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# Evidence of Lung Function for Stratification of Cardiovascular Disease Risk

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## ABSTRACT

Among adults in the United States, the prevalence of reduced lung function including obstructive and restrictive lung disease is about 20%, representing an over 40 million adults. Persons with reduced lung function often demonstrate chronic systemic inflammation, such as from elevated levels of C-reactive protein. Substantial data suggests that inflammation may have a significant role in the association between reduced lung function and cardiovascular disease (CVD); however, how reduced lung function predicts CVD as risk modification remains largely unknown. Poor lung function has been shown to be a better predictor of all-cause and cardiac-specific mortality than established risk factors such as serum cholesterol, and CVD is the leading cause of mortality among those with impaired lung function. The exact mechanism of atherosclerosis is not clear, but persistent low grade inflammation is considered as one of the culprits in clot formation. The initial presentation of coronary heart disease is either myocardial infarction or sudden death in approximately half of the individuals. Unfortunately, conventional risk factor assessment predicts only 65-80% of future cardiovascular events, leaving many middle-aged and older individuals to manifest a major cardiovascular event despite being classified low risk by the Framingham risk estimates. (**Korean Circ J 2011;41:171-174**)

**KEY WORD:** Respiratory function test.

## Introduction

In spite of a current evidence-based approach to cardiovascular disease (CVD) reduction, coronary heart disease (CHD) remains the leading cause of mortality in the industrialized world. Preventive strategies utilize risk assessment to identify those most likely to benefit from medical interventions to reduce risk for CVD events.<sup>1)</sup>

The Framingham Risk Score (FRS) is a global risk algorithm using multiple risk factors such as age, sex, smoking history, systolic blood pressure (BP), total cholesterol, and high density lipoprotein-cholesterol (HDL-C) to estimate 10-year

CHD event risk in individuals not previously diagnosed with heart disease.<sup>2)</sup> While FRS is widely used as a risk assessment tool, it is not entirely reliable in its ability to differentiate individuals regarding CVD events.<sup>3)</sup> A subject of interest is whether various novel risk markers such as C-reactive protein (CRP)<sup>4,5)</sup> or screening tests such as coronary calcium scanning<sup>6,7)</sup> can further add to the prediction of CVD events over global risk. Furthermore reduced lung function has been described as risk factor, but remains unsettled.

## Cardiovascular Disease and Inflammation

Clinical evidence accumulated since 1990 has established inflammatory processes as important contributors to atherogenesis, as well as to the vulnerability of an atherosclerotic lesion to rupture or erosion.<sup>4)</sup> Based on this evidence, protein markers of inflammation have been studied as noninvasive indicators of underlying atherosclerosis in apparently healthy individuals and of the risk of recurrent events in patients with established atherosclerotic vascular disease. The most exten-

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sively studied biomarker of inflammation in CVD is CRP, for which standardized high-sensitivity assays are widely available and since hs-CRP has also been shown to be an independent predictor of atherosclerosis among apparently healthy men and women<sup>5)</sup> and also improves prediction of CVD risk over traditional risk factors,<sup>8)</sup> measurement of hs-CRP has been proposed for measurement in asymptomatic intermediate risk individuals for further risk stratification.<sup>9)</sup> Although it is plausible that serum CRP is a nonspecific marker that is increased as part of the acute phase response to inflammation, experimental evidence has raised the possibility that CRP is a direct participant in the progression of atherosclerosis and its clinical consequences.<sup>10)11)</sup>

## Lung Function and Cardiovascular Disease

Previous epidemiologic studies have shown reduced pulmonary function to be a significant predictor of CVD,<sup>13-16)</sup> including CVD mortality.<sup>17)</sup> There is also abundant literature describing a significant relationship between lung function and all-cause mortality.<sup>18-24)</sup> Most of these studies included smokers in their samples and used forced expiratory volume in one second (FEV<sub>1</sub>) as a measure of lung function. Smoking status was shown to be causally related to mortality. However, the link between poor lung function and mortality has also been reported in never-smokers.<sup>23)24)</sup>

Poor lung function has been shown to be a better predictor of all-cause and cardiac mortality than established risk factors such as serum cholesterol.<sup>21)</sup> The cause of this relationship remains largely unknown, but low grade inflammation was present in participants with moderate and severe airflow obstruction and was also associated with increased risk of cardiac injury and this may in part explain the high rates of cardiovascular complications in chronic obstructive pulmonary disease (COPD).<sup>25)</sup> There have been recommendations for the use of subclinical disease screening measures in intermediate risk individuals, such as with coronary calcium scanning to be incorporated into risk stratification algorithms to refine the intensity of clinical management of key risk factors.<sup>6)7)</sup>

Individuals in this risk group are often quite heterogeneous and with treatment guidelines that are not always clear. A recent study<sup>26)</sup> shows the potential importance of pulmonary function assessment in risk stratification for mortality, particularly for those individuals classified into the intermediate FRS group.

