Cholesterol Embolization Syndrome

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Cholesterol embolization syndrome refers to embolization of the contents of an atherosclerotic plaque (primarily cholesterol crystals) from a proximal large-caliber artery to distal small to medium arteries causing end-organ damage by mechanical plugging and an inflammatory response. Synonyms used in the medical literature include atheromatous embolization, cholesterol crystal embolization, and atheroembolism.

Cholesterol embolization syndrome should be distinguished from the related and much more common syndrome of arterio-arterial thromboembolism in which fragments of a thrombus that forms atop an atheromatous plaque in the aorta or a large artery travel distally and occlude medium to large arteries.[1]

Cholesterol embolization syndrome is generally characterized by a multitude of small emboli (showers of microemboli) occurring over time. This is in contrast to arterio-arterial thromboembolism, which is usually characterized by an abrupt release of 1 or a few large emboli, leading to severe ischemia of target organs.

Cholesterol embolization syndrome has a variety of clinical presentations. Cholesterol emboli originating in the descending thoracic and abdominal aorta may lead to renal failure, gut ischemia, and emboli to the skeletal muscles and the skin. Dermatologic manifestations (most commonly livedo reticularis and blue toe syndrome) are usually confined to the lower extremities but may extend to the abdomen and the chest. Cholesterol emboli originating in the ascending aorta may in addition cause neurological damage that is typically diffuse and due to small infarcts. Cholesterol embolization syndrome is also characterized by a nonspecific acute inflammatory response leading to constitutional symptoms (such as fever and malaise) and abnormalities in laboratory tests (such as hypereosinophilia and elevated erythrocyte sedimentation rate). These manifestations will be discussed in detail later in the text.

History

Danish physician Fenger and his colleagues appear to have provided the first description of atheroembolism in the Danish medical brochure *Ugeskrift for Laeger* (Doctors' Weekly).[2] In 1844, they performed the autopsy of the Danish/Icelandic sculptor Bertel Thorvaldsen (1770–1844), who suffered a sudden cardiac death at age 74 years while attending the Royal Theater in Copenhagen. In their autopsy report, they noted the following:

Aorta was a bit enlarged and somewhat rough on the exterior surface. Its walls were somewhat tender and filled with a great amount of partly atheromatous, partly chalk-like deposits within the inner membrane and creating roundish irregular elevations which were partly ulcerated; a notable one was seen in the abdominal aorta above its bifurcation. A similar finding existed in both coronary arteries; in the posterior vessel 1 inch below its origin, there were several atheromatous plaques, one of which undoubtedly had ulcerated, pouring the atheromatous mass into the arterial lumen.[3]

These autopsy findings were translated into German and disseminated into a wide medical literature in 1862 by the Danish pathophysiologist Peter Ludvig Panum (1820–1885).[4]

Autopsy remained the primary way of diagnosing cholesterol embolization syndrome well into the 20th century. The first autopsy series was reported in 1945 from the New York Hospital by Flory; the average age of study patients was ≈65 years.[5] The first antemortem noninvasive diagnosis of cholesterol embolization syndrome was described in 1961 by Dr Robert Hollenhorst (1913–2008), an ophthalmologist working at the Mayo Clinic.[6] He noted yellow, highly refractile cholesterol emboli at the bifurcation of retinal blood arteries, which later became known as Hollenhorst plaques (Figure 1). Major historical developments in cholesterol embolization syndrome are summarized in Table 1.

Pathophysiology

The following 6 key elements are required for the development of cholesterol embolization syndrome:

1. Presence of a plaque in a proximal, large-caliber artery (such as the internal carotid artery, the iliac arteries, or the aorta)
2. Plaque rupture (spontaneous, traumatic, or iatrogenic)
3. Embolization of plaque debris (containing cholesterol crystals, platelets, fibrin, and calcified detritus)
4. Lodging of the emboli in small to medium arteries with a diameter of 100 to 200 μm, leading to mechanical occlusion
5. Foreign-body inflammatory response to cholesterol emboli
6. End-organ damage due to a combined effect of mechanical plugging and inflammation

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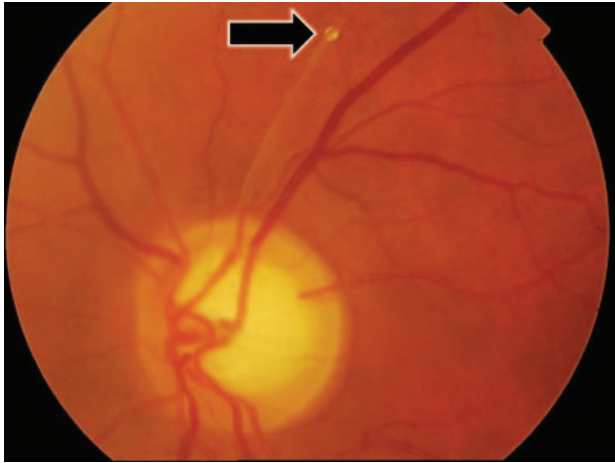DOI: 10.1161/CIRCULATIONAHA.109.886465

Figure 1. Hollenhorst plaque (cholesterol embolus) in the retinal artery (arrow). Courtesy of Dr Irene Cherfas Tsyvine, Department of Ophthalmology, New Jersey Medical School, Newark, NJ.

1. Atheromatous Plaque in a Proximal Artery

The pathophysiology of cholesterol embolization syndrome is inextricably linked to the general development of atherosclerosis. To the 18th century pathologists, atheroma (from the Greek $\alpha\theta\acute{\eta}\rho\omega\mu\alpha$) appeared as a tumor-like swelling of the arterial wall filled with material reminiscent of gruel or crushed grains (referred to in ancient Greek as $\alpha\theta\acute{\eta}\rho\eta$: athêrê). Subsequently, many terms have been used to describe these lesions in the aorta and its branches, including atheromatous deposits, atheromatous debris, atherosclerotic lesions, and cholesterol deposits. In this review, these atheromatous lesions will be referred to as plaques.

Histologically, the plaque resides within the arterial intima, is composed of a necrotic core, and is overlaid by a fibrous cap. The necrotic core is made up of cell debris, foam cells (macrophages), and various lipids including cholesterol crystals. Macrophages are loaded with oxidized low-density lipoprotein. On their death, they release cholesterol-rich material into the extracellular space. It is this low-density lipoprotein–derived cholesterol that becomes the source of cholesterol emboli.

