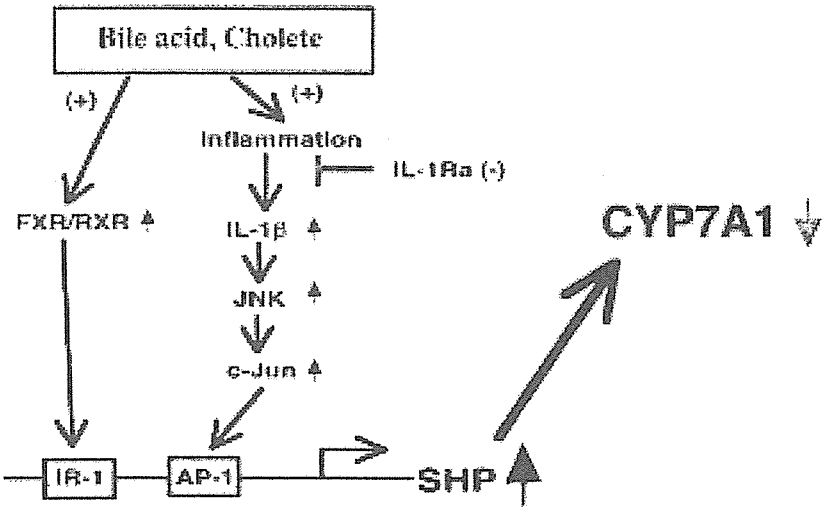

Fig.4. Model for up-regulation of SHP gene expression in the absence of IL-1Ra. Bile acids activate FXR and induce inflammation. The lack of IL-1Ra could not reduce inflammation and might induce the production of a large amount of IL-1. Then IL-1 activated the JNK signaling cascade. Activated FXR and c-Jun enhanced SHP transcription by binding to the IR-1 and AP-1 elements in the SHP promoter. Elevated SHP protein levels in turn repressed CYP7A1 transcription and the down-regulation of CYP7A1 expression increased amounts of bile acids in hepatocytes. Finally this loop formed a vicious circle in the metabolism of bile acids. See text for details.

dl, $n = 5$; $p < 0.01$), higher apoB-containing lipoprotein levels (699 ± 126 mg/dl versus 192 ± 36 mg/dl; $p < 0.01$), and decreased HDL levels (31 ± 10 mg/dl versus 54 ± 3 mg/dl; $p < 0.05$)·in IL-1Ra$^{-/-}$ mice compared to IL-1Ra$^{+/+}$ mice after 20 weeks on the atherogenic diet (Fig. 3B). Real-time PCR analysis revealed that the decreasein the IL-1Ra mRNA level was accompanied by a increase in the levels of IL-1β ($P < 0.001$), TGF-β ($P < 0.01$) and CD68 mRNA ($P < 0.001$) in the IL-1Ra$^{-/-}$ liver compared to the WT liver. Furthermore, IL-1Ra$^{-/-}$ mice failed to express mRNA of cholesterol 7α-hydroxylase (CYP7A1) ($p < 0.05$), the rate-limiting enzyme in bile acid synthesis, with upregulation of small heterodimer partner 1 (SHP) mRNA expression ($p < 0.001$) following 4 weeks on the atherogenic diet (69). Indeed, IL-1Ra$^{-/-}$ mice showed markedly decreased bile acid excretion, which is promoted in WT mice to maintain cholesterol levels while feeding on an atherogenic diet. Our results show that both bile acid and high cytokine levels in IL-1Ra$^{-/-}$ mice reduced the mRNA expression of CYP7A1 with a upregulation of SHP mRNA expression. We summarize the mechanism of these changes in Fig. 4. Several previous reports demonstrated that administration of cholic acid in mice induced SHP gene expression (70, 71) and SHP reduces CYP7A1 expression (72). Increased concentrations of bile acids in the liver could, in turn, induce inflammation and the lack of IL-1Ra, an anti-inflammatory cytokine, might worsen the inflammation in IL-1Ra$^{-/-}$ liver. Furthermore, large amounts of cytokines produced in response to severe inflammation in IL-1Ra$^{-/-}$ mice could also play an important role in the up-regulation of SHP expression. Cytokine-dependent signaling leads to the activation of c-Jun N-terminal kinase (JNK) and other mitogen-activated protein kinases (73, 74). Recently, Gupta *et al.* showed that c-Jun activated by cytokines induces SHP-1 promoter activity and mutations in the AP-1 binding site abolished bile acid responsiveness of the rat SHP promoter (75). Thus, they suggested that activation of the JNK/c-jun pathway is needed for the induction of SHP by bile acids. Furthermore, Miyake *et al.* demonstrated that bile acid-induced expression of cytokines (such as TNF-α and IL-1) by macrophages correlates with repression of hepatic CYP7A1 (76), further supporting our findings. Thus, atherogenic diet-induced inflammation with both a high IL-1 level and deficiency of IL-1Ra caused an up-regulation of SHP expression and, in turn, down-regulation of CYP7A1. The suppression of CYP7A1 causes more cholesterol to accumulate in IL-1Ra$^{-/-}$ mice. We conclude that the significant increase in SHP expression in IL-1Ra$^{-/-}$ liver is an indirect effect of loss of IL-1Ra, but IL-1Ra plays an important role in maintaining cholesterol homeostasis under conditions of cholic acid-induced inflammation.

Conclusion

During the last five years, transgenic and gene knockout studies in murine models of vascular disease have established IL-1 and IL-1Ra as pivotal players in the regulation of vascular cell functions and cholesterol metabolism. Although genetic differences between mouse and man preclude a direct translation of these findings to human disease, these studies have identified several pathways whose perturbation has the potential to significantly shift the balance between disease progression and retardation. An important goal of future studies will be more-detailed investigations of the particular genes and pro- and anti-inflammatory pathways regulated by different cytokines in atherogenesis and cholesterol metabolism. This challenge could lead to promising novel therapeutic targets for anti-inflammatory therapies, potentially even harnessing some of the sophisticated regulatory systems designed to normally limit the inflammatory response.

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Interleukin-1 and Occlusive Arterial Diseases

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Abstract: Interleukin (IL)-1 is a pro-inflammatory cytokine and a central mediator in the cytokine network, and is known to control important functions both in the immune system and inflammation. The activity of IL-1 is counter-regulated by its endogenous inhibitor, IL-1 receptor antagonist (IL-1Ra). IL-1 and IL-1Ra are produced and secreted by a variety of cells including those responsible for controlling immunity. A recent study indicated that IL-1 and IL-1Ra transcripts were expressed in the vessel wall, suggesting that these cytokines contribute to the development and progression of vascular diseases.

In this review, we will discuss the recent advances in our understanding of the mechanism of action of IL-1 in occlusive arterial diseases such as neointimal hyperplasia and atherosclerosis, specifically in a mouse model.

Key Words: Cytokine, Interleukin-1, occlusive arterial disease, atherosclerosis, lipid metabolism.

INTRODUCTION

Though hypercholesterolemia is a major risk factor for atherosclerosis and cardiovascular diseases, it is well known that serum cholesterol levels are normal in one-third of patients developing coronary heart disease. In addition, LDL-cholesterol lowering therapy with statins reduces cardiovascular events by only about 30%. This suggests that factors other than hypercholesterolemia also play important roles in the development of atherosclerotic vascular lesions.

Elevated C-reactive protein (CRP) levels and the WBC number have been recently recognized as new markers for atherosclerosis, supporting the hypothesis that atherosclerosis is a chronic inflammation of the blood vessel walls [1]. According to this hypothesis, stimuli such as hypercholesterolemia induce vascular injury and chronic inflammation, leading to the progression of atherosclerosis. Inflammatory cells and pro-inflammatory cytokines also play important roles in sustaining inflammation of the vessel walls.

