

Arrhythmogenic right ventricular cardiomyopathy: Pathology and genetics

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Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a cardiac disease of unknown etiology. It is listed among cardiomyopathies in the recent WHO classification and is characterized by transmural fatty or fibro-fatty infiltration of the right ventricle, resulting in ventricular tachyarrhythmias and high risk of unexpected cardiac arrest and sudden death, particularly in the young and in athletes.

The heart weight is usually normal and does not exceed 400 g. Right ventricular pathology is often overlooked by pathologists, despite the fact that the right side of the heart appears yellowish or whitish, suggesting a fatty or fibro-fatty infiltration of the underlying myocardium, a suspicion which is easily confirmed by cutting the right ventricular inflow-outflow, which appears lardaceous. By checking the wall transparency with a light source, the right ventricular free wall appears parchment-like. The dystrophic process of the right ventricular free wall is regional in 20% and diffuse in 80% of cases. Aneurysms of the right ventricular free wall, whether single or multiple, are reported in about 50% of cases and are considered a pathognomonic feature of ARVC. Right ventricular enlargement, whether mild, moderate or severe, is a constant feature.

The left ventricle and the ventricular septum are highly normal in the majority of cases, which explains the paradox of why these hearts are able to withstand the cardiac output of a strenuous exercise performance and at the same time are electrically vulnerable because of fibro-fatty infiltration of the right ventricle. However, following *in vitro* magnetic resonance and histological examination, the left ventricle appeared to be involved in nearly 50%. In hearts with end-stage disease and congestive heart failure, examined either at autopsy or at cardiac transplantation, biventricular involvement is a regular finding.

The histology of the free wall of the right ventricle clearly shows disappearance of the myocardium with transmural fibro-fatty replacement. The pathological process seems to start from the subepicardium and extend to the endocardium in a wave-front phenomenon. The dispersion of residual electrically conducting myocytes within the fibro-fatty tissue accounts for the delay of intraventricular impulse transmission and persistence of electrical depolarization during diastole (late potentials), as well as for onset of reentrant circuits with premature ventricular beats and ventricular tachycardia of left bundle-branch block morphology.

Evidence of patchy myocarditis with myocyte death and round cell inflammatory infiltrates was observed in two-thirds of specimens. Inflammatory cell infiltrates consist of CD45+ and CD43+ leukocytes and a few CD68+ macrophages. All stages of myocardial injury and repair are recognizable: acute cell death with sarcolysis and inflammatory infiltrates, subacute damage with matrix rich in fibroblasts and proteoglycans ("active fibrosis"), including dying myocytes with empty sarcolemma, lymphocytes and macrophages, or otherwise adipocytes replacing vanished myocytes, and, eventually, chronic

stage with hyaline fibrous tissue and adipocytes surrounding residual surviving myocytes, of variable size and degeneration.

Endomyocardial biopsy may be of help to improve the *in vivo* diagnostic accuracy of ARVC because of the peculiar topographic and histological features of the disease. In young subjects, the diagnosis is based on the finding of a certain amount of fibrous and/or fatty tissue: fibrous tissue >40%, fatty tissue >3% and residual myocytes <45%.

There is now clear-cut evidence that ARVC is an acquired, non-ischemic atrophy of the right ventricular myocardium and that electrical instability appears late in childhood. Patchy cell death with inflammatory infiltrate is visible by microscope, suggesting progressive myocyte loss followed by fibro-fatty replacement. An inflammatory theory has been put forward, and infection, toxic or immune mechanisms have been postulated. An inflammatory hypothesis does not contrast with a familial occurrence, since a genetic predisposition to viral infection eliciting an immune response has been proven in animals, with a selective involvement of the right ventricle and even development of ventricular aneurysms.

According to the dystrophic theory, the progressive loss of myocardium is secondary to spontaneous myocyte death as a result of a genetic defect. Familial occurrence suggests a genetically determined myocardial atrophy with autosomal dominant transmission and variable expression and penetrance. In this regard, the term myocardial dystrophy appears more appropriate, as in Duchenne's or Becker's skeletal muscle dystrophies, which may also be characterized by muscular atrophy with fatty infiltration ("pseudohypertrophy"). So far, six loci have been identified, two mapping to chromosome 14, one to chromosome 1, one to chromosome 2, one to chromosome 3 and one in chromosome 17, suggesting genetic and clinical heterogeneity. The specific gene defects as well as the defective coded proteins have not yet been identified.

