High prevalence of raised lipoprotein(a) in patients with refractory angina

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ABSTRACT

Background: Angina that is refractory to conventional medical therapy and revascularisation, remains challenging to manage and poses significant burden to patients. Elevated lipoprotein(a) [Lp(a)] has emerged as an important independent cardiovascular risk factor and predictor of adverse outcomes in atherosclerotic disease. The prevalence of raised Lp(a) amongst patients with refractory angina has not yet been defined.

Objective: To establish the prevalence of raised [Lp(a)] >500 mg/L in patients with refractory angina.

Methods: We conducted an epidemiological screening pilot study in 75 patients with refractory angina from a UK tertiary cardiac centre. We determined the proportion of the cohort with raised Lp(a) >500 mg/L using an isoform-insensitive method. In addition, a full fasting lipid profile (including: LDL cholesterol, HDL cholesterol, total cholesterol to HDL ratio and triglycerides) was obtained. Patients were also asked about the presence of conventional cardiovascular risk factors.

Results: Our study demonstrated that 60% of the 75 patients with refractory angina had raised Lp(a) levels of >500 mg/L. The median and inter-quartile range of Lp(a) values were 771 mg/L (162 mg/L,1260 mg/L) respectively.

Conclusions: This high prevalence of raised Lp(a) detected in our cohort with refractory angina may suggest a causal role. Further research is necessary to confirm this association and prospective studies are needed to explore the potential therapeutic benefit of Lp(a) reduction in patients with refractory angina.

Keywords: Refractory angina, Coronary artery disease, Lipoprotein (a), Risk factors
Elevated lipoprotein(a) [Lp(a)] is an important independent cardiovascular risk factor and predictor of adverse outcome in atherosclerotic disease. Lp(a) may potentially have a causal role in refractory angina, however, the prevalence of Lp(a) in this population has not yet been defined.

Our epidemiological screening pilot study provides an estimation of the prevalence of raised Lp(a) amongst patients with refractory angina. We found that 60% of our study cohort with refractory angina had raised Lp(a) > 500 mg/L.

Given that our screening programme has suggested that a substantial proportion of individuals with refractory angina have raised Lp(a); this risk factor deserves further attention as a potential target for therapy, as it may have a causal role.

Further research is necessary to confirm this association and good quality prospective studies are urgently needed to explore the potential benefit of aggressive Lp(a) reduction in patients with refractory angina.

INTRODUCTION

Cardiovascular disease remains the leading cause of death in the developed world. The majority of patients with angina, resulting from coronary heart disease (CHD) are successfully treated with conventional medical therapy and revascularisation techniques such as coronary artery bypass graft (CABG) surgery or percutaneous coronary interventions (PCI). However, there is a subset of patients who have severe disabling angina from coronary artery disease which is refractory to conventional therapy, for whom management is particularly challenging.

Refractory angina, as defined by Mannheimer and colleagues in 2002, is ‘a chronic condition characterised by the presence of angina caused by coronary insufficiency in the presence of coronary artery disease which cannot be controlled by a combination of medical therapy, angioplasty and coronary bypass surgery’. There are no accurate figures on the occurrence or frequency of refractory angina, though there is universal agreement that its prevalence is increasing. The European Society of Cardiology estimates that 15% of patients who experience angina can be characterized as having refractory angina. Estimates based on rejection rates for further intervention amongst angina patients in Europe suggest that between 30,000 and 50,000 patients per year develop the condition. Most of these patients are relatively young and have a moderately impaired left ventricular ejection fraction. An estimated 300,000 to 900,000 patients in the United States have refractory angina, with between 25,000 and 75,000 new cases diagnosed each year.

The healthcare burden of this condition is significant and the management of affected patients is challenging, with limited treatment options. Aside from conventional anti-anginal agents such as beta-blockers, calcium channel blockers and nitrates, newer pharmacological agents include ranolazine, which works by altering the trans-cellular late sodium current; and ivabradine, an If channel inhibitor. Current non-pharmacologic options for patients with refractory angina include neurostimulation (transcutaneous electrical nerve stimulation and spinal cord stimulation), enhanced external counterpulsation (EECP) therapy, laser revascularization, gene therapy, and newer procedures such as extracorporeal shockwave myocardial revascularization. Although a limited number of treatment options exist for refractory angina, further evidence to support widespread use of these treatments is required. In addition, there is a pressing need to identify further treatments and therapeutic targets.

Lipoprotein(a) [Lp(a)] is an inherited, genetically-determined form of LDL-cholesterol consisting of a cholesterol-rich LDL particle with one molecule of apolipoprotein B100 and an additional protein, apolipoprotein(a), attached via a disulphide bond. It was discovered in the 1960s by Berg. Although the exact physiological role of Lp(a) is not currently understood; an elevated Lp(a) level has emerged as an important independent cardiovascular risk factor and predictor of adverse outcome in atherosclerotic disease. Lp(a) may potentially have a causal role in refractory angina, however, the prevalence of raised Lp(a) in this population has not yet been defined.

