition that routine device manipulation may cause dissociation of the hydrophilic polymer coating, resulting in HPE. To evaluate the frequency and extent of HPE-associated morbidity and mortality,

Table 2
Overview of non-HPE iatrogenic emboli cases

Case	Endovascular procedure(s)	Clinical course	Brain infarction	Other organ(s) with CE	Death interval (d)
1. 63 M	Coronary angiography	LOC, right MCA	Extensive brain stem and rt. MCA infarcts. (CT + MRI head). Basilar and Rt. MCA M1 occluded on CTA. (✱)	Coronary arteries, spleen	0
2. 80 M	CABG	Coma	No brain pathology available. Died due to MI.	Coronary arterial occlusion with CE	1
3. 69 M	TAVI + CABG	Coma	Left MCA M3 branch (CT)	Nil	7
4. 73 M	TAVI + CABG	Sepsis, brain stem signs.	Pons + cerebellum (✱)	Colon, kidneys, coronary arteries	14
5. 75F	TAVI	Left MCA	Extensive left MCA stroke (CT). Cardiac tissue embolized to left M1 MCA artery (✱)	Left upper extremity ischemia	15
6. 66F	CABG	Cortical blindness	Bilateral occipital (CT). CCE in bilateral PCA.	Nil	90
7. 45 M	Mitral valve leaflet repair	Coma	Diffuse ischemic change (CT). Died MI.	Lung	N/A

Included are patient demographics, endovascular procedures employed, clinical course, location(s) of brain infarction and other involved organs, and the death interval after final endovascular procedure. "x" indicates cases where the presence of iatrogenic emboli was implicated in the final cause of death.

MCA: middle cerebral artery, CABG: coronary artery bypass graft, STEMI: ST elevation myocardial infarction, TAVI: transcatheter aortic valve insertion.

