

## “Cardiac incidentaloma”: Left ventricular non-compaction in a kindred with familial coronary artery disease

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### Abstract

*Whether to a greater or lesser extent, genetics often plays an important role in the development of cardiovascular diseases. Here we report a newly identified family with familial coronary artery disease (CAD) and left ventricular non-compaction (LVNC).*

*A 52-year-old male with acute coronary syndrome, in whom LVNC had been found “incidentally,” was admitted for revascularisation. From a two-dimensional echocardiogram the epicardial layer appeared to be thin and compacted, but the apical endocardial layer of the left ventricle was extremely thickened with prominent trabeculations in the endocardial layer and deep intertrabecular recesses in a channel-like structure. Family history revealed that his 47-year-old brother also had LVNC but to a lesser degree. Their mother had two false tendons in the left ventricular apex and both parents had severe CAD.*

*Left ventricular non-compaction is “incidentally” identified in a kindred with familial CAD. The disease expressivity varies among affected individuals. Whether it is coincidental or there is a genetic link is a question that awaits further investigation. (Cardiol J 2007; 14: 407–410)*

**Key words:** coronary artery disease, non-compaction myocardium

### Introduction

Coronary artery disease (CAD) is the most common heart disease and the leading cause of death in the USA and developed countries. Family history of CAD is among the most important risk factors. On the other hand, non-compaction myocardium is a rare congenital cardiomyopathy with the features of a unique spongy myocardium and

a poor prognosis in patients with heart failure, arrhythmias and complications of embolism [1–3]. Accounting for 9% of primary cardiomyopathy in children [4] and 0.014% of pathological echocardiograms in adults [3], the prevalence of non-compaction myocardium is still underestimated. Since most reports in the literature describe very severe cases, it may well be that these represent only the tip of the iceberg. With advanced imaging technology, it is likely that more asymptomatic individuals will be identified [5, 6]. Case reporting has been encouraged by investigators, since most cardiologists are still unaware of this type of cardiomyopathy, and for the purpose of large-scale collaborative studies such reports aid recognition of the nature of the disease and facilitate disease-causing gene mutation investigations. Here we report a new kindred in which left ventricular non-compaction (LVNC) was

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“incidentally” discovered during the evaluation of acute coronary syndrome in the proband.

### Case description

In January of 2007 a 52-year-old male (175 cm, 78 kg) was admitted for the sudden onset of chest pain. His HDL level was 34 mg/dl and LDL level was 126 mg/dl, although the total cholesterol level was 188 mg/dl. He was a normotensive non-smoker and did not have diabetes. Compared to the normal ECG taken nine years before, his ECG after admission showed signs of hypertrophy of the left ventricle (LV) with poor R progression and ST-T changes in the left precordial and inferior leads (Fig. 1A). Coronary artery angiography revealed two focal lesions of > 90% stenosis in the left anterior descending (LAD) artery (Fig. 1B). The patient's angina was relieved after revascularisation with percutaneous transluminal coronary angioplasty and stenting. However, the LAD stenosis alone could not explain the excessive trabeculation in the honeycomb structure and the deep perfused intratrabecular recesses associated with marked anteroapical hypokinesia demonstrated on the LV angiogram (Fig. 1C). A two-dimensional echocardiogram showed the endocardial layer of the LV to be thickened non-continuously. The epicardial layer was thin and compacted, but the apical endocardial layer of the LV was extremely thickened with prominent trabeculations in the endocardial layer and deep intertrabecular recesses in a channel-like structure (Fig. 1D). His LV was mildly dilated and left ventricular ejection fraction was 45%. Cardiac magnetic resonance imaging (Fig. 1E) was consistent with the echocardiogram, LV angiogram and ECG findings that this patient indeed had LVNC in addition to the LAD stenosis.