## Lung Function and Inflammation

Reduced lung function, as assessed by peak expiratory flow, forced vital capacity (FVC) in 1 second (FEV<sub>1</sub>) and FVC, is as-

sociated with an increase in the occurrence of vascular alterations and cardiovascular morbidity and mortality in both smokers and non-smokers.<sup>13)21)22)</sup>

Recent reports showing the relation between inflammatory markers of either fibrinogen or CRP to reduced lung function in cross-sectional and prospective studies make inflammation a possible mechanism.<sup>27-32)</sup> An increase in serum CRP over time are associated with a significant decline of lung function, consistent with hypothesis that low-grade systematic inflammation is associated with lung function impairment in young adults.<sup>29)30)</sup>

In a large elderly cohort, baseline fibrinogen levels were inversely related to FEV<sub>1</sub> and FEV<sub>1</sub>/FVC ratio, and baseline CRP levels were inversely associated with FEV<sub>1</sub> and FVC. Elevated fibrinogen level predicted greater longitudinal declines in FEV<sub>1</sub>/FVC with increasing age, and a similar, but nonsignificant association was found with CRP.<sup>27)</sup>

Individuals with COPD are at increased risk of CVDs, osteoporosis, and muscle wasting. Systemic inflammation may be involved in the pathogenesis of these disorders. A systematic review was conducted of studies which reported on the relationship between COPD, FEV<sub>1</sub> or FVC, and levels of various systemic inflammatory markers: CRP, fibrinogen, leukocytes, tumor necrosis factor- $\alpha$ , and interleukins 6 and 8 and concluded that most of inflammatory markers are associated with reduced lung function.<sup>33)</sup>

Reduced lung function with COPD and restrictive lung disease also is associated with increasing inflammatory markers such as a CRP and fibrinogen.<sup>34)</sup> However, the relation between reduced lung function with restrictive lung disease and CVD has not been well established, whereas COPD has been well demonstrated as a risk factor for CVD. COPD is being considered as a systemic inflammatory disease not limited to the pulmonary system and statins have been shown to have pleiotropic anti-inflammatory and immune modulatory effects in addition to their cholesterol lowering ability.

Three large prospective observational studies reported that patients with COPD on a statin had a substantial reduction in both morbidity and mortality compared with those with COPD who were not.<sup>35-37)</sup> In a reported non-randomized study of lung function screening with COPD, compared with those not on statins, those taking statins had a significantly reduced annual FEV<sub>1</sub> decline and reduction in COPD related hospitalization.<sup>38-40)</sup>

The current collective evidence suggests that statins have a positive impact on outcomes of COPD patients. Despite the encouraging results, all studies reported to date have limitations and should be considered as hypothesis generating only.

There are four randomized, double blinded, placebo-controlled design, clinical trials addressing the effect of statins in the US National Institute of Health trials registry as of 1 January 2009.<sup>41)</sup>

## Conclusion

Traditional global risk assessment for CVD is limited by the ability to differentiate CVD events. Reduced lung function has been described as predictor of CVD and mortality. Systemic low grade inflammation has been considered as a significant player in this association.

There have been recommendations for the use of subclinical disease screening measures in intermediate-risk individuals, such as those with coronary calcium scanning, to be incorporated into risk stratification algorithm to refine the intensity of clinical management for key risk factors. A recent study shows the potential importance of lung function measurement in risk stratification for mortality, particularly for those in the intermediate FRS group. Lung function measures provide additive prediction for all-cause mortality when combined with traditional risk assessment using FRS, particularly in individuals at intermediate risk group.

The clinical implications of lung function measurement include their use in assessing risk in individuals who are at intermediate cardiovascular risk for targeting who may best benefit from therapy.

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