Cholesterol within the plaque exists either in a soluble form (as cholesteryl ester oil droplets or solubilized in
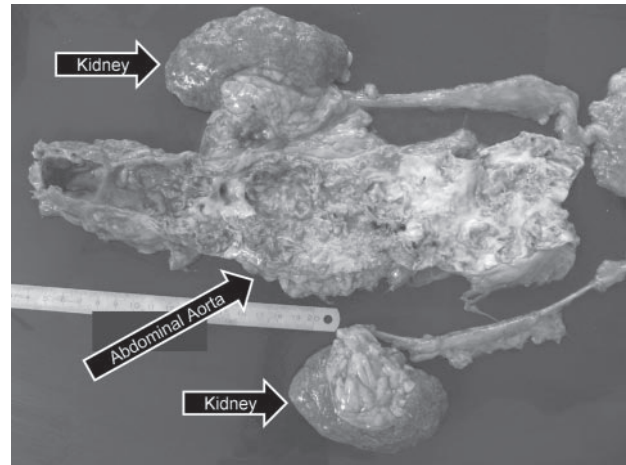
Table 1. Historical Landmarks in Cholesterol Embolization Syndrome

Year	Discovery
1862	First description of cholesterol embolization (in the left coronary artery) by Danish physicians
1945	First autopsy case series (n=267) from New York Hospital reported by Flory with classic description of multiorgan involvement
1956	Illumination of frozen sections with polarized light to identify the cholesterol crystals described
1957	Thurlbeck and Castleman first recognized atheromatous embolization as a complication of vascular surgery
1961	Hollenhorst crystals described at Mayo Clinic
1976	Blue toe syndrome first described
1990	Relationship between aortic plaque seen on TEE and embolic events first reported

Figure 2. Autopsy specimen of aorta with severe atherosclerosis. Gross pathological specimen of the abdominal aorta with severe atherosclerosis from a patient with cholesterol embolization to multiple organs. Courtesy of Dr Amy Rapkiewicz, Department of Pathology, New York University Medical Center, New York, NY.

phospholipid bilayers) or in a crystalline form (as cholesterol monohydrate crystals). Cholesterol crystals reside deep inside the plaque, and their formation represents a late stage in the progression of atherosclerosis. Crystalline cholesterol accounts for >40% of the cholesterol of a plaque.[7] With the use of radiolabeled tracers, the turnover time of cholesterol in advanced plaque is estimated to range from 442 to 934 days.[8] The deep location of cholesterol crystals within the plaque and the low turnover rate of this lipid make stabilization of ruptured cholesterol crystal–rich plaques difficult.

The cap is composed of endothelial cells, smooth muscle cells, and connective tissue. Cap rupture is the prerequisite for cholesterol crystal embolization. The cap may be destabilized by forces working from within the plaque (such as inflammation or hemorrhage within the plaque) or acting from the luminal side (such as shearing forces in systemic hypertension or mechanical disruption during vascular procedures).

Atheromatous plaques at various stages of development may coexist in the walls of the aorta and its major branches (Figure 2). Some plaques have lipid-rich cores covered by intact intima; some may be ulcerated, pouring their contents into the arterial lumen and giving rise to cholesterol emboli; and yet others are overlaid with thrombi that may shear and cause arterio-arterial thromboembolism. Thus, the same patient may have manifestations of both atheroembolism and arterial thromboembolism. The specter of coexistence of the 2 embolic phenomena in the same individual may have a major impact on the treatment of atheroembolism, as discussed below.

Plaques can be simple or complex. In the aorta, simple plaques are characterized by focal immobile lesions of the luminal wall measuring <4 mm in thickness. Complex plaques are thicker (≥4 mm), have irregular, often ulcerated luminal borders, and on occasion exhibit shaggy mobile components that represent thrombi (Movie I in the online-only Data Supplement).

The aorta is the primary location of atheromatous plaques that give rise to both cholesterol emboli and thromboemboli. The positive correlation between the severity of aortic plaque
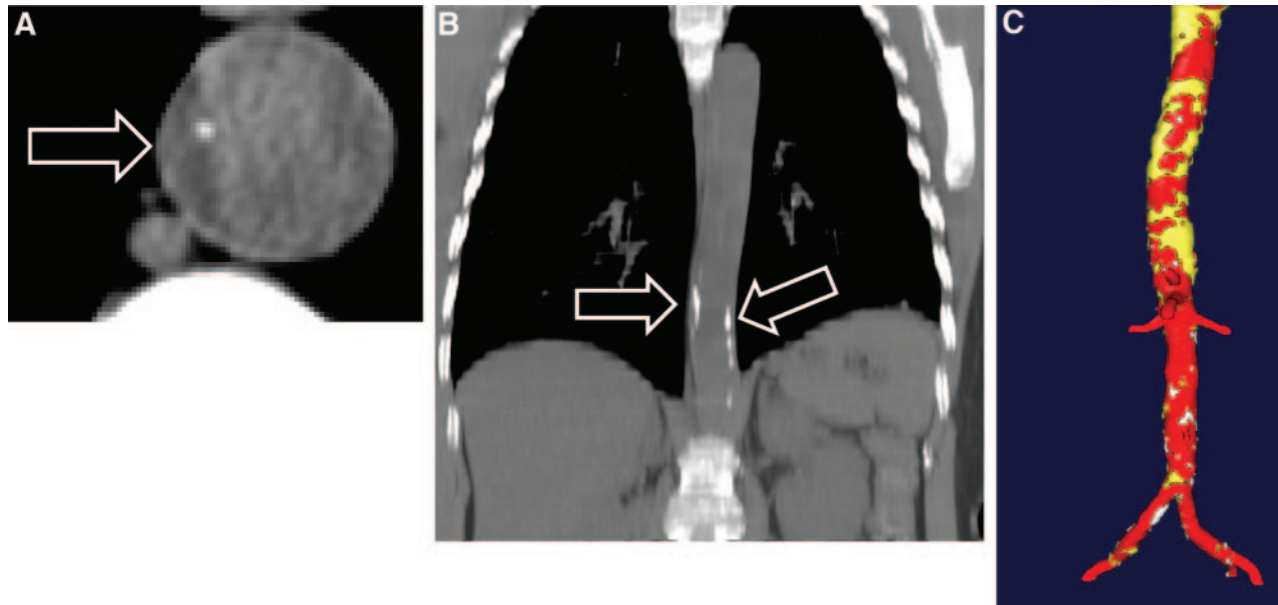
Figure 3. Aortic plaque visualized by CT. A, Short-axis view of the descending thoracic aorta at the level of the left atrium. Severe plaque (arrow) with a bright spot of focal calcification. B, Long-axis view of the descending thoracic aorta with multiple areas of calcified aortic plaque (arrows). C, Reconstructed CT image of the descending thoracic and abdominal aorta demonstrating soft (yellow areas) and calcified plaque (white areas). Courtesy of Dr Pierre Maldjian, Department of Radiology, and Dr Peter Pappas, Department of Surgery, New Jersey Medical School, Newark, NJ.

and the risk of atheroembolism was first noted in the autopsy series by Flory.[5] No atheroemboli were discovered in patients without atherosclerotic plaque erosions in the aorta. The risk of atheroembolism rose progressively with the degree of aortic plaque erosion; the risk of atheroembolism was 1.3% in patients with moderately eroded plaque and 12.3% in patients with severe plaque erosion.

