Table 2 Summary of plasma OPN levels

Disease	Origin	Changes in OPN levels	(Reference)Year
Framingham Offspring	Plasma	Age-adjusted means 729 ng/mL in men 658 ng/mL In women Increase with age	[46] 2006
Ant AMI	Plasma	At admission (420 ± 195 ng/mL) On day 2 (935 ± 464 ng/mL) Maximum around day 3 (1139 ± 482 ng/mL)	[43] 2005
CHF	Plasma CD4+ T cells	CHF vs. control (800 ± 554 ng/mL, 575 ± 229) T cells (27.3 ± 12.2, 16.7 ± 10.0)	[40] 2007
End stage of CHF	Plasma	Before and after VAD (217.4 ± 148.4 ng/mL, 412.5 ± 146.4 ng/mL) Before and after total artificial heart (TAH) (330.6 ± 151.7 ng/mL, 434.5 ± 135.2 ng/mL)	[41] 2008
CHF	Plasma	CRT responders (108 ± 47 vs. 84 ± 37ng/mL) Nonresponder (79 ± 58 vs. 115 ± 63 ng/mL)	[48] 2010
CAD	Plasma	With statins (80.57 ± 14.2) Without statins (93.47 ± 33.5 ng/mL)	[45] 2010
Stable IHD	Plasma	Median OPN (55 ng mL) Increase with age	[47] 2010

patients with cardiac dysfunction and heart failure [41]. Tamura et al. reported that plasma OPN concentrations of MI patients were significantly higher in the coronary sinus than in the aortic root and the transcardiac gradient of plasma OPN concentration correlated negatively with left ventricular ejection fraction (LVEF) and positively with LV end-diastolic and end-systolic volume indexes [42]. Suezawa reported the sequential change of plasma OPN from patients who underwent successful reperfusion after anterior-wall acute MI, which began to increase on day 2, reached a maximum around day 3, and then decreased on day 14 [43]. Plasma OPN levels may be useful in diagnosing the severity of not only ischemic heart disease, and heart failure but also arteriosclerosis [44–47]. However, there are some problems associated with measurement of plasma OPN levels. Table 2 summarizes the levels of plasma OPN. First, the source of secreting plasma OPN is not clear and plasma OPN levels are variable in each disease state. Second, since the mechanism of OPN solublization is not determined, the relationship between organs or cells and the plasma level is not clear. Third, OPN is derived from many organs, the molecular weights of which vary depending on the level of phosphorylation of OPN in the blood, and the plasma OPN level recognized by specific antibodies may also vary significantly among recognition sites and types of antibodies. For example, an antibody that recognizes the entire structure of OPN may indicate a different one from that indicated by an antibody that recognizes only the N- or C-terminus. In short, plasma OPN levels vary in each patient and an increase in the plasma OPN level may not always correspond to a local increase in OPN production. Are cardiac levels or plasma levels correlated to LV dysfunction and dimension, and how did it correlate? Although the plasma level of OPN is a biomarker to know the repair process of the injured myocardium, further studies would be needed to clarify the origin and the role of plasma OPN.

It is likely that myocardial OPN expression increases concomitantly with systolic and diastolic dysfunction in the remodeled heart. OPN has the potential to modulate different phases of injury healing and myocardial remodeling. Genetically engineered mouse studies provide evidence that increased expression of OPN may play a protective role against LV dilation after MI. However, in the infarct remodeling stage, OPN may exacerbate unfavorable fibrosis. Mineral-corticoid receptor antagonists inhibit OPN expression within the heart. CRT-induced LV reverse remodeling is reflected by changes in plasma OPN [48]. However, many questions would be raised. What is the mechanism and role of cleaved fragments of OPN in the heart? How does increased expression of OPN lead to cardiac remodeling resulting in cardiac dysfunction and heart failure? Suppressed inflammatory response and reduced response of fibroblasts could be due to decreased OPN expression in the heart? [49] What is balanced OPN expression according to the disease cause and stage? Future studies would be needed to clarify the role and the therapeutic potential of OPN in cardiac fibrosis and remodeling process.

Tenascin-C

Tenascins are a family of four multimeric ECM glycoproteins, each with distinct features; they are named TN-C, X, R, and W [50]. TN-C, found to be the first member of the family, is a typical matricellular protein, specifically expressed during the development as well as in wound healing and cancer invasion in various tissues, and may regulate cell behavior and matrix organization during tissue remodeling [51,52].

Structure and Function of TN-C

TN-C is a huge ECM molecule of about 300 kDa as an intact monomer and assembled to a hexamer. The multidomain molecule consists of an N-terminal assembly domain, followed

by EGF-like repeats, constant and alternatively spliced fibronectin type III repeats, and a C-terminal fibrinogen-like globular domain, and each subdomain has a distinct function. Several receptors including integrins, $\alpha 2\beta 1$, $\alpha 8\beta 1$, $\alpha 9\beta 1$, $\alpha v\beta 3$, $\alpha 7\beta 1$, $\alpha v\beta 6$, EGFR, Annexin II, syndecan-4 (see Refs. 52 and 53 for review) bind to the respective domains of TN-C and transmit multiple signals that could trigger various cellular functions. *In vitro* studies have demonstrated that TN-C may control the balance of cell adhesion and de-adhesion, modulate cell motility, proliferation, and differentiation and survival, although cell-type specificity is apparent, possibly using separate receptors depending on the cell [51,52]. In addition to its spatiotemporal-restricted expression, the diverse effects on culture cells have suggested that TN-C would play a significant role in tissue remodeling. However, unexpectedly, TN-C knockout (TN-C KO) mice generated independently by two different groups underwent normal development and have a normal life span and fertility, showing no distinct morphological phenotypes [54,55]. Recently more detailed investigations have shown several differences, for example, decreased bronchial branching and enlarged airspaces in lung development of mice [56], and epithelial cell clusters protruding into the ductal lumens in the prostate TN-C KO [57]. Furthermore, in various disease models, evident distinction in TN-C KO have been reported, such as attenuated fibrotic change in immune-mediated hepatitis [58], allergic inflammation in bronchial asthma [59] and arthritis [60], and reduced neointimal hyperplasia after vascular surgery [61,62].

Physiological and Pathological Significance of TN-C in the Heart

In the heart, TN-C transiently appears during the very early stage of development, often associated with cell migration and epithelial-mesenchymal/mesenchymal transformation, at several important steps such as differentiation of precardiac mesodermal cells to cardiomyocytes [63]. It is also noteworthy that TN-C might be involved in maturation of coronary arteries by enhancing recruitment of mural cells to vascular wall [64].

In the normal adult heart, TN-C is barely detected at the chorda tendinae of papillary muscles and base of valve leaflets, which are constantly subjected to mechanical loading [65]. However, TN-C reappears under various pathologic conditions such as acute MI [66–69], myocarditis [70–72], hibernating myocardium [73], ischemia-reperfusion [74], hypertensive cardiac fibrosis [75], and some cases of DCM [76,77] closely associated with tissue injury and active inflammation. During myocardial tissue remodeling, interstitial fibroblasts in the vicinity of the injured cardiomyocytes are the major source of TN-C, but cardiomyocytes themselves do not synthesize TN-C [78]. Various factors including proinflammatory cytokines and growth factors, such as TGF-β, PDGF, bFGF, IL-1β, AII, hypoxia, ROS, acidosis, and mechanical stretch, increase the synthesis of TN-C by cardiac fibroblasts *in vitro* [65,75], which suggests that TN-C may be involved in ventricular remodeling of the heart with inflammation, and in ischemia, reperfusion, and hypertension. During tissue repair after MI, TN-C molecule is expressed at the acute stage. It appears within 24 h after permanent ligation of coronary arteries of experimental animals, peaks at day 5, then becomes downregulated by day 7, exclusively localizing at the border zone between the infarcted lesion and intact myocardium [67,78,79]. Since the edge of the residual myocardium is the most active site of tissue remodeling, this characteristic localization suggests its particular role in myocardial tissue repair. As a matricellular protein, TN-C has been well known as a "de-adhesion" protein. As we have previously reported, TN-C may loosen strong adhesion of cardiomyocytes to ECM and tentatively attaches the cells, similar to a "Post-it" note [65,67]. Furthermore, TN-C has the ability to upregulate the expression and activity of MMPs [41]. These functions release surviving cardiomyocytes from their rigid linkage to surrounding connective tissue and thus help cells to reorganize their shape and arrangement at the edges of residual myocardium during tissue healing after infarction. On the other hand, TN-C may keep attachment of the cardiomyocyte during repeated cycles of contraction and relaxation, and protect against anokisis, transducing signals for survival. Another fascinating function proposed is that TN-C may act as a "shock absorber" for mechanical stress based on its elastic property [42] so that it might protect border zone myocardium subjected to the heaviest mechanical loading.

Myocardial tissue repair mostly depends on interstitial cells, especially myofibroblasts, because of the limited ability for regeneration of cardiomyocytes. Myofibroblasts play an important role in wound healing by synthesizing collagens and exerting strong contractile forces to promote wound healing [80]. Using a myocardial injury model of TN-C-KO mouse, we have found that TN-C promotes recruitment of myofibroblasts to injured sites by accelerating migration and differentiation and enhancing traction forces [78]. Furthermore TN-C promotes deposition of ECM proteins [61] and collagen fibril formation *in vivo* [81] and is essential for cardiac angiogenic function [82]. These functions would protect tissue and expedite healing and may prevent cardiac rupture and dilatation after infarction.

