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Structural analysis of chordae tendineae in degenerative disease of the mitral valve ☆

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ABSTRACT

Background: Degenerative disease of the mitral valve (DDMV) is always accompanied by lengthening and/or rupture of chordae tendineae. However, the mechanisms and the mode of chordal rupture remain controversial, and the pathologic anatomy of the apparently healthy chordae has mostly been overlooked. We analyze the structural aspects of both ruptured and intact chordae tendineae in DDMV.
Methods and Results: Structural and ultrastructural microscopic analyses indicate that both the extracellular matrix and the interstitial cells are severely affected. Degenerative chordae show alterations in the synthesis and deposition of collagen and elastin, disorganization of collagen bundles and rupture of collagen fibres, accumulation of proteoglycans and of cellular and vesicular remnants, and cell transformation into a myofibroblast phenotype. Structural disruption makes the spongiosa and the dense collagenous core separate and break. Degeneration of the chordae is segmental, affecting both chordae that are clearly abnormal, and chordae that appear healthy on visual inspection.
Conclusions: Changes in both matrix synthesis and degradation disturb the ordered collagen arrangement and modifiy the structural and physical properties of the chordae. Progressive structural disruption of the diseased chordae is the cause of chordal rupture. Mitral surgery corrects the damage, but the underlying causes of DDMV are not corrected. Thus, progression of the disease and affectation of additional chordae may be at the basis of the late complications and the recurrent mitral regurgitation which occurs several years after surgery. Our results indicate that a more aggressive approach to surgery may be needed.

1. Introduction

Degenerative disease of the mitral valve (DDMV) is one of the most frequent causes of cardiovascular morbidity and mortality in developed countries. It affects about 2.5% of the general population [1,2] and frequently requires cardiac surgery [3]. There are two main etiologic classifications of DDMV [3–6]. On the one hand, there is Barlow's disease (BD). It has a chronic evolution, affects middle-aged people, and the valves show excess of tissue and leaflet thickening (myxomatous valve). On the other hand, there is fibroelastic deficiency (FED). It affects older people, shows a short-term evolution, and the valves are thinner and more transparent than normal (pellucid valve). Although the two aetiological conditions generate different valve morphologies, the valve leaflets show in all cases rupture of the collagen fibres, disruption of the elastic fibres, and glycosaminoglycan (GAG) infiltration to different degrees [1,5,7,8]. It should be underscored that the aetiology of DDMV cannot be recognized in a large percentage of cases. Many of these cases have been considered as idiopathic [9], or they have been defined as *formes frustes* of Barlow's disease [6].

A phenomenon that always accompanies DDMV is lengthening and/or rupture of chordae tendineae. Several studies have reported that degenerative chordae show an increase in the amount of collagen and GAGs [8,10], and fragmentation of the elastic fibres [5]. This is accompanied, in the valve leaflets, by transformation of resident cells from a fibroblast to a myofibroblast phenotype [11,12]. It is currently unknown whether a similar transformation occurs in degenerative chordae. If so, it would indicate that both cellular and extracellular components are implicated in chordal disease. On the other hand, the mechanisms and the mode of chordal rupture remain controversial [13,14].

Mitral valve replacement or valve repair are considered the main surgical options to avoid the risk of heart failure [6,15–17]. Minimally invasive procedures involving replacement of ruptured chordae [18–20], or chordae transfer [21], have also been considered. However, any conservative procedure should take the pathologic anatomy of the rest of the chordae system into consideration. This has mostly been overlooked [22].

We report in this paper a study of chordae tendineae in DDMV. The following points were addressed: 1) the structural appearance of the ruptured chordae; 2) the possible mechanisms and mode of

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chordal rupture; and 3) the pathologic anatomy of the unaffected chordae. Chordae in DDMV were defined structurally, and the mode of rupture was elucidated. Furthermore, most of the apparently unaffected chordae showed structural disruption, indicating that a more aggressive approach in the surgical treatment of DDMV is warranted.

2. Material and methods

Surgically excised mitral valves (posterior leaflets or the entire valve) from twelve patients undergoing mitral surgery were used in this study (with the approval of the Ethics Committee of the University Hospital "Marqués de Valdecilla"). None of the patients had previous diagnoses of Marfan's syndrome. Clinical records of ischaemic heart disease or of infective endocarditis were absent. Four normal mitral valves (two obtained at autopsy from patients who died of cancer, and two from donors who were rejected for transplantation) were used as controls. Marginal chordae and struts were included in this study.

2.1. Light and transmission electron microscopy (TEM)

For conventional light microscopy, excised valves were fixed in 3% glutaraldehyde in PBS. Selected chordal fragments were postfixed in 1% osmium tetroxide for 1 hr, dehydrated in graded acetone and propylene oxide, and embedded in Araldite (Fluka, Buchs, Switzerland). Semithin (1 μm) sections were cut with a Leica Ultracut UCT, stained with 1% toluidine blue, and observed with a Zeiss III photomicroscope. Ultrathin sections from the same tissue blocks were stained with uranyl acetate and lead citrate and examined with a Philips EM 208 transmission electron microscope.

2.2. Scanning electron microscopy (SEM)

For SEM, selected chordal fragments, fixed in 3% glutaraldehyde, were dehydrated in graded acetone, dried by the critical point method, coated with gold, and observed with an Inspect S microscope (FEI Company).

