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Abstract

Thoracic aortas isolated from dogs were evaluated to determine the correlation between the depth of an intimal tear and the progression of aortic dissection. Thoracic aortas obtained from 99 adult mongrel dogs were used. An intimal tear (aortic pocket) was created on the aortic wall and the aorta was connected in series to a closed circuit (150 mmHg/100 mmHg and 60 beats/min). The progression of the dissection was most notable in the aortic pocket prepared in the first one-third of the external media (87.5%). There was no correlation however between the width of the pocket and the progression of dissection. Examinations of samples from surgical patients have shown that dissection usually progresses at the same site. This has been attributed to the diseased media. Our results demonstrated that dissection occurred almost always at the same site without any medial changes suggesting that whether dissection develops or not likely depends upon whether the intimal tear reaches the first one-third of the external media or not.

KEYWORDS: aortic dissection, pathogenesis, depth of intimal tear, medial degeneration

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Thoracic aortas isolated from dogs were evaluated to determine the correlation between the depth of an intimal tear and the progression of aortic dissection. Thoracic aortas obtained from 99 adult mongrel dogs were used. An intimal tear (aortic pocket) was created on the aortic wall and the aorta was connected in series to a closed circuit (150 mmHg/100 mmHg and 60 beats/min). The progression of the dissection was most notable in the aortic pocket prepared in the first one-third of the external media (87.5 %). There was no correlation however between the width of the pocket and the progression of dissection. Examinations of samples from surgical patients have shown that dissection usually progresses at the same site. This has been attributed to the diseased media. Our results demonstrated that dissection occurred almost always at the same site without any medial changes suggesting that whether dissection develops or not likely depends upon whether the intimal tear reaches the first one-third of the external media or not.

Key words: aortic dissection, pathogenesis, depth of intimal tear, medial degeneration

A ortic dissection is a serious circulatory disease that develops suddenly and is associated with high morbidity and mortality. However much about its etiology inducing factors and mechanism of propagation are still unknown (1-3). Clarification of these areas would undoubtedly facilitate a correct diagnosis aid in the selection of an appropriate treatment and consequently improve the prognosis of the disease.

In vivo histologic and hemodynamic studies of aortic dissection have been conducted which have led to several important findings (4). While in vivo experiments are the preferred method of study, it is difficult to maintain constant experimental conditions and to observe the pre- and postpropagation conditions of dissection directly.

In this study we prepared in vitro experimental models in which circulatory circuits maintained under constant circulatory parameters were connected with excised canine aortas and dissections were initiated. Only a few in vitro experiments of aortic dissection have so far been done (5, 6). The aim of the present study was to clarify the relationship between the size of the intimal tear and the progression of dissection.

Materials and Methods

All animal care outlined below complied with the "Principles of Laboratory Animal Care" (formulated by the National Society for Medical Research) and the "Guide for the Care and Use of Laboratory Animals" (NIH Publication No. 80-23, revised in 1985).

The descending thoracic aorta extending from the immediate distal end of the left carotid artery to the diaphragm was carefully dissected from 99 adult mongrel dogs (weight: 14-20 kg) that had been sacrificed with euthanyl at the conclusion of other experiments (myocardial protection, coronary blood flow measurement). Fat and loose connective tissues around the aorta were carefully dissected off from the adventitia and the intercostal arteries were ligated. Small transverse incisions 1 cm from the proximal end were made on the lesser curvature of the aortic wall by a scalpel. And pockets were created by the method of Blanton et al. (7) by using mosquito forceps, and the cuts were sutured (Fig. 1). Using a magnifying glass (X10), we made aortic pockets to the desired depth and width. This procedure was carried out in a tissue bath filled with a Krebs-Ringer dextrose solution composed of 120 mM NaCl, 4.8 mM KCl, 2.5 mM $CaCl_2$, and 1.2 mM $MgSO_4 \cdot 7H_2O$, 15 mM phos-