In general, the severity of atherosclerosis increases from the proximal to the distal portions of the aorta. As a consequence, the abdominal aorta and the ileo-femoral arteries are the most common source of atheroembolism.[9] In contrast, the subclavian artery is a rare source of cholesterol emboli, and thus atheroembolism to upper extremities is unusual.[10]

Imaging of the Aorta

Transesophageal echocardiography (TEE), computed tomography (CT), and magnetic resonance imaging (MRI) are standard clinical imaging techniques for the visualization, characterization, and quantification of atherosclerotic plaque in the aorta.[11] At present, TEE is the most commonly used imaging technique for the detection and measurement of the aortic atherosclerotic plaque.[12,13] A correlation between in vivo findings of advance atherosclerotic plaque on TEE and embolization phenomena was first reported in 1990 by Tunick and Kronzon in 2 patients with neurological events and in 1 patient with both a stroke and an embolism to a toe.[14] The importance of TEE findings of aortic plaque for the pathogenesis of systemic embolism was confirmed in subsequent case-control studies. Plaque thickness of ≥4 mm in the ascending aorta and the aortic arch emerged as an important predictor of cerebral embolization.[15–17]

However, in these studies no biopsy data were available to distinguish between atheroembolism and thromboembolism. Subsequently, several case reports of biopsy-proven choles-terol embolization to the skin and kidneys were published. In these case reports, TEE demonstrated complex atherosclerotic plaques in the descending thoracic aorta.[18,19]

CT (Figure 3) and MRI (Figure 4) can also be used to detect and characterize aortic plaques. In the initial experience, CT seemed to underestimate the atheromatous plaque burden in the aorta compared with 2-dimensional TEE (Figure 5).[20] In a series of 32 patients with a recent history of stroke or systemic emboli, the sensitivity and specificity of noncontrast dual-helical CT in comparison to TEE were 87% and 82%, respectively.[21] However, with recent technical advances, CT and MRI may now provide a less invasive and more complete evaluation of aortic atherosclerosis compared with 2-dimensional TEE.

For imaging of aortic branches and the abdominal aorta, CT and MRI have clear advantages over TEE. First, TEE has a blind spot for the region around the brachiocephalic artery because of interposition of the trachea between the aorta and the ultrasound probe in the esophagus. Second, TEE cannot visualize the abdominal aorta except for the few centimeters of proximal abdominal aorta between the diaphragm and the origin of the superior mesenteric artery.

Real-time 3-dimensional TEE, which has been introduced recently into clinical practice, provides detailed images of the aortic plaque (Figure 6). Atherosclerotic plaque can also be seen occasionally on transthoracic echocardiography in either the thoracic or abdominal aorta.

Although aortic arch atherosclerosis is common in patients with ischemic stroke, aortography (performed as an add-on to conventional cerebral angiography performed during diagnostic workup of ischemic strokes) frequently fails to identify plaque detected by transesophageal echocardiography.[22] Aortic plaque may be discovered incidentally during endoscopic ultrasound of the upper gastrointestinal tract (Figure 7),
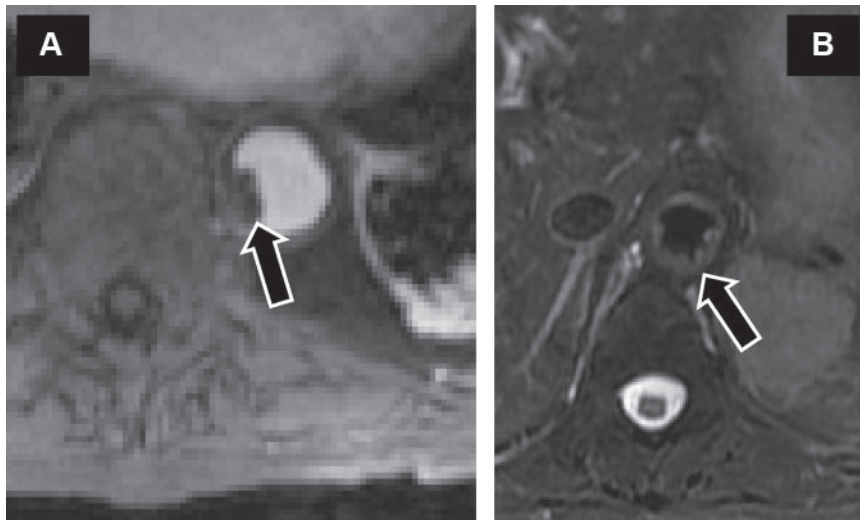
Figure 4. Aortic plaque in the descending aorta visualized by MRI. A, An axial cut obtained with the use of the volumetric interpolated breath-hold examination sequence demonstrates a large protruding plaque (arrow). Courtesy of Dr Robert Donnino, Division of Cardiology, New York University Medical Center, New York, NY. B, An axial T2-weighted image with fat suppression demonstrates extensive ulcerated plaque (arrow). Courtesy of Dr Pierre Maldjian, Department of Radiology, New Jersey Medical School, Newark, NJ.

which may pose a diagnostic challenge to a gastroenterologist unfamiliar with aortic pathology.

Abdominal aortic aneurysm is a known source of cholesterol emboli. In a prospective study of 660 patients with a mean follow-up of 15.3 ± 15 months (range, 1 to 60 months), signs and symptoms of cholesterol embolization syndrome developed in 19 patients (2.9% of patients with abdominal aortic aneurysm).[23]

2. Plaque Rupture

Plaque rupture with extrusion of the cholesterol-rich material into the arterial lumen is a prerequisite for atheroembolism. Plaque rupture may either occur spontaneously or be iatrogenic after manipulations of the arterial vessels during percutaneous or surgical procedures. It is controversial whether thrombolytic or anticoagulant therapy is an independent risk factor for plaque rupture and cholesterol embolism.

