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Methamphetamine as a Risk Factor for Acute Aortic Dissection*

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ABSTRACT: Acute aortic dissections are catastrophic vascular events that have a high rate of mortality. Aortic dissections have been associated with a variety of factors, particularly hypertension. We reviewed 84 medical examiner autopsies on individuals dying from acute aortic dissections with particular emphasis on the role of drugs. Previous case reports have associated aortic dissections with both cocaine and methamphetamine intoxication.

We found that seven of the 35 cases tested for drugs of abuse were positive for methamphetamine. Our study had no cases of solely cocaine-related dissection, although one of the cases was positive for both methamphetamine and the cocaine metabolite benzoylecgonine. No significant association was found with any other drugs. As with other studies, we found the most common risk factor to be hypertension. Surprisingly, methamphetamine use was the second most common risk factor. The association between methamphetamine use and aortic dissection is most likely due to its hypertensive effect. Although methamphetamine appears to pose a greater risk than cocaine, both drugs should be considered as possible factors in all aortic dissections.

KEYWORDS: forensic science, forensic pathology, death, aortic dissection, aortic aneurysm, methamphetamine, cocaine

Acute aortic dissections are usually major catastrophic vascular events with considerable morbidity and mortality even with current methods of medical and surgical treatment (1). Aortic dissections, sometimes called dissecting aneurysms or dissecting hematomas, are a result of intimal tears with subsequent dissection of blood between cleavage planes within the wall of the aorta. This dissection frequently leads to either a reentry intimal tear, a tear externally through the adventia, or both. Usually this process can be easily distinguished from a true aortic aneurysm. An aortic aneurysm represents a dilatation of the aorta, most often caused by atherosclerosis, which may also rupture. To avoid confusion and because aortic dissections are usually not associated with preexisting dilatation, the use of the term ''dissecting aneurysm'' should be avoided.

Aortic dissections have been associated with a number of conditions, most commonly hypertension. The association of aortic and/or coronary artery dissection and cocaine use has previously been reported (2–12). We have previously reported three deaths due to acute aortic dissection associated with methamphetamine intoxication (13). To further understand the incidence and significance of this association, we reviewed all deaths in our jurisdictions which were due to aortic dissection.

Methods

A search was made of our records for all individuals who died from aortic dissections during the ten years from 1987 through 1996. A total of 84 cases was identified, 77 of which were from the San Diego County Medical Examiner's Office. Each case was evaluated for age, sex, race, medical and drug history and the circumstances of death. The autopsy findings, particularly those regarding the cardiovascular system, were reviewed including examination of available autopsy photographs and histologic slides of the aorta. The toxicologic reports were reviewed in all cases that had postmortem toxicologic studies.

Results

The mean age of our 84 cases was 52 years (range = 18 to 90 years). One additional case, a 13-year-old, was excluded from the study because of the young age. The male to female ratio was approximately 2:1. The racial breakdown was a reflection of the make-up of our jurisdictions and showed no predilection for any particular population. Thirty of the cases had a known history of hypertension. An additional 22 cases had hypertension inferred from the heart findings at autopsy using a modification of previously published criteria (14); i.e., a heart weight greater than 450 g without significant valvular or coronary disease, or a heart weight greater than 600 g in the absence of valvular disease. Other factors previously associated with aortic dissection were identified in a few cases and included Marfan's syndrome (4), bicuspid aortic valve (6), coarctation of the aorta (1) and Turner's syndrome (1). Three cases had previous aortic grafts and two had aortic valve prostheses. We had no cases associated with syphilis, pregnancy or trauma.

Of the 84 cases of acute aortic dissection, 35 (41.7%) of them were screened for drugs of abuse. Many of our cases which were not screened for drugs were done before we were aware of the possible relationship between dissection and drugs of abuse. A few cases were not screened because of prolonged medical care. Of those tested, seven (20%) were positive for methamphetamine. None of our cases was positive for the parent drug cocaine, but one of the methamphetamine cases was also positive for the cocaine metabolite benzoylecgonine and for morphine. Two other cases were positive for morphine but not cocaine or methamphetamine. Only two of the 55 cases tested for ethyl alcohol were positive.