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phate buffer of pH 7.4, and 11.0 mM dextrose at 37 °C. And the aorta was cannulated in series to a closed circulatory circuit the same length as that found in the dog's body (Fig. 2). The average size of specimen was about 12 mm in diameter and about 14 cm in length. It took an average of about 40 min to mount the specimen on the apparatus. The circuit was constructed as shown in Fig. 2. Pressure waves were produced by a pneumatic diaphragmatic pump (Cleveland Clinic Foundation made, Cleveland, Ohio, stroke volume: 30 ml) connected to the apparatus and an artificial heart driver (Yasuhisa Koki Ltd., Model 113). The circuit was filled with saline (37 °C) tinted with black ink. By adjusting the level of the water (H) and the resistance (R) of the circuit properly, constant circulatory parameters (150 mmHg/100 mmHg and 60 beats/min, average flow velosity = about 1,800 ml/min) and arterial wave patterns were similar to *in vivo* conditions (Fig. 2). Pressure was recorded simultaneously in the circuit with catheter-tip micromanometers (Millar Instrument, Houston, Texas). The $(dP/dt)_{max}$ was also recorded and measured approximately 1,200 mmHg/sec in every experiment. At the beginning of each experiment, a video recorder (Sony TR-55) and a pressure recorder (Sanei, Model 360) were used to monitor the experiment until dissection began or until the vessel ruptured.

After completion of the experiment, the aorta was removed from the experimental apparatus and was pathologically examined in longitudinal sections stained with hematoxylin-eosin and Elastica van Gieson stain. The protocol of the study was consisted of two sets of experiment.

Experiment 1.   The depth of the aortic pocket was fixed at the middle of the media. The widths of the pockets were varied at 60°, 80°, 100°, 120°, 140°, 160°, and 180° of the aortic circumference. Six specimens were studied for each width.

Experiment 2.   Each specimen had only one tear at one of the five tear depths (1/6, 2/6, 3/6, 4/6, 5/6). The width of the aortic pocket was fixed at one-third of the circumference (120°) of the aorta, and the depth of the pocket was one of five depths. The distance between tears was one-sixth of the thickness of the aortic wall. Eight specimens were studied for each of the five groups. Cases in which dissection did not occur within 120 min after the initiation of the circulation were categorized as nondissections.

Statistical analysis.   Chi-square tests were used to compare the dissection and nondissection groups with respect to the different widths and depths of the aortic pockets. A P value of 0.05 was chosen as the
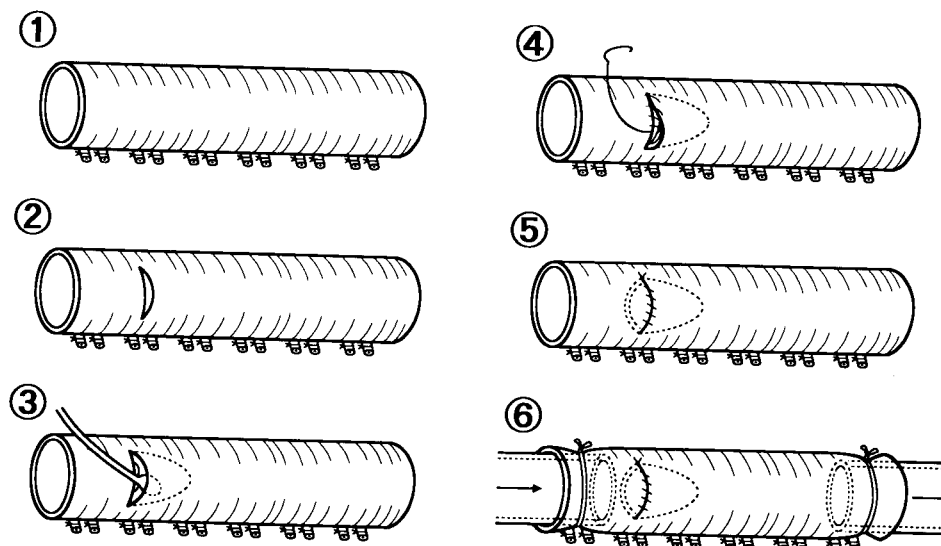