However, TNC could have double-faced effects for myocardial repair (Figure 3). In addition to loosening cell adhesion and upregulating MMPs, TN-C may enhance inflammatory responses [60] with activation of NF-kappa β [59] and cytokine upregulation [58]. While these functions are useful for clearing damaged tissue and freeing cells for rearrangement, they might cause progressive degradation of ECMs and slippage of myocytes within the LV wall, resulting in wall thinning and dilatation. Furthermore, an increase of myofibroblasts and pronounced fibrosis generate traction forces that prevent ventricular dilatation; on the other hand, excessive fibrosis would lead to stiffer and less compliant ventricles. Moreover, the situation is complicated by the fact that a compensatory system for the lack of TN-C exists [55]. For example, the recruitment of myofibroblasts in injured sites of myocardium is delayed in TN-C KO mice that are normalized by day 3 after injury [78], although the compensatory mechanism has not been identified. Therefore it is not easy to state whether TN-C is harmful, beneficial, or completely redundant for tissue reconstruction after MI. Our recent study showed ventricular remodeling in TN-C-KO mouse was significantly reduced and cardiac function was improved compared with the wild type at day 28 after permanent ligation of the coronary artery [79]. Therefore, it seems that TN-C

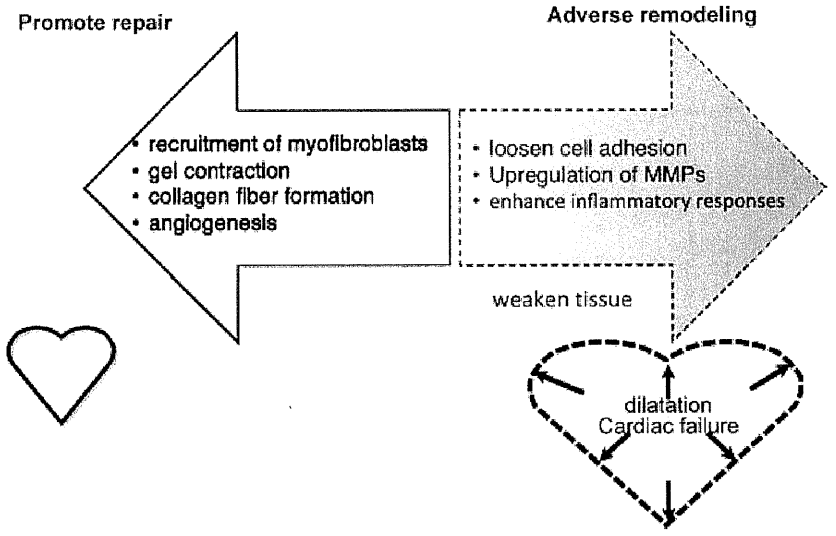

Figure 3 Possible roles of TN-C in ventricular remodeling. TN-C may weaken the adhesion of cardiomyocytes, upregulates MMP, and enhances inflammation, which might promote adverse ventricular remodeling. On the other hand, TN-C could accelerate tissue repair by recruitment of myofibroblasts, synthesizing collagens and exerting strong contractive forces, and angiogenesis, which may protect against cardiac rupture and ventricular dilatation.

exerts harmful effects on the infarcted heart at least in later stages, although the molecular mechanism remains to be elucidated.

Clinical Application

In contrast to contradictory and diverse molecular functions, the expression pattern is clear and specific. Taking advantage of this character, TN-C could be applicable for diagnosis of myocardial disease. In the mouse autoimmune myocarditis model, expression of TN-C is observed in foci of inflammation during the active stage, and disappears with healing [70]. Immunostaining of TN-C appears at a very early stage of inflammation and often is detectable before histological alteration becomes evident and localized in broader areas than those featuring inflammatory cell infiltrations [70,72]. These findings suggest that TN-C can be a sensitive marker for inflammation in myocardium. We evaluated the diagnostic value of TN-C expression in endomyocardial specimens obtained from patients with acute myocarditis, and confirmed that immunostaining for TN-C not only reflects clinical disease activity but also significantly improves the diagnostic sensitivity and accuracy of diagnosing inflammation [72]. Recently, a pathogenic role of inflammation has received considerable attention in the development and progression of heart failure [83], especially in the case of DCM [84]. Indeed, analysis of myocardial sample obtained at left ventriculoplasty, showed approximately 50% of 64 DCM patients with severe refractory congestive heart failure had significant intramyocardial inflammation associated with expression of TN-C [77]. Therefore, the precise evaluation of inflammation and distinguishing inflammatory cardiomyopathy from other types of DCM would be critical to improve management of patients. Although endomyocardial biopsy could be a direct diagnostic procedure, sampling error remains problematic even using immunostaining for TN-C [72].

While TN-C molecules are deposited in the extracellular spaces of the inflammatory lesion in the myocardium, soluble forms of TN-C are also released into the blood stream and can be measured by enzyme-linked immunosorbent assay. In fact, serum TN-C levels in patients with acute MI are significantly elevated on admission compared with normal controls, peaks at day 5, then gradually decreases, reflecting local expression in the myocardium. Interestingly, follow-up examination of 105 patients revealed that patients with high peak levels of TN-C in the acute stage after infarction have a greater incidence of ventricular remodeling 6 months later, and that the peak levels of TN-C were the most important independent predictor of major adverse cardiac events during a follow-up period of up to 5.5 years [68]. This finding may suggest that TN-C may aggravate progression of ventricular remodeling. Conversely, upregulation of TN-C might reflect complementary responses, as with brain natriuretic peptide (BNP). Our recent data that ventricular remodeling after MI in TN-C-KO mouse was reduced [79] support the former possibility.

An increasing number of reports demonstrated that elevated serum TN-C reflect the severity of heart failure, LV dysfunction, and LV remodeling in patients with DCM [85,86], LVH [87], after resynchronization therapy [88], supported by mechanical circulatory support devices [89], and that increased serum TN-C may be a marker for poor prognosis comparable with BNP [86]. Particularly interesting is that combining serum TN-C levels with plasma BNP levels is a stronger predictor of cardiac events in heart failure than either single biomarker alone (Figure 4) [86]. While BNP is secreted from cardiomyocytes in response to increasing cardiac wall tension, TN-C is synthesized in interstitial fibroblasts as discussed. Therefore, the combination of two biomarkers could enable more precise assessment of a whole heart by reflecting both cardiomyocytes and interstitial cells.

TN-C is not synthesized specifically in the myocardium; endothelial cells and vascular smooth muscle cells of various organs have the potential to synthesize TN-C. In fact, an elevated serum level of TN-C has been reported in various diseases other than heart disease, such as chronic hepatitis/liver fibrosis [90], and is suggested to be a biomarker of disease activity. The elevated levels of circulating soluble inflammatory mediators in heart failure

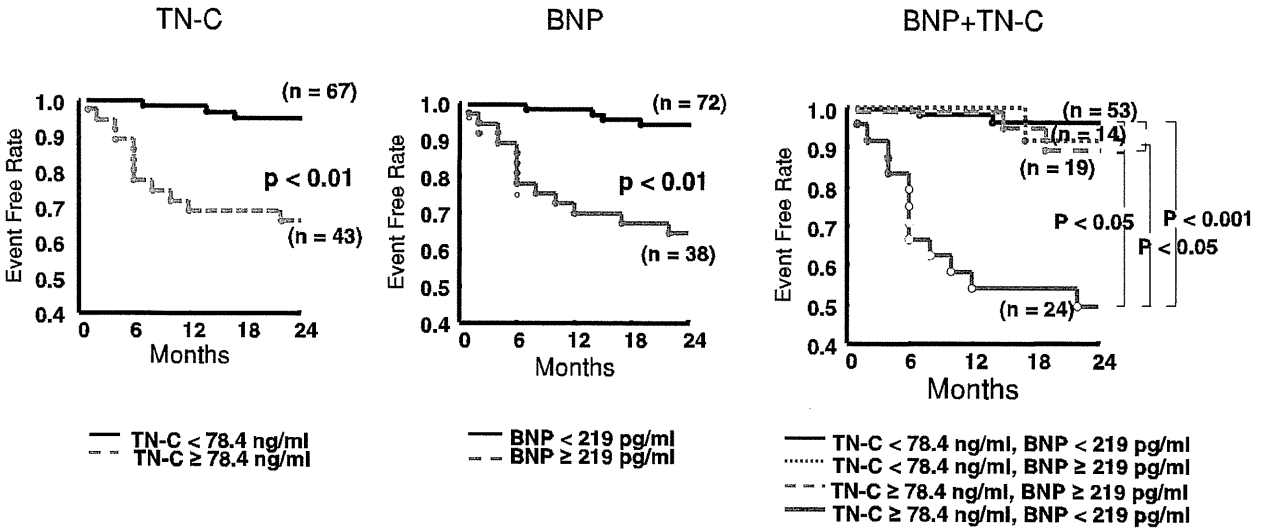

Figure 4 Kaplan–Meier analysis of cardiac event-free survival of 110 DCM patients with a BNP level ≥219 pg/mL and serum TN-C ≥ 78.4 ng/mL at discharge, and the four risk groups of patients based on serum TN-C and plasma BNP concentrations. Both BNP ≥ 219 pg/mL and serum TN-C ≥ 78.4 pg/mL at discharge had strong prognostic values for heart failure with DCM ($P < 0.01$). Cardiac event rate of the group with serum TN-C ≥ 78.4 ng/mL and BNP ≥ 219 pg/mL was significantly higher than those of the other groups. Reproduced from Fujimoto et al. [77].

patients might also stimulate endothelial cells of, for example, the liver, or lung, to secrete TN-C into the blood stream. Therefore, it may be necessary to identify the origin of serum TN-C for direct and accurate evaluation of the myocardial lesion. Molecular imaging could be a promising way. Using In^{111} labeled anti-TN-C, we successfully imaged the *in vivo* inflammatory lesion in myocarditis and MI rat models [69,71] and in primates (manuscript in preparation).

