Coronary artery disease in cystic fibrosis: An emerging concern?

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Letter to the Editor

Advances in cystic fibrosis (CF) care have significantly improved patient survival. Consequently, CF-related complications less common in younger individuals are becoming increasingly prevalent during the adult years. It is unclear whether this also applies to coronary artery disease (CAD). Although case reports of CAD exist in the literature, this topic has not been systematically studied and many CF experts believe CF patients are “protected” from CAD. However, whether this truly represents lower risk or is the result of this patient population not surviving long enough to develop CAD remains uncertain. Individuals with CF have several CAD risk factors including diabetes, high fat diets, altered lipid metabolism, decreased fat-soluble antioxidant levels, and increased systemic inflammation [1]. Recent studies have also demonstrated indirect evidence of atherosclerosis in CF, including endothelial dysfunction based on impaired flow-mediated dilatation [2], and increased vascular stiffness [3]. Chronic inflammation may be an important driver of vascular disease in CF by causing endothelial injury and increased arterial stiffness.

Coronary angiography via cardiac catheterization is routinely performed on all patients 40 years and older prior to lung transplant for cardiovascular screening at our adult CF program (Vancouver, BC, Canada), regardless of underlying cardiovascular risk factors. This provided us with a unique opportunity to retrospectively examine for coronary atherosclerosis and CAD in this older advanced lung disease CF cohort with high rates of CF-related diabetes and chronic inflammation. Charts were reviewed following institutional ethics board approval (UBC REB H16-00386).

Between 1996 and 2016, a total of 330 adults with CF were registered at our centre, with 90 (27%) being 40 years and older. During this time frame, 73 adults with CF were assessed for lung transplant and 16 (22%) were 40 years of age or older. Of the 16 patients 40 years and older, 14 (88%) underwent coronary angiography. Of the two individuals who did not undergo angiography, the reason for not pursuing the test was unclear. The clinical characteristics of included patients are summarized in Table 1 and are generally representative of a pre-transplant CF population. CF-related diabetes (CFRD), affected 64% of patients with a median duration of disease of 6 years (range 0–19 years). Of those with CFRD, 56% were insulin-dependent. Based on National Cholesterol Education Program criteria [4], dyslipidemia was present in 69% of patients. Of those individuals with dyslipidemia, 78% had low HDL and the remainder had high total cholesterol but none had triglyceride or LDL abnormalities (Table 1). No patients had a documented history of hypertension or acute coronary syndrome. Documentation of smoking status and family history of cardiovascular disease was not available for most patients.

The coronary angiography reports and “still” diagrams were carefully reviewed for evidence of luminal narrowing or complete obstruction of the coronary vessels consistent with atherosclerosis. Interestingly, no vessels had evidence of narrowing and not a single atherosclerotic plaque was documented in the 14 patients examined.
Chronic systemic inflammation has been identified as an independent risk factor for atherosclerosis. Studies involving other chronic inflammatory disease states, such as idiopathic pulmonary fibrosis [5] (IPF) and rheumatoid arthritis [6] (RA), have shown that individuals with these chronic conditions have a higher likelihood of CAD (even after accounting for age and other common cardiac risk factors). Kim et al. noted a CAD prevalence of 7% in IPF subjects (n = 460) compared to 3% in controls (n = 1925) [5]. Karpouzas et al. found coronary plaques on computed tomography (CT) angiography in 71% of adults with RA (n = 150) versus 45% of controls (n = 150) [6]. The mean age of CAD-affected groups in these studies was 65 and 53 years, respectively [5,6]. In contrast, our study suggests CAD is uncommon in CF, even among a group of relatively older patients with advanced lung disease and multiple cardiovascular risk factors. However, our population was slightly younger (median age 47 years) than those in the aforementioned IPF and RA studies [5,6].

Overall, this data is reassuring as natural history studies have shown that atherosclerotic changes often appear in coronary arteries years and sometimes decades before the onset of clinically significant coronary heart disease [7]. However, acknowledging that the macrovascular complications of diabetes can lag disease onset by about 20 years [8], ongoing studies are required to provide further reassurance as the median age of survival continues to increase.

Conflicts of interest
None.

Acknowledgements
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References

Table 1
Clinical characteristics of CF individuals aged 40 years and older undergoing lung transplant evaluation and coronary angiography (n = 14).

| Characteristic                               | Value
|---------------------------------------------|-------
| Male, n (%)                                 | 8 (57)
| Age in years, median (range)                | 47 (40–59)
| Genotype, n (%)                             |       
| F508del homozygous                         | 7 (50)
| F508del heterozygous                       | 4 (29)
| Other                                       | 3 (21)
| FEV₁ % predicted, median (range)           | 29 (11–47)
| Chronic Pseudomonas aeruginosa, n (%)      | 9 (64)
| Pancreatic insufficiency, n (%)             | 12 (86)
| CFRD, n (%)                                 | 9 (64)
| Insulin dependent, n (% of pts with CFRD)  | 5 (56)
| Dyslipidemiaa, n (%)                        | 9 (69)
| Low HDL, n (% of pts with dyslipidemia)    | 7 (78)
| High LDL                                   | 0     
| High triglycerides                          | 0     
| High total cholesterol                      | 2 (22)
| Fasting lipid profileb                     |       
| HDL in mmol/L, median (range)              | 1.06 (0.71–2.53)
| LDL in mmol/L, median (range)              | 2.22 (1.36–2.90)
| Triglycerides in mmol/L, median (range)    | 1.00 (0.47–1.70)
| Total cholesterol in mmol/L, median (range)| 3.60 (2.63–5.27)

a Lipid profiles were available for 13 patients.
b Normal values for lipid profiles based on National Cholesterol Education Program Guidelines: High-density lipoprotein (HDL) > 1.02 mmol/L. Low-density lipoprotein (LDL) < 3.44 mmol/L. Triglycerides < 1.70 mmol/L. Total cholesterol < 5.17 mmol/L.