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Aortic Atherosclerotic Plaques as a Source of Systemic Embolism

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Objectives. **Our study was designed to determine the significance of aortogenic embolism in an unselected autopsy collective.**

Background. **Although embolism arising from atherosclerotic plaques in the aorta has been acknowledged, the role of aortic atheromatosis among other well known sources of embolism remains to be further clarified.**

Methods. **We examined the proximal part of the arterial system with regard to the presence of atherosclerotic lesions as well as cardiac changes in 120 consecutive necropsy studies. Pathologic evidence of embolic events was recorded. Clinical and neuropathologic data were also surveyed in all patients.**

Results. **Among atherosclerotic lesions, fibrous plaques ($p < 0.05$) and calcified ($p < 0.0001$) and ulcerated lesions ($p < 0.0001$) as well as thrombi ($p < 0.005$) were observed significantly more frequently in the aortic arch and in the descending aorta than in the ascending aorta, whereas fatty streaks were distributed uniformly. In 40 (33%) of the 120 patients, we found pathologic evidence of arterial embolization. Multiple logistic regression analysis revealed a significant correlation between embolism and complicated atherosclerotic plaques in the aortic arch (odds ratio [OR] 5.8, 95% confidence interval [CI] 1.1 to 31.7, $p < 0.05$), severe ipsilateral carotid artery disease (OR 3.1, 95% CI 3.1 to 45.3, $p < 0.001$) and atrial fibrillation (OR 3.5, 95% CI 1.1 to 9.9, $p < 0.05$).**

Conclusions. **Complicated atherosclerotic plaques in the aortic arch represent an independent risk factor for systemic embolism similar to atrial fibrillation and severe atherosclerosis of the carotid arteries.**

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About one-fourth of cardiovascular death results from cerebrovascular disease (1). The specific cause of cerebral infarction remains undetermined in a discouragingly large number of patients (2,3). Embolism from an undetected source is, however, suspected to be the underlying cause in some of the cases with this disorder (3).

Atherosclerosis in the thoracic aorta has traditionally been regarded as a rare source of systemic embolism (4,5). Nevertheless, recent clinical and pathologic studies emphasize the relevance of these lesions as a source of systemic embolism, particularly in patients with cerebral infarction of unknown cause (6–15). In this regard, ulcerative changes are considered to be particularly highly associated with embolism (7,13,16–19).

Although echocardiographic studies addressed the role of aortic atheromatosis among other well-known sources of embolism, this subject remains to be further clarified (10). In the present study, we determined the impact of both clinical and pathologic changes on arterial embolism in an unselected series of necropsy studies.

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Methods

One hundred twenty complete necropsy studies performed at the Medizinische Universität zu Lübeck in 1993 to 1994 were included in this prospective study (65 men, 55 women; mean age [±SD] 71 ± 12 years, range 29 to 94). Extensive macroscopic examinations of the proximal part of the arterial system, the heart and the brain were performed in each case. Clinical data and laboratory findings were also surveyed in all patients.

Atherosclerotic lesions. We examined the thoracic aorta, the carotid system and the major cerebral arteries regarding the presence of atherosclerotic lesions. The vessels were removed, opened longitudinally, and prepared in a standardized way. Care was taken during the cleaning process not to lose thrombi or shaggy overlay. No special or unusual procedures were used to treat the specimens. The aorta was examined in its three segments: the ascending aorta from its origin to the orifice of the innominate artery, the arch from this orifice to a line through the orifices of the first intercostal arteries and the descending aorta from this line to the upper edge of the orifice of the celiac artery (20).

Atherosclerotic changes were classified by inspection and palpation as fatty streaks, fibrous plaques, complicated and calcified lesions (21). Complicated lesions were defined by the presence of ulceration, mural thrombi or atheromatous debris. An ulceration was defined by a disruption of the intimal surface visible on macroscopic examination (7). Mural throm-

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bus was defined as an intravascular clot that, on transection, usually disclosed lamellations known as the lines of Zahn (22). Atheromatous debris was defined by the presence of eroded atheromata containing soft, brown, grumous material that could be scraped away with ease (23). The presence or absence of each type of lesion in each of the three aortic segments was noted.