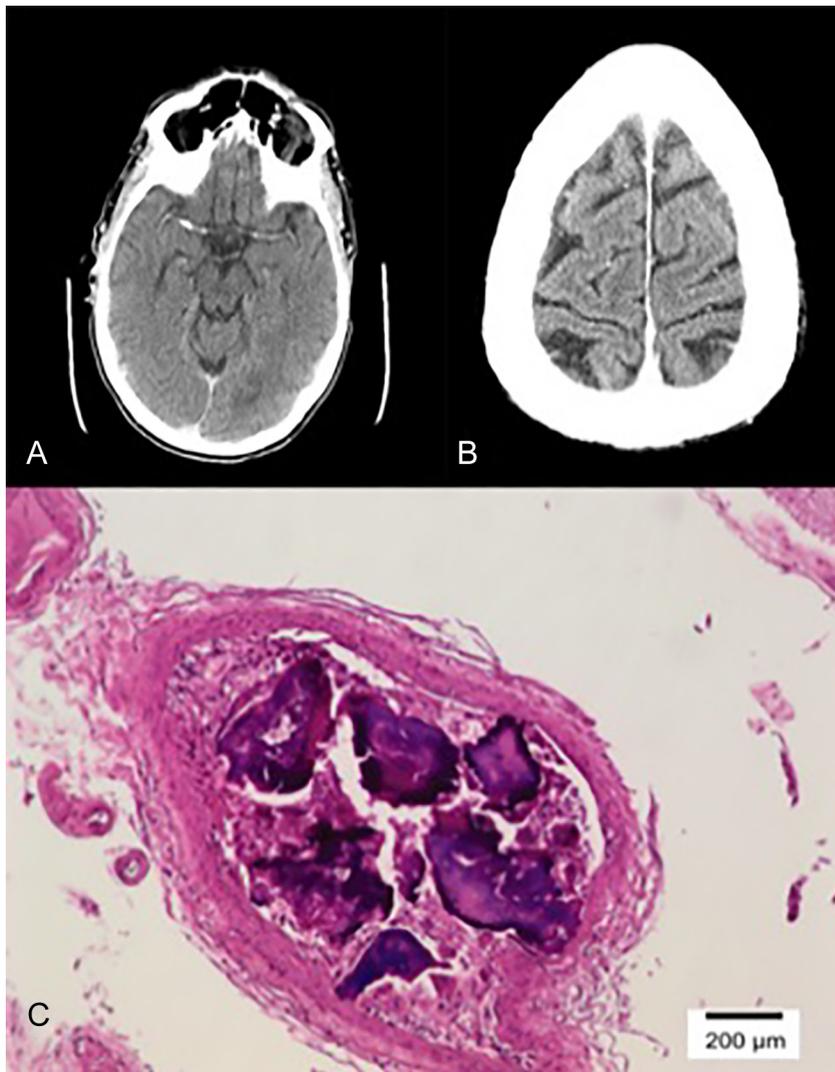


Fig. 2. Axial noncontrast head CT showing (A) hyperdense vessel sign showing irregular occlusive embolus of the right M1 artery (vessel and embolus pathology showed that this was made of a large CCE) and (B) "salted pretzel" appearance caused by multiple CCE. (C) Microscopic image (200 \times) of CCE resulting from displaced aortic valve calcifications.

we undertook a retrospective autopsy-based analysis and correlated these findings with premortem imaging studies.

In this largest documented collection of HPE-positive histologic cases to date, with companion diagnostic imaging correlation where available, we identified evidence of HPE in 23% of cases. In a heart-only study, Grundeken et al. [11] identified HPE in 10% ($n=4$) of cases while also identifying polymer material in 45% ($n=205$) of aspirated

thrombi from percutaneous cardiac interventional procedures. Mehta et al. [12] reviewed 136 hospital autopsies and identified HPE in 13% ($n=18$) cases, specifically involving the lungs ($n=18$), heart ($n=1$), and central nervous system ($n=1$). In comparison, our 25 HPE-positive cases involved a diverse range of organs, with the 3 most prevalent sites being the kidneys ($n=13$), lungs ($n=8$), and heart ($n=7$). Other reports have identified HPE in the skin [13], bowel [14], kidney

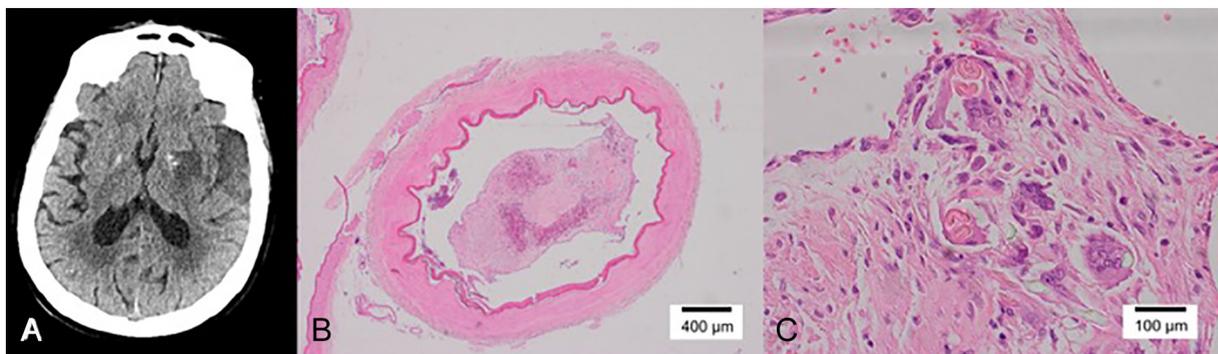


Fig. 3. (A) Axial noncontrast head CT scan demonstrating subacute infarct in the left MCA territory, including lentiform nucleus and temporal operculum. (B) Embolic tissue within left MCA (100 \times). (C) Higher magnification of embolic fragment of myocardial tissue within middle cerebral artery. Note polarizable foreign material (sutures) and giant cell reaction (200 \times).