TN-C could be a key molecule to diagnose cardiac remodeling and also might be a target for the prevention of adverse ventricular remodeling.

SPARC

Secreted protein, acidic and rich in cysteine (SPARC, osteonectin, BM-40), a 32-kDa glycoprotein, mediates cell–matrix interactions during wound healing and regulates the production and/or assembly of the ECM [10,91]. SPARC binds to collagen and it is suggested that SPARC plays a significant role in postsynthetic procollagen processing and the development of mature cross-linked collagen fibrils [11]. SPARC expression increases primarily in inflammatory cells and fibroblasts after MI. Deletion of SPARC increases cardiac rupture, dysfunction, and mortality after MI, associated with a decrease of organized, mature collagen fibers. Treatment with TGF-β prevented cardiac rupture and improved mortality of SPARC-KO after MI [92]. Pressure overload causes elevation of SPARC expression associated with increased soluble and insoluble collagen and collagen fibrils in myocardium of wild-type mice. In SPARC-KO, insoluble collagen incorporation and myocardial diastolic stiffness were decreased, although an increased fibrillar collagen content was comparable with that of wild-type mice, [93] Therefore, it is suggested that SPARC could regulate collagen fibrils formation, a critical determinant of cardiac function. However, so far, no studies reported clinical data of SPARC in patients with heart disease and its role in heart failure remain to be elucidated.

CCN Family

The CCN family is a group of at least six secreted proteins and regulates biological processes including cell differentiation, proliferation, adhesion, migration, apoptosis, and ECM production, in many cell types [94]. CCN proteins bind to $\alpha v\beta 3$, $\alpha 6\beta 1$, $\alpha v\beta 5$ integrins, fibronectin, LRP1, BMP4, VEGF, and TGF-β. The CCN family has four functional domains, an insulin-like growth factor binding protein (IGFBP) domain, a Von Willebrand factor domain, a TSP-homology domain, and a cysteine knot, heparin-binding domain. Thus, they play essential roles in development, wound healing, and angiogenesis [12,95]. CCN2 is a secreted 36–38 kDa protein, main member of the CCN family, and also known as connective tissue growth factor (CTGF). CCN2 binds TGF-β and enhances the ability of TGF-β to bind TGF-β receptors at low TGF-β concentrations and hence indirectly affects Smad-responsive promoters [96], promoting many profibrotic effects of TGF-β. CCN2 is overexpressed in numerous fibrotic diseases and the degree of overexpression correlates with the severity of disease [97]. CCN2 is highly expressed in the developing cardiovascular system. CCN2-null mice show no prominent cardiovascular defects but severe skeletal malformation [98].

CCN2 expression is increased in the hypertrophied and failing myocardium of experimental animal models [99] and

endomyocardial biopsy samples from patients [100]. A recent report suggests CCN2 may be a novel potential biomarker of cardiac dysfunction in patients with chronic heart failure [101]. CCN2 might directly promote myocyte hypertrophy and cardiac fibrosis. However, it is uncertain whether CCN2 overexpression directly leads to a fibrotic pathology or can lead to the initiation or exacerbation of fibrosis and cardiac remodeling in concert with signaling pathways.

CCN1 is essential for cardiovascular development, and deletion of CCN1 causes early embryonic lethality due to a severe defect of angiogenesis [102]. Pressure overload, ischemia, and neurohormonal factors, such as Ang II or alpha1-adrenergic stimuli, induce myocardial expression of CCN1, suggesting CCN1 may play an important role in the adaptation of the heart to cardiovascular stress. However, human clinical data have been lacking so far, as well as for other CCN members except CCN2.

TSP Family

The five current members of the TSP family can be divided in two subgroups according to their molecular structure. TSP-1 and -2 are trimeric proteins that do not contribute directly to tissue integrity. TSP-3, -4, and -5 are pentameric. It has been recognized that TSP-1 and -2 play an important role in wound healing [6–9].

TSP-1 is secreted from platelets, macrophages, fibroblasts, ECs, and SMCs, which may suppress the recruitment of inflammatory cells production, activation of inflammatory cytokines, and mediate inhibition of MMP activity. TSP1 induces a conformational change in the latent TGF-ß complex to transform it to be bioactive [103]. Furthermore, TSP-1 can inhibit angiogenesis through suppression of VEGF production and release [104]. Indeed, the absence of TSP-1 results in increases in cardiac and skeletal muscle capillary vessels [104].

Similar to TSP-1, TSP-2 inhibits angiogenesis and protease activity. Unlike TSP-1, TSP-2 does not activate TGF-β1, but may modulate collagen matrix assembly.

Expression of TSPs is low in normal heart, but expression of TSP-1, -2, -3, and -4 are increased in pressure-overloaded heart failure model and patients with cardiac hypertrophy secondary to aortic stenosis [7,105]. Paradoxically, lowering expression levels of TSP-1 has been reported in myocardial biopsy samples from patients with end-stage heart failure [106]. Coronary ligation model of TSP-1 KO mice shows an enhanced inflammatory response with subsequent expansion of granulation tissue and myofibroblast infiltration into the viable myocardium, resulting in LV remodeling [107].

In TSP-2 knockout mice, angiotensin II induced fatal cardiac rupture in as high as 70% of surviving mice with cardiac failure [108]. Moreover, lack of TSP-2 results in progressive cardiac failure and dilatation with aging [109]. Thus, the protective effects of TSP-1 and TSP-2 after myocardial injury may lead to novel therapeutic interventions to attenuate adverse LV remodeling.

Periostin

Periostin is a 90 kDa protein with four domains that are highly related in its amino acid sequence to the ancestral fasciclin gene in Drosophila and is expressed within the peri-osteum, peri-odontal ligament [110]. Periostin binds multiple ECM proteins, such as TN-C, fibronectin, collagen V, collagen I, and heparin, in addition to several integrin including $\alpha v/\beta 3$, $\alpha v/\beta 3$. Periostin plays an evolving role in collagen fibrillogenesis by directly binding collagen I [111] and/or cooperatively interacting with other molecules such as TN-C, thus affecting the structural integrity of the adult heart matrix or stretch-sensitive signaling [112]. In the embryonic heart, periostin is expressed in epicardium and valve leaflets and their supporting apparatus, and plays an important role in their development by increasing collagen compaction in the endocardial cushion tissue and promoting the mesencymal cells into fibroblastic lineage while blocking their transformation to cardiomyocyte [113,114].

Periostin is not present in the adult ventricular myocardium but the expression is increased after aortic banding and showing parallel changes in interstitial fibrosis [115]. TGFβs and BMPs are the main mediators of periostin in the development, and VEGF, CCN2, and interleukins might regulate periostin expression in the remodeling process [15].

Periostin null mice show increased susceptibility to cardiac rupture and exhibit decreased circumferential strain and passive stiffness after MI [116,117]. However, periostin-null mice that survive the initial myocardial insult were less susceptible to fibrotic scarring and exhibited better ventricular performance than wild-type controls [116,117], which is similar to the cases of TNC-KO. Recently a report has suggested periostin can induce re-entrance of the differentiated cardiomyocytes to the cell cycle following cardiac injury [118]. However, this hypothesis is still controversial [119]. Although the role of periostin in the heart is very complicated, it is clear that periostin could be a regulator of cardiac remodeling and hypertrophy and may be a reasonable pharmacological target to mitigate heart failure.

Future Directions and Conclusion

Matricellular proteins modulate cell function by interacting with cell-surface receptors, proteases, hormones, and other bio-effecter molecules, as well as with structural matrix proteins. Integrated networks of these matricellular proteins and interactions between matrix and matricellular proteins are beyond the scope of this review. Clearly, this review article does not cover all the proteins that are now considered to be matricellular. Several members of the CCN, tenascin-X, the galectins, plasminogen activator inhibitor type 1 (PAI-1), and autotaxin are excluded from this review.