Interleukin-1 (IL-1) is a major pro-inflammatory cytokine. It was originally described as a macrophage-derived, lymphocyte-activating factor and can be considered to be a link between innate and adaptive immunity [2]. IL-1 and its receptor are expressed in nearly every cell type, not only in immune cells. IL-1 is a key regulator of the host immune response and it also shows various biological activity with respect to non-immune cells. Vessel wall cells, endothelial cells, smooth muscle cells, and fibroblasts express both IL-1 and its receptor. The above strongly suggest that IL-1 is involved in the development of atherosclerosis and neointimal hyperplasia. Furthermore, recent progress in our understanding of IL-1 signaling has demonstrated the importance of the involvement of IL-1 in vascular disease, suggesting that IL-1 and its signal pathway should be a new therapeutic target for vascular disease.

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In this review, we will discuss the potential role of IL-1 in occlusive arterial diseases, such as neointimal hyperplasia and atherosclerosis, while focusing on a mouse model of occlusive arterial diseases involving the IL-1 family, mainly IL-1α, IL-1β, and IL-1 receptor antagonist (IL-1Ra)

IL-1 FAMILY

Recently, the IL-1 family has been expanded to ten members [3], though many of them have not yet had their biological functions fully elucidated. In this section, we briefly review the originally known IL-1 family: IL-1α, IL-1β, and IL-1 receptor antagonist.

IL-1α, IL-1β, and IL-1Ra genes are located close to one another on human chromosome 2. They have different amino acid sequences but are structurally related on the three-dimensional level, and act through the same cell-surface receptors. The homology between human IL-1α and IL-1β is 45% at the nucleotide level and 26% at the amino acid level. The interspecies homologies (human versus mouse) at the amino acid level are 61% for IL-1α, 68% for IL-1β, and 76% for IL-1Ra. These 3 genes all originated from a common ancestral gene during evolution.

Both IL-1α and IL-1β are produced as 31kDa precursors, which are then enzymatically cleaved into mature forms of 17kDa protein. Both lack signal peptides and are not secreted *via* the classical secretory pathway. Most IL-1α is stored in the cytosol of cells in its precursor form, where it may function as an autocrine messenger. Recently, the precursor form of IL-1α has been reported to be an intracrine activator of transcription [4]. After activation by LPS, IL-1α is translocated to the nucleus where it activates the transcriptional mechanism. Also, stable transfectants overproducing precursor IL-1α release IL-8 and IL-6, while exhibiting a highly sensitive response to TNF-α and IFNγ. These observations suggest that the blocking of the intracellular functions of IL-1α might also serve to block IL-1 activity when conducted in combination with extracellular inhibitors. There is also evidence that the IL-1α precursor is translocated to the cell surface and is thus associated with the cell

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membrane. Bound to the cell membrane, the precursor is biologically active, and can serve as a paracrine messenger for adjacent cells [5]. It is cleaved into a mature form of IL-1α of 17kDa by such extracelluar proteases as calpain, and is then released into the extracellular space.

In contrast, the IL-1β precursor (31kDa) has no biologic activity and must be cleaved to become active. It is present in the cytosol and moves into specialized secretory lysosomes where it co-localizes with procaspase-1. The next step is the conversion of the inactive procaspase-1 to activate caspase-1 by a complex of proteins termed the inflammasome [6]. In resting cells, procaspase-1 is bound to a large inhibitor molecule. During the initiation of IL-1β synthesis, caspase-1 is activated and it then processes the IL-1β precursor into its mature form (17kDa) within the cell, which is released into the extracellular space and then into the circulation. In humans, circulating IL-1 consists almost exclusively of IL-1β.

Four forms of IL-1Ra protein have been reported in both mice and humans. One of them, sIL-1Ra, is secretory but the other three lack the signal sequence and are thus retained within the cytoplasm of intact cells (icIL-1Ra) [7-10]. sIL-1Ra is synthesized as a 177-amino acid precursor with a 25-amino acid signal sequence. It is secreted exracellularly through the classical secretory pathway as protein of about 20kDa (152 amino acids). IL-1Ra resembles IL-1α and IL-1β in the amino acid sequence and three-dimensional folding pattern. IL-1Ra binds to type I IL-1 receptor (IL-1RI) with a higher affinity than that of IL-1α and β. However, it fails to recruit IL-1 receptor accessory protein, which is required for signaling, and therefore cannot activate IL-1R signaling. IL-1Ra is thus a natural negative regulator of IL-1 [11].

IL-1 RECEPTOR (IL-1R) FAMILY

IL-1α, IL-1β, and IL-1Ra bind to two receptors classified as type I (IL-1RI) and II (IL-1RII) [12]. Both type I and II receptors are members of the immunogloblin (Ig) super-family. The human IL-1RI is an 80kDa transmembrane protein with 552 amino acids. It has a single 22 amino acid transmembrane region and a long cytoplasmic tail of 212 amino acids, which participates in signal transduction. Its extracellular ligand-binding region consists of three Ig-like domains. IL-1RII is a 60kDa protein and is similar to IL-1RI in its extracellular and transmembrane regions. However, IL-1RII has a short cytoplasmic tail of 29 amino acids and it is incapable of signaling. IL-1RII actually competitively inhibits IL-1 activity by acting as a decoy receptor for IL-1.

The IL-1 receptor accessory protein, IL-1RacP, is essential to IL-1 responsiveness. IL-1RacP is a 60kDa trans-membrane protein possessing 570 amino acids. Although the extracellular portion of IL-1RacP also consists of three Ig-like domains, and IL-1RacP shares homology with IL-1RI, it does not directly bind to IL-1 or IL1Ra. IL-1α, IL-1β, and IL-1Ra bind to both types of IL-1R with high affinity, though affinities for IL-1R differ among them. IL-1α preferentially binds to IL-1RI with high affinity while IL-1β binds preferentially to IL-1RII. IL-1Ra binds to IL-1RI with higher affinity than it does to IL-1RII. Both the precursor and mature forms of IL-1α bind to its receptor with equal affinity, and their biological activities appear to be similar. The IL-1β precursor does not bind to or signal through the type I receptor, but the mature IL-1β does. Similar to the IL-1 family, the IL-1 receptor family has also been expanded to ten members [13,14]. The members of the IL-1R family are membrane-spanning proteins that possess at least one Ig-like extra-cellular domain and a Toll/IL-1 receptor (TIR) domain in the cytoplasm.

TOLL/IL-1 RECEPTOR (TIR) FAMILY

The cytoplasmic domain of IL-1R is essential for signal transduction. IL-1R and Toll-like receptor (TLR) family members share a conserved stretch of 200 amino acids in their cytoplasmic region known as the Toll/IL-1 receptor (TIR) domain. The TIR domain does not have a catalytic function and works by protein-protein interaction [15]. The TIR domain is present in a large number of proteins, and it acts as a switch in the process of cell activation during innate immunity and inflammation. The animal TIR family can be classified into three subgroups "Fig. (**1**)". TIR-I is similar to IL-1RI, having one or more extracellular Ig regions, a single trans-membrane region and a cytoplasmic TIR domain. TIR-II is similar to TLR2 and 4, possessing an extracellular region composed of leucine-rich repeats, a single trans-membrane region and a cytoplasmic TIR domain. TIR-III consists of an intracellular protein such as myeloid differentiation protein-88 (MyD88), and has a TIR domain and one or more additional domains. TIR-III acts as an adaptor molecule for signaling in the cytosol.

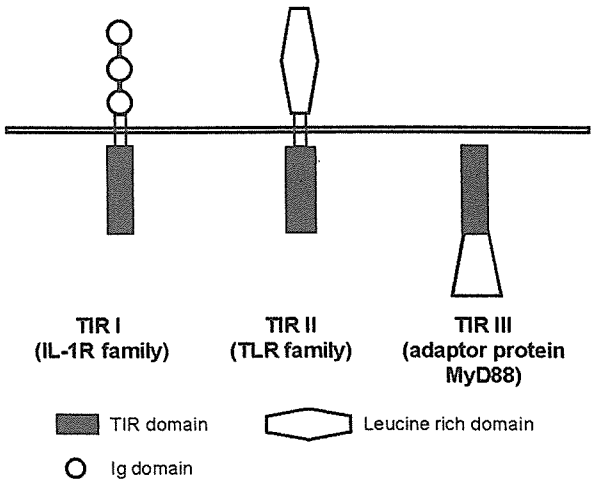

Fig. (1).