Fig. I   Technique for formation of aortic pocket. ① The descending thoracic aorta is excised from adult mongrel dogs, ② a small transverse incision of the aortic wall is made, ③ a small pocket in the medial layer is produced by using mosquito forceps, ④ proximal free edge of aortic wall and outer layer of distal aortic wall are sutured with 6-0 Prolene, ⑤ completion of aortic pocket, and ⑥ the specimen is cannulated to a closed circulatory circuit.
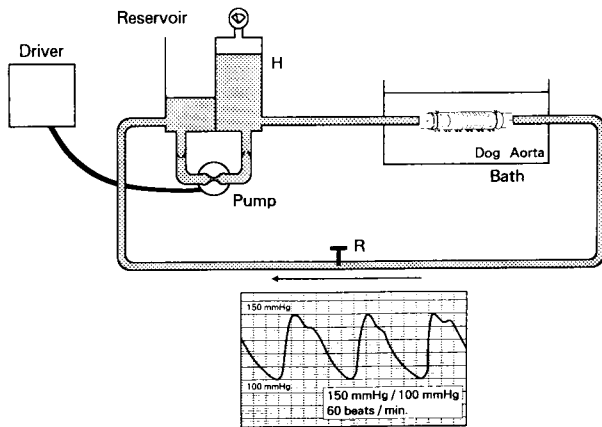
the width of the aortic pocket do not vary significantly (contingency $\chi^2 = 12.597$; df = 2; $P > 0.05$). In other words, there was no significant relationship between the width of the pocket and the progression of aortic dissection.

Experiment 2. Dissection progressed in 19 of these 40 cases (47.5 %). Fig. 5B depicts the results of the experiment. The proportions of the depth of the aortic pocket vary significantly (contingency $\chi^2 = 11.429$; df = 2; $P < 0.05$). That is, the dissection progressed more often (87.5 % of the time) when the aortic pocket was in the first one-third of the external media than when it was
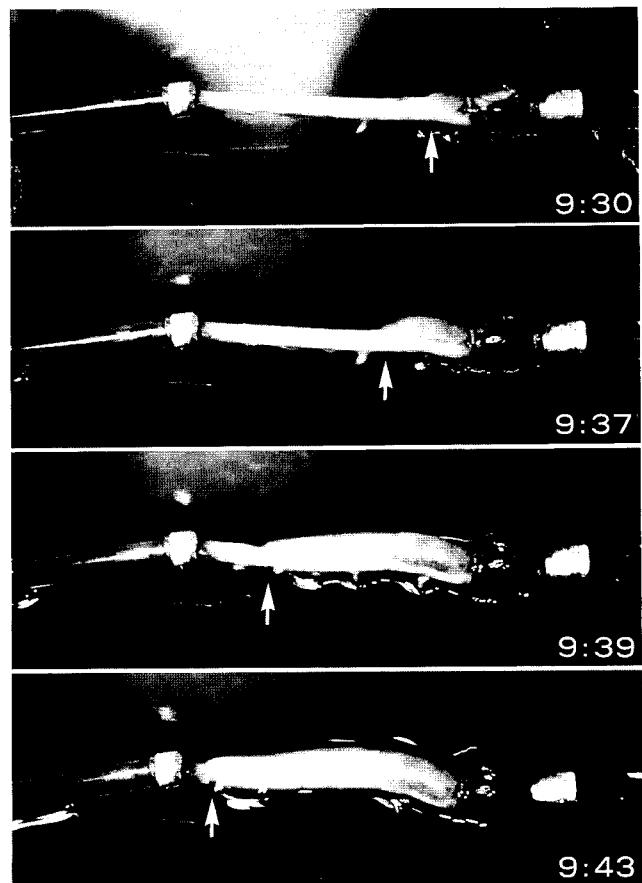

Fig. 2   Schematic drawing of the experimental apparatus. Pulsatile flow was generated by a pneumatic diaphragmatic pump and driver. By arranging the level of the water (H) and the resistance (R) of the circuit, we achieved a constant circulatory condition (150 mmHg/100 mmHg, 60 beats/min) throughout the experiments. The Reynolds number of the circuit was about 2000.

cut-off for statistical significance.

Results

We completed 82 successful trials. Of the 99 aortas, 17 were discarded because of the leakage of saline at the connection of the circuit and aorta (13 cases) and leakage from the ligated intercostal arteries (4 cases). None of the aortic pockets ruptured. Fig. 3 shows a series of photographs showing the progression of an aortic dissection. In this case, the dissection progressed from the aortic pocket (width: 120°, depth: 3/6) along the whole specimen within 13 beats. As the dissected part of the aorta became enlarged and blackened, we could easily recognize the progression from the outside of the specimen. Fig. 4 shows a representative case of dissection. After we created the aortic pocket (width: 100°, depth: 4/6), we connected aortas to the circulatory circuit and started circulation. After 45 sec, dissection started from the pocket in the direction of the flow (left to right).