In response to pressure and volume overload, ischemia, oxidative stress, and injury, the heart changes its shape, structure, and function. Matricellular proteins are upregulated in these circumstances, modulate cell function and cell–matrix interactions, and induce ECM deposition. Generally, matricellular proteins loosen cell-ECM adhesion and, possibly, cell–cell adhesion, which would help cells to move for rearrangement and allow inflammatory cells and capillary vessels to spread during tissue remodeling. Some matricellular proteins may cause myocyte hypertrophy, which may also lead to myocyte necrosis and apoptosis. Matricellular proteins have diverse functions and could exert both harmful and

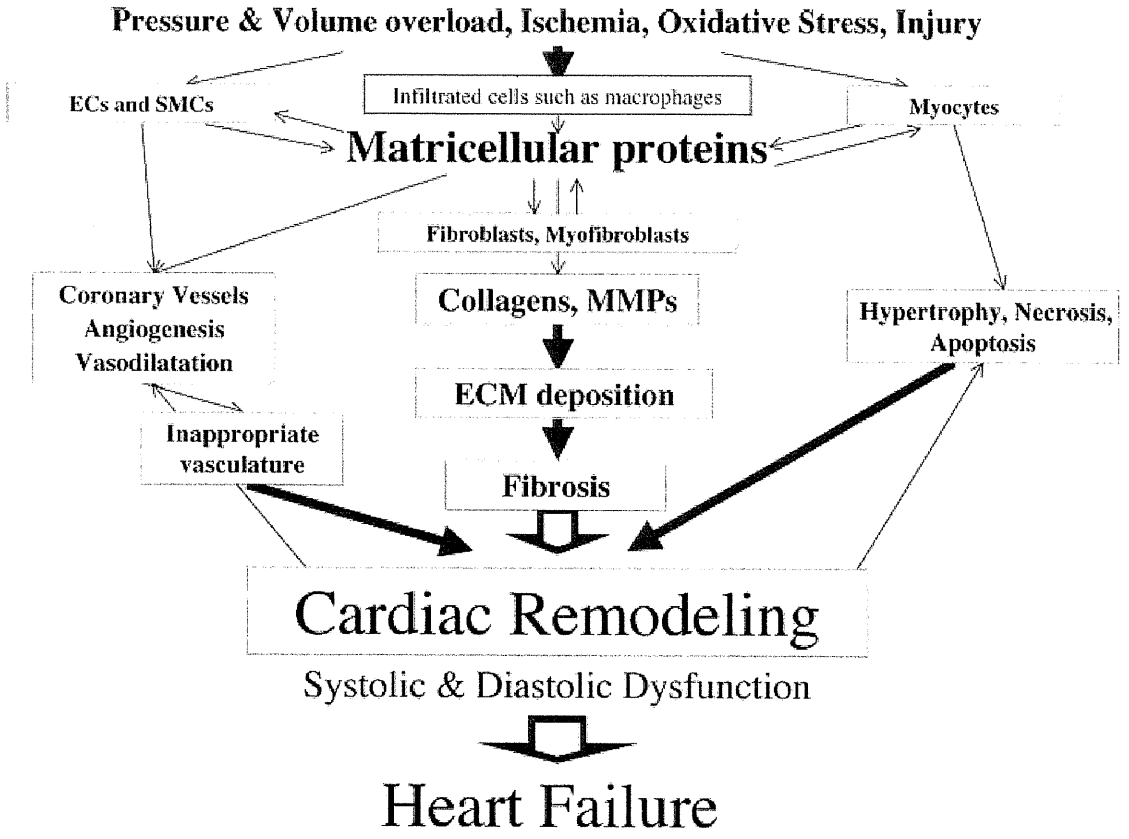

Figure 5 A hypothetical scheme showing the possible role of the matricellular proteins in cardiac remodeling and heart failure. Expression of matricellular proteins increases in response to many stresses. Matricellular proteins loosen cell–matrix adherence and induce migration and infiltration of macrophages, endothelial cells, fibroblasts, and myofibroblasts. Matricellular proteins regulate MMP activity involved in regulating ECM deposition during cardiac remodeling process leading to heart failure. MP, matricellular proteins; ECs, endothelial cells; SMCs, smooth muscle cells; TGFβ, transforming growth factor; EGF, epidermal growth factor; PDGF, platelet-derived growth factor; VEGF, vascular endothelial growth factor.

beneficial effects in a context-dependent manner during myocardial tissue remodeling. Ablation of most matricellular proteins often causes inappropriate alterations in inflammation, angiogenesis, and ECM deposition, which result in impairment of tissue repair and cardiac rupture after myocardial injury such as infarction. Meanwhile, the knockout animals which survive the acute stage show improved cardiac function with less fibrosis as observed in cases of periostin-KO and TN-C-KO.

Matricellular proteins may essentially function to maintain cardiac structure against many stresses. At the same time, they also have the potential to cause cardiac fibrosis leading to cardiac dysfunction, as shown in Figure 5. Furthermore, cardiac dysfunction enhances inflammatory cytokines, and, in turn, induces proteins production and release of matricellular, a modulator of inflammation. Further and extensive research is needed to understand and clarify the exact mechanisms of matricellular proteins during cardiac remodeling and heart failure, which should make it possible to induce desirable myocardial tissue remodeling by manipulating matricellular proteins.

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Conflict of Interest

The authors have no conflict of interest.

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Original contribution

Sarcoidosis does not belong to or overlap with immunoglobulin G4–related diseases based on an assessment of serum immunoglobulin G4 levels in cardiac and noncardiac sarcoidosis☆

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Summary Although sarcoidosis may exhibit histopathologic features similar to those of a newly emerging clinical entity, immunoglobulin G4–related sclerosing disease, sarcoidosis is currently not considered to be associated with immunoglobulin G4–related immunoinflammation. Not many studies on this association have been reported. We investigated serum immunoglobulin G4 levels among patients with sarcoidosis with or without cardiac involvement (cardiac sarcoidosis and non–cardiac sarcoidosis patients). The mean serum immunoglobulin G4 level among the 65 patients with sarcoidosis was 56.8 ± 43.0 mg/dL, which did not significantly differ between patients with cardiac sarcoidosis (54 ± 48 mg/dL, n = 12) and patients without cardiac sarcoidosis (58 ± 42 mg/dL; n = 53). Serum level of soluble interleukin 2 receptor, a potent marker that may reflect sarcoidosis activity, was elevated in cardiac sarcoidosis (910 ± 683 U/L) and noncardiac sarcoidosis (689 ± 399 U/L) but did not significantly differ between the groups. Immunohistochemistry of cardiac or lymph node specimens from patients with cardiac sarcoidosis showed only sparse or no infiltration of immunoglobulin G4–positive lymphocytes, in contrast to the moderate to severe infiltration of CD68-positive macrophages and CD45-positive lymphocytes. Although the number of study subjects was small, these findings collectively suggest that regardless of the presence or absence of cardiac involvement, sarcoidosis does not belong to or overlap with immunoglobulin G4–related sclerosing disease.
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1. Introduction

Since elevation of serum immunoglobulin G4 (IgG4) levels and tissue infiltration of IgG4-positive plasma cells were first characterized in autoimmune pancreatitis [1], similar findings have been observed in a wide variety of disorders, such as retroperitoneal fibrosis, inflammatory

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Table 1 Patient characteristics

Characteristics	Cardiac involvement (+) (n = 12)	Cardiac involvement (−) (n = 53)	*P*
Age (y)	52.3 ± 13.4	55.6 ± 16.0	NS
Men	6 (50%)	23 (43%)	NS
Body mass index	23.8 ± 3.8	22.6 ± 2.8	NS
History of smoking	5 (42%)	18 (34%)	NS
Accompanying diseases			
Hypertension	2 (17%)	15 (28%)	NS
Diabetes mellitus	2 (17%)	7 (13%)	NS
Dyslipidemia	6 (50%)	19 (36%)	NS
Coronary artery diseases	0 (0%)	4 (8%)	NS
Heart failure	11 (92%)	2 (4%)	<.001
Systolic blood pressure (mm Hg)	110 ± 24	127 ± 16	.006
Diastolic blood pressure (mm Hg)	72 ± 16	74 ± 9	NS
Heart rate (beats per minute)	74 ± 17	72 ± 8	NS
Electrocardiogram			
Complete or advanced AV block	5 (42%)	4 (8%)	.002
Ventricular tachycardia	3 (25%)	0 (0%)	<.001
Echocardiogram			
LV end-diastolic diameter (mm)	59.7 ± 14.4	47.1 ± 4.8	<.001
LV ejection fraction	41.3 ± 22.1	66.8 ± 7.4	<.001
Medication			
ACEI/ARB	4 (33%)	9 (20%)	NS
Calcium channel antagonists	1 (8%)	10 (19%)	NS
β-Blockers	4 (33%)	2 (4%)	.002
Diuretics	6 (50%)	1 (2%)	<.0001
Digitalis	3 (25%)	1 (2%)	.003
Spironolactone	2 (17%)	0 (0%)	.003
Statin	6 (50%)	14 (26%)	NS
Amiodalon	3 (25%)	0 (0%)	.001
Laboratory findings			
Brain natriuretic peptide (pg/mL)	350.9 ± 378.4	116.1 ± 242.1	.048
CRP (mg/dL)	2.43 ± 5.35	0.18 ± 0.33	.003
White blood cell count (/μL)	6860 ± 2810	5740 ± 1640	NS
Hemoglobin level (g/L)	14.5 ± 1.3	13.9 ± 1.3	NS
Platelet count (103/μL)	191 ± 57	242 ± 51	.003
Erythrocyte sedimentation rate (mm/h)	17.5 ± 9.9	13.8 ± 12.1	NS
Aspartate aminotransferase (IU/L)	38.5 ± 34.8	24.5 ± 11.7	.019
Alanine aminotransferase (IU/L)	27.3 ± 14.6	24.6 ± 15.2	NS
Blood urea nitrogen (mg/dL)	19.4 ± 6.4	15.8 ± 4.5	.022
Creatinine level (mg/dL)	0.96 ± 0.29	0.76 ± 0.23	.020

NOTE. Data are presented as mean ± SD for continuous variables.
Abbreviations: AV, atrioventricular; LV, left ventricle; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers; CRP, C-reactive protein; and NS, not significant.

abdominal aortic aneurysm [2], Mikulicz disease, and Sjoegren syndrome [3], leading to the proposal of a new clinicopathologic entity, IgG4-related sclerosing disease [4]. Although the clinical spectrum of IgG4-related sclerosing disease or its identity as a novel clinical entity has not been established, it has been proposed that diagnosis of IgG4-related sclerosing disease can be defined by elevated serum IgG4 and histopathologic features such as greater than 50% infiltration of IgG4/IgG-positive plasma cells [5]. Currently, sarcoidosis is not considered to be IgG4 related. However, a small fraction of IgG4-related sclerosing disease may be misdiagnosed as other lymphoproliferative diseases because of the resemblance of clinicopathologic pictures [6] as well as the fact that a substantial fraction of autoimmune pancreatitis, the first disease to be diagnosed as IgG4 related, may occur concomitantly with other autoimmune diseases, including sarcoidosis [7].

