Occurrence and Prognostic Significance of Ventricular Arrhythmia Is Related to Pulmonary Function
A Study From “Men Born in 1914,” Malmö, Sweden

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Background—Reduced lung function has been associated with increased rates of myocardial infarction. Whether the occurrence and prognostic significance of ventricular arrhythmia is related to lung function is largely unknown.

Methods and Results—We performed a population-based study of 68-year-old men without a history of stroke or myocardial infarction; 402 men participated. Mortality and coronary events (fatal or nonfatal) were studied in relation to ventricular arrhythmia during 24 hours, percentage of the predicted forced expiratory volume (FEV1 %pred), vital capacity (VC %pred), and the FEV/VC ratio. During 14 years of follow-up, 181 men died and 87 experienced a coronary event. Occurrence of frequent or complex ventricular arrhythmia (Lown class 2 to 5) was significantly and inversely associated with FEV1 %pred. Men with Lown class 2 to 5 and a low FEV1 %pred (below median) had significantly higher mortality (71.5 versus 26.8 per 1000 person-years; \( P = 0.0001 \)) and coronary event rates (37.7 versus 18.0; \( P = 0.02 \)) than men with Lown class 2 to 5 and a high FEV1 %pred. These associations remained significant after adjustments for potential confounders (mortality: relative risk [RR], 2.91; 95% CI, 1.68 to 5.04; coronary events: RR, 2.16; 95% CI, 1.07 to 4.37). In men without frequent or complex arrhythmia (Lown 0 to 1), a low FEV1 %pred was not significantly associated with mortality (RR, 1.37; 95% CI, 0.92 to 2.05) or coronary events (RR, 1.24; 95% CI, 0.67 to 2.27) after adjustments for confounders. The FEV/VC ratio showed similar associations with arrhythmia, mortality, and coronary events.

Conclusions—Lung function is inversely associated with the occurrence of ventricular arrhythmia. The increased incidence of myocardial infarction and death associated with arrhythmia was mainly limited to men with a low FEV1 %pred or FEV/VC. We suggest that lung function should be considered when assessing the prognostic significance of ventricular arrhythmia. (Circulation. 2001;103:3086-3091.)

Key Words: electrocardiography ■ arrhythmia ■ lung ■ ventilation

Several prospective studies have reported inverse relationships between lung function (ie, vital capacity [VC] or forced expiratory volume [FEV]) and the incidence of myocardial infarction and death.1–5 These associations have remained significant when other cardiovascular risk factors have been taken into account, and results have been similar in studies of lifelong nonsmokers.1–3 The nature of this relationship is unclear. Reduced pulmonary function and cardiovascular diseases could share common causes, or the associations could reflect interactions between the pulmonary and cardiovascular systems.

Frequent or complex ventricular arrhythmia (VA), as documented on 24-hour ambulatory ECG recordings, commonly occur among elderly individuals both with and without evidence of cardiovascular disease.6–12 VA has been associated with increased mortality and coronary event rates in several studies of individuals with coronary heart disease, whereas the results from studies of apparently healthy subjects are inconsistent.8–12 The relationships between the occurrence and prognostic significance of VA and lung function in healthy individuals are largely unknown.

This follow-up of the population-based cohort “Men Born in 1914” sought to study the associations between lung function and occurrence of VA and to assess whether the prognostic significance of VA varied between groups defined in terms of lung function.

Methods
A total of 621 men representing a random 50% sample of all 68-year-old men living in Malmö, Sweden, were invited to a health examination close to their 68th birthday.6,9,13 Five hundred men (80.5%) participated, and 456 (91%) took part in the 24-hour ambulatory ECG registration. After excluding men with history of myocardial infarction or stroke (according to questionnaire or hospital records), 402 remained. The project was approved by the...
Assessments of Health Status
Blood pressure was measured in the morning with the subjects in a sitting position. Pressure was measured to the nearest 5 mm Hg with a mercury sphygmomanometer and a 12×26-cm rubber cuff. History of angina pectoris was assessed by means of the Rose questionnaire.

Daily tobacco consumption was estimated by means of a self-report questionnaire and categorized into consumption of 1 to 14 g/day and ≥15 g/day. Men who had stopped smoking at least 1 month before the investigation were counted as ex-smokers.

The consumption of beer, hard liquor, and light and strong wine (in decilitres per month) was noted. The men were categorized according to alcohol consumption into consumers of more or less than 2.50 liters per week (corresponding to half a bottle of wine per day or 750 mL of whiskey per week).14

Physical activity during leisure time was assessed in a structured interview and classified into “vigorous” physical activity (ie, regular physical training, such as heavy gardening, tennis, and swimming at least 2 to 3 hours per week) or “nonvigorous” physical activity (eg, reading, watching television, walking, and light gardening).15 Information on physical activity was missing for one subject.

