



Assessment of subclinical atherosclerosis and intraplaque neovascularization using quantitative contrast-enhanced ultrasound in patients with familial hypercholesterolemia



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ABSTRACT

Objective: Patients with heterozygous familial hypercholesterolemia (FH) are at severely increased risk of developing atherosclerosis at relatively young age. The aim of this study was to assess the prevalence of subclinical atherosclerosis and intraplaque neovascularization (IPN) in patients with FH, using contrast-enhanced ultrasound (CEUS) of the carotid arteries.

Methods: The study population consisted of 69 consecutive asymptomatic patients with FH (48% women, mean age 55 ± 8 years). All patients underwent carotid ultrasound to evaluate the presence and severity of carotid atherosclerosis, and CEUS to assess IPN. IPN was assessed in near wall plaques using a semi-quantitative grading scale and semi-automated quantification software.

Results: Carotid plaque was present in 62 patients (90%). A total of 49 patients had plaques that were eligible for the assessment of IPN: 7 patients (14%) had no IPN, 39 (80%) had mild to moderate IPN and 3 (6%) had severe IPN. Semi-automated quantification software showed no statistical significant difference in the amount of IPN between patients > 50 years and patients ≤ 50 years and between patients with a defective low-density lipoprotein receptor (LDLR) mutation and patients with a negative LDLR mutation. Plaques with irregular or ulcerated surface had significantly more IPN than plaques with a smooth surface ($p < 0.05$).

Conclusion: Carotid ultrasound demonstrated atherosclerotic plaque in 90% of asymptomatic patients with FH without known atherosclerosis. IPN assessed with CEUS, was present in 86% of these patients. Irregular and ulcerated plaques exhibited significantly more IPN than plaques with a smooth surface.

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1. Introduction

Heterozygous familial hypercholesterolemia (FH) is the most prevalent autosomal dominant inherited disorder of the lipoprotein metabolism, resulting in increased LDL cholesterol levels. Patients with FH are at severely increased risk of developing atherosclerosis at relatively young age. The introduction of statin treatment has

partly reduced the risk of myocardial infarction and stroke in patients with FH [1–4]. Still, patients with FH receiving long term statin treatment may have a substantial amount of subclinical atherosclerosis [5]. There is a large variation in the extent and severity of atherosclerotic disease, and therefore presymptomatic evaluation of atherosclerosis may be especially useful in patients with FH.

Carotid ultrasound is a widely available, low-cost and free from ionizing radiation imaging modality for the evaluation of (subclinical) atherosclerosis. Previous studies have demonstrated that ultrasound assessment of carotid intima-media thickness and plaque provides valuable information for monitoring the response to treatment and for risk-stratification in patients with FH [6,7]. Contrast-enhanced ultrasound (CEUS) is an advanced form of ultrasound imaging using a microbubble contrast agent to provide

Abbreviations: CEUS, contrast-enhanced ultrasound; CIMT, carotid intima-media thickness; FH, familial hypercholesterolemia; IPN, intraplaque neovascularization.

