Age-Related Pulmonary Crackles (Rales) in Asymptomatic Cardiovascular Patients

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ABSTRACT

PURPOSE The presence of age-related pulmonary crackles (rales) might interfere with a physician's clinical management of patients with suspected heart failure. We examined the characteristics of pulmonary crackles among patients with stage A cardiovascular disease (American College of Cardiology/American Heart Association heart failure staging criteria), stratified by decade, because little is known about these issues in such patients at high risk for congestive heart failure who have no structural heart disease or acute heart failure symptoms.

METHODS After exclusion of comorbid pulmonary and other critical diseases, 274 participants, in whom the heart was structurally (based on Doppler echocardiography) and functionally (B-type natriuretic peptide <80 pg/mL) normal and the lung (X-ray evaluation) was normal, were eligible for the analysis.

RESULTS There was a significant difference in the prevalence of crackles among patients in the low (45-64 years; n = 97; 11%; 95% CI, 5%-18%), medium (65-79 years; n = 121; 34%; 95% CI, 27%-40%), and high (80-95 years; n = 56; 70%; 95% CI, 58%-82%) age-groups (*P* <.001). The risk for audible crackles increased approximately threefold every 10 years after 45 years of age. During a mean follow-up of 11 ± 2.3 months (n = 255), the short-term (≤3 months) reproducibility of crackles was 87%. The occurrence of cardiopulmonary disease during follow-up included cardiovascular disease in 5 patients and pulmonary disease in 6.

CONCLUSIONS Recognition of age-related pulmonary crackles (rales) is important because such clinically unimportant crackles are so common among elderly patients that, without knowledge of this phenomenon, their existence might interfere with the physician's management of cardiopulmonary patients.

INTRODUCTION

Heart failure is a common problem, especially in elderly patients.[1] The appearance of pulmonary crackles (rales), defined as discontinuous, interrupted, explosive respiratory sounds during inspiration, is one of the most important signs of heart failure deterioration.[2] Many older patients with asymptomatic cardiovascular disease seem to have pulmonary crackles, even in the absence of apparent cardiac dysfunction or comorbid pulmonary disease. The prevalence and pathologic importance of crackles in apparently normal persons are controversial.[3-5] Moreover, little is known about these issues in patients with asymptomatic cardiovascular disease. Frequent age-related pulmonary crackles might interfere with the physician's management of patients with suspected heart failure or presumed pulmonary disease. Because diagnostic and therapeutic decisions may be made on the basis of the finding of crackles, knowledge of their occurrence would be clinically important. In this study we examined the characteristics of pulmonary crackles among adult patients, stratified by decade, with stage A cardiovascular disease status as defined by the American College of Cardiology/American Heart Association 2001 chronic heart failure guidelines,[6] ie, patients at high risk for congestive

Conflicts of interest: none reported

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heart failure, but without structural heart disease or symptoms of heart failure, who were also free from comorbid pulmonary disease.

METHODS

Study Design and Patients

This prospective study was performed in the cardiology outpatient clinic of Nishida Hospital (Oita, Japan) between June 2005 and November 2006. Adult outpatients (aged 45 years and older) undergoing treatment for cardiovascular disease, including metabolic syndrome, were first screened by research nurses, who obtained consent and recorded a brief cardiac and pulmonary history and current complaints. Patients were not eligible for this investigation if they reported acute cardiopulmonary complaints or if they had a current diagnosis or history of structural heart disease, decompensated heart failure, chronic pulmonary disease, or recent episode (less than 3 months) of acute respiratory disease. No patient was suspected either clinically or after examination or investigation to suffer from connective tissue diseases.

All screened patients had a physical examination, blood chemistry tests, a 12-lead electrocardiogram (ECG), and a simple chest radiograph. At this second step, patients were excluded if they had high serum creatinine levels (≥1.2 mg/dL), abnormal ECG rhythm (atrial fibrillation or left bundle branch block), or radiographic abnormalities. Finally, all the patients screened at the second step underwent a cardiac Doppler echocardiogram and blood sampling for analysis of serum B-type natriuretic peptide (BNP) levels. At this final step, patients were excluded if they had abnormal findings on a Doppler echocardiogram[7,8] or high BNP levels (≥80 pg/mL).[9,10]

Because the sensitivity of a simple chest radiograph alone might be insufficient for assessing the structural normalcy of lung tissue, some study patients underwent thoracic high-resolution computed tomography (CT).[11-13]

We observed a substantial number of participants from 6 to 12 months. During this follow-up period, the short-term (3 or fewer months) reproducibility of the presence or absence of pulmonary crackles and the occurrence of critical cardiovascular or pulmonary disease were evaluated. The protocol was approved by the ethics committee of Nishida Hospital, and all patients provided informed consent.

