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Vasculitis of Vasa Vasorum and Aneurysm Formation in Kawasaki Disease: Predilection for Coronary Arteries Lesions

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Abstract: *Backgrounds*. The mechanism causing coronary artery lesions in Kawasaki disease (KD) has not yet been fully clarified. *Objective*. We hypothesized that the main coronary artery (MCA) segment perfused by the vasa vasorum (VV) arose from the atrial and ventricular branches of peripheral coronary arteries in the myocardium (Type 1 VV externa) is more prone to aneurysm formation than that perfused by Type 2 VV originated from the ostium. *Methods and Results*. We reviewed the coronary angiography and two-dimensional echocardiogram (2DE) data of KD patients in our hospital and measured the distances from the left coronary ostium to the proximal point of the aneurysm in the left MCA (D1) and to the MCA bifurcation (D2). We found that the ratio of the distances (D1/D2) was negatively correlated with the patients' age of KD onset, indicating that longitudinal extension of the left MCA aneurysms coincided with the development of Type 1 VV externa. We performed a literature review of KD cases with extracardiac aneurysms and found that 15 patients also had giant aneurysms in the MCA. Also, 8 of 9 extracardiac aneurysm cases whose clear 2DE images were available in the reports, the giant MCA aneurysms seemed to have developed at positions immediately adjacent to the ostium. We assume that the giant coronary aneurysms might be a consequence of the coincidence of aneurysms in the MCA segments perfused by Type 1 and 2 VV externas and reflect a severe inflammation where Type 2 VV externa which is less susceptible to blood flow reduction than Type 1 VV externa is affected. *Conclusions*. Vasculitis in VV externa with the unique structure originating from and distributing most richly across coronary arteries might induce a vicious circle of hypoperfusion of VV externa and reduced coronary blood flow.

Keywords: Coronary Artery Aneurysm, Coronary Artery Ischemia, Coronary Blood Flow, Coronary Vasa Vasorum, Endothelial Dysfunction

1. Introduction

Kawasaki disease (KD) is a diffuse disease in the systemic vascular system affecting the venules and capillaries as well as the aorta with activation of the immune system [1] which is a central feature of KD [2]. The incidence of coronary artery aneurysm (CAA) in KD is 15-25% [3]. The foremost causes of death are CAA rupture, thrombotic occlusion, and chronic coronary insufficiency.

Degeneration of the endothelial cells in KD has been elucidated early on as primary lesion in blood vessels [4-7]. There are other reports on the development of coronary artery lesions [8-15].

Recently, Onouchi Y et al. analyzed susceptibility genes to KD and found *ITPKC* and *CASP3* functional polymorphisms were associated with coronary artery aneurysm (CAA) formation [16-18].

The majority of research efforts for vascular lesions have focused on the inner and medial vascular layers (e.g., internal elastic lamina), which are, in fact, affected at the early stage of vascular lesions.

In our autopsy case with ruptured aneurysm of the left main coronary artery in KD, the pathogenesis of coronary aneurysm formation was ascribed to the vasa vasorum vasculitis, resulting in the hypoxia and necrosis of the host vessel [19, 20].

Indeed, experimental manipulation of the adventitia and, more specifically, of the vasa vasorum (VV) could lead to medial edema, degeneration, and ischemic necrosis, followed by later intimal thickening due to proliferation of smooth muscle cells and VV proliferation [21-25]. Moreover, hypoperfusion of the adventitial VV develops an abdominal aortic aneurysm [26].

Clarke reported two types of VV externa in the coronary artery [27]. One is Type 1 VV externa originating from atrial and ventricular branches of peripheral coronary arteries in the myocardium and develops toward the ostium along the main coronary artery (MCA) during childhood [28]. Kwon HM et al. [29] described that the VV externa of pigs runs longitudinally along vessel walls from coronary branch points. The other (what we refer to as Type 2 VV externa) originates from the coronary ostium and grows toward the coronary artery's proximal portion within about 1 cm from the ostium before reaching adulthood [27].

This study aimed to elucidate the association of vasculitis of vasa vasorum and aneurysm formation in the host vessel.

2. Background

We hypothesized that potential heterogeneities in the structure, development and spatial density of the adventitial VV among different vascular beds may be an underlying mechanism of the different frequencies of aneurysm formation and that VV vasculitis causes hypoperfusion most severely on the aorta and medium-sized arteries.