IL-1-INDUCIBLE SIGNALING PATHWAY

After binding with IL-1α or β, IL-1 RI and IL-1RacP form a signal-transducing complex, which then recruits Tollip, MyD88, and IRAK (IL-1-receptor-associated kinase)" Fig. (**2**)". IRAK is a serine/threonine kinase which possesses a death domain (DD) [16]. The DD of IRAK-1 interacts with the DD of MyD88. IRAK-4 is then recruited through DD interaction with MyD88 DD and phosphorylates IRAK-1. This phosphorylation weakens the IRAK-1-MyD88 DD interaction and releases the IRAK-1-TRAF-6 (TNF-receptor-associated factor) complex. The IRAK-1-TRAF-6 complex then binds to TAK-1 (TGFβ-activated kinase). TAK-1

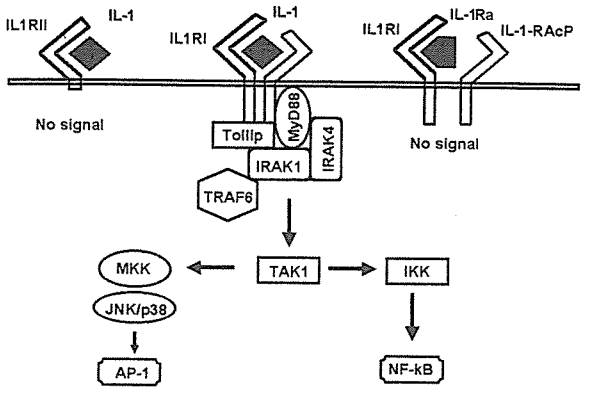

Fig. (2).

phosphorylates and activates IKK (inhibitory κB kinase) complexes and MKK leading to the activation of both the NF-κB and MAPK pathways. MKK3 activates AP-1 *via* the JNK/p38 cascade and IKK activates NF-κB. These two transcription factors, AP-1 and NF-κB, translocate to the nucleus and then activate many of the cytokine-inducible genes.

MULTIPLE BIOLOGICAL EFFECTS OF IL-1 ON VESSEL WALL CELLS

Endothelial cell (EC) function changes are known to be the initial step of the pathogenesis of atherosclerosis. ECs seem to be the major target cells of IL-1 in the vessel [17]. IL-1 stimulates the production of cytokines, chemokines, growth factors, and vasoactive mediators in ECs and induces the expression of adhesion molecules on ECs. Furthermore, it increases the expression of clotting factors and inhibitors of fibrinogenesis, resulting in a procoagulant state of the ECs. IL-1 also influences a variety of functions in smooth muscle cells (SMCs). In addition, it stimulates their proliferation [18]. IL-1 increases the production of growth factors in SMCs and induces the expression of adhesion molecules and integrin on them.

IL-1 expression is also regulated by various stimuli other than immune signals. In this regard, macrophages from LDL-R-/- mice produced an excess of IL-1α and β that was twice as great as that from the macrophages of wild type mice after LPS stimulation [19]. Also, the uptake of oxidized low-density lipoproteins by peripheral-blood monocytes resulted in an increase in IL-1 production by these cells. These findings indicate that hypercholesterolemia increases IL-1 production by macrophages.

Shear stress has been seen to regulate IL-1 expression in vessels. Jiang *et al.* demonstrated that IL-1β expression was markedly up-regulated in vein grafts in a rabbit jugular vein carotid interposition graft model, which resulted in neointimal hyperplasia [20]. They also found that IL-1 production was more marked under low shear stress and that the production of IL-10, an anti-inflammatory cytokine, increased under high shear stress, an interesting observation. These results suggest that shear stress modulated the pro- and anti-inflammatory cytokine balance.

PLASMA LEVELS AND TISSUE EXPRESSION OF IL-1 IN CARDIOVASCULAR DISEASE

In humans, most of the IL-1 activity detected in the circulation tends to involve IL-1β, whereas that associated with the cell membrane more often involves IL-1α. In normal human subjects, the plasma concentration of IL-1β is usually less than 40 pg/ml and circulating levels of IL-1Ra tend to range from 200 to 300 pg/ml. Elevated plasma IL-1 levels have been reported in various cardiovascular diseases related to atherosclerosis, such as angina [21], abdominal aortic aneurysm [22], hypertension [23], and hypercholesterolemia [24]. The reason for such elevated plasma IL-1 levels has not yet been elucidated. Recently, activated platelets have been reported to produce IL-1β [25,26], suggesting that activated platelets might be a reason for elevated plasma IL-1β levels in hypercholesterolemia [24]. Further, IL-1β production in platelets has been seen to decrease after treatment with either statin or low dose aspirin. These observations indicate a link between inflammation and the prothrombotic state observed in hypercholesterolemia.

The IL-1 family is also expressed in both the normal and atherosclerotic artery. The main components of atheroscletic plaque are ECs, SMCs, and macrophages. All these cells were observed to express IL-1 but each with a different pattern. The predominant cells expressing IL-1α and β mRNA were foam cells in the intima. ECs expressed mRNA for IL-1α, IL-1β, and IL-1Ra and SMCs expressed IL-1α mRNA [27-29]. However, intimal SMCs expressed both IL-1β, and IL-1Ra in different time courses, but not IL-1α. These findings suggest that both IL-1α and IL-1β participate in the development of atherosclerosis. However, the roles of IL-1α and IL-1β may be different when atherosclerosis is progressing.

EFFECTS OF IL-1 SYSTEMS ON NEOINTIMAL HYPERPLASIA IN ANIMAL MODELS

Neointimal hyperplasia may be an early stage of atherosclerosis, and it is also related to restenosis after percutaneous coronary intervention. Several studies have reported a relationship between the IL-1 system and neointimal hyperplasia, which was observed using different methods (Table 1).

(1) IL-1β

Shimokawa *et al.* showed that adventitial treatment with IL-1β induced an increase in neointimal hyperplasia of about 10-fold and a vasospastic response in the porcine coronary artery [30]. Histological analysis revealed an increase in SMCs in the intima and an accumulation of inflammatory mononuclear cells at the adventitial surface. The neointimal hyperplasia due to IL-1β was blocked by a neutralizing antibody to PDGF, suggesting that IL-1-induced neointimal hyperplasia was substantially mediated by PDGF. These results are consistent with the findings of a previous *in vitro* study, which noted that the proliferative effect of IL-1 β with respect to SMCs was mediated by other growth factors, mainly PDGF [31].

Table 1. Effects of IL-1 Systems on Neointimal Hyperplasia in Animal Models

Animal model	Age	Methods	Effects	Changes	Possible mechanisms	Ref.
porcine		local treatment	neointima ↑	+1000%	SMC ↑ PDGF ↑	30
IL-1Ra -/- C57BL6/J	8W	cuff	neointima ↑	+250%	adventitial cell ↑ SMC ↑	32
IL-1RI-/- B6x129	8W	CCA ligation	neointima↓	-90%		33

CCA ligation; unilateral common carotid artery ligation.

(2) IL-1Ra

We previously reported on neointimal formation in a model of femoral artery injury due to an external vascular cuff in IL-1Ra -/- mice [32]. The increase in intimal thickness in the Il-1Ra-/- mice was 2.5-fold that in IL-1Ra+/+ mice and large accumulations of inflammatory mononuclear cells were found in the adventitia of the IL-1Ra-/- mice. These results indicate that IL-1Ra inhibited neointimal hyperplasia.

(3) IL-1RI

Another model that we will consider is the unilateral common carotid artery ligation model. A ligated common carotid artery has a low shear stress, which results in remodeling and neointimal hyperplasia [33]. In this model, TNFα and IL-1α mRNA were upregulated in the common carotid artery ligated on one side and the IL-1RI-/- mice showed a greater decrease in neointimal area than the WT control. These results indicate that the IL-1 system plays an important role in neointimal formation.