Recent studies have suggested that cardiac involvement, although less common, may be one of the features of IgG4-related sclerosing disease [8,9]. Sarcoidosis with cardiac involvement, termed *cardiac sarcoidosis*, is reported to be more prevalent in Japan than in the United States and is responsible for approximately 58% to 85% of deaths from sarcoidosis [10-12]. To date, there has been little information

available regarding whether serum IgG4 levels are increased in patients with sarcoidosis, especially those who have been diagnosed with cardiac involvement. Therefore, we analyzed serum IgG4 levels in 65 patients with sarcoidosis, including 12 patients with cardiac sarcoidosis.

2. Materials and methods

2.1. Study patients and diagnosis of cardiac sarcoidosis

The study was approved by the Ethical Committee of the Osaka Medical College, Osaka, Japan, and Hayama Heart Center, Kanagawa, Japan. Sixty-five patients with active sarcoidosis who attended our hospital and/or Hayama Heart Center between 2002 and 2010 were enrolled in the current study. Among these patients, 12 (6 men and 6 women) were diagnosed as having cardiac sarcoidosis according to the diagnostic guidelines proposed by the Japan Society of Sarcoidosis and Other Granulomatous Disorders [13].

2.2. Laboratory measurements

Serum IgG4 levels, soluble interleukin 2 receptor (sIL-2R), and C-reactive protein (CRP) were measured by turbidimetry (SRL, Tokyo, Japan), enzyme-linked immunosorbent assay, and a latex agglutination immunophotometric assay. Serum levels of angiotensin-converting enzyme (ACE) were measured by the Kasahara method [14]. The upper reference ranges of IgG4, sIL-2R, and ACE were 105 mg/dL, 519 U/mL, and 21.4 U/L, respectively.

2.3. Histologic and immunohistochemical examinations

Biopsy specimens of 5 of the 12 patients with cardiac sarcoidosis enrolled in the study were available. In addition, a biopsy specimen was available for 7 other patients with cardiac sarcoidosis. Specimens of left ventricular (LV) myocardium or lymph nodes were obtained from surgically excised LV muscles, biopsy, or autopsy. Sections of paraffin-embedded specimens with a thickness of 4 to 6 μm were incubated with antibodies against cell surface markers (CD45 [Leica, Newcastle, UK], CD38 [Leica], and CD68 [DAKO, Glostrup, Denmark]) or IgG4 (Cappel, Cochranville, PA), and antigens were visualized by using the 3,3-diaminobenzidine tetrahydrochloride method (ScyTek Laboratories, Logan, UT).

Table 2 Biomarkers

Characteristics	Cardiac involvement (+) (n = 12)	Cardiac involvement (−) (n = 53)	*P*
Immunoglobulin G4 (mg/dL)	53.5 ± 48.5	57.5 ± 42.1	NS
sIL-2R (U/mL)	910 ± 683	689 ± 399	NS
ACE (U/mL)	19.1 ± 10.8	19.4 ± 7.5	NS

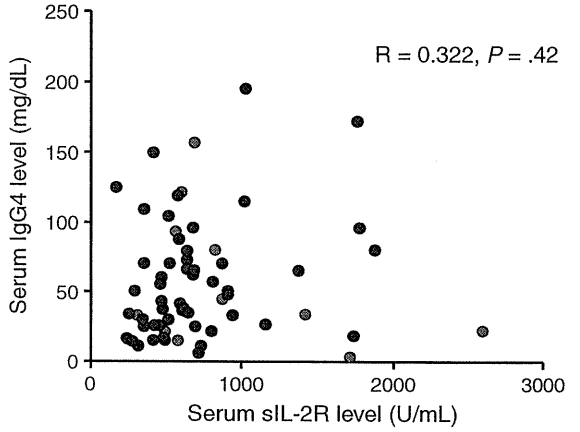

Fig. 1 Scatter plot of serum IgG4 and sIL-2R levels in patients with sarcoidosis. Patients with cardiac sarcoidosis and non–cardiac sarcoidosis patients are represented by red and blue circles, respectively.

2.4. Statistical analysis

Data are expressed as mean ± SD for continuous variables and as number (percentage) for categorical variables. Spearman correlation analysis was performed to estimate correlations between variables. Comparison between 2 groups was performed by Wilcoxon rank sum test or unpaired Student *t* test. $P < .05$ was considered to be statistically significant.

3. Results

3.1. Patient characteristics

The mean age and prevalence of male sex did not significantly differ between the groups (Table 1). Compared with non–cardiac sarcoidosis patients, heart failure, complete atrioventricular block, and ventricular tachycardia were found to be more prevalent in patients with cardiac sarcoidosis. Use of cardiac medications, such as β-blockers, diuretics, digitalis, spironolactone, and amiodarone, was more frequent in patients with cardiac sarcoidosis.

3.2. Laboratory data

Serum levels of CRP, aspartate aminotransferase, blood urea nitrogen, and creatinine were significantly higher in patients with cardiac sarcoidosis. No statistical difference was found between serum levels of IgG4, sIL-2R, and ACE of patients with cardiac sarcoidosis and non–cardiac sarcoidosis patients (Table 2). Among the 12 patients with cardiac sarcoidosis, 2 (17%), 9 (75%), and 3 (25%) had IgG4, sIL-2R, and ACE levels higher than the upper normal

Table 3 Histologic and immunohistochemical findings in tissues from patients with cardiac sarcoidosis

Case	Age (y)	Sex	Tissue examined	Sampling	Preoperative clinical diagnosis	Echocardiogram		Serum data		Immunohistochemistry			
						LV diastolic diameter	LVEF (%)	IgG4 (mg/dL)	sIL-2R (U/mL)	CD38	CD68	CD45	IgG4
1	60	M	Myocardium	Excised LV	DCM	88	24	NA	NA	1+	3+	3+	-
2	63	M	Myocardium	Excised LV	DCM	85	21	NA	NA	2+	3+	3+	1+
3	51	F	Myocardium	Excised LV	Unclassified CM	62	29	NA	NA	2+	3+	3+	1+
4	51	F	Myocardium	Excised LV	DCM	68	35	NA	NA	1+	3+	3+	-
5	36	M	Myocardium	Excised LV	DCM	73	8	23.3	2600	2+	3+	3+	1+
6	45	M	Myocardium	Excised LV	DCM	81	11	121	601	2+	2+	3+	-
7	49	F	Myocardium	Biopsy	Unclassified CM	66	24	21.4	491	2+	3+	3+	-
8	55	M	Myocardium	Biopsy	DCM	69	26	NA	NA	NA	2+	3+	-
9	48	F	Myocardium	Excised LV	DCM	83	28	NA	NA	1+	3+	3+	-
10	43	F	Myocardium	Autopsy	DCM	71	22	NA	NA	1+	2+	2+	-
11	72	M	Lymph nodes (mediastinal)	Biopsy	DCM, MDL	56	41	14.6	577	2+	3+	3+	-
12	54	F	Lymph nodes (cervical)	Biopsy	Unclassified CM	44	40	93.5	567	2+	3+	3+	1+

Abbreviations: LV, left ventricle; DCM, dilated cardiomyopathy; CM, cardiomyopathy; MDL, mediastinal lymphadenopathy; LVEF, LV ejection fraction; IgG, immunoglobulin G; and NA, not assessed.

limit, respectively. Among the non–cardiac sarcoidosis patients, 7 (13%), 32 (60%), and 22 (42%) had IgG4, sIL-2R, and ACE levels higher than the upper normal limit, respectively. The correlation between IgG4 and sIL-2R was found to be nonsignificant (Fig. 1).

3.3. Histologic and immunohistochemical analysis

Of the 12 patients whose serum IgG4 levels were available, the histologic specimens of 5 patients were also available (Table 3). The gross photograph from one of the patients (case 10 in Table 3) demonstrates dilated and partially thinned LV wall with scar lesion formation, and sarcoid granulomas and interstitial fibrosis are shown microscopically in these lesions (Fig. 2). In the patients listed in Table 3, the cardiac tissue showed sarcoid granulomas with multinucleated giant cells in cases 1 to 10 (Supplementary Figure). On the other hand, in cases 11 and 12, the cardiac tissues had been obtained by endomyocardial biopsy, which showed granulomatous degeneration with inflammatory cell infiltrates, and multinucleated giant cells that occasionally contained asteroid bodies can be observed. In the latter 2 cases, although multinucleated giant cells were not apparent (Supplementary Figure), cardiac sarcoidosis was diagnosed with the histopathologic findings in lymph node tissues showing sarcoid granulomas and the presence of cardiomyopathy. In the tissue sample of a patient (case 6), who had slightly elevated levels of IgG4 and sIL-2R, increased infiltration of CD45-positive T lymphocytes and CD68-positive macrophages was observed. In contrast, CD38-positive B lymphocytes and IgG4-positive cells were sparse (Fig. 3). In lymph node specimens from another patient with cardiac sarcoidosis (case 11) who had normal serum IgG4 levels, increased infiltration of CD45-positive T lymphocytes and CD68-positive macrophages was found; however, IgG4-positive cells as well as CD38-positive B lymphocytes were sparse (Fig. 4). IgG4 staining of heart specimens that were judged to be 1+ (Table 3) is shown in Fig. 5.