Blood samples to determine lipid and glucose levels were drawn after a minimum fasting period of 8 hours. Total plasma cholesterol levels were analyzed at the laboratory of the Malmö University Hospital with standard methods. Diabetes mellitus was defined as a fasting plasma glucose level ≥7.0 mmol/L or medication for diabetes mellitus. All cases were validated by review of hospital records. Information on diabetes was missing for 3 men.

Ambulatory 24-Hour ECG Recordings
The procedures for the 24-hour ECG recordings and analyses of arrhythmia were described previously.6,8 An electrocardiographic tape recorder (Oxford Medilog II, FM type) with 2 bipolar electrodes in the V2 and V6 positions was used. An interactive computer (Oxford Medilog MA 14/20) was used to interpret the type of ventricular extrabeats. In addition, all tapes were analyzed by the same well-trained technician.

VA was categorized with respect to number and type according to Lown and Wolf.16 Frequent or complex VA was defined as Lown grade 2 to 5.6,9

Lung Function
FEV in 1 second and static VC were determined with a Bernstein type of spirometer12 and corrected to body temperature, atmospheric pressure, and water saturation. Experienced technicians at the Department of Clinical Physiology performed the tests. The best of 2 (or more if not congruent) measurements were used. All curves were inspected with respect to technical defects. If necessary, the tests were repeated until 2 acceptable measurements were obtained. FEV and VC were adjusted for body height and are presented as percentages of the predicted values (FEV1,0pred and VC,0pred). The predicted values are based on the distribution in 260 nonsmokers aged 68 years from the present cohort. The equations follow.

1. Predicted FEV (liters) = 3.51 + (0.0375 × height in cm)
2. Predicted VC (liters) = 5.85 + (0.0575 × height in cm)

Mean height, FEV, VC, and FEV/VC ratio in the present cohort were 174.4 ± 6.4 cm, 2.93 ± 0.69 liters, 4.1 ± 0.71 liters, and 70.9 ± 9.8%, respectively.

Mortality and Coronary Event Rates
All probands were followed from the baseline examination until their death or December 31, 1996. Median follow-up time was 13.3 years (range, 0.3 to 14.3 years). A coronary event was defined as a fatal or nonfatal myocardial infarction (ICD-9 codes 410A to 410X) or death from ischemic heart disease (ICD-9 codes 410 to 414). Cause of death was based on autopsy in 59% of the cases. Data linkage with the National Cause of Death Registry, the Swedish Hospital Discharge register, and the Malmö Myocardial Infarction Register18 was used to retrieve cases.

Statistics
The association between VA and quartile of lung function was tested with logistic regression. Cox regression19 was used to compare the survival and coronary event rates and to adjust them for potential confounders. The fit of the Cox model was confirmed by plotting the hazard functions in different categories of risk factors over time. Because the number of events was limited in the present study, only potential confounders were selected in the multivariate analysis.20 Potential confounders were identified by significance testing, with 1-way ANOVA and Pearson’s χ2, of the cardiovascular risk factors in categories of VA and lung function. P ≤ 0.20 was used as a criterion for potential confounding.20 To estimate whether the combined absolute effect of VA and poor lung function departed from additivity, a synergy index was calculated from the adjusted relative risks (RRs).21 A synergy index > 1 indicates a synergistic effect. If the synergy index is 2, this indicates an effect twice what could be expected from additivity.

Results
Occurrence of VA
The occurrence of VA and the coronary event and death rates in relation to Lown class are presented in Table 1. There were 143 men (35.6%) with VA (Lown class 2 to 5).

Occurrence of VA was significantly and inversely associated with FEV1,0pred and FEV/VC (Table 2). The trends remained significant after adjustments for tobacco consumption, former smoking, alcohol consumption, angina pectoris, physical activity, and diabetes (Table 2). Systolic blood pressure, body mass index, and cholesterol were not associated with FEV1,0pred or FEV/VC and were thus not considered potential confounders. However, the results were also significant after further adjustments for these risk factors. Twenty-seven men (6.7%) had FEV1,0pred values <60%; 14 of these 27 men (52%) had VA.

Survival and Coronary Event Rates
A total of 181 men (45%) died during follow-up, and 87 men (21.6%) experienced a coronary event; 35 of these 87 men died within 1 day. The coronary event and death rates were inversely associated with FEV1,0pred, VC,0pred, and FEV/VC.
Arrhythmia and Lung Function

Death and Coronary Event Rates in Relation to VA and Lung Function

The unadjusted death and coronary event rates in categories of VA and FEV1 QPushButton are illustrated in Figures 1 and 2. The increased coronary event and death rates among men with VA and FEV1 QPushButton, VCQPushButton, or FEV/VC values below median remained statistically significant after adjustments for potential confounders (Table 4). The increased mortality rate among men with Lown grade 0 to 1 and FEV1%pred values below median: RR, 2.15; 95% CI, 1.08 to 4.28; VA and FEV1 QPushButton values below median: RR, 2.61; 95% CI, 1.35 to 5.05; VA and VCQPushButton below median: RR, 1.70; 95% CI, 0.82 to 3.41).