METHODS

We identified patients with refractory angina from cardiology outpatient clinics and cardiac catheterisation lists at Royal Brompton and Harefield NHS Foundation Trust. Patients included had to
satisfy the following requirements:

- A diagnosis of refractory angina for more than three months.
- Two or more episodes of angina per week.
- Previous history of myocardial infarction, coronary artery bypass graft surgery, percutaneous coronary intervention (PCI) or any combination of the above.
- Prescribed optimal medical therapy including at least two oral anti-anginal agents.
- Established on statin therapy.

Such patients were invited to a screening clinic and had venous blood samples taken for Lp(a) using an isoform-insensitive method (Lp(a) Ultra: a quantitative immunoturbidimetric method), as well as a full fasting lipid profile including: LDL cholesterol, HDL cholesterol, total cholesterol to HDL ratio and triglycerides. Patients were also asked about the presence of conventional cardiovascular risk factors such as smoking history, family history, diabetes mellitus and hypertension.

We determined the distribution (median, interquartile range; given non-parametric distribution of values) of Lp(a) levels as well as LDL cholesterol, HDL cholesterol and triglyceride levels in the group. We also calculated the proportion of patients (%) with: Lp(a) raised >500 mg/L, LDL cholesterol >2 mmol/L despite optimised statin therapy. The proportion of patients with positive family history, hypertension, diabetes mellitus, smoking history and male gender were also defined.

RESULTS

Seventy five patients with refractory angina who fulfilled the above inclusion criteria were screened for their fasting lipid profiles including Lp(a) as well as conventional cardiac risk factors. Of the 75 patients tested, 60% had raised Lp(a) levels of >500 mg/L (Figure 1).

Given that the Lp(a) levels were not normally distributed we calculated the median and inter-quartile range of values which were 771 mg/L (162 mg/L, 1260 mg/L)(see Figure 2a). Fifty per cent of the patients with refractory angina had LDL cholesterol levels of >2 mmol/L. Comparably, 47% of patients with Lp(a) >500 mg/L also had LDL cholesterol level of >2 mmol/L. The median and inter-quartile range of LDL cholesterol levels were 2.02 mmol/L (1.57 mmol/L, 2.75 mmol/L) respectively (see Figure 2b). LDL cholesterol values were calculated using the Friedewald equation and were not corrected for the cholesterol in Lp(a). The median and inter-quartile range for HDL cholesterol levels were 1.11 mmol/L (0.93 mmol/L, 1.30 mmol/L); and the median and inter-quartile range for triglyceride levels were 1.30 mmol/L (0.90 mmol/L, 2.00 mmol/L) (see Figure 2c).

Of the 75 patients, 65% had a positive family history of coronary artery disease (CAD) amongst first degree relatives (Table 1) whereas in patients with raised Lp(a) (>500 mg/L) family history was marginally higher at 73% (Table 1). Heterozygous familial hyper-cholesterolaemia (FH) was confirmed in 6 of the 75 patients ie. 8% of the cohort.

Similarly the incidence of hypertension amongst the total 75 patients with refractory angina was comparable to the subset of patients with raised Lp(a) >500 mg/L at 69% and 64% respectively (Table 1), which is consistent with the findings of Solanki and Kumar.9

![Figure 1. Percentage of patients with refractory angina with Lp(a) >500 mg/L. Total patients = 75.](image)
We also examined the prevalence of other conventional cardiac risk factors such as diabetes mellitus, smoking history (current and previous smoking history) and male gender. Forty per cent of the 75 patients had diabetes mellitus. Thirty nine per cent of the 75 patients had a history of smoking. Ninety one per cent of the total cohort were male and of those 58% had raised Lp(a) \( \geq 500 \text{ mg/L} \).

Whereas of the female patients, 71% had raised Lp(a). The ethnic origin of the patients in our cohort was 56% Caucasian, 39% Asian, 4% Greek/Cypriot extraction and 1% Afro-Caribbean.

**DISCUSSION**

These findings suggest an association between raised Lp(a) and refractory angina which may implicate Lp(a) in having a causal role in the aetiology of this condition. Ideally, the relevance of this observation
needs to be further substantiated by testing a control group of patients with CHD but without refractory angina. In addition, further research is needed to explore raised Lp(a) as a risk factor for refractory angina or accelerated coronary artery disease and to determine the clinical and symptomatic benefit of aggressively lowering Lp(a) in such individuals. Given that our screening programme has suggested that a substantial proportion of individuals with refractory angina have raised Lp(a), this risk factor deserves further attention as a potential target for therapy.