EFFECTS OF IL-1 SYSTEMS ON ATHEROSCLEROSIS IN ANIMAL MODELS

We studied the effect of IL-1 on the formation of more advanced atherosclerotic lesions in addition to neointimal hyperplasia in various mouse models (Table 2).

(1) IL-1β

A deficiency of IL-1β reduced foam cell lesions in ApoE-/- mice by approximately 30% over the number counted in control mice [34]. Further, the mRNA levels of VCAM-1 and MCP-1 in the aorta of IL-1β-/-ApoE-/- mice decreased by more than those in IL-1β+/+ApoE-/- mice. These results indicate that IL-1β has an atherogenic action by which the expression of VCAM-1 and MCP-1 in the aorta is enhanced, leading to an increase in the recruitment of monocytes and macrophages into the intima.

(2) IL-1Ra

The systemic treatment of ApoE-/- mice with IL-1Ra was seen to decrease the size of foam cell lesions [35]. Such treatment resulted in an IL-1Ra plasma level of 1-2 μg/mL and did not interfere with lipid metabolism. Furthermore, despite differences in the size of the lesions and lesion cellular composition , macrophages and SMCs appeared to be similar to those of the control mice.

Devlin *et al.* examined the role of IL-1Ra in atherosclerosis using IL-1Ra knockout and transgenic (Tg) mice [36]. An IL-1Ra deficiency tended to induce an increase in the size of foam cell lesions while IL-1Ra over-expression decreased lesion size. Interestingly, IL-1Ra only modified the atherosclerotic lesions when the mice were fed a cholate-containing diet. Since the presence of cholate in the diet increases inflammation and fibrosis [37], IL-1Ra might play an important role in modifying the state of chronic inflammation in the vessel walls.

We studied the effects of IL-1Ra on atherogenesis in ApoE-/- through the use of IL-1Ra-/- mice [38]. In our study, the body weight of IL-1Ra-/-ApoE-/- mice was significantly less than that of either IL-1Ra+/+ApoE-/- or IL-1Ra+/-ApoE-/- mice. Furthermore, though total cholesterol levels were elevated, HDL-cholesterol levels were lower in the IL-1Ra-/-ApoE-/- mice than in either the IL-1Ra+/+ApoE-/- or IL-1Ra+/-ApoE-/- mice. We therefore compared the atherosclerotic lesions between IL-1Ra+/+ApoE-/- and IL-1Ra+/-ApoE-/- mice finding that the IL-1Ra serum levels in the IL-1Ra+/-ApoE-/- mice (about 160pg/mL) were approximately half of those in the IL-1Ra+/+ApoE-/- mice (about 320pg/mL). At 16 weeks of age, the atherosclerotic lesions had increased more in the IL-1Ra+/-ApoE-/- mice than in the IL-1Ra+/+ApoE-/- mice. However, at 32 weeks, the size of the lesions in the IL-1Ra+/-ApoE-/- mice was similar to that in the IL-1Ra+/+ApoE-/- mice, though the cellular compositions of the plaque were completely different. The lesions in the IL-1Ra+/-ApoE-/- mice contained a larger number of macro-phages but less SMCs than those in the IL-1Ra+/+ApoE-/- mice. These results suggest that IL-1Ra has little effect on the suppression of atherosclerotic plaque size but it does modulate plaque composition during the progression of atherosclerosis. Macrophage richness is a characteristic feature of unstable plaque and this suggests that IL-1Ra plays an important role in plaque stability. It also suggests that IL-1Ra could be a useful drug for the treatment of unstable angina.

(3) IL-1RI

The above observations suggest that the IL-1 system works as a modifier of inflammation induced by hypercholesterolemia or a high fat/cholesterol/cholate diet. Current epidemiological data suggest that dental infections (periodontitis) trigger or potentiate atherosclerosis. This may be due to the systemic consequences of infection or the effect of direct vascular invasion by microorganisms. It was recently

Table 2. Effect of IL-1 System on Atherosclerosis in Animal Models

Animal model	Diet	Age	Methods	Lesion area	Changes	Plaque composition	Possible mechanisms	Ref.
IL-1β-/- ApoE-/-	normal	4W-24W		↓	-30%		MCP-1↓ VCAM-1↓	34
ApoE-/-	16%fat 1.16%chol 0.5%cholate	8W-12W	IL-1Ra systemic	↓	-60%			35
IL-1Ra-/- C57BL6/J	15%fat 1.25%chol 0.5%cholate	4W-16W		↑	+300%			36
IL-1RaTg LDLR-/-	21%fat 0.15%chol	4W-16W		→	–			36
	15%fat 1.25%chol 0.5%cholate	4W-16W		↓	-40%			36
IL-1Ra+/- ApoE-/-	normal	4W-16W		↑	+180%		MCP-1↑ IL-1β↑ ICAM↑ VCAM↑	38
		4W-32W		→	unstable plaque↑	SMC↓ Mφ↑		38
IL-1RI-/- ApoE+/-	15%fat 1.25%chol 0.5%cholate	4w-34W		↓	-80%			40
		4w-34W	10W bacterial exposure	↓	-93%			40
	normal	4w-34W		↓	-80%			40
Myd88-/- C57BL6/J	21%fat 0.15%chol no cholate	8W-16W			M: -65% F: -40%	collagen (M)↓ (I)→ SMC→ Mφ↓	MCP-1↓ Gro-1↓ MIP-1β,2↓	41

reported that infection by P. gingivalis, a putative periodontal pathogen, accelerates atherosclerosis in heterozygous ApoE-deficient mice [39]. Further, the complete absence of IL-1RI was observed to markedly reduce the progression of atherosclerosis in ApoE-/-mice subjected to a high fat/cholate diet and P gingivalis injections [40]. The severity of atherosclerosis was less in IL-1RI-/-ApoE+/- mice than it was in IL-1RI+/-ApoE+/- mice, regardless of whether mice were fed normal chow or a high fat/cholate diet, and irrespective of whether they were inoculated with P gingivalis or not. It is notable that the observed rates of reduction of atherosclerosis differed between IL-1β-/- mice and IL-1RI-/- mice, suggesting that IL-1α also plays an important role in the development of atherosclerosis.

The above results confirmed the crucial role of IL-1 in the inflammatory cascade involved in the progression of atherosclerosis and suggest that both bacteria and diet mediate the response through an IL-1 signaling pathway.

(4) MyD88

After IL-1 binds to IL-1R, IL-1R and IL-1RacP form a signaling complex that recruits MyD88. MyD88 transduces the cell signaling events downstream of IL-1R as well as TLRs. MyD88 is essential for the signaling and biological activity of IL-1 and it may also be involved in atherogenesis.

MyD88-/-ApoE-/- mice had 40-65% less atherosclerosis than their ApoE-/- counterparts [41]. The diminished atherosclerosis in the Myd88-/- mice was associated with a smaller number of macrophages in the arterial wall than in the control mice. This effect can be attributed to a decline in the expression of such arterial chemokines as MCP-1 and decreased macrophage recruitment for the arterial intima. It is notable that IL-1β, but not IL-18, induced MyD88-dependent MCP-1 protein secretion by bone marrow-derived macrophages, while TNF-α induced similar levels of MCP-1 in the wild –type and MyD88-/- cells. These findings suggest that the IL-1-IL-1R- MyD88 signal pathway may play an important role in the progression of atherosclerosis.

TARGETING IL-1 IN VASCULAR DISEASE

Modulation of cytokine activity is a new therapeutic strategy for various chronic inflammatory diseases. In this regard, blocking of TNFα activity is widely used in the treatment of rheumatoid arthritis (RA) and has been very effective. Recently, IL-1 receptor antagonist (anakinra) has been approved for the treatment of patients with RA, though

treatment with this agent has been not as effective as blocking TNFα. However, the safety of an IL-1 blockade by anakinra is well established and opportunistic infections are much less of a problem than in the case of TNFα blockade. In fact, there have been no reports of opportunistic infections in long-term anakinra use in RA patients. This attests to the safety of the long-term blocking of IL-1 activity [42].