Experiment 1. Dissection progressed from the aortic wall in 30 of these 42 cases (71.4 %). Fig. 5A depicts the results of the experiment. The proportions of

Fig. 3   A series of photographs showing the progression of an aortic dissection. In this case the dissection began at 9 min 30 sec after the circulation was started, and progressed along the whole specimen within 13 sec. Arrows show the leading edge of the dissection.
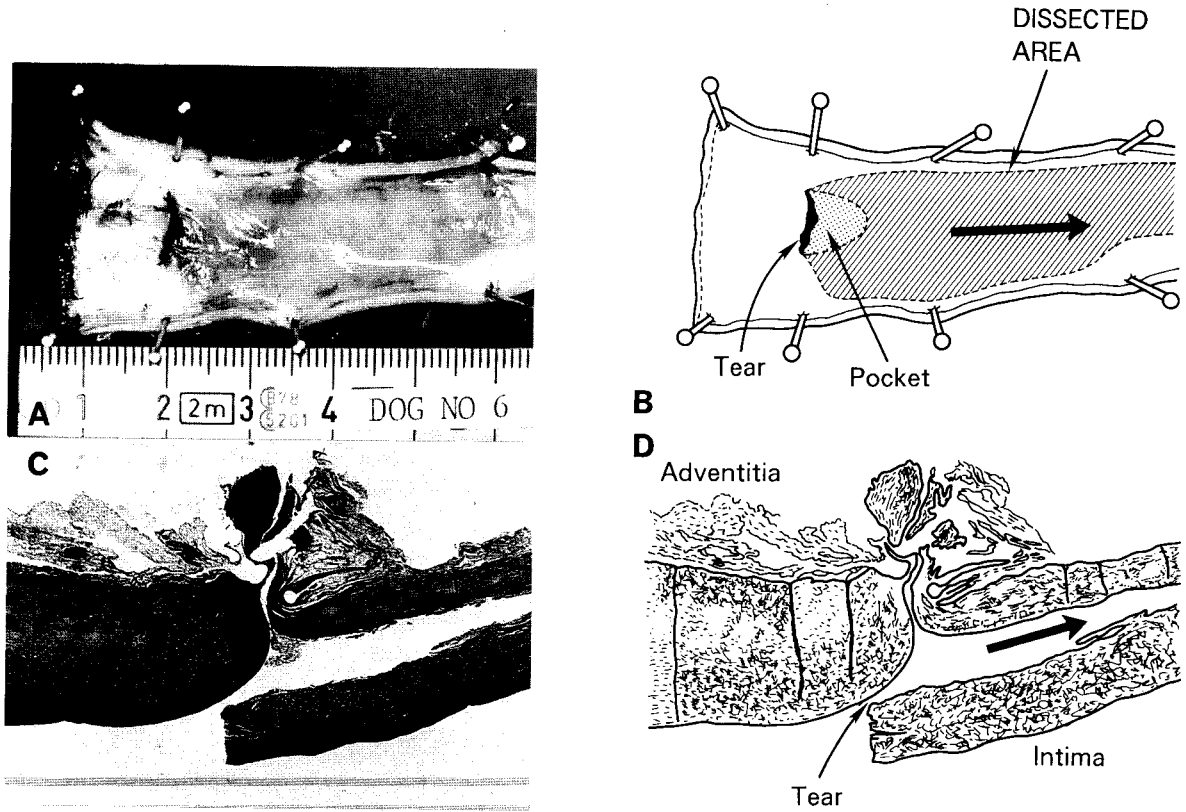
Fig. 4   A representative case of aortic dissection. **A**: Photographs of an aorta of a dissected case. **B**: Shematic drawing of Fig. 4. A. **C**: Histology of this case through the plane of the dissection. The adventitia is at the top and the tear is propagating from left to right. The intimal tear is in the first one-third of the external media (Original magnification X80, Elastica van Gieson stain). **D**: Schematic drawing of Fig. 4. C.
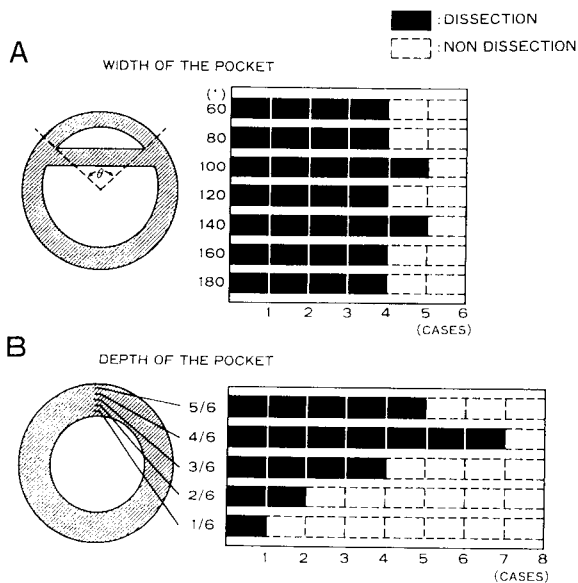

