Microcirculation and Metabolism in the Vascular Wall concerned with the Vasa Vasorum

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In the case of investigating metabolism in the vascular wall, it is important that mechanism of microcirculation in the vascular wall and influence of its disturbance are elucidated.

So, we have reported the anatomical structure of the vasa vasorum, the vascular lesions caused by obstruction of the arterial and venous vasa vasorum, influence of inflammation, result of adding cholesterol on the vascular lesions produced by obstruction of the vasa vasorum and influence of bradykinin on the vasa vasorum.

In this paper, on the basis of above experiments, relation between microcirculation and metabolism in the vascular wall was investigated, with the work of anatomical structure of the lymphatics in the abdominal aorta of the dog and effects of obstruction of lymphatics in the abdominal aorta and the periaortic tissue of dogs.

Anatomical structure and mechanism of microcirculation in the vascular wall

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In the normal abdominal aorta of dogs, rich network of arterioles in the periarterial tissues anastomosed with a longitudinal plexus of the adventitial vasa vasorum. From the adventitial plexus, the arterioles penetrated to the media and formed secondary plexus in the two-thirds of the media\(^1\) (Fig. 1, 2). The blood coming from outer side through these ways reaches near inner one-third of the media, and then flows out with fluids coming from its own lumen through venous side of the vasa vasorum. Venous side of the vasa vasorum run parallel with arteries and formed rich network in the same depth as arterial ones\(^3\) (Fig. 1, 3).

It has been said recently that lymphatics themselves do not distribute to the media\(^7,8\) although there are still different opinions concerned with the depth of its distribution\(^9\) By the observation using microangiography or injection of India ink, lymphatics start on the border of the media and adventitia, and also form rich network and then collect into the large lymphatics.
in the periaortic tissue (Fig. 1, 4). Anastomosis of lymphatics to venous vasa vasorum could be also observed by microangiography in this investigation.

**Obstruction of arterial vasa vasorum**

In one week after the obstruction of the arterial vasa vasorum, thickening of the intima and splitting of the internal elastic membrane became progressively prominent. In the media, there was degeneration and disappearance of muscle and elastic fibers which appeared to begin from the outer one-third of the media.

At the 4th week after the operation, the lesion became more severe. The edematous intimal thickening more progressed. There are marked increase of the collagenous fibers. In this affected region metachromasia-positive substance
Fig. 4. Transparent specimen of transverse section of 1 mm thick in the abdominal aorta of the dog. Plexus of lymphatics is seen in the adventitial layer. India ink was injected into the external iliac lymph node for visualization of lymphatics. × 15.

Fig. 5. Thickening of the intima, destruction of the internal elastic membrane are observed. Fraying and splitting of the elastic fibers are recognized in the media. Four weeks after obstruction of the arterial vasa vasorum. Elastica-Van Gieson. × 50.

(toluidin blue of pH 7.0 and 4.1) increased, but all layers were stained homogeneously by PAS method. In the media, the elastic fibers were almost frayed and disappeared (Fig. 5).

In general, severe vascular lesions tended to be observed in parallel well with the occlusion of the vasa vasorum in microangiogram.

It seemed reasonable that the above-mentioned vascular damages were produced as a result of stagnation of interstitial fluids, hypoxia, disturbed nutrition, decreased metabolic activity and hyperpermeability in the aortic wall following an obstruction of the vasa vasorum.

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Obstruction of the venous side of the vasa vasorum

During 3 days to 2 weeks after the operation obstructing venous side of the vasa vasorum, degeneration of muscle cells followed destruction of elastic fibers was observed in the inner one third of the media, especially in the region near to the internal elastic lamina. Cystic degeneration was also observed in these inner one third of the media. These lesions seemed to be produced by stagnation of interstitial fluids. These areas were stained red by Mallory-Azan’s method. Metachromasia was positive in the damaged regions. However, thickening of the intima was slight (Fig. 6).

In general, vascular lesions were more less than those obtained by an obstruction of the arterial side of vasa vasorum.\(^1,2\)

If venous side of the vasa vasorum is disturbed, the plasma in the outer coats of the aorta may, therefore, flow out through lymphatics distributed abundantly in the outer coats and periarterial layers. Since there is no connection between vasa vasorum of the inner side of the media and lymphatics of the outer coats of the aorta, flow of plasma might be disturbed mainly in this particular layer where vascular lesions were consistently observed in early stage after operation.