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TABLE 1—*Study results.*

	All Cases	Meth. Positive	Drug Test Negative
Total Number	84	7	28
Males	57	6	19
Mean age	52	41	46
Hypertension history	30	4	10
Drug Abuse history	8	6	1

TABLE 2—*Aortic dissection classification.*

Dissection Type*	All Cases	Methamphetamine Cases	Drug Negative
Type I	54	5	15
Type II	17	1	5
Type III A & B	13	1	8

* In Types I and II the origin is in the ascending aorta. The difference is that Type I extends to the arch or beyond. In Type III the origin is in the descending aorta.

The study results are summarized in Table 1 with comparison of the methamphetamine positive and drug negative cases.

The mean heart weight for the 84 cases was 494 g, which is considerably higher than the normal expected mean weight, but is similar to heart weights reported in other studies (14,15). All of our dissections originated in the thoracic aorta. The DeBakey classification of these dissections based on the site of tear and extension of the dissection is shown in Table 2. The mechanism of death was rupture with hemopericardium in 58 of the 84 cases. Ten cases had left hemothorax and four had a right hemothorax. In nine cases the mechanism of death was dissection extending into one or more of the coronary arteries resulting in coronary occlusion. In one case the exact rupture site was not specified. In two cases no rupture was observed.

Histology—The number of aortic sections and special stains varied considerably from case to case. A total of 55 cases had microscopic sections of the aorta available with an average of approximately three aortic sections per case. In addition, many of the cases had special stains for elastic fibers, mucosubstances or fibrosis. We independently reviewed the microscopic slides in addition to reviewing the microscopic descriptions in the autopsy reports specifically looking for evidence of cystic medial necrosis (CMN), laminar necrosis (LN) and atherosclerosis. We defined CMN as the combination of pools of basophilic material and fragmentation of elastic fibers (Fig. 1). In the original autopsy reports only a few cases were given the diagnosis of CMN. However, many more cases had features of CMN either described under the microscopic report or noted in our observations. We found that approximately two-thirds of the cases had features of CMN. LN was defined as focal loss of nuclei and muscle fibers in a laminar pattern without fibrosis (Fig. 2). No cases were originally diagnosed with laminar necrosis, but we noted in retrospect, features of LN in 21 of the 55 cases. We also noted that 19 of the cases had microscopic findings of atherosclerosis, although this was rarely near the site of dissection.

Discussion

We did a retrospective study of acute aortic dissections in two medical examiner populations expecting that our cases might differ from previous studies based on hospital cases. Our cases had a bias toward individuals who died rapidly or outside of medical attendance and specifically included only those who died from their dissections. Our findings, however, were similar to previously reported studies. Our mean age of 52 years is comparable to the mean age of 55 years reported by Wilson and Hutchins (15). Our study had 68% males, very close to their 65%. Either by history or pathologic findings 62% of our cases had hypertension. Previous reports have ranged from 58 to 90% (14) of cases with hypertension. We had one case of Marfan's syndrome by history and another three cases in which the diagnosis was made at autopsy. This resulted in an incidence of 4.8% which is within the reported range of 2.6 to 4.9% (15,16).

We did find a slightly higher percentage of Type I aneurysms (65.5%) compared to other studies (46 to 54%) (14,16), with a concomitant reduction in the number of Type III aneurysms. We had theorized that we would have more cases with ascending aortic tears and hemopericardium due to our bias toward those who die suddenly or rapidly. However, in the accumulated study of Hirst et al. (16), 70% of the acute cases had hemopericardium, which is almost identical to our 69%.