Several different strategies are available for reducing IL-1 activity: (1) production and secretion, (2) circulating IL-1, (3) receptor binding, and (4) intracellular signaling.

(1) Blocking IL-1 Procession and Secretion

IL-1 is highly inflammatory cytokine and its production is tightly regulated. For instance, monocytes do not release IL-1β without stimulation. Though monocytes start to synthesize the IL-1β precursor upon stimulation, less than 50% of the total IL-1β precursor amount is cleaved into mature IL-1β by capase-1 and released into the extracellular space. The processing and secretion of the IL-1β precursor are coupled together (IL-1β inflammasome) and the regulation of caspase-1 activity is important for IL-1β secretion from cells [43]. Thus, inhibitors of caspase-1 will prevent the processing of the IL-1β precursor into the active cytokine and thereby reduce its secretion. Recently, an orally-active caspase-1 inhibitor has been developed [44] and shown to be effective in protecting against cartilage destruction in an animal model [45] as well as in blocking a hypersensitive response in monocytes from familial cold autoinflammatory syndrome patients [46]. Further, human vascular smooth muscle cells have been observed to express an endogenous caspase-1 inhibitor and a serine proteinase inhibitor (serpin) PI-9 [47]. In this study, PI-9 expression was abundant in the unaffected artery but was reduced in atherosclerotic lesions which showed an increase in IL-1β expression. These observations suggest that a caspase-1 inhibitor would be a very attractive strategy for preventing inflammation in the vessel wall and atherosclerosis. However, the actual effect of a caspase-1 inhibitor on occlusive arterial diseases has not been reported on yet.

(2) Neutralization of Circulating IL-1

Since body fluid cytokine levels are relatively low in most autoimmune diseases, cytokine neutralization is easily and rapidly accomplished. There are several methods for neutralizing circulating cytokines, one of them the use of anti-cytokine monoclonal antibodies. Soluble cytokine receptors are another means of blocking circulating cytokines but the effectiveness of this approach for IL-1 is limited, because of the two components of the IL-1 receptor system. Recently, an innovatory method of binding cytokines with high affinity has been developed, using what are known as cytokine traps [48].

The cytokine trap consist of the Fc portion of human IgG1 and the extracellular domains of two distinct receptor components fused together. In complex multi-component receptor systems such as IL-1, the cytokine binds with low affinity to the first receptor component and then recruits a second receptor component. The component formed from these two receptors binds the cytokine with higher affinity than does either of the isolated receptor components individually. The IL-1 trap consists of the extracellular domain of IL-1 AcP and IL-1RI arranged in line and then fused to the Fc portion of human IgG1. The IL-1 trap binds IL-1β more tightly than IL-1Ra and IL-1RI and is about 30 times more potent in blocking IL-1β than IL-1Ra and 250-500 times more potent than soluble IL-1RI in this respect. The administration of an IL-1 trap to RA patients was well tolerated and pharmacokinetic analysis indicated a plasma half-life of 7.5 days. This suggests that a once per week dosing interval is appropriate for an IL-1 trap and that it is acceptable for clinical use. However, there have been no reports of an IL-1 trap preventing the progression of neointimal hyperplasia and atherosclerosis in animal models.

(3) Blocking of Receptor Binding

IL-1Ra is a natural IL-1 inhibitor. It binds to the IL-1 receptor with high affinity and competitively blocks the binding of IL-1 to its receptor. It is reasonable to use IL-1Ra for anti-IL-1 therapy and in fact, the recombinant IL-1Ra preparation, anakinra, has reduced the severity of RA in patients. However, IL-1Ra has several weak points. First, to achieve 50% inhibition of IL-1, the amount of IL-1Ra required is about 100 times that of IL-1 [49]. Second, IL-1Ra is rapidly excreted by the kidneys and the plasma half-life is relatively short (4-6 hr). Third, IL-1 receptors are expressed on all cells except red blood cells and generated every day, necessitating the administration of large daily amounts of IL-1Ra. For instance, a plasma level of IL-1Ra of more than 5 μg/mL over 24 hr was required to relieve arthritis symptoms in a collagen-induced arthritis model [50]. On the other hand, a plasma level of 2 μg/mL decreased atherosclerosis in ApoE-/- mice when the IL-1Ra was systemically administered. These results indicate that atherosclerosis is more susceptible to the effect of IL-1Ra than RA.

We previously reported that IL-1Ra might modulate plaque stability in IL-1Ra+/-ApoE-/- mice. Further, widespread coronary inflammation and multiple atherosclerotic plaque rupture were recently detected in acute coronary syndrome [51,52]. These findings indicate that the coronary artery overall (and also other systemic vessels) needs to be treated and stabilized. In view of this, the administration of IL-1Ra could be an effective treatment for acute coronary syndrome.

(4) Blocking of Intracellular Signaling

IL-1 signaling is also tightly regulated. IL-1-stimulated cells express several molecules which negatively regulate IL-1signaling such as ST2, MYD88s, and IRAK-M. ST2 is a member of the TIR family and possesses extracellular immunoglobulin domains (TIR I). In this regard, normal peritoneal macrophages from mice expressed little detectable surface ST2, though ST2 was clearly detected at 4 hr after LPS stimulation and was sustained for at least 48 hr following the stimulation. Macrophages from ST2-deficient mice were seen to produce large amounts of IL-6 and TNF-alpha in response to IL-1, suggesting that ST2 is a negative regulator of IL-1R signaling. The inhibitory effect of ST2 on IL-1R signaling is due to sequestration of the adaptor MyD88. MyD88s (splice variant of MyD88) and IRAK-M is induced after treatment of monocytes with LPS [16,53,54]. Myd88s and IRAK-M work as natural inhibitors of MyD88

and IRAK and shut down the signaling of IL-1R. These molecules may therefore be potential therapeutic targets for reducing IL-1 activity.

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心膜疾患，腫瘍

1

心膜炎

荒川　宏・大鈴文孝

心膜は心臓と大血管を密に包む臓側心膜と壁側心膜からなる折り返しのある嚢状の形態を呈し，上方は大血管の外膜と気管支筋膜に連なる．心筋側は1層の中肺葉由来の内皮細胞からなり，大血管へ数センチ移行した部位から反転し壁側心膜になる．壁側心膜は厚さ約2 mm程度で，細胞成分に乏しくコラーゲン線維や弾性線維が主成分で，心臓の大部分を覆っている．この2層の膜に包まれた心膜腔には約35～50 mLの心膜液を含んでいる．壁側心膜は胸腔と結合することで胸腔内での心臓の位置を一定に保っている．心膜には機械的，化学的受容体を含む神経が発達している[1]．

急性心膜炎は心膜の炎症性疾患であるが，その際に心膜液貯留を呈することがある．原因は**表1**に示すように多種多様であるが，臨床症状と検査所見から診断される．原因検索に際し感染性と非感染性に分けて鑑別診断を行う．一般病院では特発性や悪性腫瘍によるものが多く，高度先進医療を行っている病院では悪性疾患の治療に合併する感染症や放射線治療後に生じるものが多い[2]．実際にはウイルス抗体価の測定が十分行われていないこともあって，特発性と診断されるものの中にはウイルス性心膜炎が多く含まれている可能性がある．

I　急性心膜炎

■治療のための診断と検査

1 症　状

通常胸痛を主訴とし，原疾患となる症状，例えば感染症が原因であれば先行する発熱など感染症状を伴う．胸痛は前胸部の鋭く激しい痛みで，呼吸，体動で増悪する（通常前傾座位で軽減，仰臥位で増悪）．痛みは左肩・背部に放散するが，時には無痛性のこともある．