3. Methods

3.1. Distance Ratio

We studied whether the longitudinal extension of the left main coronary artery (LMCA) aneurysm coincided with the development of the VV externa (here named as Type 1 VV externa) (Figure 1).

Subjects: we retrospectively analyzed data from patients treated at our university hospital over 19-year periods from 1972 to 1980 and 1988 to 1999. We included KD patients with CAA in the LMCA.

Coronary angiograms and two-dimensional echocardiogram (2DE) images were analyzed. We measured the distances from the left coronary ostium to both the proximal point of the aneurysm in the LMCA (D1) and its bifurcation point (D2) (Figure 2). We defined the distance ratio as y=D1/D2 × 100, and assessed the correlation between the distance ratio and ages either at KD onset or the coronary imaging. We evaluated the correlation between the distance ratio and (A) the day of illness when the patients underwent coronary angiography or echocardiography or (B) the patients' age at KD onset.

A single regression test was performed to analyze the linear correlations between the two parameters by using Microsoft Excel. Statistical significance was set at a P value < 0.05.

3.2. A Literature Review of KD Cases with Extracardiac Aneurysm

Sometimes, aneurysms of arteries other than coronary arteries, i.e., iliac and axillary arteries, are seen in KD. VV perfuses such arteries has a similar structure to Type 2 VV externa. Considering that vasculitis of Type 1 VV is more likely to cause ischemic necrosis and damage coronary arteries than Type 2 VV, we hypothesized that KD cases with extracardiac aneurysms had severer vascular inflammation than those without. We also hypothesized that the vasculitis of Type 2 VV externa could cause aneurysms in its perfusing LMCA region when the inflammation is highly severe, and the giant aneurysms neighboring the ostium are the consequences of the fusion of aneurysms in LMCA areas perfused by Type1 and 2 VV externa. To investigate the comorbidity of coronary and extracardiac aneurysms in KD patients, we conducted a literature search for previous reports in 1983 – 2016 in PubMed. We also searched case reports of extracardiac aneurysms in the 'A Bibliography of KAWASAKI DISEASE' distributed by the Japan Kawasaki Research Center. The papers of extracardiac aneurysm cases with clear 2DE images of their coronary arteries were then selected.

This study conformed to the Declaration of Helsinki principles.

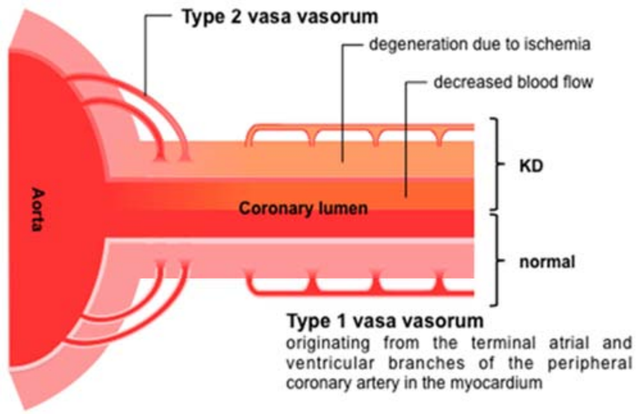

Figure 1. *Two-dimensional imaging of the aorta and LMCA An illustration of the origins and running course of VVs of the main coronary arteries described by Clarke et al. [27]. The upper half represents KD with the decrease of coronary blood flow and the medial edema and degeneration in the coronary artery. Type 1 VV=vasa vasorum externa originating from atrial and ventricular branches of peripheral coronary arteries, and Type 2 VV=vasa vasorum externa arising from the ostium.*