We are unaware of any previous studies which included analyses for drugs. Our incidence of 20% methamphetamine positive cases of those tested for drugs appears significant, and is much higher than what we would expect from just random sampling. We found only a few differences between the methamphetamine positive cases and the others. Two significant differences were a younger mean age (41 years) for the methamphetamine cases and a known history of drug abuse (6 of the 7 cases). The mean heart weight of 492 g for the methamphetamine positive cases is slightly higher than the 474 g for those tested but drug negative, but this is of questionable significance because of the relatively low number of

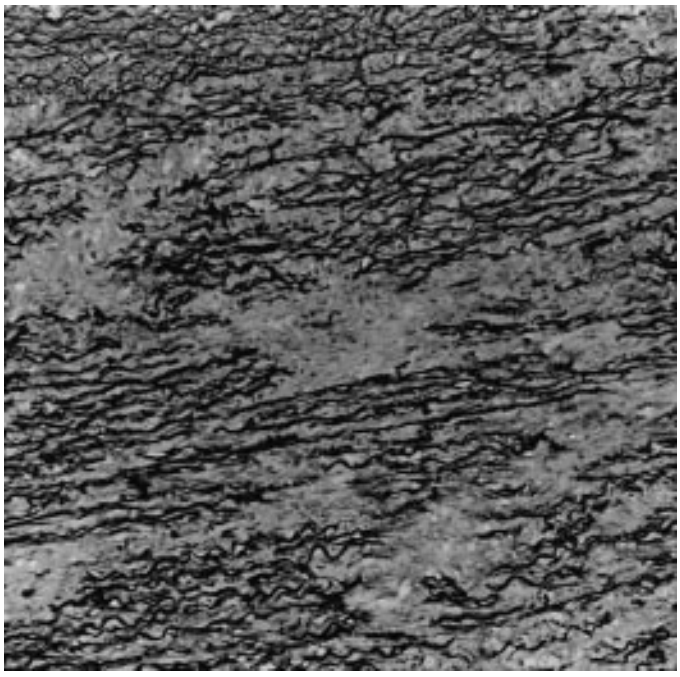

FIG. 1—*Cystic medial necrosis of aorta showing elastic fiber fragmentation around areas devoid of elastic fibers (elastic stain, original magnification ×100).*

FIG. 2—*Laminar necrosis characterized by a lack of nuclear staining and cellular detail within a layered band of the aortic wall. (Hematoxylin-eosin, original magnification ×100).*

cases involved. The only significant difference noted microscopically was a lower percentage of atherosclerosis in the methamphetamine cases, which is probably only a reflection of their younger age.

The anatomy of an aortic dissection includes the intimal tear, cleavage of the aortic wall and possible ruptures which may be internally, back into the aortic lumen, or externally, through the wall into a body cavity. The plane of dissection usually occurs between the middle and outer thirds of the media, and there probably are structural reasons for this (17). In the case of a reentry intimal tear, the dissection channel may become endothelialized and result in a double-barreled aorta. Two essential elements, hypertension and medial degeneration, have been identified for the development of an aortic dissection (18). All studies have shown a high incidence of hypertension. Hypertension appears to be essential for either the initiation of the intimal tear or the propagation of the dissection, or both. It may also contribute to the rupture of the dissection. The other requirement, and perhaps the more important, is some type of defect in the aortic wall. A study by Tiessen and Roach (19) showed that extremely high, nonphysiological pressures are required to cause dissection in a normal aorta.

Several different types of aortic wall changes have been studied as the possible defect responsible for dissection. It is generally agreed that atherosclerosis is not important in the course of aortic dissection. It has been pointed out that intimal tears only rarely occur in atherosclerotic plaques and that dissections most commonly occur in the thoracic aorta, whereas atherosclerosis is most severe in the abdominal aorta (16). One study did show a statistical correlation with atherosclerosis (15), but it seems that atherosclerosis has only a minor role at best.