Fig. 5 (left)   Effects of aortic pocket on the progression of the aortic dissection. **A**: Correlation between the width of the pocket and the progression of the aortic dissection. **B**: Correlation between the depth of the pocket and the progression of the aortic dissection.

in any other layer.

Discussion

Predisposing factors reported in the literature for aortic dissection include hypertension, atherosclerosis, congenital connective tissue disease of the media, the occurrence of an intimal tear, and pulse wave variations (1–3). However, the relationship between the disease and these factors has long been disputed. Nevertheless, no

clear agreement exists regarding the pathogenesis of this disorder. We believe that to examine the pathological samples of dissected cases is important and informative to determine the etiology of the disease. In dissected cases we can find that the plane of cleavage in aortic dissection (dissecting aneurysm) is almost invariably in the first one-third of the external media of the aortic wall. This finding has been reported by various investigators, such as Hirst et al. (1) (who investigated 505 cases of dissecting aneurysm), Gore and Seiwert (8) (who conducted pathological analyses on 85 cases), and Hashimoto et al. (9). In fact, dissection in the same region was confirmed in most of the 17 cases in which pathological samples of the periphery of the initial intimal tear were examined at our institute over the past 20 years. "Why does the dissection develop so frequently in the first one-third of the external media?" Studies on the dissecting layer are considered to be useful in clarifying the pathogenesis of dissection and are also clinically important because any further progression of the dissection may cause rupture by tearing to the adventitial side, or reentry by tearing to the intimal side.

On the other hand, during careful post-mortem inspection of the human aorta of non-dissected cases, we can usually find the intimal tear that does not cause dissection. All intimal tears do not necessarily develop into dissection. The question of what sort of intimal tear causes the dissection is one of the keys to understanding the pathogenesis of aortic dissection.

There must be many predisposing factors in the medial layer for the development of aortic dissection. To clarify those factors, we examined the disease using an experimental model that more closely resembles the in vivo environment. To clarify the relationship between the intimal tear and the progression of aortic dissection by experimental model, we made medial pockets of various depths in extracted canine aortas and looked for the presence or absence of the development of dissection when the vessels were connected with the circuit under constant circulatory parameters. From this experiment we found that dissections developed in the first one-third of the external media in normal adult mongrel dogs, and that there was no correlation between the width of the tear and the progression of the dissection. From these results, it was assumed that weakness of the medial wall might not always be necessary for the development of dissection. Rather, the fact that aortic dissection progresses at the first one-third of the external media is in itself important

regarding the mechanism of aortic dissection. Braunstein (10) studied 35 cases of aortic dissection and came to the same conclusion. Subsequently, he reported that dissection layers in most cases were observed at the first one-third of the external media, and moreover, that dissection runs through media without any histological abnormalities. He also concluded that the most important factor in aortic dissection is the formation of the intimal tear. Our results support his view.