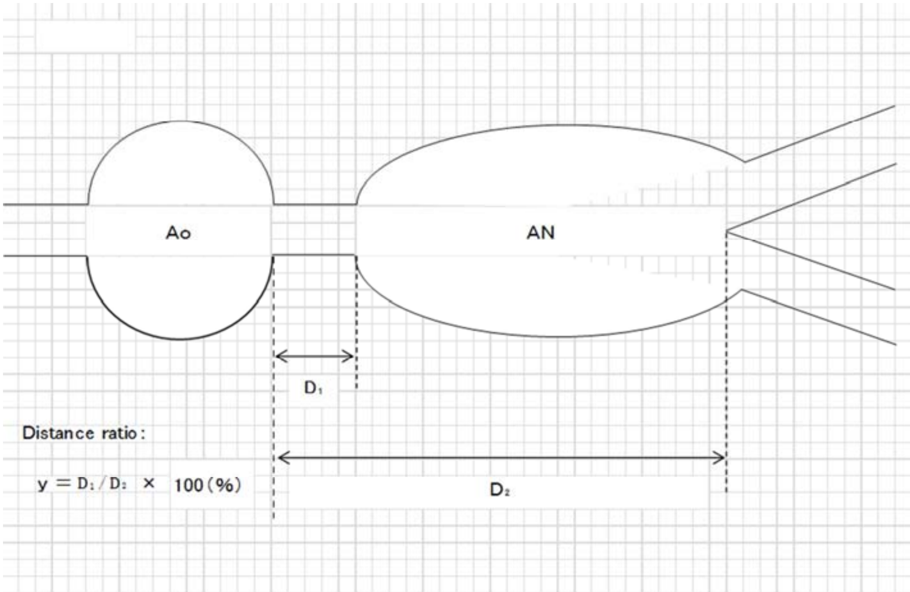

Figure 2. Imaging of an aneurysm in the LMCA and the calculation of the distance ratio Illustration of the calculation for the Distance ratio of an aneurysm in the coronary arteriograms and 2DE images. Ao=aorta, AN=aneurysm.

4. Results

4.1. Distance Ratio

Sufficient data were available for analysis of coronary artery images in all 63 cases without extracardiac aneurysms. Mean age at KD onset (x) was 2 years 6 months (median, 1 year 3 months old; range, 2 months to 7 years 5 months). Mean age at the time of angiography or echocardiography was 5 years 7 months old (median, 2 years 6 months; range, 1 month to 36 years 6 months). The distance ratio (y) was negatively correlated with age (x) at KD onset but was not correlated with age at the time of angiography or echocardiography (Figure 3). The linear regression equation was as follows: y=47.634 – 2.775x (P=0.008, R=0.326).

4.2. Extracardiac Aneurysm Is Associated with the Giant CAA

Except for cases without descriptions about CAA, all 73 patients with extracardiac aneurysms from the literature revealed an LMCA aneurysm. At KD onset, the median age was 4 months in the 51 male patients (range, 7 weeks to 6 years) and 22 female patients (range, 4 weeks to 3 years 5 months). There were 15 cases with descriptions of giant coronary aneurysms in the reports. Among them, clear images of LMCA were available for 9 patients for assessment (Table 1).

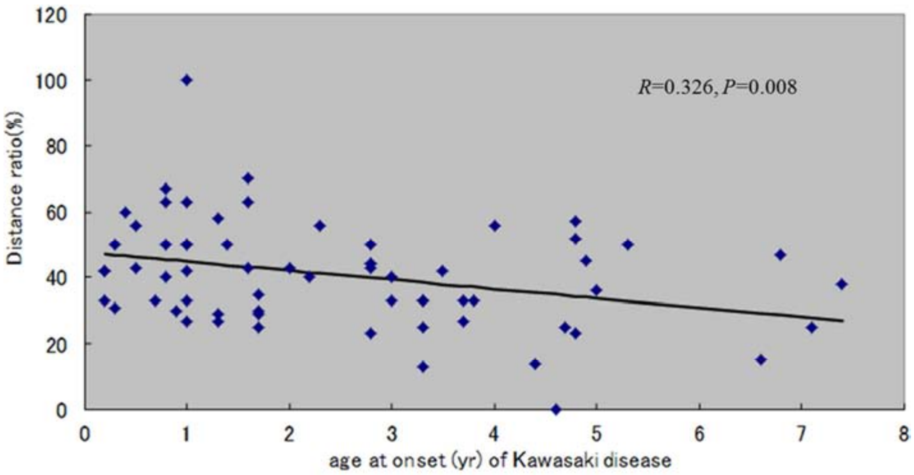

Figure 3. Relation between the distance ratio and the age at KD onset Plots of the relation between Distance ratio of aneurysm (%) and age at onset (yr) of Kawasaki disease in the 63 patients. The Distance ratio of the LMCA aneurysm is negatively correlated with the age at KD onset.

The male-to-female ratio of the 9 cases was 7: 2. The median day at the time of angiography or echocardiography after KD onset was more than 3 months (range, 1.7 months to 1 year 4 months).

Eight of 9 coronary artery aneurysms were located immediately after the ostium (Figure 4). The remaining one was located at a short distance from the ostium, probably resulting from the regression of aneurysm [30].