表1　心膜炎の原因

1．特発性
2．感染性
　ウイルス性（エコーウイルス，コクサッキーA・Bウイルス，アデノウイルス，サイトメガロウイルス，HIVなど）
　細菌性（肺炎球菌，ブドウ球菌，連鎖球菌，大腸菌，サルモネラ，マイコプラズマ，インフルエンザ菌など）
　結核
　真菌
　リッケチア
　ライム病
3．非感染性
　腫瘍性
　　二次性（肺癌，乳癌，ホジキン，悪性リンパ腫，白血病など）
　　原発性（中皮腫，肉腫など）
　自己免疫疾患（関節リウマチ，SLE，強皮症など）
　急性心筋梗塞（急性期）
　心筋梗塞後症候群（Dressler症候群），心膜切開後症候群
　薬剤性（procainamide，isoniazid，hydralazine，penicillin，ciclosporineなど）
　放射線被曝
　外傷
　尿毒症・人工血液透析
　その他
　　粘液水腫
　　アミロイドーシス
　　サルコイドーシス

（文献1，2より引用改変）

2 身体所見

通常心膜摩擦音が聴取され，診断上重要な所見である．これは臓側および壁側心膜の接触で生じ，典型的には圧雪するときの音に似ている[1]．心膜摩擦音は前収縮期，収縮期，拡張早期の三相からなる．

3 心電図

心電図所見は診断上重要でaV_R，V_1を除く全誘導でST segmentが上昇する（**図1**）．ST segmentの上昇は特徴的で上に凹の上昇をみる．数日から

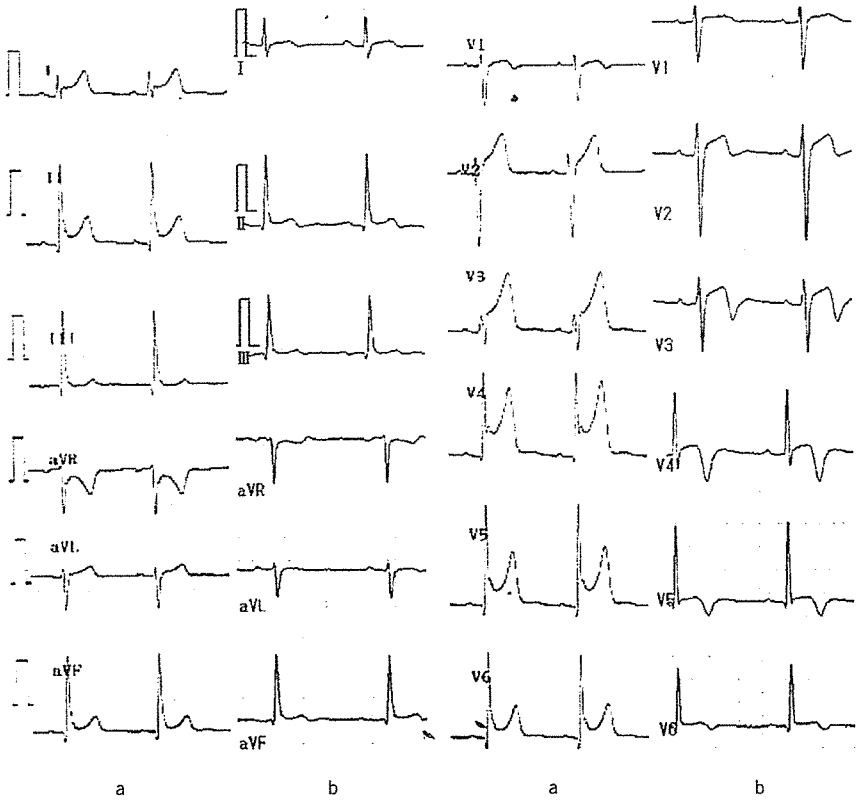

図 1　急性心膜炎の心電図

17歳，男性．急性心膜炎発症第1病日の心電図 (a)，aVR を除くほぼ全誘導で ST 上昇を認める．第9病日には ST は低下傾向を示し V_3-V_5誘導では陰性 T 波を認めた (b)．NSAID の対処療法で軽快した．

数週間で ST segment 上昇は基線に戻り，その後陰性 T 波は数週間から数ヵ月間持続する．PR segment の低下は ST segment の上昇がなくてもみられ，急性心膜炎に特異的であるが，しかし頻度は低い[3]．QRS voltage が低いときには心膜液貯留を疑う．

4 胸部 X 線写真

合併症がなければ特有の所見はみられない．多量の心膜液が貯留すれば心陰影の拡大，心筋炎を伴えば肺うっ血，また原因となる肺炎，肺結核や悪性疾患があれば随伴所見として観察される．

5 心エコー図

特発性急性心膜炎では心エコー所見は正常である．場合によっては少量の心膜液を観察できることがあり，悪性疾患などが原因であれば大量の心膜液が貯留する．心筋炎を伴うと心機能の低下がみられ，心筋梗塞に伴う場合は局所壁運動の低下がみられる．

6 血液検査

特発性急性心膜炎では炎症所見としてのリンパ球主体の白血球増加，血沈の亢進がみられる．CK-MB やトロポニン T の上昇は心筋炎の合併を示唆する．

細菌性心膜炎では急激な経過をたどることが多い．左方移動を伴う好中球増加がみられ，心膜液ではグルコースの低下，蛋白，LDH の上昇がみられ，心膜液からの細菌培養が診断に役立つ．

HIV ウイルスによる心膜炎は HIV ウイルス患者の約 20%にみられ，多くは無症候性であるという[1]．HIV 患者では HIV 以外に心膜炎の原因とし

て合併する結核，マイコバクテリア，サイトメガロウイルス，リンパ腫，Kaposi 肉腫なども原因となり多種多様である．

結核による心膜炎では心膜液からスメアにより結核菌が検出されることはまれで，培養に出しても結核菌が検出される確立は低い．心膜生検からの病理所見が診断確率を上げる．心膜生検の PCR は培養より早く結果が分かるので診断に有用である．しかしエビデンスに基づいた心膜生検の適応は確立されていない．皮内テストの強陽性，心膜液中のアデノシンデアミナーゼの高値（＞40 μ/L）は感度，特異度が高い[4]．

転移性・原発性腫瘍による心膜炎では心膜液中の細胞診に診断価値がある．

膠原病に伴う場合は関節リウマチの病勢に一致して心膜炎が起き，心膜液中の低グルコース，好中球の増加，リウマチ因子の増加，補体価の低下がみられる．SLE では心膜炎は診断基準の項目の一つであり，心膜液検査所見では高蛋白，低グルコース，白血球の増加がみられる．

■治療の一般方針

特発性急性心膜炎は比較的予後はよい．安静と aspirin（1～4.5 g/日），indomethacin（50～75 mg/日）や ibuprofen（600 mg/日）などの非ステロイド抗炎症薬（NSAID）が用いられる．胸痛がなくなるまで服薬を続け，通常 1～3 週間程度で治癒する．特発性急性心膜炎はあくまでも除外診断であるので，初期治療に反応せず，多量の心膜液が貯留する場合は他の原因を精査すべきである．

NSAID で十分鎮痛効果が得られない場合は副腎皮質ステロイドを使用する．副腎皮質ステロイドの効果が出るまで鎮痛目的で麻薬を使用する場合もある．通常 prednisolone 60 mg/日を 2 日間服用させ，以後約 1～2 週間かけて漸減させる．

colchicine は NSAID に反応しない症例や再発性心膜炎に対し使用され有効であるとの報告があるので試してみるべき治療法である．2～3 mg/日のローディングを行った後 1 mg/日を服用させることを推奨している報告もあるが[5]，2 mg/日以上服用させると下痢などの副作用で継続困難となるので 0.5～1 mg/日程度を服用させることが好ましい．また催奇性があるので服用中は女性のみならず男性も避妊に心がける必要がある．いずれにしても特発性急性心膜炎に対する確立した治療ガイドラインはない．

合併症として心膜液貯留がみられるが通常心タンポナーデになるほどの大量貯留することはまれであるので，大量に貯留する場合は特発性以外の原因を検索する必要がある．タンポナーデになる場合は心膜液ドレナージが必要となる．

原因疾患が明らかな場合は原疾患に対する治療を行う．

膠原病の中で関節リウマチによる心膜炎は NSAID によく反応する．SLE による場合は副腎皮質ステロイドでコントロールできるが再発する場合は免疫抑制薬を用いる．