Evaluation by Auscultation

A single senior cardiologist (H.K.) auscultated carefully the anterior to posterior basilar sites in each hemithorax in seated patients who were asked to perform periodic slow deep respiration. The cardiologist who performed the auscultation was blinded to chest radiograph, Doppler echocardiogram, and high-resolution CT findings. Pulmonary crackles were defined as discontinuous, interrupted explosive sounds during inspiration.[14] Audible crackles were classified as fine or coarse crackles according to their dominant acoustic nature.[14] Some previous studies reported that basilar crackles are often heard during the first few deep breaths, even in apparently normal persons.[4,15] In our study, only inspiratory crackles that appeared recurrently during consecutive respiratory cycles were accepted as the presence of crackles. We graded such basal crackles from 0 to 4 based on the longitudinal extension from the lung base upward to the apex[16]: a score of 1 indicates crackles over one-quarter of the lung height and a score of 4 indicate crackles over the entire lung height. Additionally, we defined bilateral transverse extension of crackles over two-thirds of the hemithorax as diffuse crackles.

Other Main Measurements

We obtained high-resolution thoracic CT scans[12,13] with 1-mm collimation, 130 kVp and 200 mA, by using a high-frequency reconstruction algorithm (X-Vision/GX, Toshiba Co, Ltd, Tokyo, Japan). A single senior pneumologist (O.M.) who was blinded to other clinical tests evaluated the CT image. Serum BNP was measured using the Shionoria assay method.[17] The Doppler echocardiogram was performed using a commercially available real-time, wide-angle phased-array system (Aloka SSD-2000, Aloka Co, Ltd, Tokyo, Japan).

Statistical Analysis

Continuous variables are expressed as mean values plus or minus standard deviations, and categorical data are expressed as frequencies and percentages. We assessed differences among the 3 study groups stratified arbitrarily by age by using 1-way analysis of variance for continuous variables with Bonferroni's correction for multiple comparisons; they were analyzed using the Kruskal Wallis H test for categorical data and the Mann-Whitney U test with Bonferroni's correction for multiple comparisons as the post hoc test. We used a 2-tailed unpaired Student's t test and a χ^2 test for comparisons between patients with and without pulmonary crackles. Using logistic regression analysis, we determined the presence or absence of pulmonary crackles by taking univariate predictors of the appearance of crackles and using iterative modeling procedures to arrive at the most efficient model. The threshold for entry of variables into the model was $P < .10$. We calculated odds ratios (OR) and 95% confidence intervals (CI), and a 2-tailed P value of $< .05$ was considered sig-

nificant. Statistical analyses were performed using SAS Statistical Software, version 8.2 (SAS Institute, Inc, Cary, North Carolina).

RESULTS

Patients Selection

Of the 385 study participants with current treatment for hypertension, diabetes, or dyslipidemia, 52 were excluded because of high serum creatinine levels (n = 7), abnormal ECG rhythm (n = 13), chest radiograph abnormality of the lower lung (n = 15), or any combination of these (n = 17). Chest radiograph abnormalities consisted of localized infiltration or reticular opacities in the lower lung field in 16, pleural thickening in 3, and both in 4. After exclusion, the remaining 333 patients underwent a cardiac Doppler echocardiography and measurement of serum BNP levels. At this step, a total of 59 patients were excluded from the analysis because of abnormal Doppler echocardiogram findings (n = 11), high BNP levels (n = 14), or both (n = 34). Doppler echocardiogram abnormalities included left ventricular systolic dysfunction (ejection fraction <50%) in 9 patients, segmental wall motion abnormality in 4, hypertrophy of the septal or left ventricular posterior wall (≥12 mm) in 10, left ventricular dilatation (≥140 mL) in 14, abnormal peak early-to-atrial velocity (EA) ratio of Doppler-derived left ventricular diastolic dysfunction in 13, and major valvular regurgitation in 27 (2 or more abnormali-

ties in 18 patients). After this final exclusion process, 274 asymptomatic adult patients with sinus rhythm in whom the heart was assumed to be structurally normal (determined by Doppler echocardiography) and functionally normal (determined by serum BNP), and with structurally normal lungs as evaluated by a simple radiograph, remained eligible for analysis.