4. Discussion

In the current study, we measured serum IgG4 levels in 65 patients who were diagnosed with sarcoidosis. The mean serum IgG4 level was 56.8 ± 43.0 mg/dL, and 9 (14%) patients had an IgG4 level above the upper reference range (105 mg/dL). In addition, among the 12 patients with cardiac sarcoidosis, 2 (17%) had an IgG4 level above the upper reference range. The mean IgG4 level did not differ significantly between patients with cardiac sarcoidosis and non–cardiac sarcoidosis patients. On the other hand, 41 (63%) of the 65 patients with sarcoidosis had increased serum levels of sIL-2R, a marker that may reflect sarcoidosis

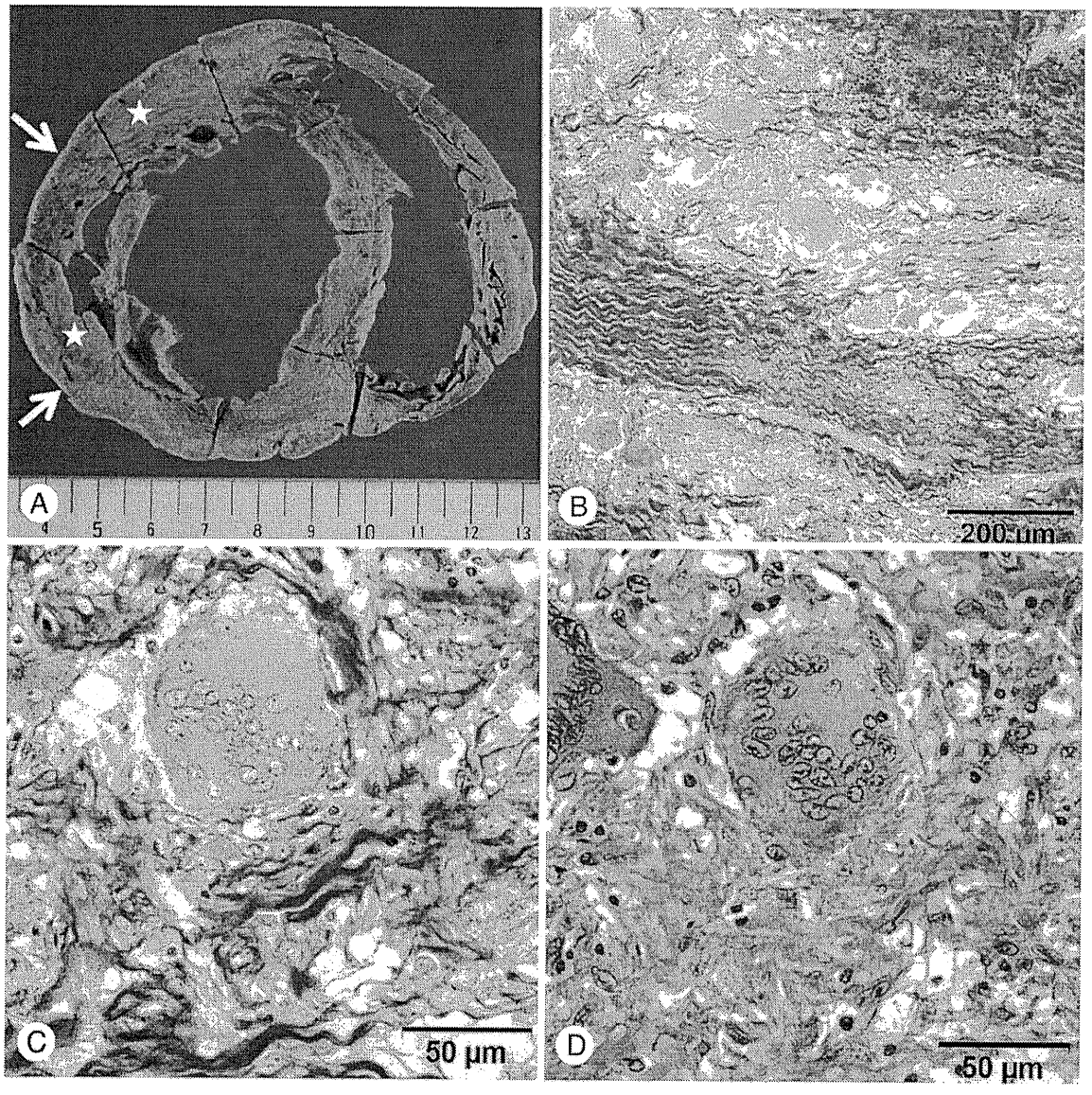

Fig. 2 Gross anatomy and histologic findings of cardiac sarcoidosis (case 10 in Table 3). A, Macroscopic analysis. The dilated LV wall showed thinning (arrows), and the scar-like white lesion was observed (asterisks). B, C, and D, Microscopically, many sarcoid granulomas and interstitial fibrosis were evident. B and C, Masson-trichrome staining. D, Hematoxylin-eosin staining. (Original magnification: ×100 in B and ×400 in C and D.)

activity [15], although the mean sIL-2R level did not differ corresponding to the presence or absence of cardiac involvement. Together with the finding that the relationship between serum IgG4 and sIL-2R was insignificant, these results suggest that serum IgG4 levels may not represent a biomarker for or reflect the disease activity of sarcoidosis, regardless of cardiac involvement.

IgG4-related sclerosing disease is a newly emerging disease entity, and a certain fraction of various lymphoproliferative disorders, such as Mikulicz disease, Sjoegren syndrome, and Castleman disease, may be IgG4 related [3,16]. However, whether IgG4-related sclerosing disease is truly a separate clinical entity needs to be elucidated, and if yes, the extent covered by this disease requires further evaluation to avoid diagnostic confusion [16]. We propose the possibility that other disorders that occasionally present similar clinical features, such as sarcoidosis, Wegener granulomatosis, and malignant lymphoma, should be ruled out before the diagnosis of IgG4-related sclerosing disease or alternatively, IgG4+ multiorgan lymphoproliferative disease is made [5].

As previously discussed, sarcoidosis is one of the diseases that should be distinguished from IgG4-related sclerosing disease. Whether a certain fraction of IgG4-related sclerosing disease has been misdiagnosed as sarcoidosis or whether a certain fraction of sarcoidosis overlaps with IgG4-related

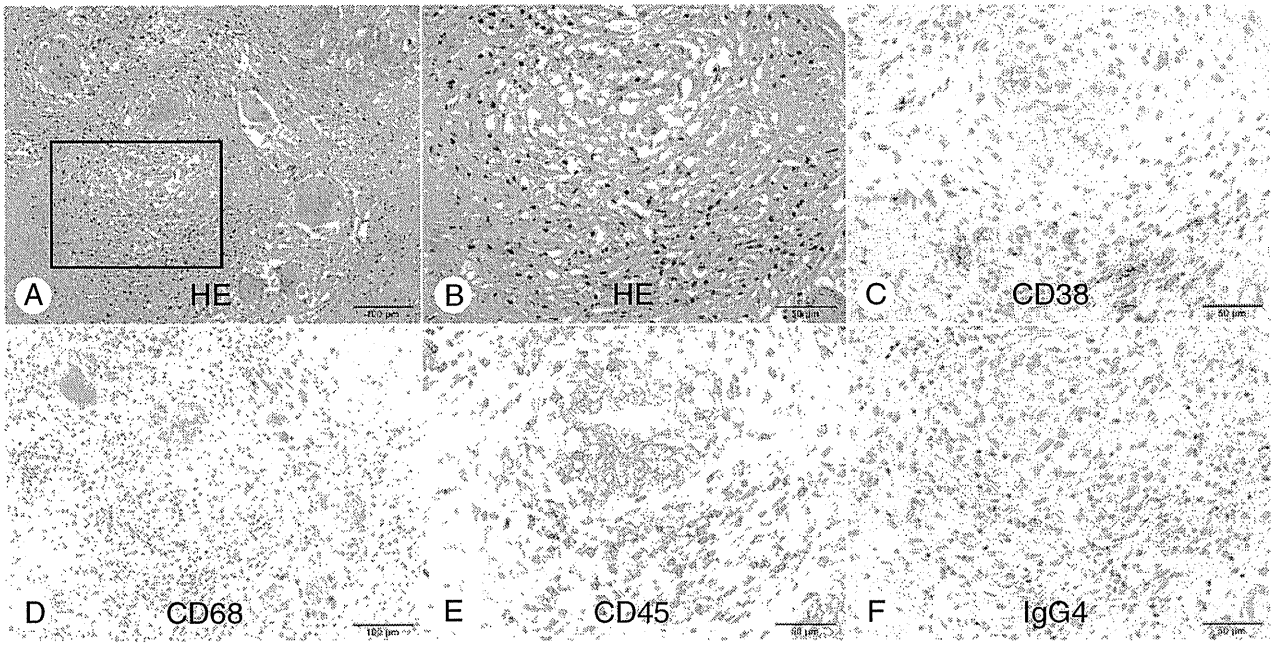

Fig. 3 Histologic and immunohistochemical analyses of the cardiac specimen from a patient with cardiac sarcoidosis (case 6 in Table 3). All panels were from serially cut sections. A, Hematoxylin and eosin staining. Large noncaseating sarcoid granulomas are observed. They are mainly composed of lymphocytes, macrophages, multinucleated giant cells, and interstitial components. B, Higher-magnification image of the boxed area in A. C, CD38 staining showing CD38-positive B cells. D, CD68 staining. CD68-positive macrophages and multinucleated giant cells are observed. E, CD45 staining showing CD45-positive T cells. F, IgG4 staining. (Original magnification: ×40 in A and D and ×100 in B, C, E, and F.)