尿毒症のような腎不全末期での心膜炎は BUN やクレアチニンレベルが高いほどみられ，胸痛はあっても軽度か，無症候性心膜液貯留で初めて診断されることもある．透析開始後にみられる心膜炎では胸痛・発熱・呼吸困難・白血球増多などの症状がみられる．鎮痛目的には NSAID を使用するが，いずれも透析により大部分は改善する．心タンポナーデに陥れば心膜液ドレナージや心膜開窓術が必要となる．

細菌性心膜炎では感受性のある抗菌薬を使用する．結核性心膜炎では isoniazid，streptomycin，rifampicin を併用するが，副腎皮質ステロイドの使用については確定した見解がない．

心筋梗塞急性期に心膜炎をみることがあるが，心筋梗塞後 1 週間目から数ヵ月の間で発症する心膜炎は心筋梗塞後症候群（Dressler syndrome）と呼ばれ，発症に自己免疫学的機序の関与が疑われている．心膜液貯留をみるがタンポナーデになることはまれである．心筋梗塞急性期の心膜炎では NSAID やステロイドは創傷治癒を遅らせたり，心筋の壁厚が減少し心筋破裂の頻度が増したりするので，できるだけ使用は避けるべきである．使用する場合 aspirin 少量療法が望ましい．心筋梗塞後症候群では aspirin や NSAID，ステロイドが極めて有効である．

悪性疾患による心膜液貯留ではしばしば心タンポナーデを起こすことがある．心膜液ドレナージ

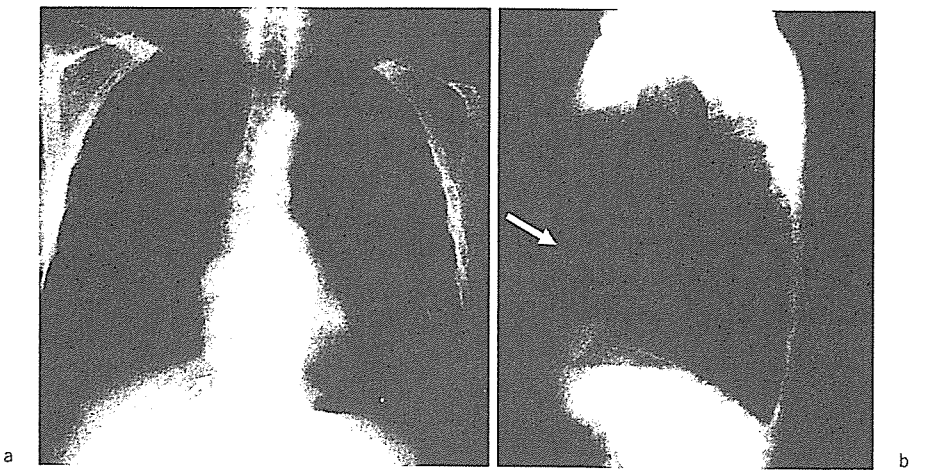

図 2　心膜石灰化の胸部 X 線写真
a：正面像，b：側面像．心膜石灰化（矢印）を認めるが，収縮性心膜炎には陥っていない．

後も心膜液が再貯留することがあり，心膜腔内にテトラサイクリンや抗悪性腫瘍薬を注入し心膜癒着術を行うことがある．それでも貯留する場合は心膜開窓術を行う．

II　慢性収縮性心膜炎

心膜の線維性肥厚・癒着が高度に生じ，心腔が十分拡張できないため，心腔内の充満が制限される状態ある．したがって左右心房心室の拡張期圧が上昇して等圧となる．心房の圧は上昇し拡張早期の心室充満は異常に速くなる一方で，拡張中期からの心室内への充満が硬くなった心膜により抑制されるので心室の充満は拡張早期でほぼ完了する．収縮能は通常保たれている．肥厚した心膜に遮られて呼吸による胸腔内圧の変動が心膜腔や心腔に伝達されないので，呼吸による体静脈圧や右房圧の減少がみられず，右房への静脈還流は増加しない．吸気時には胸腔内圧が減少し，この変化は肺静脈に伝わるが左房には伝達されない．その結果肺静脈と左房の圧較差は減少するので左心系の充満が減少する．左心系の充満の減少が心室中隔の左方への変位を生じて右心系へ充満の増加をもたらす．呼気では逆の現象がみられる．一部の症例で吸気により静脈圧のさらなる上昇（Kussmaul 徴候）をみるが，慢性収縮性心膜炎に特徴的ではなく，右心不全，拘束型心筋症でもみられる[1]．

慢性収縮性心膜炎の原因として，特発性のほかに，従来結核が多かったが，最近では感染症，開心術後，放射線療法後にみられることが多い．発症までには数年かかるといわれているが開心術3〜4ヵ月後に収縮性心膜炎に陥った症例を経験しており，急性心膜炎から収縮性心膜炎に移行する場合もある．

■治療のための診断と検査

右心系のうっ血症状（肝腫脹，腹水貯留，浮腫）や低心拍出に伴う症状（全身倦怠感，易疲労性，労作時呼吸困難）が中心となる．身体所見では頸静脈怒張，Kussmaul 徴候，Friedreich 徴候（怒張している頸静脈が拡張早期に虚脱），Broadbeny 徴候（横隔膜付着付近の肋間腔の収縮期陥没），心膜ノック音（拡張早期II音の後に聴取される過剰音），心膜摩擦音，M 字または W 字型頸静脈波（上昇した右房圧による a 波増高，右室収縮中の右房圧上昇を反映した V 波増高，心房収縮後の右房圧の急激な減少による X 下降，右室拡張に伴う右房圧減少を反映した Y 下降）が観察される．

胸部 X 線写真では石灰化した心膜（図 2）がし

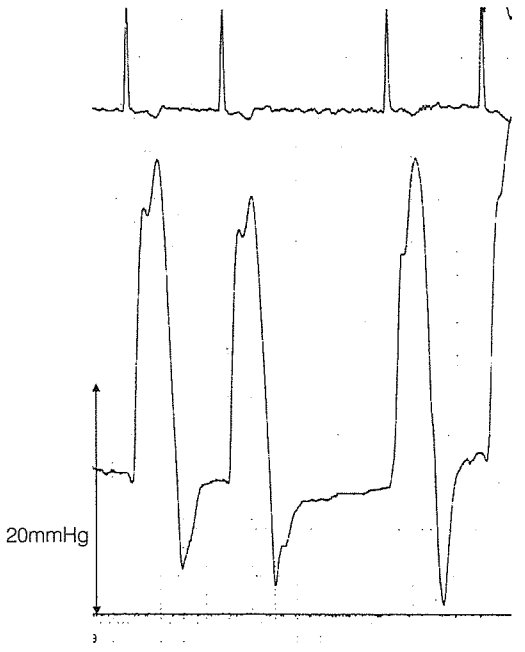

図 3 心膜切開後3ヵ月で発症した収縮性心膜炎の右心室圧
拡張期に dip and plateau を認める．左室圧は示さないが左室拡張期圧も右室拡張期圧とほぼ同じ圧を認めた．

ばしば認められるが，かならずしも収縮性心膜炎の血行動態状態を反映しているわけではない．心臓カテーテル検査では平均右房圧が上昇し，前述のMないしW字型波形が観察される．右心室拡張期圧は拡張中期からの心室内への充満が硬くなった心膜により抑制されることを反映し，dip and plateau型（図3）を呈する．右室拡張期圧は左室拡張期圧とほとんど等しくなる．心エコー図では肥厚した心膜が認められることがある．また心室の拡張早期の呼吸性左方移動（septal bounce）は収縮性心膜炎に特徴的で，肝静脈・下大静脈の拡大と呼吸性変動の減少はうっ血の所見として観察される．拘束性心筋症ではseptal baunceはみられないので鑑別に役立つ．ドプラ心エコー法では心室流入拡張早期波の減衰時間の短縮（<160 msec），左室流入拡張早期波高の（吸気で減少し呼気で増大する）呼吸性変動をみとめ右室ではその逆の変動がみられる[6]．