Clinical Characteristics

Table 1 displays the baseline clinical characteristics of the study participants and the 3 categories stratified by age-groups (low = 45-64 years; n = 97, medium = 65-79 years; n = 121; and high = 80-95 years; n = 56). Men made up 28% of the participants. There were significant differences in demographic features across the 3 age-groups. The higher the age-group, the more likely patients were to have venous insufficiency or edema in the lower leg and higher mean values of serum BNP and creatinine. The prevalence of a smoking habit was not different across the 3 age-groups.

Characteristics of Pulmonary Crackles by Age

The overall prevalence of audible pulmonary crackles was 92 of 274 study patients (34%; 95% CI, 31%-36%). Among these 92 patients with audible crackles, 79 patients (86%) had predominantly fine crackles, and the remaining 13 patients (14%) had predominantly coarse crackles. Table 2 displays the prevalence of audible pulmonary crackles across the 3 age-groups. The higher the age-group, the more frequently the

Table 1. Demographic Characteristics of Study Patients Classified by Age-Group

Characteristics	All Patients (n = 274)	Low (45-64 Years) (n = 97)	Medium (65-79 Years) (n = 121)	High (80-95 Years) (n = 56)
Age, years	69.2 ± 12	56 ± 9.8	73.1 ± 4.1	83.7 ± 3.5
Men, No. (%)	77 (28)	34 (35)	28 (23)	15 (27)
Current or previous smoker, No. (%)	48 (18)	21 (22)	18 (15)	9 (16)
Treatment				
Hypertension, No. (%)	225 (82)	78 (80)	97 (80)	50 (89)
Dyslipidemia, No. (%)[a]	87 (32)	34 (35)	45 (37)	8 (14)
Arrhythmia, No. (%)	39 (14)	16 (16)	14 (12)	9 (16)
Stable angina pectoris, No. (%)	26 (9)	4 (4)	16 (13)	6 (11)
Diabetes mellitus, No. (%)	24 (8)	9 (9)	9 (7)	6 (11)
Third heart sound, No. (%)	4 (1)	0 (0)	3 (2)	1 (2)
Venous insufficiency, No. (%)[b]	58 (21)	9 (9)	26 (21)	23 (41)
Leg edema, No. (%)[c]	33 (12)	6 (6)	15 (12)	12 (21)
Left ventricular ejection fraction, %	61.2 ± 7.1	61.9 ± 6.5	60.9 ± 7.1	60.8 ± 7.8
Serum creatinine, mg/dL[c]	0.8 ± 0.24	0.73 ± 0.21	0.78 ± 0.21	0.8 ± 0.23
BNP, pg/mL[b]	31.6 ± 19.1	23.4 ± 17.2	33.1 ± 18.3	42.4 ± 19.8

BNP = serum B-type natriuretic peptide.

[a] P <.01 among groups in low, medium, and high age-groups.
[b] P <.001 among groups in low, medium, and high age-groups.
[c] P <.05 among groups in low, medium, and high age-groups.

patients had audible pulmonary crackles. Audible pulmonary crackles in such patients were often fine and localized to the lower quadrant of the lung field irrespective of the location, ie, anterior, lateral, or posterior on the thoracic wall. Increasing age was associated with the extension of crackles from the unilateral to bilateral hemithorax. Fourteen patients (5%) had grade 2 crackles. Only 3 patients (1%) had diffuse transverse and grade 2 longitudinal extensions of the pulmonary crackles. Other abnormal lung sounds heard at the basal lung included local wheeze in 3 patients.

CT Findings

Thoracic high-resolution CT was performed in 55 participants who had audible crackles, including 35 of 39 (90%) patients with bilateral crackles and 20 of 53 (38%) patients with unilateral crackles. CT findings of the lower lung field appeared normal in 20 of 55 participants (36%). Minimal or focal subpleural interstitial changes were detected in 27 patients (49%), solitary septal thickening in 6 (11%), and small nodules in 2 (4%). One patient was suspected to have a pathologic pulmonary condition based on the CT findings, which indicated extensive bibasal fibrotic/reticular abnormalities.[12,13] This patient was an 83-year-old man who had diffuse and grade 2 pulmonary crackles and whose condition was diagnosed as unclassifiable interstitial pneumonia[12,13] during the follow-up period.

Among 19 patients without crackles, focal subpleural interstitial changes on a CT scan were found in 3 patients (16%), focal septal thickening in 1 (5%), and small nodules in 1 (5%). Of the 74 study patients examined by CT, none showed heart failure-related CT findings,[11] such as pulmonary edema, pleural effusion, and venous engorgement.