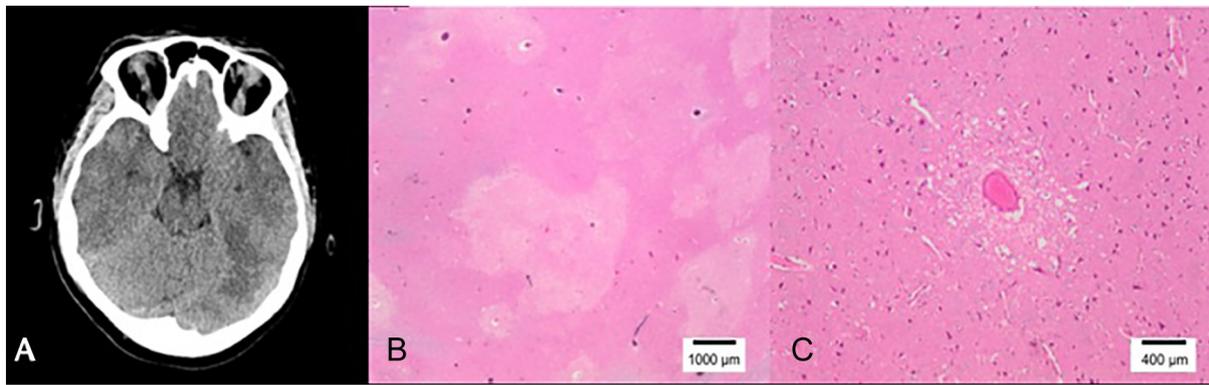


Fig. 4. (A) Axial noncontrast head CT showing diffuse infarction and edema secondary to air embolism. (B) Corresponding histopathology showing geographic perivascular brain injury (40 \times) and (C) marked perivascular edema (100 \times).

[15], and myocardium [16] and implicated as a cause of death in the brain [17].

It has been demonstrated that routine use of polymer-coated endovascular devices can result in dissociation of polymer from the device surface [18]. As such, it seems that with any hydrophilic polymer-coated endovascular device, there is the potential for polymer to slough and embolize. As shown in Fig. 1, the polymer material can present with variable tinctorial quality and granularity, even within a single individual. This is likely due to differences in the polymer material used between different instruments during endovascular procedures.

There remains a great deal of uncertainty to what extent these small polymer emboli may be harming patients. HPE results in focal vascular occlusion, normally at the level of the arterioles. Scattering of these emboli may result in diffuse, though subclinical, ischemic or hypoxic insult. For three cases in our study, the HPE were determined to have caused death by resulting in extensive cerebral and myocardial infarctions, as demonstrated by numerous foci of HPE within the same region as infarcted heart and brain tissues (Table 1).

HPE do show visible evidence of resolution in the postprocedural period. The greatest interval between procedure and death detected in our study group was 41 days, while others have reported polymer dissolution over weeks to months [16,18,19,20].

One limitation of our study is that we only assessed HPE in hospital autopsy cases, a patient group that may be biased due to the multiple comorbidities and worsened preprocedural clinical status of many of these patients. Within this high-risk group, the HPE may have initiated a cascade of events that could have led to greater morbidity and mortality than in individuals with fewer risk factors and more stable clinical status. Regardless, we propose that any individual undergoing an endovascular procedure with a polymer-coated device is at some undefined risk of HPE. Due to the inconsistency of pre- and postprocedural patient imaging in our case group, it is difficult to draw firm conclusions on the utility of CT or MRI as a means of detecting HPE-associated infarction. Notably, in the three cases where we identified HPE in the brain (Table 1), there was also radiographic evidence of regional brain infarction.

Improved recognition and reporting of HPE are necessary to better understand the contribution of these complications to morbidity and mortality. The United States Food & Drug Administration (FDA) recently acknowledged that there are deficiencies in international endovascular device standards, resulting in devices in the market that have the potential to slough polymer coating material [21]. Furthermore, there were over 500 medical device reports related to failure of these devices over a nearly 2-year period (2015–2016), including 9 patient deaths related to dissociation of device coatings [21]. Although the FDA contends that overall benefits of these polymer-coated devices outweigh the risks, confirmed histologic findings of HPE need to be reported to government medical device regulators. We remain hopeful that

clinicopathologic analysis will contribute to enhanced design and standards for use of these important medical devices.