THE ROLE OF LIPOPROTEIN(A) IN CARDIOVASCULAR DISEASE:

A large epidemiological study showed that the relative risk of CHD per 3.5-fold higher Lp(a) level adjusted for age and sex only was 1.16 and 1.13 (95% CI: 1.09-1.18) following further adjustment for systolic blood pressure, smoking, history of diabetes and total cholesterol.10

Elevated Lp(a) is believed to promote atherosclerosis via Lp(a)-derived cholesterol entrapment in the intima, inflammatory cell recruitment and/or via the binding of pro-inflammatory-oxidised phospholipids, such as oxidised LDL.11 In addition, elevated Lp(a) is felt to be pro-thrombotic via the inhibition of fibrinolysis with enhancement of clot stabilisation as well as via enhanced coagulation via the inhibition of tissue factor pathway inhibitor.11

An increased level of Lp(a) is highly heritable. Two variants of the LPA locus on 6q26-27 encoding Lp(a) lipoprotein (rs10455872) and (rs3798220) were strongly associated with both an increased level of Lp(a) and risk of coronary disease.12

Approximately one in five individuals have plasma levels above 500 mg/L (80th percentile), and about one in four individuals have plasma levels above 320 mg/L (75th percentile). Lp(a) levels less than 300 mg/L are considered normal.10

The prevalence of raised Lp(a) in refractory angina has not previously been defined. Our pilot screening programme suggests that a significant proportion of patients with refractory angina and progressive coronary disease have raised Lp(a) as an underlying risk factor.

THE TREATMENT OF LIPOPROTEIN(A)

Most patients with raised LDL cholesterol can be adequately treated with appropriate dietary measures and lipid-lowering drug therapy.13 However, the conservative therapy of elevated Lp(a) is unsatisfactory.14 Data assessing the impact of statins on Lp(a) are limited and highly variable15 and overall, statins are ineffective at significantly lowering Lp(a). Nicotinic acid based treatment (eg. Tredaptive) was previously felt to be modestly effective at lowering Lp(a), however the European Medicines Agency have withdrawn it based on findings from the HPS2-THRIVE trial showing that this drug does not reduce major adverse cardiac events and causes a higher incidence of serious non-fatal side effects.15

The proprotein convertase subtilisin kexin type 9 (PCSK9) monoclonal antibody, Evolocumab (AMG 145) offers a potential future pharmacological approach to Lp(a) reduction. Recently the effect of evolocumab (AMG 145) on Lp(a) was assessed from a pooled analysis of data from 1,359 patients involved in 4 phase II trials.16 Evolocumab treatment for 12 weeks resulted in significant (p < 0.001) mean (95% confidence interval) dose-related reductions in Lp(a) compared to control: 29.5% (23.3% to 35.7%) and 24.5% (20.4% to 28.7%), with 140 mg and 420 mg, dosed every 2 and 4 weeks, respectively.16 This data lends further support to studying the impact of PCSK9 inhibition on Lp(a) in a phase III clinical outcomes trial. In addition, it would be useful to assess the impact of monoclonal antibodies to PCSK9 in patients with exclusively raised Lp(a), as the majority of patients assessed in

| Table 1. Percentage of study patients with positive family history of CAD & percentage of study patients with hypertension. |
|---------------------------------------------------------------|
| Patients with Refractory Angina (n = 75) | Patients with Refractory Angina and Lp(a) > 500 mg/L (n = 45) |
| Percentage (%) with positive Family History of CAD | 65 | 73 |
| Percentage (%) with Hypertension | 69 | 64 |

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these phase II studies had concomitant raised levels of LDL cholesterol given that the impact on LDL cholesterol was also being assessed.

Another potential pharmacological treatment that holds promise for the future are anti-sense oligonucleotides (ASO) directed to apolipoprotein (a) [Apo(a)], thereby reducing Apo(a) and Lp(a) levels. So far, animal studies have shown that this may provide an effective approach to lower elevated Lp(a) levels. However, further human trial data is necessary to determine the safety and efficacy of this treatment before it can be established for widespread use.

Lipoprotein apheresis is a selective lipid-lowering extracorporeal treatment by which excess atherogenic ApoB100-containing lipoproteins, including Lp(a) and LDL cholesterol, are removed from blood or plasma. It remains the most effective means of lowering Lp(a) currently available.17 To the best of our knowledge, to date no randomised controlled trials have been performed to objectively assess the clinical and symptomatic benefit of Lp(a) reduction in patients with refractory angina. As such, we are in the process of conducting a prospective, randomised controlled cross-over study of patients with refractory angina and raised Lp(a) in the absence of raised LDL cholesterol, randomised to undergo lipoprotein apheresis or ‘sham’ apheresis with assessment of myocardial perfusion, carotid atherosclerosis, endothelial vascular function, thrombogenesis, oxidised phospholipids and their antibodies, exercise capacity, angina symptoms and quality of life at the beginning and end of treatment. Our study aims to address whether lowering Lp(a) is beneficial in patients with refractory angina and raised Lp(a) and will assess the mechanisms of this treatment effect on numerous clinical parameters. Results of this trial are expected to be available at the end of 2015.

CONCLUSION
Refractory angina remains a challenging dilemma faced by patients and clinicians. Although there are a handful of treatment options open to affected patients including a few newer pharmacological agents, enhanced external counter-pulsation (EECP) therapy and neuro-stimulation techniques, there remains a pressing need to explore further therapeutic targets and options. Our pilot screening programme demonstrates that there is a high prevalence of Lp(a) in this population, suggesting that it may potentially have a causal role. Further research is necessary to confirm this association and good quality prospective studies are urgently needed to explore the potential benefit of aggressive Lp(a) reduction in patients with refractory angina.

Conflicts of interest
None

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