Spontaneous Atheroembolism

The rate of spontaneous rupture may be gleaned from older pathoanatomic series published before the widespread use of arterial cannulation for cardiovascular imaging and repair. In the first autopsy series of atheroembolism published by Flory in 1945, the incidence of spontaneous thromboembolism was 3.4% (9 of 267 patients with advanced arteriosclerosis of the aorta).[5] In an autopsy series of 2126 individuals published in 1978, evidence of spontaneous atheroembolism was found in 16 patients (.075%; cited as 0.79% in the study), 9 men and 7 women with an average age of 76.7 years.[24] In a general autopsy series of 372 patients reported in 1991, spontaneous plaque rupture was found in 7 patients (1.9%), all affected individuals were older than 60 years, and 6 were men. Therefore, the reported incidence of spontaneous atheroembolism is low (0.79% to 3.4% in the aforementioned 3 autopsy studies), and the phenomenon is most frequently observed in elderly patients.[25]

In an antemortem retrospective study of 519 patients with complex aortic plaque seen on TEE, atheroembolism occurred in 1% of patients in the 3-year follow-up period. The rate of cholesterol embolism was markedly lower than the 20% rate of arterio-arterial thromboembolic complications in the same group of patients.[26]

Cardiac Catheterization and Angioplasty

Clinically apparent atheroembolism is an uncommon complication of cardiac catheterization. In a prospective study of
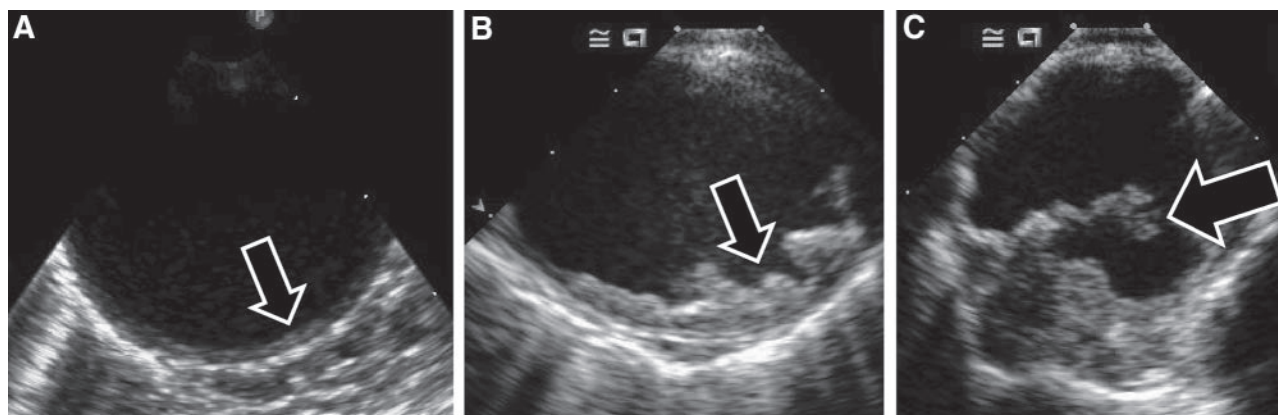
Figure 5. Aortic plaque in the descending thoracic aorta visualized by 2-dimensional TEE. A, Simple atherosclerotic plaque, measuring ≈2 mm in this patient. B, Complex atherosclerotic plaque with deep ulcerations (arrow). C, Complex atherosclerotic plaque with a mobile component (arrow) that represents a thrombus. Please also see Movie I in the online-only Data Supplement, which demonstrates severe atherosclerosis of the descending thoracic aorta with a large mobile component.
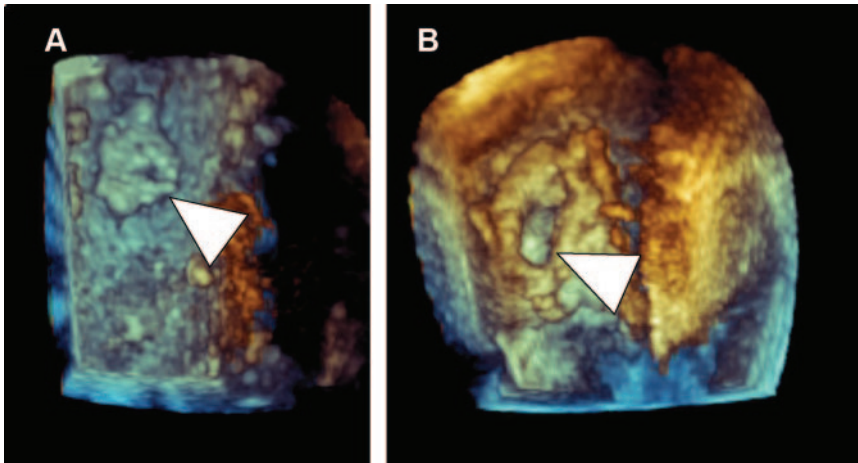
Figure 6. Aortic plaque in the descending thoracic aorta visualized by 3-dimensional TEE. A, Protruding plaque. B, Ulcerated plaque.

1786 consecutive patients aged ≥40 years, who underwent left-heart catheterization in Japan, cholesterol embolization syndrome (defined as livedo reticularis, blue toe syndrome, digital gangrene, or renal failure) was found in 25 patients (incidence of 1.4%). There was no significant difference in the risk of atheroembolism between femoral and brachial approach, suggesting that the ascending aorta is the predominant source of cholesterol emboli.[27] In another prospective study that examined renal failure as the only manifestation of cholesterol embolization syndrome after cardiac catheterization, the incidence was also relatively low. Among 263 study patients, renal failure was attributed to cholesterol emboli in 5 patients (incidence of 1.9%).[28]

Cholesterol embolization during coronary angioplasty is uncommon. In a prospective study of 1579 patients undergoing coronary angioplasty in the United States, clinical evidence of cholesterol embolization was found in 1 patient (0.06% of cases).[29] Interestingly, in a prospective study of 1000 patients undergoing percutaneous revascularization procedures via the femoral approach, plaque debris was retrieved from >50% of all guiding catheters.[30]

Surgical manipulation of the aorta and its major branches carries the highest risk of cholesterol emboli. Atheromatous embolization as a complication of vascular surgery was first

Figure 7. Severe aortic plaque (arrow) visualized by endoscopic ultrasound in the descending thoracic aorta (AO). Courtesy of Dr Zamir Brelvi, Division of Gastroenterology, New Jersey Medical School, Newark, NJ.

recognized in the 1950s.[31,32] The high risk persists in the modern era of cardiovascular surgery.