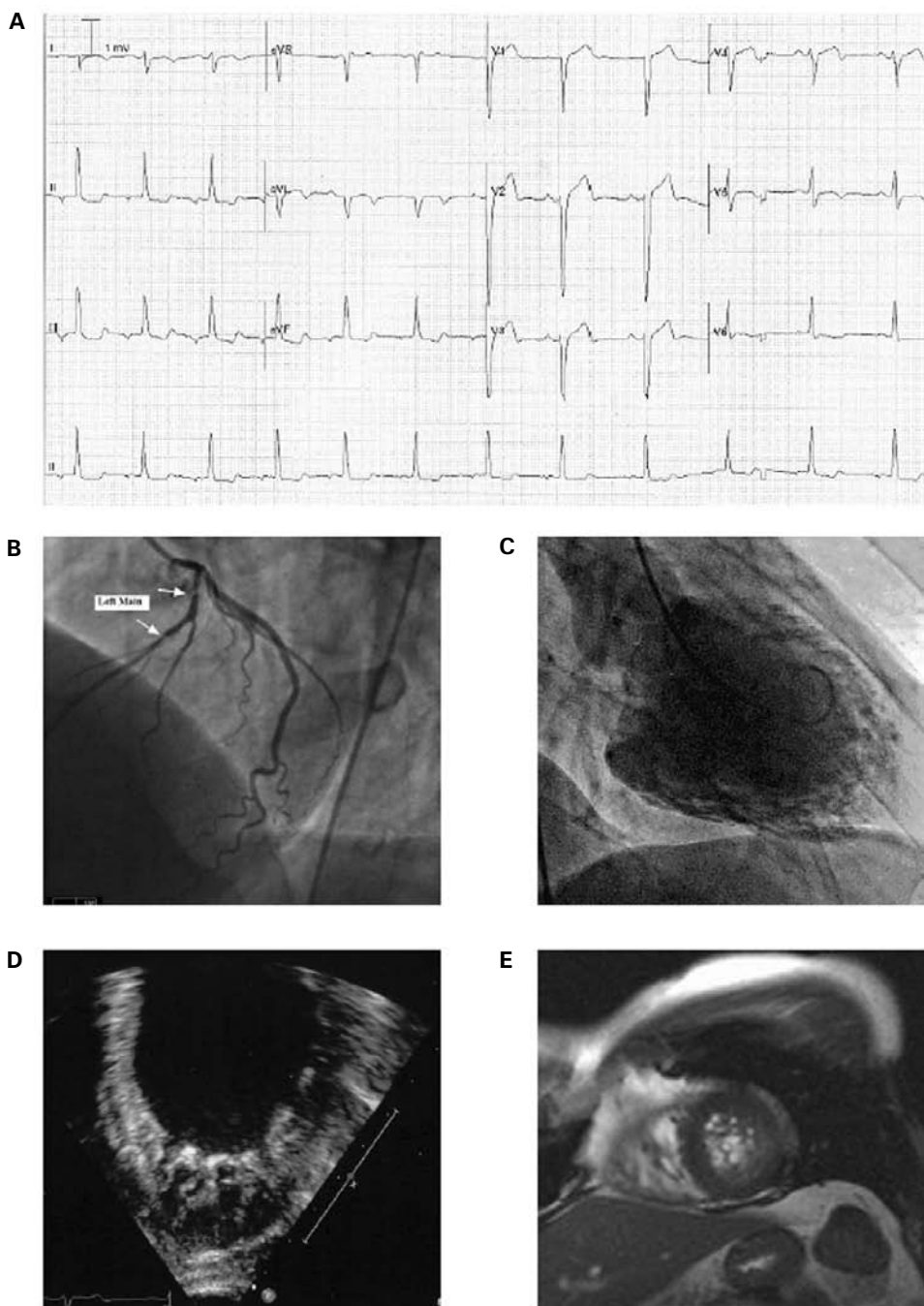
Subsequent family screening identified his 47-year-old brother as having LVNC, although less pronounced. His total cholesterol level was 250 mg/dl (LDL 153 mg/dl) and triglyceride level was 313 mg/dl. ECG was normal. He had been asymptomatic and declined further evaluation. Two false tendons in the LV apex were found in the mother. She had moderate hypertension and hypercholesterolemia (237 mg/dl). The father had mild hypertension and type-2 diabetes but with negative LVNC findings. Both parents had undergone coronary artery bypass grafting because of severe CAD. No abnormalities were identified in the 16-year-old son of the proband. None of the first-degree blood-related family members had dysmorphic features or other congenital heart anomalies.

### Discussion

The term “incidentaloma” usually refers to an adrenal neoplasm incidentally found during another investigation. Incidentaloma could, however, be applied to different incidental findings, as in this case of LVNC discovered during the evaluation of CAD [7]. Family screening identified the proband's younger brother as also having LVNC. Both parents had severe CAD and the mother might also be a silent LVNC gene carrier. Our experience raised questions about the true prevalence of LVNC. These two brothers were asymptomatic with respect to LVNC, which could have remained unrecognised if the proband had not developed acute coronary syndrome [7]. Thus we consider LVNC a “cardiac incidentaloma”.