Table 1. *Extracardiac aneurysm with Kawasaki disease.*

No.	Age at onset of KD	Sex	Distance from coronary ostium to AN	DI at coronary angiography	Extracardiac AN
1	3y3m	M	No description		R. axillary artery
2	5m	F	No description		Distal abdominal aorta- Bil. common iliac arteries
3	2y4m	F	Immediately after	7m	Distal abdominal aorta Bil. femoral arteries R. axillary artery Bil. common iliac arteries
4	1y	M	Indistinct immage	4m	Bil. axillary arteries
5	2y1m	M	Immediately after	> 75d	Bil. common iliac arteries L. internal iliac artery
6	1y1m	F	Immediately after	> 50d	Bil. Axillary arteries
7	4m	M	Immediately after	3m	Bil. axillary arteries Bil. internal iliac arteries Abdominal aorta
8	8m	M	Gap*	> 6m	R. axillary artery Bil. common iliac arteries
9	11m	M	Immediately after	2m	Bil. axillary arteries Bil. common iliac arteries
10	2y5m	M	Immediately after	3m	Bil. axillary arteries Bil. common iliac arteries
11	2m	M	Indistinct immage	2m 22d	Bil. axillary arteries Ascending aorta Abdominal aorta
12	2m	M	Indistinct immage	3m 18d	Bil. axillary arteries Abdominal aorta
13	4m	M	Immediately after	1y 4m	Bil. axillary arteries Abdominal aorta Bil. common iliac arteries Bil. internal iliac arteries
14	2m	M	Immediately after	2m 16d	Bil. axillary arteries L. subclavian artery
15	1m19d	M	No discription	6m	Gangren of 4 toes of the left foot

KD: Kawasaki disease, AN; aneurysm, DI; day of the illness, m; month, d; day, R; right, Bil; bilateral, L; left

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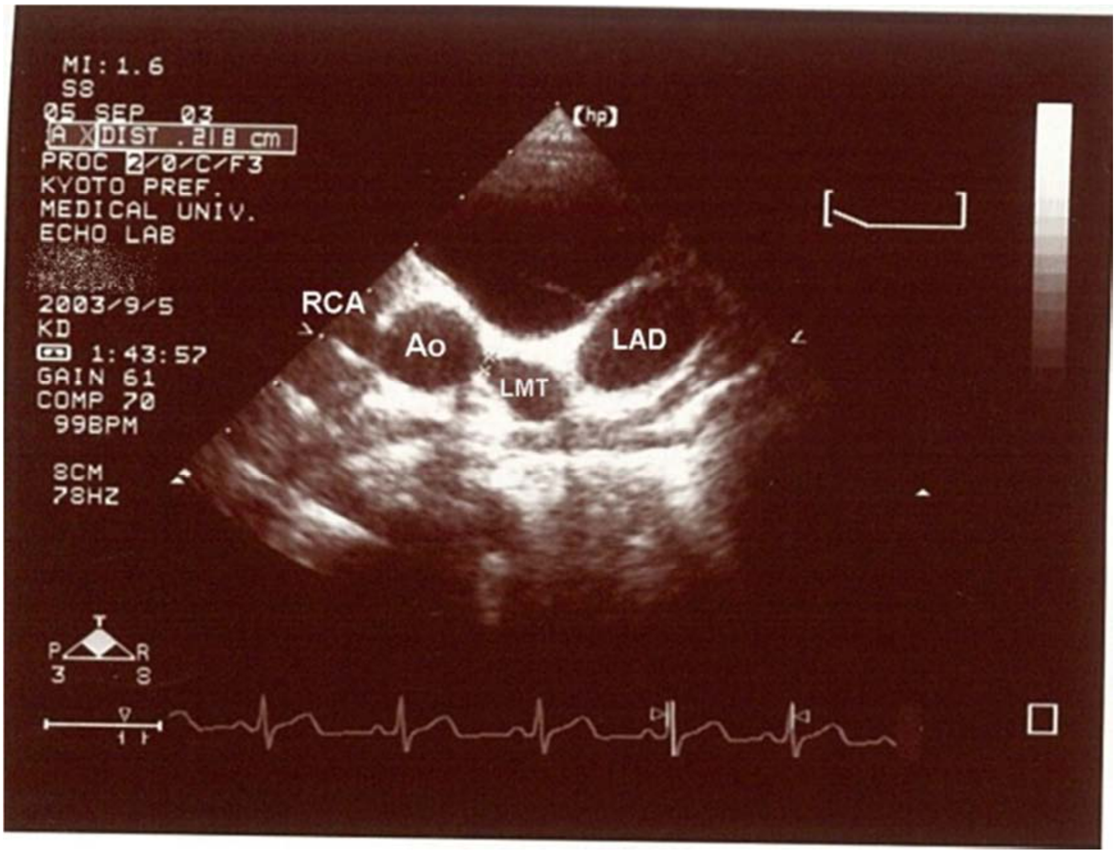