Cardiac Surgery
In an autopsy study of 221 patients with a mean age of ≈66 years (58.8% were men) who had undergone myocardial revascularization or valve operations between 1982 and 1989, cholesterol embolization or abnormalities consistent with cholesterol embolization were noted in 48 patients (21.7% of the autopsy series), whereas thromboemboli were found in 14 of them (6.3%). Cholesterol embolization was 3 times more common in patients undergoing coronary revascularization surgery (43 of 165 patients, or 26.1%) than in those undergoing valve surgery (5 of 56 patients, or 8.9%). The risk of cholesterol embolization after cardiac surgery was strongly related to the degree of atherosclerosis in the ascending aorta, whose severity, in turn, was directly related to patients' age. Brain was the most common destination site of cholesterol emboli (8 of 48 patients) followed by the spleen (5 patients), kidneys (5 patients), and pancreas (3 patients). Thirty of the 48 autopsied patients had multiple atheroembolic sites.[33]

Off-pump coronary artery bypass grafting has been shown in 1 randomized trial to lead to less microembolization and retinal damage than older bypass techniques using a cardiopulmonary bypass machine.[34] At least some of the microemboli that arise during coronary artery bypass grafting surgery are cholesterol emboli, as discussed later in the text.

Aortography and Abdominal Aortic Surgery
The prevalence of the reported risk of cholesterol embolism after aortic imaging and surgery depends on whether the risk was judged from clinical or postmortem studies. In a retrospective clinical study of 1011 patients undergoing infrarenal aortic and infrainguinal vascular surgery in the 1990s, the clinical, radiological, or pathoanatomic diagnosis of atheroembolism was established in 2.9% of patients; angiography alone rather than vascular surgery was responsible for the vast majority (84.6%) of cases.[35]

This is in sharp contrast to older autopsy series. In 1 series of patients undergoing abdominal aortography in the 1970s, 30% of patients experienced postprocedural cholesterol embolism.[36] In another autopsy series of patients who died after resection of abdominal aortic aneurysm in the 1950s,
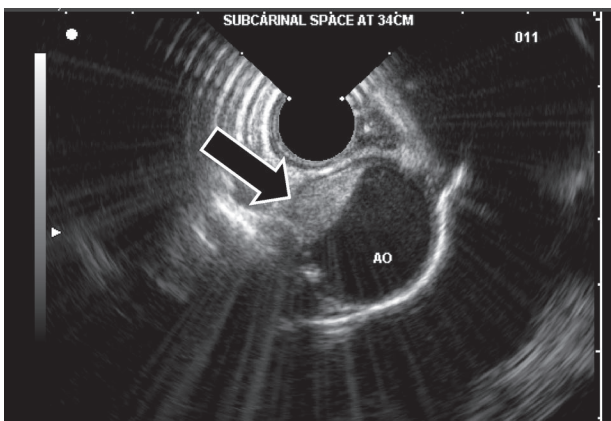
procedure-related cholesterol embolization was found in 77% of patients.[37] Such a high risk is likely a combination of procedural factors and a selection bias toward older patients with more advanced atherosclerosis.

Carotid Interventions

Cholesterol embolization syndrome has been observed after both surgical carotid endarterectomy and percutaneous carotid stenting. In major trials of carotid endarterectomy, the rate of perioperative stroke and death has ranged from 2.0% to 7.5%, with more than half of the events being mild to moderate strokes. Most perioperative events are ischemic strokes and due to cholesterol embolization syndrome or hypoperfusion from carotid clamping. This is in contrast to events in the later postoperative period, which are related to thromboembolism from the newly debrided arterial surface or dissection of an intimal flap.[38]

Carotid stenting is emerging as an alternative to carotid endarterectomy in patients with significant carotid artery stenosis. Numerous microemboli can be shed during carotid angioplasty.[39] The risk of periprocedural neurological complications due to embolism after carotid stenting is ≈5%; the risk is substantially lowered by the use of embolism protection devices.[40–42]

Thrombolytic Therapy

In 1984, the first case of thrombolytic therapy–associated cholesterol embolization syndrome was published.[43] In a subsequent systematic review of articles published in English from 1980 to 2007, a total of 30 cases of thrombolytic agent–associated cholesterol embolization syndrome were identified. In most of these cases, thrombolysis was given for acute myocardial infarction (28 patients); in the remaining 2 patients, it was used for deep venous thrombosis.[44] On the basis of these case reports, a causal relationship between cholesterol embolism and thrombolysis has been hypothesized.

However, in a prospective study of 60 patients, all of whom underwent skin and muscle biopsies, there was no statistically significant difference between the patients who received thrombolytic therapy and those who did not.[45] Unfortunately, the large clinical trials of thrombolytic therapy, such as the Third International Study of Infarct Survival (ISIS-3) trial[46] and Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO),[47] did not systematically track cholesterol embolization syndrome as a separate complication category.

Anticoagulant Therapy

It has been hypothesized that anticoagulation may lead to plaque hemorrhage, plaque rupture, and subsequent cholesterol embolization syndrome.[48] However, from the published case reports, it is unclear whether cholesterol embolization syndrome was causally related to anticoagulants or simply occurred in patients who happened to be receiving anticoagulation therapy.

In the retrospective observational study of 519 patients with severe atherosclerotic plaque of the thoracic aorta visualized by TEE, there was no statistically significant difference in the rate of cholesterol embolization syndrome in patients who received warfarin compared with those who did not.[26] However, the event rate of cholesterol embolization syndrome was low; only 5 patients developed it (3 of 313 patients taking warfarin [1%] and 2 of 206 patients receiving no warfarin therapy [1%]).[49]

To date, there are no randomized clinical trials whose primary outcome was cholesterol embolization syndrome related to anticoagulant therapy. However, 2 clinical trials have indirectly addressed the issue: the French Study of Aortic Plaques in Stroke (FSOAPS) and the third iteration of the Stroke Prevention and Atrial Fibrillation trial (SPAF-III).