Non-compaction myocardium has attracted much scientific and clinical interest in recent years because it is related to the early steps of cardiovascular development. At the embryonic stage the spongy nature of the myocardium allows diffusion of oxygen and nutrients into the cardiomyocytes. Recent studies have revealed that mutations of the encoding genes [8–11] could lead to the arrest of myocardial morphogenesis, resulting in a persistent spongy myocardium after birth and the development of non-compaction cardiomyopathy in some, if not all, individuals. In the absence of direct communication to the epicardial coronary artery system, the region of the non-compaction myocardium is perfused directly from the LV cavity. Owing to decreased coronary flow reserve, segmental wall motion abnormalities are common [12].

Cardiac development is complex and the sequential process is regulated by cardiogenic transcriptional factors and growth/differentiation factors. Ventricular trabeculation and compaction are important processes in morphogenesis and are closely associated with cardiac growth regulation at mid-gestation. At a certain stage of embryonic cardiac development trabecular myocytes in the developing myocardium undergo “compaction” and gradually become part of the compact wall, papillary muscles, interventricular septum and conductive system. Bone morphogenetic proteins (BMPs) belong to the transforming growth factor  $\beta$  (TGF- $\beta$ ) family and are linked to multi-step cardiac development. For example, BMP10 is transiently present in the developing trabecular myocardium. Upregulation of BMP10 could result in the overproduction of ventricular trabecule and non-compaction in a FKBP12-deficient mouse model [10]. BMP10 has a close relationship with transcriptional factors



**Figure 1.** **A.** The atrial pacing ECG of a 52-year-old male proband shows 1) the deep S wave (27 mm) in V2 (SV2 + + RV6 > 35 mm) and the strained ST-T pattern in the inferior leads meet the modified Sokolov-Lyon Index of left ventricular hypertrophy; 2) ischemic T wave inversion in leads I, aVL and V4–5, and 3) right QRS axis with poor R progression in V3–5. **B.** The LAO view of left coronary artery of the proband shows two focal lesions, suggesting severe left anterior descending stenosis. The upper lesion is eccentric and the lower is concentric. The remaining vessel branches, including circumflex and intermediate arteries, are smooth. Multi-view of motion film (not shown) is consistent with the diagnosis. **C.** The left ventricular angiogram is characterised by the excessive trabeculation in the honeycomb structure. Motion film (not shown) revealed the deep perfused intratrabecular recesses associated with marked anteroapical hypokinesis. **D.** From the two-dimensional echocardiogram of the proband the left ventricular apex reveals an extremely thickened endocardium with prominent trabeculations and deep intertrabecular recesses in a channel-like structure and a thin compact layer of epicardium. At the site of maximal wall thickness the ratio of non-compacted endocardium/compacted epicardium is > 2.3. The left ventricle is mildly dilated with left ventricular ejection fraction of 45%. **E.** Short-axis view of cardiac magnetic resonance imaging at the left ventricular apical level shows diffuse spongy tissue.

NKX2.5 and MEF2C to balance with negative cell cycle regular p57<sup>kip2</sup> in the developing heart at mid-gestation. BMP10 also contributes epithelial mesenchymal transformation and a coronary vessel network develops within the subepicardial mesenchyme [13]. One of the myocyte enhancer MEF2 transcription factors, MEF2A, is highly expressed in the endothelium of the coronary arteries. The defective coronary arteries are, owing to MEF2A mutations, more prone to inflammation and thrombosis, especially under environmental risk factors, eventually leading to CAD [1, 14, 15].

In this kindred dyslipidemia is present in 4/5 of first-degree blood-related family members, including two LVNC siblings. Thus the coincidence of LVNC and CAD due to familial dyslipidemia is likely. Nevertheless it may also be speculated that the gene mutation(s) controlling cardiac development may be responsible for both the non-compaction myocardium and the development of defective coronary endothelium. The latter is susceptible to coronary atherosclerosis and stenosis, especially in the presence of hypercholesterolemia. Continued investigation into family pedigree expansion, follow-up and gene mutational research may help uncover the disease-causing mechanism.

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