From the facts above mentioned, it was shown that obstruction of venous side of the vasa vasorum brought disturbance of microcirculation in the vascular wall and caused vascular lesions.

Obstruction of the lymphatics in the vascular wall

In the cases of partial obstruction of lymphatics only produced by injecting various density of gelatin-HCl solution (5 or 10% gelatin, 1/2 or 1 normal HCl) into lymphatics in the periaortic tissue and aortic wall, slight vascular lesions seemed to be caused by stagnation of interstitial fluids were able to be observed in the inner media as those of obstruction of venous side.\(^3\) However, in 2-12 weeks after the operation, there were the regions where granulation tissue increased around the obstructed lymphatics in the periaortic tissue so that disturbance of drainage of interstitial fluids progressed. In these changed region, marked thickening of the intima were observed. Stagnation of interstitial fluids in these area was especially evident near the internal elastic lamina (Fig. 7). This area were stained well by pH 4.1 of toluidin blue and PAS method but stained only partially by PTAH method and not stained red by Mallory-Azan’s method.

Degeneration and necrosis of muscle cell were recognized in the media, but elastica in the media and internal elastic membrane were reserved relatively well.

In the case of partial obstruction of lymphatics, interstitial fluids may flow out through the
venous side of the vasa vasorum. Lymphatics have rich anastomosis to the vein in normal situation and lymphatico-venous communications are fully operable two weeks after obstruction of the lymphatics in their proximal part as Takashima and Benninghoff\textsuperscript{10} reported. So vascular lesions was limited only in inner coats and its degree was slight in the region of partial obstruction and marked destruction of vascular wall could not be produced until flowing out of interstitial fluids was disturbed extensively such as figure 7.

\textit{Influences of bradykinin on the microcirculation.}

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From these obstructing experiments, it is considered that hyperpermeability may play an important part on the vascular lesions. So influences of bradykinin on the microcirculation were examined.

After the local application of 5 gamma of bradykinin, leakage of blood or its component containing fluorescent dye was also seen at branches of the venous vasa vasorum of the carotid artery, as many investigations have reported in the capillaries and venules of the various tissues (Fig. 8). Dogs injected with homologous serum protein combined with fluorescent dye showed no anaphylactic reaction. In microangiograms, only the arterial side of the vasa vasorum is recognized by our method injecting corpuscular barium through the lumbar arteries (Fig. 2). However, simultaneous demonstration of arterioles, capillaries and venules by injecting corpuscular barium after the injection of bradykinin into the vasa vasorum was observed which implies a decreased peripheral vascular resistance by the peptide (Fig. 3), and bradykinin would play an important part in the regulation of regional blood flow.

The fact that bradykinin administered locally caused remarkable increased permeability of the venules suggests an important role of venular side of the vasa vasorum in a hyperpermeable state.

Bacterial infection

When new factors were added on vascular lesions caused by disturbance of the vasa vasorum, the lesions became more marked and variagated.

It was easy to cause inflammation in the abdominal aorta which had been destructed prior by disfunction of the vasa vasorum, though inflammation could not occure in the healthy abdominal aorta by injecting Staphylococcus via femoral artery or femoral vein.

In 1 week after the operation that a mixture of thrombin, gelatin-saline and Staphylococcus was injected into the vasa vasorum of the abdominal aorta so that disfunction of the vasa vasorum and inflammation in he wall were produced, a thickening of the intima was observed. In the media there were marked destruction and disappearance of muscle and elastic fibers (Fig. 9). Bleeding into these outer one-third of the media occurred. At the second week after the operation, in the severely damaged area, inflammation progressed markedly and organization of the large hematoma in the outer two-thirds of the media was observed, although elastic fibers in the inner one-thirds of the media and the internal elastic membrane were reserved pretty well (Fig. 10). These lesions were more rapid and severe than those of previous experiments.
In contrast with previous experiment having no inflammation, the cause of these severe damage seemed to be hyperpermeability risen by various chemical mediator at inflammation.