The French Study of Aortic Plaques in Stroke was a prospective observational study of 331 patients aged ≥60 years with brain infarction; some patients were treated with warfarin and some with antiplatelet agents at the discretion of the patient's physician. In the entire cohort, there was only 1 case of cholesterol embolization syndrome, which occurred in a patient who was not receiving warfarin.[50]

In the third iteration of the Stroke Prevention and Atrial Fibrillation trial, which was a prospective open-label randomized trial, adjusted-dose warfarin (international normalized ratio, 2 to 3) was compared with low-dose warfarin (international normalized ratio, 1.2 to 1.5) plus aspirin (325 mg/d) for stroke prevention. The authors of the study concluded that risk of cholesterol embolism syndrome in elderly patients with atrial fibrillation and aortic plaque who receive adjusted-dose warfarin (international normalized ratio, 2.0 to 3.0) is "relatively low."[51]

Among the 140 patients with no atherosclerotic plaque in the thoracic aorta, none developed cholesterol embolization syndrome in either treatment group. Among patients with atherosclerotic plaque on TEE, 1 of 117 patients treated with adjusted-dose warfarin developed apparent cholesterol embolization syndrome (the diagnosis was established on clinical grounds; no biopsy was performed), whereas none of the 121 patients taking low-dose warfarin plus aspirin developed the syndrome. However, the exact impact of warfarin therapy on the rate of cholesterol embolization syndrome could not be fully ascertained from this trial because there was no control group; all patients received some form of warfarin therapy.

In summary, on the basis of current data, one cannot definitively either prove or disprove the causal relationship between cholesterol embolization syndrome and anticoagulation and/or thrombolytic therapy. Nonetheless, the package insert for Coumadin (Bristol-Myers Squibb, Princeton, NJ), a brand-name version of warfarin, states that "therapy with Coumadin may enhance the release of atheromatous plaque emboli, thereby increasing the risk of complications from systemic cholesterol microembolization, including the 'purple toes syndrome.' Discontinuation of Coumadin therapy is recommended when such phenomena are observed."[52] In our own practice, we do not recommend the use of anticoagulation therapy in patients with cholesterol embolization syndrome unless there is a separate indication such as atrial fibrillation or mechanical prosthetic valve.

3. Embolization of Cholesterol Crystals and Plaque Debris

Despite the multitude of reports on the risk of plaque rupture leading to cholesterol embolization in a variety of clinical scenarios (Table 2), the true incidence and prevalence of cholesterol embolism are unknown. Atheroembolism is characterized by showering of numerous cholesterol microemboli

Table 2. Risk of Cholesterol Embolization in Various Clinical Settings

Clinical Context	Type of Study	Incidence of Atheroembolism, %
Spontaneous atheroembolism	Clinical	0.79–3.4
Cardiac catheterization	Clinical	1.4–1.9
Coronary angioplasty	Clinical	0.6
After cardiac surgery	Autopsy	≤22
After aortography	Autopsy	≤30
After AAA resection	Autopsy	≤77

AAA indicates abdominal aortic aneurysm.

to a variety of tissues and organs. Atheroembolism becomes evident only after clinically significant end-organ damage has occurred. In other words, there is no specific diagnostic test to detect cholesterol embolism per se. It is likely that a large number of atheroembolic episodes never become clinically apparent and that those episodes recognized clinically are only the "tip of an iceberg" of atheroembolism.

4. Lodging of Cholesterol Emboli in Peripheral Arteries

After traveling through arterial circulation, atheroemboli lodge in the arterioles and small arteries. Cholesterol crystals per se can be visualized only if biopsy specimens are specially processed with liquid nitrogen to preserve the crystals.[53] Under polarized light, cholesterol crystals demonstrate birefringence (double refraction of polarized light). In routinely processed biopsy specimens, cholesterol crystals are washed away. Characteristic ovoid or crescentic clefts within the lumen of affected arterioles or small arteries remain (Figure 8).

5. Inflammatory Response

Cholesterol emboli not only mechanically occlude the vessel but also trigger an inflammatory reaction. The details of the inflammatory response have been well documented in an animal model. The response is a 3-step process consisting of (1) acute inflammation, (2) foreign body reaction and intravascular thrombus formation, and (3) endothelial proliferation and eventually fibrosis.

During the acute inflammatory phase, the walls of the affected arterioles and small arteries are infiltrated by polymorphonuclear leukocytes and eosinophils. Within the next 24 to 48 hours, mononuclear cells appear; they become giant cells, and they phagocytize cholesterol crystals. Around the same time, there is intraluminal thrombus formation. In the final stage, there is endothelial proliferation and intimal fibrosis. The net result is narrowing or even obliteration of the arterial lumen, leading to tissue ischemia. Cholesterol emboli may remain lodged for months because they are often resistant to scavenging by macrophages.[54]

6. End-Organ Damage

Virtually any organ or tissue can be affected by cholesterol embolization syndrome. However, the following organs are most commonly involved: the brain, the kidneys, the gastrointestinal tract, and the skin and skeletal muscles of the lower extremities.
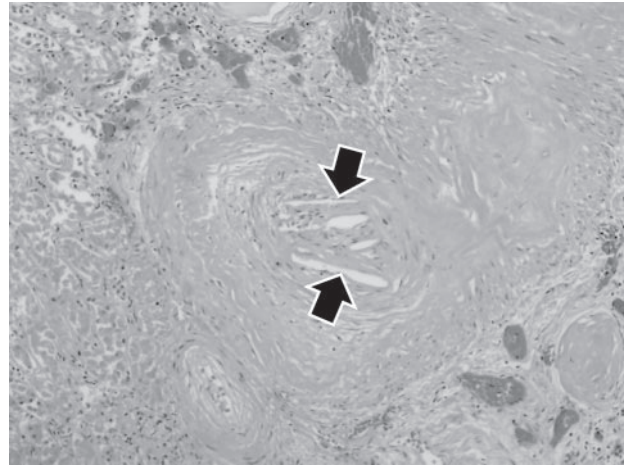

Figure 8. Histopathology of cholesterol embolization. Characteristic empty clefts (arrows) are seen within the obliterated lumen of a small artery in the kidney. Hematoxylin-eosin stain; magnification ×200. Courtesy of Dr Amy Rapkiewicz, Department of Pathology, New York University Medical Center, New York, NY.

Central Nervous System

Showers of cholesterol emboli originating in the ascending aorta, aortic arch, or carotid and vertebral arteries either spontaneously or during intravascular interventions (such as cardiac catheterization, cardiac surgery, carotid endarterectomy, or carotid stenting) lead primarily to diffuse brain injury, often characterized by confusion and memory loss rather than focal neurological deficits. Cholesterol emboli are often large enough to occlude the penetrating arterioles of the cerebral cortex.[55] Brain imaging typically reveals small ischemic lesions and border zone infarcts.[56]

Transcranial Doppler (TCD) ultrasonography, which was first described in 1982, can be used to detect microemboli in the cerebral circulation.[57] Microemboli are detected as high-intensity transient signals superimposed on standard spectral Doppler flow velocity tracings of red blood cells in cerebral arteries. Cholesterol crystals are only 1 form of cerebral microemboli; others are made of fat, air, calcium deposits, and other materials. TCD ultrasonography cannot distinguish cholesterol from other cerebral microemboli.