Predictors of Pulmonary Crackles

Table 3 displays the comparison of the clinical variables between study patients with (n = 92) and without (n = 182) pulmonary crackles. A logistic regression analysis was performed for presence or absence of pulmonary crackles, with age, leg venous insufficiency, leg edema, serum creatinine, and serum BNP as independent variables. Age was the only independent predic-

tor of the presence or absence of pulmonary crackles (Table 4). For the appearance of crackles, the adjusted OR of age per 10 years was 3.23 (95% CI, 2.22-4.70; $P <.001$). Other variables were not significant predic-

Table 2. Appearance of Pulmonary Crackles Classified by Low, Medium, and High Age-Groups

Pulmonary Crackles	Age-Group (Years)			P Value		
	Low (n = 97)	Medium (n = 121)	High (n = 56)	Low vs Medium	Low vs High	Medium vs High
Incidence, No. (%)	11 (11)	42 (34)	39 (70)	<.001	<.001	<.001
95% CI, %	5-18	27-40	58-82			
Location				<.001	<.05	NS
Unilateral, No. (%)	10 (10)	23 (19)	20 (36)			
Bilateral, No. (%)	1 (1)	19 (16)	19 (34)			
Longitudinal extension				NS	NS	NS
Grade 1, No. (%)	9 (9)	35 (29)	34 (61)			
Grade 2, No. (%)	2 (2)	7 (6)	5 (9)			
Transverse extension						
Diffuse type, No. (%)	0	1 (0.8)	2 (4)	NS	NS	NS

NS = nonsignificant.

Table 3. Comparison of Clinical Variables of Patients With and Without Pulmonary Crackles

Variable	Pulmonary Crackles		P Value
	Present (n = 92)	Absent (n = 182)	
Age, years	76.9 ± 7.8	65.3 ± 11.2	<.001
Men, No. (%)	24 (26)	53 (29)	NS
Current/previous smoker, No. (%)	15 (16)	33 (18)	NS
Third heart sound, No. (%)	3 (3)	1 (0.5)	NS
Venous insufficiency, No. (%)	27 (29)	31 (17)	<.05
Leg edema, No. (%)	17 (18)	16 (9)	<.05
Left ventricular ejection fraction, %	61.1 ± 7.1	61.5 ± 7.9	NS
Serum creatinine, mg/dL	0.79 ± 0.21	0.75 ± 0.19	<.1
BNP, pg/mL	36.4 ± 19.6	29.1 ± 19.0	<.01

BNP = serum B-type natriuretic peptide.

Table 4. Predictors of Pulmonary Crackles Determined by Logistic Regression Analysis

Parameter	OR	95% CI	P Value
Age per 10 years	3.23	2.22-4.70	<.001
Venous insufficiency	1.02	0.499-2.08	.961
Leg edema	1.43	0.597-3.41	.425
Serum creatinine	1.29	0.314-5.26	.727
BNP	0.997	0.981-1.01	.731

BNP = serum B-type natriuretic peptide; CI = confidence interval, OR = odds ratio.

tors of the presence or absence of pulmonary crackles. Leg edema was strongly associated with the presence of peripheral venous insufficiency in the study population ($\chi^2 = 27.2$, $P < .001$).

Follow-Up

A clinical follow-up was obtained for 255 patients over a mean of 11 ± 2.3 months. At the short-term follow-up of 1.75 ± 0.8 months, the reproducibility of pulmonary crackles was 87%. The occurrence of critical cardiopulmonary disease during the entire follow-up included congestive heart failure in 3 patients, acute coronary syndrome in 2, bacterial pneumonia in 5, and unclassifiable interstitial pulmonary pneumonia in 1. Among the 5 patients with cardiovascular events, 2 patients with crackles at study entry (diffuse and grade 2 crackles in 1 patient) developed congestive heart failure during follow-up, and the remaining 3 patients were free from crackles at study entry. Among 5 patients with subsequent complicating pneumonia, 2 patients had unilateral grade 1 pulmonary crackles, but the other 3 patients were free from crackles at study entry.

DISCUSSION

Our study has shown that elderly patients with stage A cardiovascular status[6] frequently have audible pulmonary crackles, even in the absence of apparent cardiac dysfunction and comorbid pulmonary disease. Characteristically, crackles in such patients are fine and are almost always restricted to an area localized to the lower quadrant of the lung field. Diffuse basal crackles involving the bilateral hemithorax were exceptional phenomena in this study. These age-related crackles, except for the diffuse type, are not considered clinically significant over the medium-term follow-up; however, the possibility of new-onset heart failure or occult interstitial or other types of active lung disease must be kept in mind on subsequent evaluations.