To examine the reason of the fact that dissection develops more easily when we make the aortic pocket at the first one-third of the external media. Many experimental studies have been done to test the hypothesis that a mechanical weakness must be present in this region of the external media for dissection to occur (11, 12). Hirst and Johns (13) infused saline into human and canine aortic walls and measured the pressure necessary to form a bleb. The pressure was 505–586 mmHg in the canine aorta and 290–586 mmHg in the human aorta. They also reported that differences of associative strength were not noted among different layers of the media. Millazo (14) measured the tension necessary to tear slits in various layers of the media using a segment of the normal aorta. Subsequently, he reported that no one layer was more easily torn than another in the normal aorta. As such, mechanical weakness in the first one-third of the external media has not been demonstrated. Concerning the blood supply and nourishment of the aortic wall, we find two routes: from the vasa vasorum and from the permeation of aortic intima. The vasa vasorum arises from a branch of the aorta, and penetrates the adventitia and the first one-third of the external media, and then ends with branches of the middle and external media. From this fact, it is speculated that when disorders of the vasa vasorum occur, the first one-third of the external media may degenerate (15). Although Wilens et al.(16) showed that the ligation of the vasa vasorum caused degeneration at the central site of the media, it did not lead to dissection. The other hypothesis presupposes that hematoma due to hemorrhage in the vasa vasorum with the retiform structure at the first one-third of the external media may be the cause of aortic dissection. However, the frequency of the latter type is very low, 4 % as reported by Hirst et al. (1) and 1.9 % as noted by Hume and Porter (17). Therefore, it seems very unlikely that disorders of vasa vasorum cause aortic dissection.

Up to now, many pathological examinations of aortic dissection have been performed. Of those, Erdheim (18)

was the first who listed idiopathic cystic medionecrosis with abnormal deposit of mucoid substance in place of the smooth muscle, collagen fiber, and elastic lamella as a cause of aortic dissection. In many cases, pathological changes in the media are assumed to promote the development of dissection, and the lesions are said to be characteristically at the first one-third of the middle and external media and to be restricted to the ascending aorta and arch region. However, histologically notable changes are not detected in many cases (12), and pathological changes, so-called idiopathic cystic medionecrosis, are found in only about 20 % of the cases, with no specific changes observed in the remaining 80 % (19). Cellina (20) observed the disappearance of nuclei in the band-like smooth muscle cells at the first one-third of the external media mainly in lesions of the aorta of patients 70 to 85 years old. Moritz (21) reported notable deposits of mucoid substance at the first one-third of the middle and external media in the ascending aorta of three individuals with dissecting aneurysms of the aorta. Rottino (22) noted deposits of mucoid substance at the same region of the media. Therefore, medial lesions such as cystic medial necrosis, which is said to be specific for aortic dissection, are seen at the first one-third of the middle and external media, but not very often at the same region of the external media. It has also been found that dissection progresses even in the absence of medial lesions (23).

As stated above, it is difficult to demonstrate the easiness of dissection at this layer from the pathological examination. Rather, though it is only speculation, it seems that study of the disease from hemodynamics or reological aspects is mostly needed, and studying diseased aorta using our dissection model may clarify the mechanisms underlying the progression of aortic dissection.

So far, only Baardwijk and Roach (6) have conducted a study similar to the present experiment. In their experiment, the speed of dissection was affected by blood pressure and by the depth of the intimal tear. Their results showed that the deeper the intimal tear, the slower was the speed of dissection. Their explanation was that while the medial region from the intima is an elastin layer structure, the region from the adventitia is fibrous, so that tears do not occur easily at the adventitial side. However, in their experiment, the pulse flow factor was not regarded to be important in the occurrence of dissection, and no flow system was adopted. Clinically (23, 24), as is shown by the fact that the frequency of proximal

dissection is less than that of antegrade dissection, we believe that flow factors cannot be ignored in the progression of dissection. This may explain the difference between their results and ours on this point. Prokop *et al.* (5) conducted an experiment in which a tygon tube with cement was connected to the circulatory circuit to cause dissection. Subsequently, they reported that dissection did not occur with non-pulsatile flow in the circuit, but did occur in pulsatile flow. Because the tube used in their experiment was less expansible and flexible than the aorta, their results differed what can be expected *in vivo*. However, the changes in blood pressure do appear to be an important contributing factor in the occurrence and development of dissection.

Our results and those of the many above mentioned reports indicate the following developmental course for aortic dissection. First, a small tear is formed on the internal surface of intima because of, for example, hemodynamic sheer stress, nutrient disorders or connective tissue disease of the intima. Through this intimal tear, blood enters into the aortic media which is probably affected by medial lesions such as sclerotic disorders or idiopathic medial degeneration. A hematoma then occurs at this site and expands within the media. This site then dilates outward, and the lateral pressure increases, causing increased tension of the aortic wall. When blood enters the wall to the dissection face at the first one-third of the external media, it is assumed that dissection may progress through the aorta.

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