The severity of stenosis in the carotid arteries was classified according to Fisher et al. (24). Severe carotid artery disease was defined by a stenosis greater than 75%, occlusion of the vessel or ulceration, independent of the degree of stenosis. The presence of a plaque that included the entire circumference of the vessel and caused a moderate to severe occlusion was required for the diagnosis of severe atherosclerosis of any of the major cerebral arteries (25).

Cardiac source of emboli. The following morphologic cardiac changes, known to be correlated with systemic embolism, were searched for: intracardiac thrombi, recent myocardial infarction, left ventricular aneurysm, infective or marantic endocarditis, mitral or aortic stenosis, prosthetic heart valves or patent foramen ovale (26). We included only subjects whose cardiac rhythm had been accurately documented.

Systemic embolism. Pathologic evidence of an acute or subacute systemic parenchymal infarction with or without the presence of an intravasal embolus was required for the diagnosis of an embolic process (27). A cerebrovascular event was assumed in the presence of a focal or global neurologic deficit with sudden onset and lasting more than 24 h (28). The clinical diagnosis of peripheral or visceral embolism required ischemic manifestations with sudden onset and angiographically or surgically proven arterial occlusion (29).

Infarct subtypes. Complete examination of the brain was performed by neuropathologists who had no knowledge of the pathologic results. An etiologic classification of cerebral infarction was undertaken, and clinical and pathologic evidence of the presumed mechanism of cerebral infarction was assessed in each case (3,7). Causes were classified as "atherosclerotic" (as evidenced by severe cerebrovascular atherosclerosis), "cardioembolic" (as defined by the presence of a cardiac source of emboli with no severe cerebrovascular atherosclerosis), "mixed" (defined as both atherosclerotic and cardioembolic), "other" (rare and unusual causes of cerebral infarction) or "undetermined" (in the absence of any of the conditions mentioned above).

Clinical data. The patient's chart was reviewed in detail, and the circumstances surrounding all illnesses and the death of each subject were also sought by scrutiny of all available medical information (history, cardiac and neurologic evaluations, cardiac rhythm, laboratory findings and results of invasive and noninvasive diagnostic and therapeutic procedures). The cardiovascular risk factors considered in this study were hypertension, diabetes mellitus, smoking and hypercholesterolemia. We analyzed the relation between these risk factors and calcified plaques observed in the descending aorta.

Statistics. Statistical comparison between groups was performed using the chi-square test. Multiple logistic regression analysis was performed to determine predictors of arterial embolism. Cardiac sources of embolism as well as arterial lesions in the thoracic aorta and in the carotid system were included in this analysis. Data were controlled for age and gender. Ninety-five percent confidence intervals were calculated for the odds ratios; $p < 0.05$ was considered to be significant. The data were analyzed using the SPSS statistical package.

Results

Neuropathologic findings. Pathologic evidence of cerebrovascular disease was found in 42 (35%) patients. Of these, 36 (86%) had cerebral infarction, and 6 (14%) intracranial hemorrhage.

Clinical data. Review of patients' charts revealed that clinical symptoms of stroke had occurred in 24 of the 36 patients who had pathological evidence of cerebral infarction. The remaining 12 patients (33%) had no history of stroke. Pathologic evidence of extracerebral embolism was found in 12 patients (10%), of whom 10 had visceral and 2 had peripheral embolism. Premortem diagnosis of extracerebral embolism was accurately made only in three cases, including two cases of peripheral embolism and one mesenteric infarction.

Atrial fibrillation was documented in 40 (33%) patients. Of these, 20 (50%) patients had evidence of arterial embolization. Atrial fibrillation was found more frequently in patients with than in those without cerebral infarction (50% vs. 26%, $p < 0.05$). It had occurred in 7 of 12 patients with silent cerebral infarction.

Regarding cardiovascular risk factors, calcified plaques were present in the descending aorta of 34 (87%) of 39 patients with hypertension, and of 27 (90%) of 30 patients with diabetes ($p < 0.05$, respectively).

Pathologic findings. The presence of intimal changes was assigned to a total of 360 segments of the thoracic aorta (120 patients × 3 segments). All types of intimal lesions except fatty streaks were found significantly less frequently in the ascending aorta, compared to the arch and the descending aorta (Table 1). The finding of complicated plaques included ulcerations in all and thrombi in 17 (14%) patients. Among patients who had mural thrombi, pathologic evidence of systemic embolism was found in six patients. In five (4%) patients, in addition to an extensive ulcerative disease with superimposed thrombi, we found eroded atheromas with atherosclerotic debris. These were located in the descending aorta and in the aortic arch. Evidence of systemic embolism was found in all of these patients.