Figure 4. *Two-dimensional echocardiogram of the patient with an extracardiac aneurysm An ilustration of 2DE of our 1.6 year old patient with extracardiac aneurysm. This echocardiogram shows giant aneurysms proximal to both coronary ostia, combined with a giant aneurysm in the LAD. Ao=aorta, LMT (LMCA)=left main trunk, LAD=left anterior descending artery, RCA=right coronary artery.*

5. Discussion

Fujiwara described that the vascular inflammation in KD first takes place as perivasculitis and vasculitis on microvessels (arterioles, venules, and capillaries) and small arteries including VV of three MCAs [1]. In the MCAs, acute perivasculitis, inflammation of the adventitia, and acute endarteritis were observed, but inflammatory changes of the media were not detected in the early stage. The inflammatory tissue was edematous and infiltrated chiefly with neutrophils, eosinophils, and lymphocytes. They insisted that the origin of angiitis exists in the microvessels.

Amano S et al. [4] demonstrated that the arteries' primary lesions were intimal endothelial degeneration and increased vascular permeability. They also pointed out the degeneration of the VV's endothelial cells and infiltration of the small or moderate number of lymphocytes, large mononuclear cells, and neutrophils. Subendothelial accumulation of mononuclear cells followed by the VV vasculitis, periarteritis, and inflammation of adventitia was observed [31]. Landing et al. [32] described that the inflammation of the coronary arteries begins at the adventitia.

Neutrophils activated by G-CSF, TNF-alpha, and GM-CSF adhere to damaged endothelium [33]. Adherent factor changes and both mononuclear cells and macrophages massively gather to the endothelium. ICAM-1 and CD 44 [34] mediate to transmigrate them into the media through the endothelium. Neutrophils produce massive ROS [35] and cause endothelial damage in KD [36]. In the early stage in KD, activated by the proinflammatory cytokine [15], neutrophils adhere to the endothelial cells and secrete MRP-8, 14 and induce the thrombogenic and inflammatory reaction on the endothelial cells of the microvessels [37].

Proinflammatory cytokines are massively produced in KD. Monocytes/macrophages secrete TNF, which is an important predisposing factor [38]. Furthermore, proinflammatory cytokine directly causes endothelial damage.

Neutrophils express VEGF isoforms only in the early stage of acute KD [9], whereas mononuclear cells express VEGF isoforms predominantly at 2-4 wk after onset [14]. VEGF has been considered to be one of the mediators of microvascular permeability in KD [9]. Mononuclear cells which acceleratory express VEGF, massively infiltrate at the intima of the coronary arteries in 10 to 12 days of illness.

Oxygen and nutrients are supplied to inner thirds of media through luminal endothelium, and adventitia to middle thirds of media through VV externa in the mammalian vessel wall [39, 40]. Infiltration of the cells in the early stage of KD more severe in the adventitia than the intima [41].

These observations suggested the difference of perfusions from VV in the adventitia and luminal endothelium [42].

Hypoperfusion of the media due to reduced blood flow associated with VV vasculitis with the thrombotic obstruction [37] induces hypoxia. Hypoxia triggers HIF-1alfa and VEGF secretion from smooth muscle cells of the media [43], resulting in VV proliferation. VEGF has been identified as a cytokine that regulates differentiation, proliferation, migration, and survival of cells in the microvascular endothelium [41, 44]. These characteristics are important since they imply that the VV may regulate their tone and vascular perfusion in a manner similar to small coronary arteries, as was demonstrated by Scotland et al. [40, 45]. It seems possible that, due to reduced transendothelial permeation, infection, inflammation or thrombosis, the smooth muscle tone of proximal vasa vasorum is selectively increased and results in blood flow reduction and hypoxia [39].