Release of thousands of microemboli has been demonstrated by TCD during or immediately after carotid endarterectomy or angioplasty.[58] A study of 41 patients who underwent TCD and MRI of the brain before and after carotid endarterectomy demonstrated new brain lesions in 8 patients (almost 20% of the study group). However, only 3 patients have clinical evidence of stroke or transient ischemic attack.[59]

In a study of 57 patients undergoing coronary artery bypass grafting, there were 22 to 2072 (mean±SD=326±47) high-intensity transient signals per patient detected by TCD. The embolization rate was the highest at the initiation of cardiopulmonary bypass, and total embolic events were highest during aortic clamping. Although transcranial Doppler ultrasonography could not distinguish between various types of microemboli in this study, cholesterol emboli were likely a significant portion of microemboli.[60]

Cholesterol emboli originating in the ascending aorta, aortic arch, and great arteries of the neck may also lead to

retinal artery occlusion. Amaurosis fugax is the typical clinical manifestation of retinal artery involvement. The presence of the Hollenhorst plaques on retinal examination is the tell-tale sign of the disease.

Kidney

Cholesterol crystal embolization to the kidneys, also referred to as atheroembolic renal disease, primarily affects the arcuate and interlobar renal arteries. These small arteries may be completely obliterated or may demonstrate some residual lumen. In rare instances, the cholesterol crystals lodge in the afferent arteries and glomeruli. However, characteristic histopathological clefts may not be found in all renal biopsies because cholesterol crystal embolization has patchy distribution.[61]

In a series of 259 patients aged ≥60 years who underwent renal biopsy setting of acute renal insufficiency, cholesterol embolization was present in the biopsies of 18 patients (6.9% of all cases). Prebiopsy clinical diagnosis of cholesterol embolization syndrome was correct in only 3 patients.[62]

In a review of 221 patients with histologically proven cholesterol embolization syndrome, renal involvement was seen in 50% of cases. Elevations of serum creatinine and proteinuria are the predominant manifestations of renal atheroembolism, occurring in 83% and 54% of renal atheroembolism cases, respectively.[63] In addition, renal ischemia caused by the inflammatory response to cholesterol emboli may lead to accelerated and hard-to-control systemic hypertension.[64]

Renal atheroembolism can lead to acute, subacute, and chronic renal failure. In acute and subacute forms, one can often elicit an inciting event that had led to massive release of cholesterol emboli (such as iatrogenic manipulation of the aorta during vascular procedures). In contrast, chronic forms are likely due to spontaneous low-grade release of cholesterol emboli over long periods.

Renal impairment after cholesterol embolization to the kidney may reside anywhere on the spectrum from spontaneous resolution to end-stage renal disease requiring dialysis. In an observational study of 354 renal patients in whom atheroembolism was confirmed by renal biopsy or suggested by concomitant presence of retinal Hollenhorst plaques, progression to dialysis was observed in >30% of patients at the end of a 2-year follow-up. In addition, the 1-year and 2-year survivals were markedly diminished (83% and 75%, respectively) and lower than after acute myocardial infarction or initiation of maintenance dialysis in the general population.[65]

Gastrointestinal System

The prevalence of cholesterol embolization syndrome of the gastrointestinal system has been reported to vary between 18.6% and 48% of all cases.[66] Gut ischemia is the primary mode of presentation with often intractable intestinal blood loss, which is typically chronic and results predominantly from superficial mucosal ulcerations or erosions or from mucosal infarcts. Such lesions are usually only microscopic and may be missed easily by endoscopic or radiological studies.[67] In more advanced cases, there may be massive bleeding from pseudopolyp formations, ulceration, and/or perforation of hollow viscera due to ischemic colitis.[68] Cholesterol embolization syndrome may also result in acalculous necrotizing cholecystitis[69] and acute pancreatitis in elderly patients.[70]

Skin

The frequency of cutaneous findings ranges from 35% to 96% on the basis of 6 case series of cholesterol crystal embolization. The highest rates of cutaneous involvements have been reported in patients who also had renal manifestations of cholesterol crystal embolization.[71] In the most comprehensive dermatologic series of patients with cholesterol crystal embolization composed of 223 patients, skin manifestations were seen in 35% of patients; the most frequent findings were livedo reticularis (49% of patients with skin manifestations), gangrene (35%), cyanosis (28%), ulceration (17%), nodules (10%), and purpura (9%). In almost all patients, the skin of the lower extremities was involved; only in the minority of patients did the lesions also extend to the trunk and rarely to the arms.[72]

Livedo reticularis is characterized by reddish blue spots distributed in fishnet or lacy patterns. The spots represent deoxygenated blood in venous plexuses subtended by narrowed arterioles. Although commonly seen in cholesterol embolization syndrome, livedo reticularis is not a pathognomonic finding. It is simply a manifestation of skin ischemia and may be observed in any condition with narrowed arterioles (such as polyarteritis nodosa, systemic lupus erythematosus, treatment with vasoconstriction agents, and cholesterol embolization syndrome).

In the lower extremities, cholesterol embolism may lead to sudden development of purple or blue toes and other regions of the foot.[73] Because of the frequent occurrence of blue toes in cholesterol embolization, the term *blue toe syndrome* is occasionally used as a synonym of cholesterol embolization syndrome. Although the term *blue toe syndrome* was first used in the context of cholesterol embolization syndrome,[74] the skin changes are merely a reflection of microvascular ischemia and, like livedo reticularis, are not exclusive to cholesterol emboli. Blue toe syndrome may also occur in vasculitis (eg, polyarteritis nodosa), hypercoagulable states (eg, antiphospholipid syndrome), hyperviscosity states (polycythemia vera), and endocarditis.[75]

Toe and foot cyanosis in blue toe syndrome is often more prominent in dependent leg areas, and it may blanch with moderate pressure. When both extremities are involved, the skin changes are usually asymmetrical. If microvascular ischemia is severe, tissue necrosis may develop, spanning from small superficial ulceration to gangrene.