Most attention has been given to cystic medial necrosis (CMN), also know as cystic medial degeneration or cystic medionecrosis. Reports of the incidence and significance of this condition have varied widely. Part of the problem is that it is defined differently in different studies. In our own study we found inter-observer bias in how we interpreted the definition. Furthermore, in some cases we had inadequate sampling, a lack of special stains, or suboptimal quality of the staining so that an opinion was difficult to render. Previously reported incidences ranged from 10% (15) to 62% (16). Our number was close to the upper end of this range. CMN has been reported as an aging process (20,21) and has also been found in control populations (15). We believe that CMN represents a nonspecific response to microscopic aortic wall injury regardless of the cause. It may be an important cause of aortic wall weakness in some cases, but it is neither specific nor necessary for aortic dissection.

Another microscopic finding reported in some cases of aortic dissection is laminar necrosis. Laminar necrosis (LN) has been found in 8 to 31% of cases (14,15). The incidence is usually less than that of CMN, but not always. Some of this variation in numbers again may be due to differing criteria or the subjective factors inherent to microscopic observations. To add to the confusion, LN is sometimes referred to as ''medionecrosis.'' In our study we encountered many of the same difficulties in diagnosing LN that we had with CMN. In any case, this phenomenon is seen in the minority of dissections and is not the primary cause of aortic degeneration. In fact, it has even been suggested that it is not a cause at all but a result of the aortic dissection (15).

It has also been suggested that the medial weakening responsible for aortic dissection may not be detectable by routine light microscopic techniques (22,23). It may be an ultrastructural or biochemical defect related to alterations in collagen (24) or elastin. However, a specific or consistent defect accounting for aortic dissection has yet to be shown. We tend to think that no one specific defect is responsible for aortic dissection. It is likely that the cause is a combination of one or more of these alterations resulting in weakening of the aortic wall.

All of the conditions previously identified as associated with aortic dissection can be explained by their contribution to hypertension, aortic wall degeneration or both. In fact, there is some suggestion that hypertension itself may contribute to medial degeneration (21,25). Therefore, both methamphetamine and cocaine should be risk factors based on their pharmacological actions which include hypertension. This hypertensive effect may be important in the initiation of the intimal tear or the propagation of the dissection. In addition, an acute hypertensive episode caused by either drug could certainly initiate the rupture of a dissection. Surprisingly, we did not find any dissections solely associated with cocaine, but this may be a result of our relatively low number of cases tested. One should also consider that persons reported as cocaine users may also use methamphetamine. One of the previously reported

cocaine-associated aortic dissections also had amphetamines detected in her urine (12). During the study period we had approximately the same number of cocaine positive cases per year as methamphetamine cases in San Diego County, so the discrepancy is not a result of a population bias. Furthermore, methamphetamine has not been found at all in any death in Jefferson County during this study period, although cocaine certainly has. Therefore, our findings seem to indicate that methamphetamine is a greater risk factor for aortic dissection than cocaine.

We believe methamphetamine is a greater risk factor because it has a much longer half-life, thus prolonging the hypertensive effect. It is also possible that methamphetamine has a direct effect on the aorta leading to medial degeneration. Methamphetamine and cocaine have physiological effects similar to epinephrine. It was observed long ago that the injection of epinephrine into rabbits produced changes in the aorta resembling cystic medionecrosis and occasionally produced aortic dissection (16).

Conclusion

We reviewed all cases of death due to aortic dissection in our offices from 1987 through 1996. We particularly wanted to assess the role of drugs in the 84 cases identified. Although not all of our cases were tested, we identified several cases in which the dissection was associated with acute methamphetamine intoxication. We believe this association is significant and indicates that drug abuse, specifically that of methamphetamine, is a risk factor for the development of aortic dissection. Although previously reported, our study did not show a similar association with cocaine, a drug of similar physiological effects. Nevertheless, we feel that both methamphetamine and cocaine use should be considered and sought in all persons with aortic dissections. In addition, aortic dissection should be added to the growing list of cardiovascular complications resulting from methamphetamine abuse just as it has for cocaine.

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