In acute KD, the migration and proliferation of endothelial cells have been demonstrated to be markedly enhanced by cytokines [46, 47]. Inflammatory cells accumulate at damaged endothelium and degrade basement membrane [48], resulting in the dissemination of inflammatory cells and substances into the media. Thus inflammation in the media is induced and, combined with hypoxia and ischemic necrosis, leads to the cytokine storm and necrotizing panarteritis [4]. We consider that reduced blood flow of the atrial and ventricular branches of the coronary artery, selective blood flow reduction in proximal VV [45], local hypoxia in the media by insufficient oxygen supply [4, 19], dissemination of inflammatory cells and substances, and cytokine storm and necrotizing panarteritis [4] sequentially occur.

Earlier work defined two general subsets of $CD4^+$ T lymphocytes, Th1 and Th2, determined by the relative activity of two members of the signal transducer and activator of transcription (STAT) family of proteins, STAT4 and STAT6, respectively. In turn, the relative activity of STAT4 versus STAT6 is determined by the prevailing cytokine milieu (Ramagnani, 2006). Th1 cells secrete proinflammatory cytokines, for example, IL-2, IL-12, IFNgamma, and TNFalfa, whereas Th2 cells secrete primarily anti-inflammatory cytokines.

Among them, T lymphocytes remarkably activated due to SNP of *ITPKC* gene [16] may play a pivotal role in the necrotizing panarteritis in the media of KD.

CAL is the most severe and the most frequent in the cardiovascular lesions of KD. However, the reason of preference for the coronary arteries remains to be clarified. Histopathologic changes similar to the coronary arteries are also often observed in the aorta and medium-sized arteries with VV in KD [49]. However, aneurysms develop more commonly in the coronary arteries [50].

Coronary arteries have the highest VV density among different vascular beds [51], which indicates that the coronary artery wall demands much oxygen. Because having 70 times higher endothelial surface area than luminal endothelium [51], endothelial dysfunction in the VV level might impact vascular wall perfusion more than luminal endothelial dysfunction of the host vessel. We considered endothelial dysfunction in the VV vasculitis in the developing MCA of infants and young children may promptly lead to depression of oxygen and nutrients supply to the MCA.

Distance ratio

The distance ratio was negatively correlated with age at KD onset. Type 1 VV externa arises from the point of MCA bifurcation and develops longitudinally toward the ostium [27, 29]. In a previous study by Clarke, VVs of coronary arteries were investigated among children older than 3years old [27]. However, VVs in the MCA were observed in infants and young children [19, 52]. VV is assumed to play a central role in the oxygen and nutrients supply to the MCA wall. Vasculitis of Type 1 VV externa might lead to blood flow reduction and then hypoxia in the adventitia and media of the MCA. Additional effects of inflammatory cell infiltration might cause necrosis and aneurysm formation.

Thus, we consider that the longitudinal sizes of the LCMA aneurysms reflect the length of Type 1 VV externa.

Extracardiac aneurysms were associated with giant CAAs.

Amano et al. [53] studied the distribution of the vascular lesions in KD and noted aneurysms were observed in the aorta and medium-sized arteries with VV. On the other hand, inflammation was observed in the intima but not in the adventitia of interlobaris denis which have no VV [54].

Because of the structural difference from Type 1 VV externa of LMCA, blood flow in the VVs of the aorta and extracardiac arteries is not easy to reduce at VV vasculitis. Therefore, it might be possible that KD cases with extracardiac aneurysms might have much severer systemic inflammation in the acute phase, and arteries perfused by Type 2 VV were also affected. Results of the literature review in this study that all extracardiac aneurysm cases had CALs are supporting this idea. Ichinose et al. described [55] that giant aneurysms developed as a consequence of a merge of usual-sized CALs formed proximally each other. The finding that the beginning of the giant aneurysms was in the vicinity of the ostium also supports our hypothesis of the genesis of giant aneurysms.

As aforementioned, Type 1 VV externa arises from the atrial and ventricular branches of the peripheral coronary arteries, supplying oxygen and nutrients to the media's outer thirds. Therefore, the supply of oxygen and nutrients to the coronary artery wall is greatly influenced by the coronary artery function itself.

Ritman et al. [39] and Scotland et al. [40] described that endothelial dysfunction and an increased vascular tone of the VV may be enhanced due to inflammation and the reduced bioavailability of nitric oxide, secondary to the increase in endogenous oxidative stress.

VV arteritis is considered to result from continuous extension of vasculitis of peripheral coronary arteries, or to be a part of the generalized vasculitis of the arterioles and small arteries in the early stage of KD [1] or both. We propose a pathogenesis scheme on a predilection for CALs in KD (Figure 5): the vicious circle of blood flow reduction between coronary arteries and the VV.