Severe atherosclerosis of major cerebral arteries was not significantly more frequent in patients with than in those without cerebral infarction (28% vs. 15%, p = NS). Severe atherosclerotic changes of internal carotid arteries were found in 15 (42%) of 36 patients with cerebral infarction compared to 12 (14%) patients without cerebral infarction ($p < 0.001$). Carotid atherosclerosis was ipsilateral to the infarct focus in 11 cases. Comparing atherosclerotic involvement of the aortic

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Table 1. Frequency and Distribution of Positive Findings of Atherosclerotic Lesions in Three Aortic Segments

	Fatty Streaks (n = 271)	Fibrous Plaques (n = 44)	Calcifications (n = 229)	Ulcerations (n = 128)	Thrombi (n = 17)
Ascending aorta	88 (32%)	6 (14%)	47 (20%)	13 (10%)	0 (0%)
Aortic arch	94 (35%)	19 (43%)	92 (40%)	54 (42%)	5 (29%)
Descending aorta	89 (33%)	19 (43%)	90 (39%)	61 (48%)	12 (71%)
p value	NS	< 0.05	< 0.0001	< 0.0001	< 0.005

arch and the carotid system revealed, in 59% of the patients with severe carotid artery disease, the simultaneous presence of complicated plaques in the aortic arch.

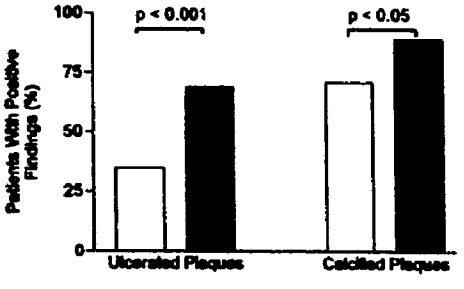
In patients with cerebral infarction, calcified plaques in the aortic arch were found in 32 (89%) patients, and complicated plaques in 25 (69%) patients, respectively. Both calcified lesions ($p < 0.05$) and complicated lesions ($p < 0.001$) were found significantly more frequently in patients with than in those without cerebral infarction (Fig. 1). Ulcerated plaques were found in 9 of 12 patients in whom cerebral infarction had not been diagnosed clinically.

Infarct subtypes. Cerebral infarction was classified according to the presumed mechanism as atherosclerotic in 6 (16%) patients, as cardioembolic in 9 (25%) patients, as mixed in 11 (30%) patients, as other cause in 2 (5%) patients and as infarct of undetermined cause in 8 (22%) patients. The prevalence of complicated plaques in the aortic arch tended to be higher in patients with infarct of undetermined cause than in those in whom a cause of cerebral infarction could be determined (75% vs. 68%).

Correlation between clinical and pathologic variables and systemic embolism. Pathologic evidence of systemic embolism was found in 40 (33%) patients including 28 patients with cerebral and 12 patients with extracerebral involvement. Of these, in 12 (30%) patients the cause remained undetermined (8 with cerebral and 4 with extracerebral embolism). In patients with systemic embolism, the prevalence of complicated plaques in the aortic arch was significantly higher than in those without embolism (68% vs. 34%, $p < 0.0005$).

A multiple logistic regression analysis was performed to determine clinical and pathologic variables associated with systemic embolism. A significant association was found between systemic embolism and complicated lesions in the aortic arch, severe atherosclerosis of carotid arteries and atrial fibrillation (Table 2).

Figure 1. Prevalence of ulcerated plaques and calcified plaques in the aortic arch of patients with cerebral infarction (**solid bars**) compared with those without cerebral infarction (**open bars**).



Discussion

Inherent to the aging process is atherosclerotic vessel disease. Complicated lesions in the aorta occur in half of the men and in one-third of the women of middle age, and their prevalence continues to increase in the subsequent decades of life (7,20,27,30–33). Systemic embolism arising from aortic atherosclerotic plaques has, however, been considered to be most unusual (4,5). The purpose of this clinicopathologic study was to demonstrate the relevance of aortic atherosclerosis as a source of embolism among other pathologic and clinical abnormalities in an unselected patient collective.