■治療の一般方針

慢性収縮性心膜炎の唯一の根治治療は心膜切除術である．当初，薬物治療として利尿薬や塩分制限がうっ血性心不全に対し有効であるが次第に効果が薄れてくる．収縮能は保たれているのでジギタリスのような強心薬は効果が期待できない．利尿薬を使用していると循環血液量が減少して頻脈がみられるようになるが，このとき心拍数を遅くし拡張期を長くするような薬物は避けるか，投与する際に注意を要する．

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理　論　編

エイジングによる疾患

第4章　2　動脈硬化（血管疾患）

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はじめに

超高齢化社会を迎えようとしている現代において，加齢に対する関心は高まるばかりである．死因の約60%を3大死因（悪性新生物，心疾患，脳血管疾患）が占め，うち半分を動脈硬化性疾患（心血管疾患）が占めるようになった現在，近代医学教育の礎を築いたWilliam Osler博士の「人は血管とともに老いる」という格言は，極めて示唆に富む．

動脈とは？

動脈はサイズに関わらず，内膜，中膜，外膜の3層構造から成り立ち，内膜と中膜は内弾性板により，中膜と外膜は外弾性板により隔てられる．弾性板はコラーゲン（膠原線維）やエラスチン（弾性線維）などから成り立ち動脈の弾力性や強靱さを維持している．内膜には血液と接して重要な役割を果たす血管内皮細胞があり，中膜には血管の収縮，弛緩を調節する血管平滑筋細胞がある．外膜には血管自身を栄養とする細動脈や細静脈，リンパ管，諸種の結合織細胞や神経などがある．動脈の機能的，形態的特徴は中膜にあり，弾性動脈と筋型動脈，小動脈，細動脈，毛細血管に分類される．弾性動脈は中膜の弾性板が豊富で，大動脈，それから分枝する腕頭動脈，鎖骨下動脈，総頸動脈や総腸骨動脈などがあたる．心臓の拍動に連動し，心室の収縮時には動脈壁が拡張，拡張時には収縮して血流を一定に保持するための補助ポンプとしての機能をもつ．筋性動脈には上腕動脈，大腿動脈，膝窩動脈，橈骨動脈，冠状動脈，腸間膜動脈，脳動脈などが属し，内径1.0 mm以下のものまでの広範囲にわたる．筋性動脈では中膜は平滑筋細胞から成り，血液量を調節するため動脈の直径を変えることができる．弾性動脈では壁は受動的に血圧の変動に耐え，平滑筋細胞は弾性膜の緊張度を調節するのが中心であるのに対し，筋性動脈では中膜の平滑筋細胞の収縮が血管の内径を変化させる．小動脈とは直径が1 mm以下，100 μmまでのものをいい，中膜は平滑筋細胞から構成されている．細動脈は小動脈とともに，血圧を調節する血流に対し末梢抵抗の基本的要因をつくりだすための循環上，生理学的に重要な部位であり，直径20～100 μmの太さで，中膜には1～2層の平滑筋細胞層が存在する．毛細血管では中膜に相当する平滑筋細胞は消失し外膜もみられなくなるが，内皮細胞は薄く内径はあまり変化せずに枝分かれして広範な血管網をつくる．毛細血管は様々な物質やガスが通り抜けるところである．

動脈硬化とは？

動脈硬化には，粥状硬化，細動脈硬化，メンケベルグ型動脈硬化の3つのタイプがある．細動脈硬化は，主に細動脈壁の内膜と中膜が傷害される．細動脈の壁が厚くなり，内腔が狭くなると，細動脈が血液を供給している器官は，十分な量の血液を得られなくなり，臓器障害が生じる．この細動脈の障害は，主に高血圧や糖尿病の患者に多くみられる（網膜症，腎症など）．メンケベルグ型動脈硬化は，細動脈以上

の動脈に生じる．動脈壁内へのカルシウムの蓄積が動脈壁を硬化させるが，内腔は狭くならず，50歳以上の男女に普通に認められる．粥状硬化は最も多いタイプの動脈硬化で，単に動脈硬化というとこのタイプを指すことが多い．この章で述べる動脈硬化もこれにあたる．粥状硬化はatherosclerosisであり，内膜に起こる粥腫形成atherosisと中膜を中心に起こる壁硬化sclerosisの両者を意味している[1]．内膜の変化（後述）はplaque ruptureをきっかけに急性冠症候群などを発症させるため注目されている．一方，中膜に生じる変化は動脈壁の硬化あるいは動脈コンプライアンス低下として認められるが，この動脈コンプライアンス低下も血行動態あるいは粥状硬化の進行に様々に影響するため臨床的に重要である．これら内膜の変化，中膜の変化は独立して存在するのではなく，粥状硬化病変の2つの要素として共存する．この粥状硬化については従来の臨床医学的アプローチとともに，最近は分子生物学的なアプローチも盛んに行われている．

臨床医学的アプローチ

1 粥状硬化のエイジングプロセス

粥状硬化は冠動脈や脳動脈などの比較的太い動脈に好発し，心筋梗塞，脳梗塞，大動脈瘤などの原因となる．10歳代の冠動脈では，偏心性の内膜肥厚を認めるが，これは生理的な適応肥厚と考えられている．さらに20歳頃にはコレステロールが内皮下に蓄積し，泡沫細胞とよばれるコレステリルエステルを貯留したマクロファージの集積が認められる．これを脂肪線条（fatty streak）という（Ⅰ-Ⅱ型）．30歳頃には泡沫細胞に加えて細胞外脂質（粥腫，atheroma）の貯留が認められる（Ⅲ-Ⅳ型）．壮年期以降になると線維性肥厚が始まる（Ⅴ型）．細胞外脂質貯留（lipid core）に線維化を伴うものをⅤa型（fibroatheroma），石灰化が強いものをⅤb型（calcific lesion），細胞外脂質貯留が軽微なものをⅤc型（fibrotic lesion）という．最終的に病変は亀裂，破裂，血腫，出血，血栓が合併し，脳梗塞や心筋梗塞などの心血管疾患の原因となる（Ⅵ型）．このうち，内膜が潰瘍などで欠損したものをⅥa型（surface defect），血腫・出血があるものをⅥb型（hematoma・hemorrage），血栓性のものをⅥc型（thrombus）と細分類している（図1）[2]．以上の粥状硬化の進行過程は年余の経過をたどり進行し，冠動脈危険因子がその進行速度を修飾する．その他ライフスタイルや遺伝的要素などの影響を受けるため，動脈のエイジングは個体差が非常に大きく，暦年齢とは一致しない．

2 エイジングによる動脈の構造的リモデリング

エイジングに伴う動脈の変化は拡張と壁の肥厚を主体とし，組織学的には内膜の過形成，中膜エラスチンの層構造の破壊，コラーゲンや間質基質の増生を含んだ肥厚からなり，しばしば石灰化を伴う．エイジングによって中膜のエラスチンはエラスターゼなどで分解され，反対に細胞外マトリックスは産生増加する．慢性的にエラスチン分解と細胞外マトリックスの増加の繰り返しという複雑な過程を経て，30歳頃には中膜のエラスチンが断裂・変成して石灰沈着が認められるようになる．50歳を過ぎると中膜平滑筋細胞は萎縮・減少し，石灰化は進行し血管壁はさらに硬化していく．その結果，末梢血管抵抗が高くなり，収縮期血圧の上昇，拡張期血圧の低下，脈圧の拡大を認めるようになる．若い頃は血管腔に強い圧がかかっても元の周径に戻れた血管も，エイジングにより弾性力がなくなり周径は徐々に拡張していく．このような動脈壁は圧に対して脆弱となり，大動脈瘤や大動脈解離などの重篤な疾患の原因となる．数々の臨床試験の結果からエイジングと弾性動脈の肥厚，拡張に関係があることが実際に示されている．そのなかでも頸動脈の内膜中膜複合体（intima-media thickness：IMT）は心血管疾患のリスクとして注目されている（図2）[3]．

3 エイジングによる血管の機能的変化

エイジングによる動脈壁の肥厚とエラスチンに代わ