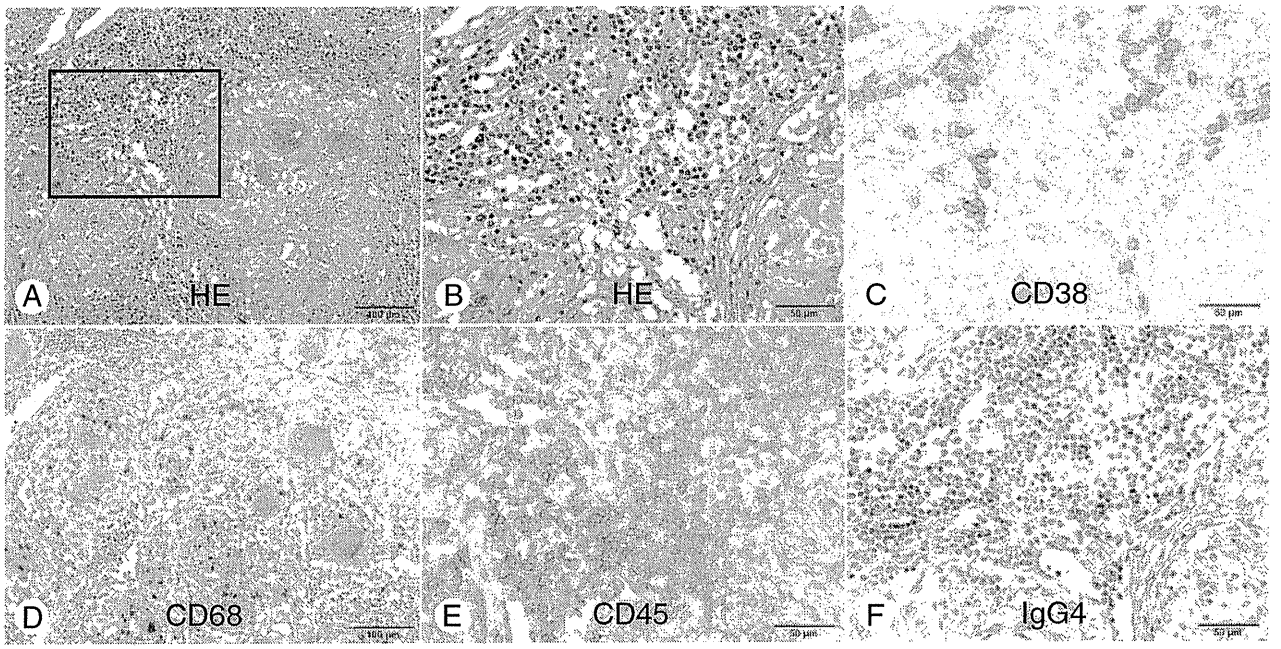

Fig. 4 Histologic and immunohistologic analyses of the mediastinal lymph node from a patient with cardiac sarcoidosis (case 11 in Table 3). All panels were from serially cut sections. A, Hematoxylin and eosin staining. B, Higher-magnification image of the boxed area in A. C, CD38 staining. D, CD68 staining. CD68-positive macrophages and multinucleated giant cells are observed. E, CD45 staining. F, IgG4 staining. (Original magnification: ×40 in A and D and ×100 in B, C, E, and F.)

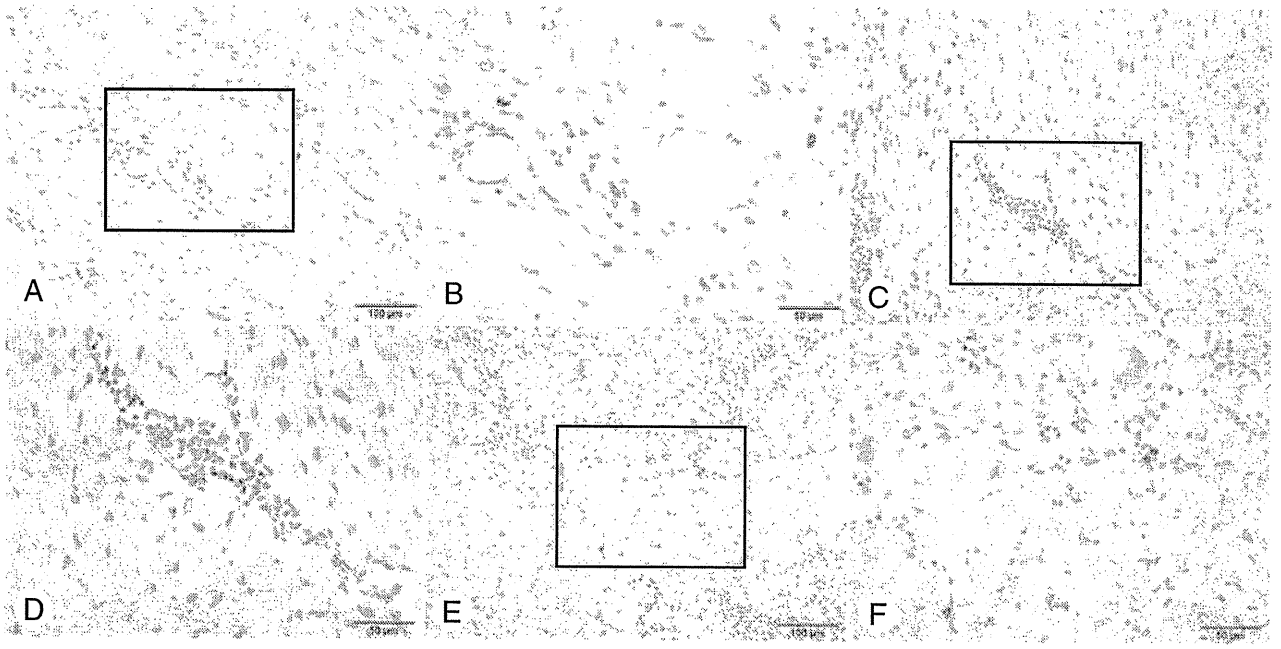

Fig. 5 IgG4 staining. Images of cardiac specimens that were judged to be "1+" on IgG4 staining are shown. A, Cardiac specimen from case 2. B, Higher-magnification image of the boxed area in A. C, Cardiac specimen from case 3. D, Higher-magnification image of the boxed area in C. E, Cardiac specimen from case 5. F, Higher-magnification image of the boxed area in E. (Original magnification: ×40 in A, C, and E and ×100 in B, D, and F.)

sclerosing disease has not been fully discussed so far. Our data suggest that sarcoidosis, which had been diagnosed as such at our institute, may not be a misdiagnosis of or overlap with IgG4-related sclerosing disease. Given that a population of greater than 50% IgG4-positive infiltrated plasma cells is a prerequisite condition for diagnosing IgG4-related sclerosing disease [5], this notion is supported, especially in cardiac sarcoidosis, by the findings from immunohistochemical analysis such as the absence or sparse presence of IgG4-positive cells in sarcoid granulomas in cardiac tissue and lymph nodes (Figs. 2 and 3), even in the presence of mildly elevated serum IgG4 levels. In addition, it has recently been reported that IgG4-related sclerosing disease may be characterized by predominant activation of the T-helper 2-mediated immune reaction [17]. In contrast, our previous finding indicated that cardiac sarcoidosis is characterized by activation of the T-helper 1-mediated immune response [18].

The strength of the current study is that we could perform immunohistochemical analysis on several cardiac tissues obtained from left ventriculoplasty, enabling the screening of numerous cardiac tissue samples from a variety of locations from patients presumably having extensive granulomatous degeneration of the heart. However, our study has several limitations. First, histologic assessment was not possible for all patients with cardiac sarcoidosis who were subjected to serum IgG4 measurement. Second, granuloma-positive noncardiac tissue was not stained for IgG4 in non–cardiac sarcoidosis patients; therefore, the prevalence of histologic IgG4 positivity is not available for these patients. Third, although none of the patients with cardiac sarcoidosis had a history of corticosteroid therapy at the time of blood sampling and/or tissue acquisition, a few non–cardiac sarcoidosis patients had already been taking steroid drugs at the time of blood sampling.

In conclusion, among the 65 patients diagnosed with sarcoidosis, the mean serum IgG4 level was 56.8 ± 43.0 mg/dL. The mean serum IgG4 level and the prevalence of an IgG4 level above the upper reference range did not significantly differ between patients with cardiac sarcoidosis and non–cardiac sarcoidosis patients. Immunohistochemical staining of cardiac and lymph node samples from patients with cardiac sarcoidosis showed only sparse or no infiltration of IgG4-positive lymphocytes, in contrast to the moderate to severe infiltration of CD68-positive macrophages and CD45-positive lymphocytes. In conclusion, it appears that among patients with sarcoidosis, especially among patients with cardiac sarcoidosis, the infiltration of IgG4-positive lymphocytes is, when present, only sparse, supporting the notion that sarcoidosis does not belong to or overlap with IgG4-related sclerosing disease.