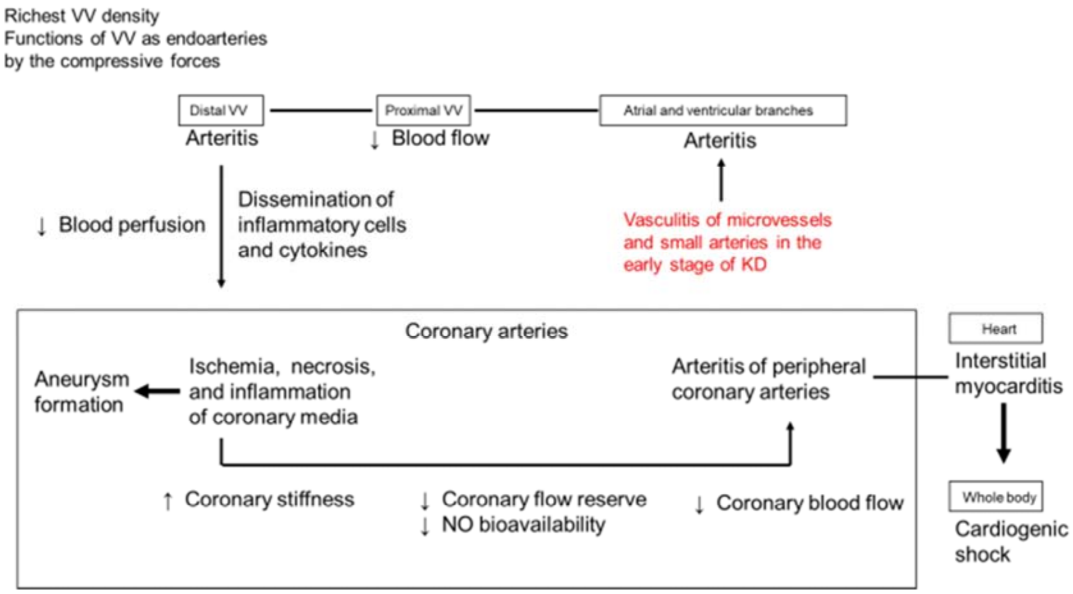

Figure 5. *Vicious circle.*

VV vasculitis
↓
VV blood flow↓→hypoxia in the media→stiffness of epicardial coronary artery↓→
Coronary blood flow↓→peripheral coronary flow↓→blood flow of atrial and
Ventricular branches↓→VV blood flow↓→

Medial degeneration and necrosis, resulting in the increased stiffness, may attribute to insufficient oxygen and nutrients supply due to the VV vasculitis. Previously, we reported a decrease of coronary reserve in patients with CALs [56]. We considered that the observation was a consequence of increased vascular resistance of peripheral coronary arteries. Now we are assuming that increased stiffness of the epicardial coronary artery due to the increased oxidative stress may also contribute to the phenomenon.

A recent study has further provided evidence that local oxidative stress, as assessed by net production of isoprostanes across the LAD artery territory, has a role in the reduction of nitric oxide bioavailability to humans with coronary endothelial dysfunction [57].

Study limitation

Many of the giant coronary aneurysm cases in this study were those affected with KD when 2DE had not become popular. Therefore, for these patients, a relatively long time since the onset of KD had elapsed when 2DE was conducted. In some patients, aneurysms might have regressed, and the regression could be supposed to weaken the correlation between the distance ratio and the patients' age.

Furthermore, although we proposed ischemic necrosis in the arterial wall as the pathogenesis of aneurysms in KD, we could not obtain direct experimental evidence in hypoxic condition in the vascular wall. We reported the low incidence of aneurysm formation in patients with neutropenia in KD and proposed granulopoiesis for treatment of KD [58].

Research into the biology of ischemia or ischemia/perfusion injury has increased in recent years [59]: consequently, many therapeutic strategies have been proposed [60-63].

6. Conclusions

Coronary arteries liable to aneurysms in KD have the highest VV density, indicating their higher oxygen and nutrients requirement. VV dysfunction might predispose oronary arteries to hypoxia in the media.

The role of VV, the vicious circle between coronary arteries and their VV, intra- and intervascular heterogeneity of the vascular bed, and the strength of the systemic inflammation might be a determinant of the difference in the coronary outcome in KD.

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