Relevance of complicated atherosclerotic lesions. The clinical relevance of complicated atherosclerotic lesions lies in the risk of producing arterioarterial emboli in addition to the well-known entities of occlusive disease (13,34,35). Eroded atheromatous plaques in the aorta may account for dislodgement of cholesterol crystals, which could lead to disseminated atheromatous emboli (16,36–38). Ulcerative changes in the aorta are a common finding in patients with cholesterol emboli (7,16,18,23,39–47). Thrombi that form on ulcerated atherosclerotic plaques represent an alternative form of atheroemboli that may occlude major arteries and produce a clinical picture indistinguishable from emboli of cardiac origin (5,6,16,17,34,35,44). Ulcerative changes are considered to be highly correlated with embolism (7,13,16,17,19,48). Furthermore, the formation of thrombi on nonulcerative lesions, namely on calcified and fibrous plaques, has also been reported (5,49). Severe atherosclerosis of the ascending aorta may account for stroke during coronary artery bypass grafting (45,50). Blauth et al. (27) observed a direct correlation between severe atheromatosis in the thoracic aorta and embolic events in patients who died in a period of 8 years after undergoing cardiac surgery. Atheroembolic events occurred in 37% of the patients with severe atherosclerosis but in only 2% of the patients without a significant atherosclerotic disease of the thoracic aorta.

Complicated plaques in the aortic arch as a source of systemic embolism. In our study most of the complicated lesions were found in the aortic arch and in the descending aorta, whereas the ascending aorta appeared to be the least prevalent site of atherosclerotic involvement. A consistent

Table 2. Multiple Logistic Regression Analysis of Presence of Systemic Embolism on Clinical and Pathologic Findings

	Odds Ratio	95% CI	p Value
Age	0.9	0.9–1.0	NS
Gender	0.6	0.2–2.1	NS
Fatty streaks in ascending aorta	0.6	0.2–2.0	NS
Fibrous plaques in ascending aorta	0.1	0.01–2.5	NS
Calcified plaques in ascending aorta	1.2	0.5–3.3	NS
Complicated lesions in ascending aorta	0.2	0.03–1.6	NS
Fatty streaks in aortic arch	2.4	0.2–25.6	NS
Fibrous plaques in aortic arch	9.5	0.9–98.5	NS
Calcified plaques in aortic arch	0.5	0.07–4.6	NS
Complicated lesions in aortic arch	5.8	1.1–31.7	< 0.05
Fatty streaks in descending aorta	0.3	0.04–3.7	NS
Fibrous plaques in descending aorta	0.1	0.02–2.2	NS
Calcified plaques in descending aorta	3.3	0.4–26.2	NS
Complicated lesions in descending aorta	1.0	0.2–5.7	NS
Severe ipsilateral carotid artery disease	11.7	3.1–45.3	< 0.001
Atrial fibrillation	3.5	1.1–9.9	< 0.05
Cardiac source of emboli	2.1	0.2–21.3	NS

CI = confidence interval.

topographic distribution of complicated lesions has been reported by Sternby (20), who performed a pathologic study on 1,486 subjects who were autopsied at the Malmö General Hospital between 1961 and 1962. Evaluation of atherosclerotic involvement of various aortic segments using computed tomography showed that intimal changes were found predominantly in the aortic arch, in the middle descending thoracic and the infrarenal abdominal aorta (51). The least prominent intimal changes appeared in the ascending aorta. In five of our patients we found eroded atheromas with atherosclerotic debris in the aortic arch and in the descending aorta. Once the material was removed, an ulceration was found in the aortic intima, often more than 1 cm in diameter. All mural thrombi that we found were also situated on ulcerated plaques. Fisher et al. (24) found mural thrombi in the aortic arch and in the descending aorta in 21 (12%) of 178 autopsied subjects, which is very similar to the prevalence of 14% found in our study.