4.2. Calcified emboli

CE are an infrequent cause of embolic stroke [22]. Nevertheless, they pose a therapeutic challenge with regards to both intravenous thrombolysis [22,23] and endovascular embolectomy [24,25] and may require surgical embolectomy in extreme circumstances [3]. Presumably, CE originate from calcified aortic and/or mitral valves as well as calcified atherosclerotic plaques [22,26,27], and it is recognized that CE may be spontaneous [22,25]. Although advanced imaging with MRI may show new embolic-looking acute ischemic lesions, the exact composition of the embolic material and extent of tissue ischemic damage may remain unclear. In contrast to previous pathological studies investigating spontaneous CE in AS patients [28], our autopsy series characterizes post endovascular procedure associated CE and their attributed ischemic damage. As expected, our patients with procedural-related CE had higher loads of emboli in their intracranial vasculature compared with those observed in spontaneous cases [28]. Moreover, two patients had large-caliber CE resulting from complete occlusion of basilar and M1 segments of the MCA arteries with subsequent death. We attribute the source of the iatrogenic CE to dislodgment and displacement of calcified material from calcified aortic valves and ulcerated aortic atherosclerotic plaques during therapeutic and investigative procedures. Stroke resulted from the CE and clinically presented from the effects of the sudden, hyperacute vascular occlusion following the endovascular procedure, as the catheter passed through the aortic valve in patient number 1 and immediately postprocedure in patient 5 (with right and left MCA syndromes). Their noncontrast CTs of head revealed hyperdense vessel signs as well as “salted pretzel sign” [6] (Fig. 3B). In two cases (numbers 3 and 5), head CT was performed to investigate continued comatose state and revealed new embolic strokes.

4.3. Tissue embolism

Iatrogenic tissue embolism is thought to be a rare phenomenon, although its true incidence is likely underreported due to the relative difficulty of histologic confirmation. Two recent case reports describe aortic valvular tissue embolization to the brain during endovascular aortic valve replacement [29,30]. Additionally, in a case report with some similarities to our own, Murphy et al. [31] describe a case of myocardial embolism causing stroke resulting from an open septal myomectomy. These cases serve to illustrate the potential for any intravascular material, whether foreign or endogenous, to potentially result in downstream vascular occlusion and infarction/stroke.

4.4. Air embolism

CAE is a recognized, although uncommon, complication of cardiovascular surgery. Diagnosing CAE during an endovascular procedure may be challenging. A syndrome consisting of reduced postoperative vigilance, frequent epileptic seizures, and focal neurological deficits in the presence of an apparently normal CT scan and often isolated cortical infarction on MRI is suggestive of such a diagnosis [32]. Even with careful neuropathologic examination postmortem, it remains difficult to distinguish severe and abrupt hypoperfusion from CAE [33]. Both processes show significant edema and hemorrhagic transformation of the ischemic territories most likely due to blood brain barrier interruption [34]. In our case, without the documentation of air within the left side of heart by transesophageal echo and the evacuation of air from the aorta intraoperatively, it would not have been possible to attribute air embolism as the cause of death in this case because the radiologic and pathologic findings were indistinguishable from those seen in ischemic hypoxic encephalopathy or to a profound episode of hypotension. This has been previously described: in a neuropathologic study of brain damage complicating open heart surgery, Brierly suspected air embolism in 7 of 46 patients and commented that it was “virtually impossible to distinguish the neuropathology of a severe and rapid reduction in cerebral blood flow from that of air embolism” [33]. Air embolism associated with ventricular assist devices was documented in 1 of 33 patients in an autopsy series [35]. Therapy in our case followed published guidelines [36] but was unsuccessful. Damage to the blood brain barrier has been implicated experimentally [34,37]. The perivascular cortical vacuolation (Fig. 4b and 4c) in our case is indicative of perivascular edema and is supportive of such a mechanism for brain injury. Prompt diagnosis of CAE followed by immediate corrective measures may have some benefit [36]; however, more definitive prognostic variables and the role of hyperbaric treatment remain unclear.

5. Conclusions

In conclusion, we describe the first autopsy-based retrospective clinicopathologic analysis to assess iatrogenic embolism complicating cardiovascular procedures with premortem diagnostic imaging correlation. In reviewing 110 autopsy cases wherein the decedent had a recent endovascular procedure, we identified 25 decedents with HPE, 7 decedents with CE, and single occurrences of tissue embolism and air embolism. To our knowledge, this is the largest collection of HPE findings to date. Patients with heavily calcified aortic valve and aorta seem to be at high risk for clinically significant iatrogenic emboli. We advocate for greater awareness of these underrecognized and occasionally fatal complications of endovascular procedures. The use of targeted postprocedural imaging has a role in aiding identification of iatrogenic embolic infarcts. The use of autopsy remains the gold standard for confirmation of the embolic cause.

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