*Fat deposition*

The vascular system of dog has rich network of the vasa vasorum as that of human beings does. So it has been reported to be pretty difficult that fat deposition was able to be seen experimentally in the abdominal aorta of dog.13

However, in this series, fat deposition was able to be observed at early periods such as 2 weeks postoperatively in the abdominal aorta of which

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Fig. 12. The straight line represents the group administered cholesterol with thiouracil and the dotted line represents the other group administered with cholesterol only.

Fig. 13. Schema shows that disturbance of microcirculation causes various conditions and vascular lesions are produced giving influence on each other.

The vasa vasorum had been obstructed (Fig. 11), though the value of serum cholesterol was in a relatively low level (Fig. 12). In the other arterial system there was no deposition of fat.

In rabbits, dogs and monkeys, many investigations have been done that fat deposition...
could be observed at pretty short periods by preexisting lesions in the outer coats by various method. These experiments succeeded to shorten the periods of lipid deposition with moderate hypercholesteremia and all reports confirmed that injury of the arterial wall was necessary preexisting conditions for accumulation of lipids. Jellinek et al. observed by using an electron microscope dilatation of lymph vessels in the aortic adventitia and the endothelial cells of the lymph vessels containing lipid droplets in albino rats fed by an atherogenic diet, and they confirmed that the increased vessel wall transport apparently imposed greater requirements on lymph drainage so that an insufficiency of lymph supply may have easily developed and disturbance of lymph drainage may largely contribute to the aggravation of arteriosclerotic lesions. All these investigators considered that reasons of accumulation of lipids after arterial lesions were disturbance of flow of tissue fluid and lymph, storage of interstitial fluids, disturbed nutrition, and hyperpermeability caused by disturbance of the vasa vasorum or degeneration of the media as this report.

From these facts, it seemed to be reasonable that disturbance of the vasa vasorum may play an important role as underlying conditions in deposition of fat into the vascular wall.

**Discussion**

**Etiologic factors causing initial disturbance of the vasa vasorum**

Etiologic factors causing initial disturbance of the vasa vasorum in the human body had been discussed previously as follows. Continuous spasm of the vessels by hypertension, emotional stress changed environment and cold may decrease the blood flow and obstruct the vasa vasorum. Aging phenomena also may produce the disturbance of flow in the vascular wall as Clark described. Arthus reaction such as rheumatic fever allergy hypersensitive inflammation may become the cause of disturbance of the vasa vasorum. Bacterial infection also may become etiologic factor. Further, many experiments have been done that disfunction of the vasa vasorum was produced by chemical agents: bradykinin, hystamine, tyramine, epinephrine, nicotine, and cholesterol.

**Etiologic factors causing vascular lesions**

In the case of obstructing arterial vasa vasorum, it might be considered that the cause of destruction progressed from the outer one-third of the media was disturbance of nutrition and hypoxia, and these lesions caused disturbance of microcirculation in the vascular wall, storage of interstitial fluids and hyperpermeability. On the other hand, it was suggested that the cause of edematous thickening of the intima observed simultaneously in the early stage was hyperpermeability. Metabolic activity also may change from the facts of increasing acid mucopolysaccharaid in these regions.

The cause of vascular lesions produced by disturbance of flowing out through venous side of the vasa vasorum or lymphatics was seemed to be mainly storage of interstitial fluids with decreased metabolic activity and hyperpermeability. In the case of infection of Staphylococcus, it was able to consider that one of the important factors cusing such severe destruction in the vascular wall was hyperpermeability risen by various chemical mediator acting in inflammation because only inflammation was the factor added on the obstruction of the arterial vasa vasorum.

From the base of above facts, disturbance of microcirculation in the vascular wall causes storage of interstitial fluids, hypoxia, disturbance of nutrition, decrease of metabolic activity and increase of permeability. By these factors, vascular lesions were produced. These vascular lesions may become preexisting condition for accumulation of fat or bacterial infection. It was thought that each factor gave an influence on each other and vascular lesions progressed more severely (Fig. 1.3).

**Summary**

It was studied by various methods that disturbance of microcirculation in the vascular wall caused vascular lesions. Influences of disturbed microcirculation on the metabolism in the vascular wall and etiological factors for vascular lesions were discussed.

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**References**


