S
omnaneous coronary artery dissection is an unusual cause of myocardial ischaemia and sudden death. Its aetiology is difficult to determine. No specific cardiac risk factors have been associated with its occurrence. The underlying mechanism is not completely understood but predisposing factors may include extracellular matrix (ECM) disorders. ECM organisation depends on the amount and maturation of its various components—collagens, elastic fibres, and proteoglycans. Many lysine and proline residues in the excreted procollagen and tropoelastin chains are hydroxylated by lysyl and proline hydroxylases or oxidised by lysyl oxidase (LOX). Hydroxylation and oxidation are essential for subsequent cross linking and lead to polymerisation of elastic and collagen fibre during development. This polymerisation supports the mechanical properties of the arterial wall.

We describe the first case of human arterial wall lesion related to LOX deficiency and support the hypothesis of vascular wall fragility caused by an ECM cross linking defect.

CASE REPORT
A 38 year old man with no medical history and no cardiovascular risk factor presented in June 2002 with a two week history of effort dyspnoea without chest pain. Blood pressure was 120/70 mm Hg and cardiovascular examination was normal. The patient’s height was 183 cm and weight 72 kg. The morphological study showed a normal arm span, without arachnodactyly or dolichostenomelia but with increased proximal upper limb girdle laxity. The patient described an increase in upper limb girdle laxity in both his mother and maternal grandmother but no familial history of cardiovascular disease. Ophthalmological and skin examination were normal. ECG showed a subepicardial anterior ischaemia. All serum biological concentrations were normal. Transthoracic echocardiography was normal. Coronary angiography found an intimal flap in the first segment of the proximal left anterior descending coronary artery with no atherosclerotic lesion. Other coronary arteries and aorta were normal. Spontaneous coronary artery dissection was diagnosed. Bypass surgery was performed. Eighteen months later the patient was free of symptoms.

One year after the onset of the disease a skin biopsy of the anterior part of the right arm was taken for immunohistological and polymerase chain reaction (PCR) study to investigate ECM components (collagens I, III, and IV, elastin, and fibrillin-1) and cross linking enzymes (LOX and lysyl oxidase-like 1). The skin biopsy was compared with a sample of the same area obtained from an age matched man with no cardiovascular risk factors. PCR amplification was performed with human LOX specific primers and glyceraldehyde-3-phosphate dehydrogenase primers used as controls as previously described.

Skin histological morphological examination showed disorganisation of the elastic fibres of the ECM (fig 1A, B). Immunohistological analysis found a decrease of elastin and collagen I immunodetection. These results were confirmed by confocal analysis (elastin staining green and collagen I staining red) (fig 1A, B). Immunodetection of fibrillin 1 and collagen III and IV to investigate Marfan’s syndrome and the vascular Ehlers-Danlos syndrome, respectively, were normal. LOX (fig 2A, B) immunodetection was dramatically decreased compared with the control. Conversely, lysyl oxidase-like expression was normal. The important decrease in LOX mRNA expression relative to the control sample was confirmed by PCR semiquantitative analysis (fig 2C).

DISCUSSION
Arterial dissection is a rare vascular wall disease. ECM disorganisation is suggested to be a predisposing factor. Many ECM proteins are candidates to induce this vascular wall fragility. Some of them, such as collagen III or fibrillin I, are clearly related to connective disorders with vascular abnormalities. For example, in the Ehlers-Danlos syndrome type IV, related to an α-1 chain mutation in collagen III, disorganisation of the collagen network results in aneurysms and dissections of the coronary and cervical arteries. On the other hand, Marfan’s syndrome, related to a fibrillin-1 mutation, leads to elastic fibre disorganisation that results in aneurysms or coronary and cervical artery dissection. However, ECM diseases are a heterogeneous group and most of cases are not related to a known inherited genetic disorder of connective tissue.

Skin is a connective tissue that allows non-invasive investigations of ECM diseases. Skin ECM disorganisation without identified disease was previously reported in coronary artery dissections. Moreover, skin fibroblast

**Abbreviations:** ECM, extracellular matrix; LOX, lysyl oxidase; PCR, polymerase chain reaction.
cultures suggested abnormal collagen metabolism in spontaneous coronary artery dissection. Genetic and histopathological studies of dissections focused on ECM component defects or increased degradation. Conversely, post-transcriptional protein maturation through cross linking enzymes has rarely been investigated. Protein cross links lead to polymers of insoluble collagen and elastin. A collagen cross linking deficiency was described during the lysyl hydroxylase deficit observed in the Ehlers-Danlos syndrome type VI. Elastin cross link insufficiency was not previously investigated, whereas skin elastic fibre disorganisation is commonly described in spontaneous dissection. In our patient we found a dramatic LOX decrease. LOX initiates the cross linking of collagens, mainly collagen I, and of elastin by catalysing oxidative deamination of the ε amino group in certain lysine and hydroxylysine residues. In our patient the ECM network disorganisation associated with the decreased immunostaining of elastin and collagen I was probably caused by a LOX expression deficiency. A LOX deficit is observed in genetically modified animals and is usually related to copper deficiency in humans. The cardiovascular lesions found during LOX deficiency were cardiac enlargement, aortic fissures and rupture, medial thickening of the aorta, and intramural haemorrhages in thoracic, carotid, and coronary arteries leading to coronary artery thrombosis and myocardial infarction. No significant change was observed in the steady state levels of LOX mRNAs in fibroblasts isolated from patients with Marfan’s syndrome, Menke’s syndrome, cutis laxa, and pseudoxanthoma elasticum. Moreover, the human LOX gene, located on chromosome 3q22–31, has not been associated with vascular wall disease.

This case report provides new insight into the pathophysiology of connective tissue disorders that are often evoked in spontaneous coronary artery dissection. Mutations and polymorphisms of the LOX gene remain to be further investigated in this disease.

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