It is frequently said that skin manifestations in cholesterol embolization syndrome occur in the presence of palpable regional pulses because cholesterol emboli occlude small arteries and arterioles rather than large palpable arteries. In other words, if the aforementioned skin manifestations occur in the presence of palpable pulses, they are much more likely to be due to cholesterol embolization syndrome rather than to other forms of peripheral arterial disease of the lower extremities. However, patients with cholesterol embolization syndrome concomitantly often have other manifestations of advanced atherosclerosis, including peripheral arterial disease, which may independently lead to diminished peripheral pulses. Manifestations of the blue toe syndrome often coexist with the more diffuse cyanotic mottling of livedo reticularis (Figure 9).[76,77]
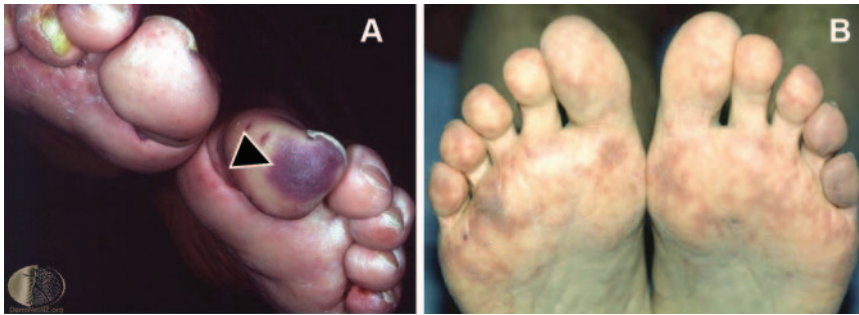
Figure 9. Skin manifestations of cholesterol embolization syndrome. A, Blue toe syndrome (arrowhead). Courtesy of Dr Amanda Oakley, New Zealand Dermatological Society Incorporated; image reprinted with permission from DermNet NZ.org.[76] B, Livedo reticularis. Courtesy of Dr Gregory J. Raugi, University of Washington, Seattle; image reprinted with permission from eMedicine.com.[77]

Diagnosis

Clinical presentation of cholesterol embolization syndrome is often a combination of signs and symptoms specific to end-organ damage (described above) and a systemic inflammatory response. Cholesterol crystals trigger an inflammatory response after they lodge in the small arteries of the target organ. Constitutional signs and symptoms such as fever, weight loss, anorexia, fatigue, and myalgias are frequent manifestation of the inflammatory response. Laboratory tests may also show an abnormality in inflammatory markers such as a rise in leukocyte count, erythrocyte sedimentation rate, and C-reactive protein or a decrease in serum complement levels (hypocomplementemia). The patient may also develop anemia or thrombocytopenia.

Hypereosinophilia has been reported in up to 80% of the patients with cholesterol embolization syndrome. The duration and magnitude of hypereosinophilia in cholesterol embolization syndrome are variable. Hypereosinophilia often occurs only during the first few days, and the proportion of eosinophils may vary from 6% to 18% of the total leukocyte count.[78] The exact mechanism of hypereosinophilia in cholesterol embolization syndrome is not known; it is believed that cholesterol embolization syndrome is a form of cytokine-mediated eosinophilic disorder.[79] One of the cytokines may be interleukin 5 derived from vascular endothelium.[80] It is important to emphasize that hypereosinophilia is not pathognomonic for cholesterol embolization syndrome because it may occur in a variety of other disorders such as systemic vasculitides, acute interstitial nephritis, and radiographic contrast-induced renal injury.

Because none of the aforementioned clinical or laboratory findings are specific for cholesterol embolization syndrome, a high degree of clinical suspicion is required in establishing the diagnosis. One should always consider the possibility of cholesterol embolization syndrome when one encounters acute renal failure, hypereosinophilia, livedo reticularis, and/or blue toe syndrome in a patient (often an elderly man) who has other manifestations of advanced atherosclerosis, particularly if the patient had recently undergone a vascular procedure such as cardiac catheterization.

Histopathological confirmation by biopsy is the only definitive test for cholesterol embolization syndrome.[81] Although biopsy of any target organ can be obtained in theory, biopsy of the affected skin or skeletal muscles is preferred. However, biopsy is performed rather infrequently because it may lead to poor healing at the sampling site.

Treatment

Although cholesterol embolization syndrome been recognized as a separate clinical entity for many years, there is still no specific therapy for this disorder.[82] Treatment goals are 2-fold: supportive care for end-organ damage and secondary prophylaxis against another episode of cholesterol embolization syndrome. Because cholesterol embolization syndrome is a manifestation of atherosclerosis, modification of traditional risk factors such as smoking, hypertension, and serum cholesterol should be advised strongly.

There is some evidence that statin therapy decreases the risk of cholesterol embolization syndrome. In a retrospective observational study of 519 patients with severe atherosclerosis of the thoracic aorta on TEE, multivariate analysis demonstrated that statin use was independently protective against recurrent embolic events.[26] Unfortunately, there has been no randomized trial of statin therapy in patients with severe aortic plaque.[83]

There is no direct evidence that antiplatelet agents prevent the recurrence of cholesterol embolization syndrome. However, their use seems reasonable because such agents have been shown to prevent other adverse cardiovascular events such as myocardial infarction, the leading cause of death in patients with atherosclerosis.[84] Similarly, angiotensin-converting enzyme inhibitors or direct angiotensin receptor blockers should be considered.[85,86]

Given the uncertainty of the impact of thrombolytic and anticoagulant therapy, it has been suggested that one should not initiate such a therapy in patients with cholesterol embolization syndrome. However, anticoagulation should probably be continued if there is a separate indication[87] (such as the presence of a mechanical prosthetic valve or atrial fibrillation). Finally, the risk of cholesterol embolization syndrome should be judged carefully against any benefits of diagnostic or therapeutic interventions involving the aorta or its branches such as angiography, percutaneous revascularization, and surgeries of the heart and/or the arterial tree.

Surgical therapy for cholesterol embolization syndrome has been shown to be effective in decreasing the rate of further embolism. A variety of surgical techniques have been described, such as aortic bypass; aortoiliac, femoral, or popliteal endarterectomy and patch; infrainguinal bypass; extra-anatomic reconstruction; upper-extremity bypass; and upper-extremity endarterectomy and patch.[88,89]

Stent graft repair of abdominal aortic aneurysms is emerging as an alternative to surgical repair. Stenting, in addition to protecting the patient from aortic rupture, may also be an

effective strategy to prevent future cholesterol embolization from abdominal aortic aneurysm.[23] Other embolizing arterial lesions (such as those in the iliac or subclavian arteries) may also be treated with endoluminally placed stent grafts to prevent future cholesterol embolism.[90]

Disclosures

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