

post-run cTn concentrations. Post-run cTn concentrations did not correlate with NT-proBNP concentrations. Furthermore, post-run cystatin C levels were increased in 27% of the runners. The number of subjects with elevated post-run creatinine levels was 1.6 to 1.8 times higher than for cystatin C, as creatinine results could be influenced by physical activity. Cystatin C concentrations did not correlate with cTn and would thereby suggest that exercise-induced cTn elevation is not caused by a reduced renal clearance. Future research is required in order to explain exercise-induced cTn elevations.

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## The occurrence of CFTR mutations in patients with bronchiectasis

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### Introduction

Homozygosity or compound heterozygosity for mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene causes cystic fibrosis. In Western European countries approximately 1 in 30 people is a carrier of a disease causing CFTR mutation. Carriership of such mutations is known to be harmless, however, recent data have shown that carriership might have health implications in later life, especially concerning lung function and chronicity of lung infections. Bronchiectasis is a lung disease that causes abnormal stretching and enlargement of the bronchi and is often found to be idiopathic. Recent advantages in lung imaging facilitate the diagnosis of bronchiectasis, however this did not lead to the expected increase in the number of patients. On the contrary, it was found that the occurrence of bronchiectasis has dropped significantly in the last decades. The decrease might be due to the successful treatment of lung infections with antibiotics and current vaccination programs prevent-

ing such infections. Nowadays, it is thought that the cause of the disease in the remaining patients is of a congenital nature.

A gene likely to be involved in the development of bronchiectasis is CFTR, because it encodes the transmembrane chloride channel between the epithelial cell and the lumen. A low chloride level causes extremely viscous mucus, which in turn causes clogging of the airways and predisposes to lung infections. Healthy individuals carry two correct copies of the gene, while Cystic Fibrosis (CF) patients have two mutated, dysfunctional alleles. It is believed that one working copy of the gene is enough to function normally.

Contradictory results have been published on the occurrence of CFTR mutations in patients with bronchiectasis. Several papers have shown that an increase of mutations was found, up to 60%, while others have found 0 to 4% (which does not deviate from the expected population frequency of 3.3%) (1, 2). However, in many reports, especially those yielding high numbers of mutations, patients with adult-onset CF were included in the analysis. We have started a study investigating 36 CFTR mutations and the polythymidine tract variation in adult patients with bronchiectasis of an idiopathic nature.

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## Methods

So far, twenty-two adult patients with bronchiectasis that visited the St Antonius Hospital Nieuwegein (mean age 55 years (range 32-72 years)) were selected for analysis. The diagnosis of bronchiectasis was confirmed on high resolution computed tomography (HRCT) (figure 1). DNA was extracted from 150 µl whole blood on the MagnaPure (Roche) and analysed for CFTR mutations with the Inno-Lipa CFTR19 and CFTR17+Tn update kit (Innogenetics) following the manufacturers instructions. In short the protocol consists of an initial multiplex PCR with subsequent hybridisation of the PCR-product to allele-specific probes on strips. Together, per patient, thirty-six CFTR mutations and the variation in the polythymidine tract were analysed on these strips.

The coverage of the mutational analysis was calculated by adding up the frequencies of those mutations that were previously determined in cohorts of Dutch CF patients (3-5). The described frequency of fourteen mutations that were on the Inno-lipa assay adds up to a total of 86.2%. For 22 mutations the frequency was unknown, and estimated to be 0.1%. In total it is estimated that the combined InnoLipa assay covers 88.4% of the CFTR mutations present in the Netherlands.

## Results

In 22 bronchiectasis patients we found three mutations (13.6%) in the CFTR gene. The difference with the expected population frequency of CF mutations that can be detected with the assay (2.9%) is significant ( $p < 0.05$ , Fisher exact). One patient carried the R117H mutation and two of the patients carried the R1162X mutation. Both these mutations have very low expected frequencies in the Dutch population (0.01 and 0.03% respectively). The patients with the R117H mutation was 67 years old, while the patients with the R1162X mutation was 46 and 33 years old. Both R117H and R1162X have not been detected before in bronchiectasis patients (6).

## Conclusion

We believe that mutations in the CFTR gene predispose to the development of bronchiectasis. Enlargement of the patient population in the future is needed to determine the contribution of CFTR mutations to bronchiectasis. Further study will also unveil whether the association is primarily found with specific, rare CFTR mutations, such as R1162X. Two of the three patients with a mutation were relatively young, which fits the idea that present-day bronchiectasis is more likely to have a genetic cause. Specifically the younger



**Figure 1.** Typical HRCT pattern of a bronchiectasis patient, with a diffuse pattern of airway clogging.

patients with bronchiectasis should always be analysed for CFTR mutations, this might provide useful insights in the cause and the development of the disease.

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