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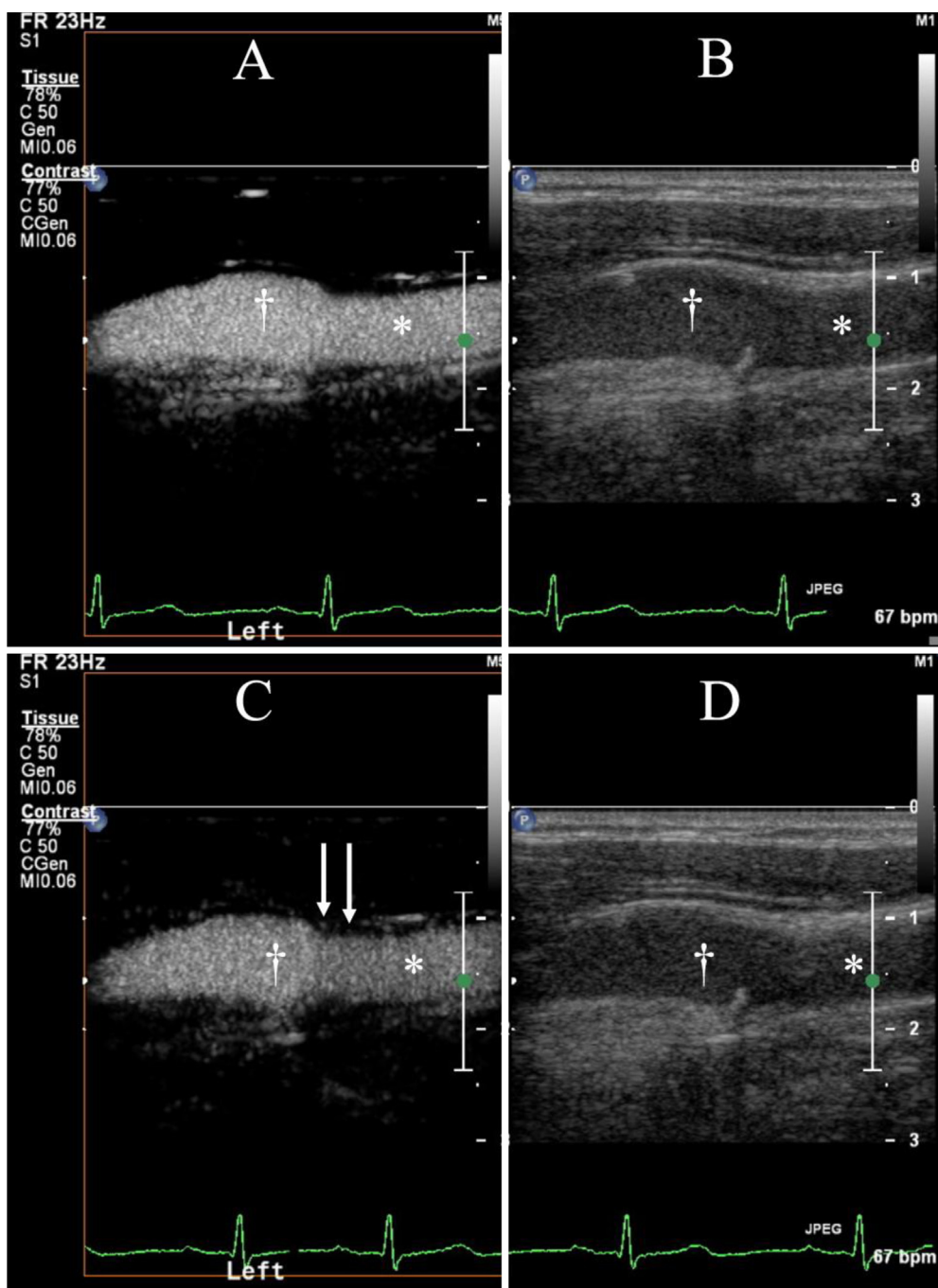


Fig. 1. Example of side-by-side contrast enhanced ultrasound (CEUS) examination. *common carotid artery, †carotid bulb. Panel A: CEUS clip of the left carotid artery shortly after contrast injection. Panel B: corresponding B-mode clip of the left carotid artery recorded simultaneously with the CEUS clip. Panel C: A CEUS clip of the same carotid artery recorded a few seconds following contrast administration. The arrows indicate contrast-enhancement in a small atherosclerotic plaque in the carotid bulb. Panel D: corresponding B-mode clip of the left carotid artery recorded simultaneously with the CEUS clip.

improved detection of plaques and can be used to visualize intra-plaque neovascularization (IPN) [8–10]. Recent data indicate that IPN is a marker of plaque instability. A recent pathology study of unstable carotid lesions demonstrated that IPN and intraplaque hemorrhage are predictors of rupture of atherosclerotic plaques [11]. This confirms the suggestion that these histological characteristics are considered to be components of the vulnerable atherosclerotic plaque [12]. Information on IPN in patients with FH is at present not available, but may be relevant for a better understanding of the pathophysiology of atherosclerosis, development of new treatment approaches, and risk stratification. The aim of this

study was therefore to assess the prevalence of subclinical atherosclerosis and IPN in a consecutive group of patients with FH. Carotid ultrasound was used to evaluate the presence and severity of carotid atherosclerosis, and CEUS was used to assess IPN.

2. Methods

2.1. Patient population and study protocol

The study population consisted of 69 asymptomatic patients with heterozygous FH. Inclusion criteria were: heterozygous FH,

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