2.3. Histochemistry

Selected chordal fragments were dehydrated in graded ethanol and embedded in Paraplast (TYCO, Mansfield, USA). Thick (8 μm) serial sections were stained with either hematoxylin or eosin for a general assessment of tissue structure, Martin's trichrome for connective tissue, orcein for the detection of elastic fibres, or Sirius red for the detection of collagen [23].

3. Results

The gross morphology of normal and degenerative valves is shown in Fig. 1. The regular appearance of the control valve (Fig. 1a) contrasts with the thickened (Fig. 1b) and with the thinned (Fig. 1c) leaflets. Focal areas of leaflet calcification were observed in the latter two cases. Ruptured chordae were also observed in these two cases, but were more frequent in valves with thinner leaflets (Fig. 1c). Of note, a short history of dyspnoea was the most frequent cause of consultation, irrespective of the presence of previous cardiac symptoms. In most cases, ruptured chordae were found during echocardiographic exploration and/or surgery (also, see [1,5,24]).

We first examined the ruptured chordae. Under SEM, they showed a blunt appearance, or they were broken into threads (Fig. 1d). Most threads corresponded to the spongy layer of the chordae, which was usually separated from the dense collagenous core (Fig. 1e). At the areas of rupture, the chordae showed partial or total loss of endothelium, and complete disorganization of collagen and elastin material (not shown, but see [22,25]).

Next, attention was focussed on the intact chordae. Under a binocular microscope, many intact chordae showed a normal, regular appearance. In many other cases, however, the chordae presented irregular surfaces, lucent areas, and alternating thicker and thinner segments. Any affected chorda could show one, two, or all three modifications. When thinner and thicker segments obtained from the same chorda were analyzed under the light microscope, the dense collagenous core could show a regular appearance (Fig. 2a, b), or large structural disruption (Fig. 2c, d). In the latter cases, collagen bundles appeared disorganized, presenting areas of different density and compaction. On the other hand, the spongiosa could be fairly normal (Fig. 2b), irregularly thickened (Fig. 2a), or the boundaries between the spongiosa and the dense core were difficult to discern (Fig. 2c, d) due to structural disruption. Very often, the spongiosa appeared detached from the dense core (Fig. 3a). Elastin fibres were very prominent at the areas of detachment. Also, the smooth appearance of the dense core could be interrupted (Fig. 3a), indicating the beginning of core disruption (Fig. 3a, inset). In other cases the dense

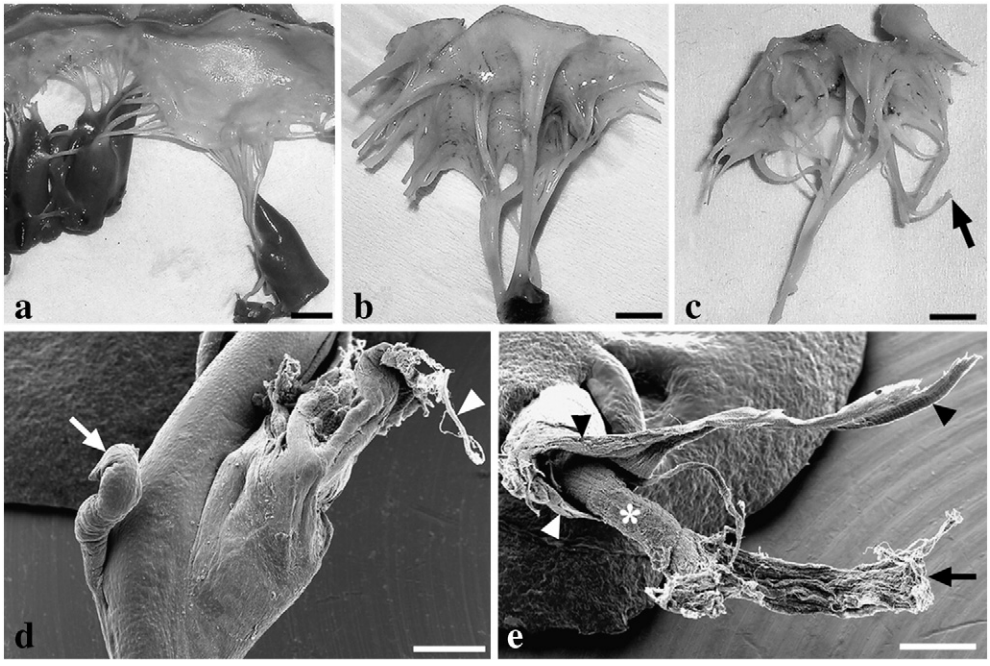

Fig. 1. a: Control mitral valve. b: Degenerative valve. Leaflet and chordal thickening are evident. c: Degenerative valve. Note chordal elongation and leaflet thinning. Arrow, ruptured chorda. d: SEM. Degenerative valve. Ruptured chordae show a blunt appearance (arrow) or appear broken into threads (arrowhead). e: SEM. This ruptured chorda shows a blunt end (arrow). The spongiosa (arrowheads) is separated from the dense collagenous core (asterisk). Collagen bundles appear disorganized. Magnification bars: a–c, 1 cm; d–e, 250 μm.