It has been recently suggested that the progressive myocyte death in ARVC might represent programmed cell death. Abnormal, recurrent bouts of apoptosis may lead to progressive myocardial disappearance in ARVC followed by fibro-fatty replacement of the right ventricular free wall. However, the finding of apoptosis should be viewed with caution due to autolytic phenomena or delay in fixation. We recently studied the *in vivo* occurrence of apoptosis in endomyocardial biopsies of ARVC patients by using both the transmission electron microscope and TUNEL method. Apoptotic myocytes were found in 35% of cases, with a mean apoptotic index of 24.4 (9.8). Apoptosis appeared to be significantly related to clinical history duration (less than 6 months) and presence of "acute" symptoms. Recent studies have demonstrated that apoptosis can not only be triggered not the "internal clock", it has been recently demonstrated that apoptosis may be induced by cytotoxic T lymphocytes. The "acute" symptoms and signs associated with apoptosis in ARVC patients might reflect viral infection, autoimmunity or other inflammatory noxae that trigger apoptosis.

Whatever the etiopathogenetic mechanism, recurrent bouts of apoptosis may destroy the myocardium, which is then replaced by fibro-fatty tissue, and may enhance the electrical ventricular vulnerability. Cell death and inflammation act as acute arrhythmic trigger in the setting of the chronic substrate of fibro-fatty replacement. This evidence may open new avenues not only in the understanding of the disease, but also to conceive new diagnostic and therapeutic strategies. As agents inducing apoptosis are used in tumor therapy, agents inhibiting apoptosis might also stop or slow down myocyte loss in ARVC, thus preventing the ominous electrical instability of the ventricular myocardium and eventually heart failure.

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Pathology of large vessel vasculitides

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Vasculitides can be classified according to the size of the vessels involved. Large vessel vasculitides are found in Buerger's disease, temporal arteritis, Takayasu's disease, Behçet's disease, infectious arteritides, rheumatologic and miscellaneous diseases. The arterial involvement presents pathological characteristics which contribute to diagnosis of the disease.

Buerger's disease is a thrombotic arterial and venous disease which is associated with smoking in young nonatherosclerotic patients and is prominent in lower and upper limb arteries of 1-5 mm diameter. Most arterial lesions are sampled during surgical bypass surgery at the stage of nonspecific organized thrombosis. However, a characteristic pattern of Buerger's disease is no or minimal arterial wall damage. Venous involvement is mainly superficial thrombophlebitides.

Temporal arteritis belongs to the giant cell arteritides. It prominently involves the branches of the external carotid artery, mainly the temporal artery. Other sites can be involved: the aorta in about 10% of cases, and large arteries of limbs, with a risk of thrombosis, aneurysms and rupture. Temporal artery biopsy is diagnostic in less than 50% of cases. It is a focal inflammatory process with or without giant cells prominent in the internal part of the media. Steroid treatment does not change inflammation in biopsies for up to 4 weeks.

Takayasu's disease, also called aortic arch syndrome or non-specific aortoarteritis, belongs to the group of giant cell arteritides. It involves mainly the aorta, but also frequently the pulmonary, the subclavian, the carotid and the renal arteries. It is characterized by a marked thickening of the arterial wall. Aneurysms and stenoses are commonly observed. In the inflammatory stage, the inflammation is made of mononuclear and giant cells, and is prominent in the external part of the media where it destroys the elastic fibers. In the fibrous stage, thickening and stenosis are generated by fibrosis of the intima and mainly of the adventitia with a fibrous ring where inflammation may have disappeared.

Behçet's disease is based on a systemic vasculitis phenomenon. In addition to multiorgan involvement, vein involvement is frequent, and arterial lesions are observed in 2-30% according to the series. Both systemic and pulmonary arteries are involved. It is a very aggressive involvement destroying the vascular wall with a risk of arterial rupture, pseudoaneurysm and thrombosis. The inflammatory process is often massive with an infectious-like pattern.

Infectious arteritides: the most frequent concern in infectious vascular pathology is now infection after vascular surgery, mainly infection in prostheses. In native arteries, primary infectious arteritis is the bacterial involvement of a preexisting vascular lesion such as aneurysm or atherosclerosis, Gram-negative germs being frequently responsible; secondary infectious arteritis or mycotic aneurysm is now rare and depends on the septic embolism from endocarditis, Gram-positive germs being frequently responsible. It is a thrombotic and destructive phenomenon. Syphilitic and tuberculous aortitides are now very infrequent: they may be a diagnostic problem with rheumatologic disease-associated aortitis.

Rheumatologic and miscellaneous diseases: arteritis, mainly aortitis can be observed in rheumatologic or in systemic diseases such as rheumatoid arthritis, ankylosing spondylitis, Reiter's syndrome, relapsing polychondritis, and Cogan's syndrome. Kawasaki syndrome is mainly responsible for coronary artery involvement.

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