Synergy Index

The synergy index for death and coronary event rates in categories of VA and FEV1 QPushButton below median (5.3 and 3.3, respectively) and FEV/VC below median (4.0 and 4.7, respectively) suggests synergistic effects. The effects of VA in combination with VCQPushButton below median were close to what could be expected from additivity (1.05 and 1.08, respectively).

Analysis of Men With VA

To assess whether lung function was associated with adverse prognosis among men with VA, the analyses were performed separately in this group. Men with VA and low FEV1 QPushButton (ie, below median) had significantly higher mortality (71.5 versus 26.8 per 1000 person-years; P<0.0001) and coronary event rates (37.7 versus 18.0; P=0.02) than men with VA and high FEV1 QPushButton. The RRs for mortality and coronary events were 2.91 (95% CI, 1.68 to 5.04) and 2.16 (95% CI, 1.07 to 4.37), respectively.
respectively, after adjustments for potential confounders. The corresponding RRs for men with VA and FEV/VC below median were 1.46 (95% CI, 0.88 to 2.42) and 2.51 (95% CI, 1.20 to 5.28) for mortality and coronary events, respectively; for men with VA and VC%pred below median, they were 1.92 (95% CI, 1.17 to 3.14) and 1.27 (95% CI, 0.67 to 2.42), respectively.

**Discussion**

As expected from other studies, VA often occurred among 68-year-old men and was associated with increased mortality and coronary event rates. However, the occurrence of VA was inversely associated with respiratory function. Furthermore, the increased risk associated with arrhythmia was mainly limited to men with, in relative terms, reduced lung function.
The FEV/VC ratio is generally considered the most specific measure of pulmonary obstruction in dynamic spirometry. Because FEV1%pred and FEV1%pred showed the strongest associations with VA and coronary events, the associations with arrhythmia and coronary events seem to be related to the degree of pulmonary obstruction. The results also suggest that the effects of arrhythmia and low FEV or FEV/VC are multiplicative, whereas additive effects could explain the increased coronary risk associated with arrhythmias and low VC.

VA was categorized by Lown class; men with frequent or complex arrhythmia made up Lown grades 2 to 5. Most men were in Lown class 1 (<720 ectopic beats per 24-hour period) or class 4a (couplets). Although the coronary event and death rates were generally higher in men with Lown class 2 to 5, it is not clear whether all types of frequent or complex arrhythmia show the same associations with lung function and coronary events.

The observed relationship is compatible with several hypotheses. An etiological factor (for example, smoking) could cause both reduced lung function and heart disease manifested as VA. Individuals could have different susceptibility to this exposure. The results in the present study, however, were adjusted for smoking habits. Previous studies have reported associations between reduced FEV and increased incidence of cardiovascular disease and death after adjustments for pack-years or change in tobacco consumption.5,22

Another possibility is that reduced lung function, independently of smoking, is associated with an increased occurrence of coronary atherosclerosis. VA has been associated with increased mortality among individuals with coronary heart disease. A reduced lung function has previously been associated with the development of atherosclerosis.23 Inflammatory processes seem to play key roles in the development of both atherosclerosis and reduced pulmonary function.24,25 It is possible that susceptible individuals have a greater tendency to react with low-grade inflammation, which in turn could cause both atherosclerosis and reduced lung function.

A third possibility is that the association between VA and lung function reflects interactions between heart and lung disease. It is well known that ventricular failure can cause pulmonary vascular engorgement and interstitial edema, which may become chronic. This reduces the compliance of the lungs and, thereby, the lung volumes. Reduced lung function could thus be a marker of heart disease. However, only men who were free from a history of myocardial infarction or stroke were included in this population-based study. The associations were similar after excluding men with a history of angina pectoris. The fact

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<th>TABLE 4. All-Cause Mortality and Coronary Event Rates in Relation to VA and 3 Measures of Lung Function</th>
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*Adjusted for tobacco consumption, former smoking, angina pectoris, physical activity, alcohol consumption, and diabetes.
that FEV1$_{\text{pred}}$ and FEV/VC showed stronger associations with coronary events than VC$_{\text{pred}}$ also speaks against this hypothesis.

Hypoxia is an unlikely explanation for the association between lung function and coronary events. This study is based on a sample from the general population, and few men would be considered abnormal from a clinical perspective. Furthermore, the associations between VA and coronary events were seen over the entire distribution of lung function, and the associations were similar among men with FEV1$_{\text{pred}}$$<60\%$.

Vital status was updated by data linkage with the National Cause of Death Registry. No subject was lost to follow-up. The Malmö myocardial infarction register has continuously recorded and validated all patients in Malmö since 1972. According to other epidemiological studies from the city, there is no reason to believe that biased retrieval or validation of end points confounded the results.

Moderately reduced lung function is associated with an increased occurrence of VA. The increased incidence of myocardial infarction and death associated with arrhythmia was mainly limited to men with, in relative terms, low FEV1$_{\text{pred}}$ and FEV/VC. We suggest that lung function should be considered when assessing the prognostic significance of VA.

**Acknowledgments**

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**References**

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