Supplementary data

Supplementary materials related to this article can be found online at doi:10.1016/j.humpath.2011.07.002.

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臓器移植の病理

心臓移植

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特集　臓器移植の病理

心臓移植

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はじめに

1997年の臓器移植法制定後，心臓移植は1999年に第1例目が行われて以来，多い年でも年に10例程度と少ない状況が続いていた．2010年の臓器移植法改正による臓器提供条件の緩和によりこの年の心臓移植症例は23例と倍増した．今後もこの傾向は続き，心臓移植認定施設も増加すると考えられる．これに伴い摘出レシピエント心の検索やその後の心内膜心筋生検（以下；心筋生検）による拒絶反応の評価を求められる病理医も増えると考えられる．今回は心臓移植に際しての病理医の役割，また移植後拒絶反応の評価法とその最近の話題を紹介する．

Ⅰ．レシピエント摘出心の検索

心臓移植待機症例は移植前にその適応を判定するため画像検査などで詳細に検索がなされているが，移植前に行われる心筋生検だけでは病理学的な評価が不十分なことも多く，移植時に摘出されたレシピエント心の検索は最終確定診断や移植前に確認できなかった情報を得るためにも重要である．

1．心臓移植手術の流れ

ドナー提供情報が臓器移植ネットワークに入り，対象症例が決定すると臓器の摘出・搬送・移植までのスケジュールが速やかに決定する．レシピエントの選択はドナーとレシピエントのクロスマッチ等の免疫学的項目とともに体格や心臓サイズが近いことも考慮される．心臓サイズは10％の誤差内が理想とされている．

病理検査部門でもこの情報を共有し，ドナー心の到着時間，手術開始時間，レシピエント心摘出時間を認知しておくことが望ましい．特に凍結標本など新鮮な検体を採取したい場合は術中より待機し，摘出後すぐに処理に取り掛かれるようにする．

2．レシピエント摘出心の検索

心臓移植待機患者のほとんどは重度の心不全状態であり，補助人工心臓 ventricular assist system（VAS）を装着して待機していることが多い．そのためレシピエント心はこの装置の装着部（脱・送血管）が付随した状態で切り取られる．術式は modified bicaval 法[1]で行われることが多く，両心房後壁はレシピエント体内に残した状態で切り取られ提出される．つまり多くの場合，摘出心は房室接合部から心室寄りの部分のみであることが多い（**図1**）．また心外膜面はVAS装着手術による線維性癒着を伴っていることが多い．当施設ではレシピエント心は肉眼写真を撮影後，清潔状態で凍結用標本を採取し，その後両心室短軸横断面標本を作製．両心室，弁尖，冠動脈，刺激伝導系（房室結節以下）の組織標本を作製している．

3．レシピエント心の病理学的検索例

実際の症例を呈示する．40歳代女性．うっ血性心不全により入院し，薬物治療などが奏効せず左室補助人工心臓（LVAS）が植え込まれ，約3年間移植待機状態であった．経過中に施行された心筋生検では細胞肥大，変性と間質線維化が目立ったものの特異的所見に乏しく，他の検査結果と総合して拡張型心筋症と診断されていた．移植時のレシピエント心の病理学的検索では，両心室短軸横断面において心内膜の高度の肥厚と心外膜側を主体とした広範囲の置換性線維化を認めた（**図2a**）．組織学的には細胞の配列異常・錯綜配列が目立ち，心筋間には肥厚した小動脈もみられ，拡張型心筋症よりは拡張相肥大型心筋症を考える所見であった（**図2b**）．このようにレシピエント心の病理学的検索は移植前の評価を見直すよい機会であり，近年我が国で新たに提唱された疾患である中性脂肪蓄積心筋血管症もレシピエント心を注意深く検索した結果，見出された疾患である[2]．

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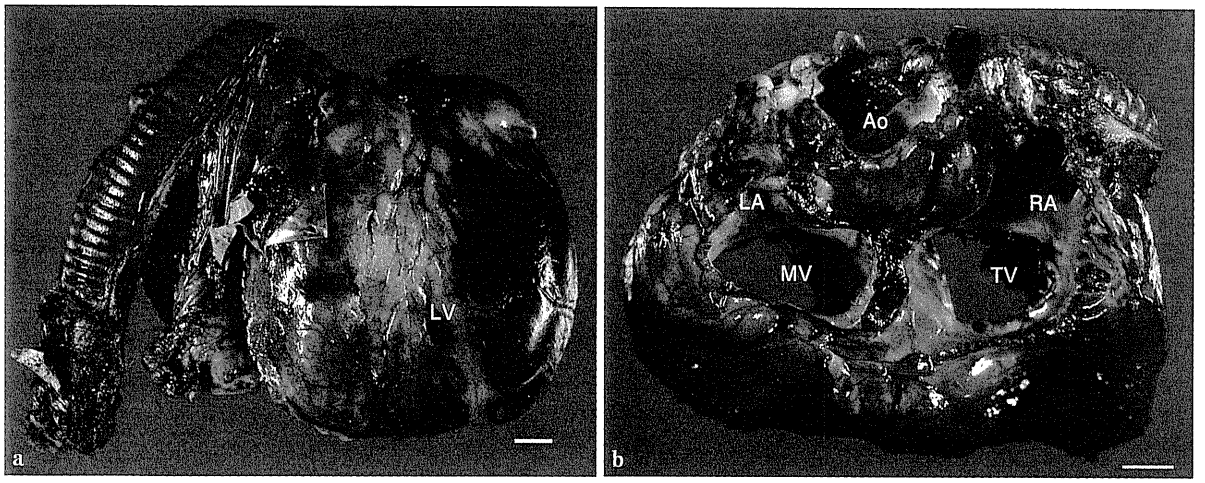

図1　摘出されたレシピエント心（10歳代，男性）　a：前面からみた像，b：心房切離面（頭側より俯瞰）．心房は大きく切り取られ，心尖部も一部切り取られている．大動脈に縫着されている人工血管は補助人工心臓の送血管である．三尖弁輪には形成術が施されている．Ao：大動脈，LA：左房，LV：左室，MV：僧帽弁，RA：右房，TV：三尖弁．bars＝1 cm．

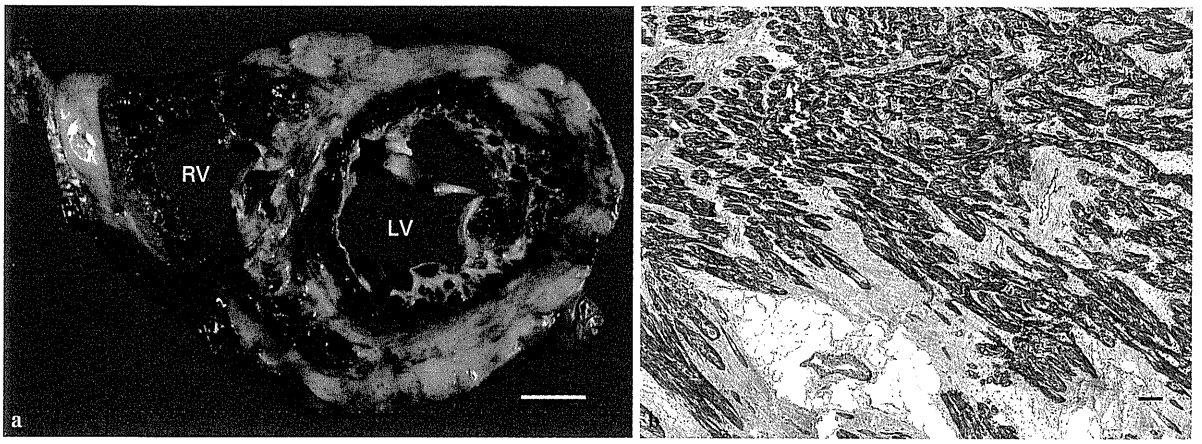

図2　移植時のレシピエント心　a：心室の横切面（bar＝1 cm）．心外膜側を主体に広範囲に置換性線維化がみられる．b：左室の組織像．置換性の線維化とともに錯綜配列も観察される．肥厚した小動脈（SICAD）もみられる（Masson染色，bar＝100 μm）．

Ⅱ．拒絶反応の診断

他臓器と同様に心臓移植後も注意深い免疫抑制剤の調節が必要である．心筋生検は心臓移植後の拒絶反応の評価において重要な位置づけにある．通常移植後7日目頃に初回の生検を行い，3週間目までは毎週施行する．その後問題となる所見がなければ2週間，4週間，8週間と間隔を空け，術後1年までは3ヵ月ごとに行い，その後は6ヵ月ごとに施行している．当施設では拒絶反応評価の心筋生検は，右頸部の総頸静脈から挿入した生検鉗子（バイオトーム）により右室の中隔から4片ほど採取している．検体は通常午前中に採取し，夕刻にはHE染色とMasson染色および蛍光抗体染色（移植早期のみ）を仕上げ同日中に判定するようにしている．標本作製にあたっては採取された組織片の全体を観察できるよう3段階の連続切片を作製している．判断すべき組織学的所見は細胞性拒絶と抗体関連性拒絶（液性拒絶）である．

1．細胞性拒絶 cellular rejectionの判定

Tリンパ球主体の炎症細胞によるドナー心への拒絶反応であるが，標本内の炎症細胞の同定と，心筋細胞傷害の有無を見極めることが重要である．評価はThe International Society for Heart & Lung Transplanta-