Pathologic evidence of an embolic event was found in 40 (33%) of our patients. In as many as 30% of these, no cause could be determined. In patients with systemic embolism, the prevalence of complicated plaques in the aortic arch was significantly higher among those with than among those without an embolic event (68% vs. 34%). Pathologic evidence of systemic embolism was found in all of our patients with atheromatous debris and in six patients with mural thrombi. Thrombi may form on ulcerated plaques in the thoracic aorta and can reliably be detected by transesophageal echocardiography (6,13,19,42,49,52). Consistent with our results, several reports have described the association between complex atherosclerotic plaques in the thoracic aorta and cerebrovascular and peripheral embolic events (6,9–11,14,27,52). In a multiple logistic regression analysis, we found a significant association between arterial embolization and the presence of complicated lesions in the aortic arch, severe atherosclerosis of the ipsilateral carotid artery and atrial fibrillation, indicating that the potential of complicated aortic atherosclerosis to cause embolism resembles that of other well recognized embolic sources.

Complicated plaques in the aortic arch as a source of cerebral infarction. Earlier studies relied heavily on clinical syndromes and risk factors in the diagnosis of stroke subtype (53,54). However, in as many as 29–40% of cases of cerebral infarction, the cause remains unknown (2,3). In this study, pathologic evidence of cerebral infarction was found in 36 (30%) patients. Prevalence of complicated and calcified plaques in the aortic arch was significantly higher among patients with than in those without cerebral infarction. Complicated lesions in the thoracic aorta are well correlated with calcified lesions, suggesting that plain radiography could be useful for rough screening of atherosclerotic changes (13). Furthermore, we subdivided cerebral infarction according to the presumed mechanism. In 22% of patients with cerebral infarction, the cause remained undetermined. The prevalence of complicated plaques in the aortic arch of patients with cerebral infarction of undetermined cause tended to be higher than in those with a known cause. Similar findings have been reported by Amarenco et al. (6,7), who observed a higher prevalence of ulcerative changes in the aortic arch of patients with cerebral infarction of unknown cause.

Parallelism of arterial lesions. Comparing the atherosclerotic involvement in the aortic arch and in the carotid arteries revealed the presence of advanced lesions in the aortic arch in more than half of our patients with severe carotid artery disease. A similar parallelism has previously been reported by Fisher et al. (24). Katz et al. (52) described the carotid bruit as a marker for the presence of protruding atheromas in the aortic arch. Our findings suggest that these patients may be susceptible to cerebral emboli arising from arterial lesions in the carotid system as well as in the aortic arch.

Pathologic findings in silent stroke. A mild neurologic deficit is to be expected in 29% of cases with cerebral embolism (55). Cerebral cholesterol embolization usually results in a mild or inapparent clinical course, and infarction in border-zone areas has also been described (18,23,40,41,45,47). In 12 (33%) of our patients cerebral infarction was clinically not diagnosed. Ulcerative plaques in the aortic arch were found in 9 of the 12 patients with a silent cerebral event, and 7 patients had a history of atrial fibrillation.

Cardiovascular risk factors. The atherogenic influence of hypertension is more strongly marked in the aorta than in the extraaortic vessel beds (56). A strong association between hypertension and calcified plaques in the descending aorta has also been reported in the Framingham study (57). In our study, association was found between the calcified lesions in the descending aorta and the presence of hypertension and diabetes. One result of the more frequent use of angiography and noninvasive Doppler studies has been the finding that cerebral infarcts attributed to atherosclerotic stenosis or occlusion of large arteries occur at a lower frequency than formerly believed when greater reliance was placed on the risk factors of

age, hypertension and other signs of atherosclerosis (58,59). Therefore, it is to be assumed that atherosclerotic angiopathy might not only lead to atherosclerotic stroke but may also be the cause of aortogenic cerebral embolism.

Study limitations. A potential limitation of this study was the relatively small sample size, which resulted in a small number of patients per stroke subtype. However, the distribution of our patients in these subtypes was in accordance with the results from other studies. Another limitation concerns the cardiovascular risk factors that could not be collected completely in all patients. Finally, this study was performed on subjects who underwent routine autopsy, and no unusual techniques were used. Despite careful preparation of the vessels, small mural thrombi and atheromatous debris might have been lost. Thus, the frequency of thrombi and atheromatous debris might have been underestimated in our patients. However, the prevalence of mural thrombi in the present study was similar to that previously reported (24).

Clinical implications. Our findings emphasize the potential of complicated atherosclerotic lesions in the aortic arch in producing systemic embolism, which appears to be as potent as atrial fibrillation. These changes could account for a substantial number of cases with cerebral infarction of unknown cause. Therefore, exploration of thoracic aorta should be included in the workup of patients with embolic events, particularly when no source can be identified.

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