The prevalence and pathologic significance of crackles in apparently normal persons is subject to controversy.[3-5] Although some investigators report that crackles do not occur in normal persons, others disagree. The observations in this study are somewhat consistent with the findings of Cabot et al,[3] who reported frequent detection of "crepitant rales" in middle-aged or elderly patients with "normal chests" examined during the first few breaths after shallow tidal breathing. Our findings show that the risk ratio of pulmonary crackles increases approximately threefold every 10 years after 45 years of age in patients with cardiovascular disease and apparently normal heart function. Minimal interstitial changes in some patients with crackles were found with high-resolution CT

examination.[12,13] Many of our older patients had likely been exposed to various environmental agents over the years, including probable infectious lung disease, which might contribute to the interstitial changes seen on CT or subsequent production of crackles. Such CT findings in the lung with age could be due to environmental pollutants rather than simply aging alone.

In patients with cardiovascular disease, physical examination is the primary step in evaluating the presence and severity of fluid retention in those with possible heart failure.[2,6] The appearance of pulmonary crackles is among the most important signs of congestive heart failure. The accuracy of detecting crackles for diagnosing the deterioration of heart failure, however, varies greatly across studies: sensitivity 13% to 70%, specificity 35% to 100%, positive predictive value 19% to 100%, negative predictive value 17% to 85%.[18] This variable accuracy among studies might be explained by at least 2 factors, ie, the population studied and the definition of crackles.[19]

First, the utility of a test is always determined by the nature of the population studied and can only be generalized if it is representative of other populations likely to be of interest. Thus, although pulmonary crackles ought to be a very specific sign, sometimes they are not, perhaps because crackles related to heart failure are so easily confused with those of interstitial fibrosis, pneumonia, and bronchitis.[4,14] Recognition of age-related crackles is important because such crackles are so common among apparently normal elderly patients with cardiovascular disease that their existence in the population of interest would additionally aggravate the specificity for diagnosing heart failure status.

Second, the criteria required for determining the crackles related to heart failure also affect the accuracy of the test results for heart failure diagnosis. Many previous studies, except several,[16,20,21] lacked definite criteria for diagnosing the presence of crackles related to heart failure, and the mere presence or absence of the crackles was often expressed as the definition. The nature of the age-related crackles in our study, ie, restriction to the lower quadrant of the lung field, would partly support the notion of Stevenson et al[16] that physical evidence of pulmonary congestion might be specific for grade 2 or 4 crackles, not for grade 1, but such strict criteria resulted in low sensitivity for diagnosing congestive heart failure.

The physical signs of heart failure in the elderly are often difficult to interpret.[22-24] Superimposition of changes caused by aging or other diseases, such as frequent leg edema in association with peripheral venous insufficiency in the elderly, might obscure the typical signs observed in younger patients. Age-related crackles in elderly patients with cardiovascular disease might

be mistakenly diagnosed as a sign of heart failure deterioration, and a danger exists when diuretic therapy is inappropriately instituted.[4,14] Elderly patients with chronic heart failure and previous decompensation often have persistent pulmonary crackles, even during stable periods,[22] associated in some cases with the age-related phenomena, not heart failure status. Whether crackles are related to cardiac dysfunction should be interpreted in light of other clinical tests including, for example, Doppler echocardiography,[7,8] serum BNP measurement,[17,22,25] or thoracic CT scans.[12,13]

This study had several limitations. First, more commonly accepted theories[26,27] for the production of crackles are associated with airway and air-space opening. The pathogenesis of crackles remains unexplained because the CT examination, undertaken in this study to exclude pathologic lung diseases, might not be suitable for exploring the genesis of crackles. Second, our study defined patients with cardiovascular disease as "functionally normal" based on their plasma BNP levels, but this diagnostic test might not be perfect. Because age, sex, and renal function affect serum BNP levels,[25,28] BNP level cannot be used to strictly define functional cardiac status. In this study, we adopted a cutoff level of BNP at less than 80 pg/mL for functionally normal hearts because a BNP level of 80 to 100 pg/mL is widely accepted as a cutoff level for ruling out heart failure status regardless of age.[9,10] Importantly, logistic regression analysis did not identify BNP levels as the independent predictor of the appearance of crackles in the this study population. Third, left ventricular diastolic function was not examined precisely, and only one index of Doppler-derived E/A ratio[6] was adopted for identifying diastolic dysfunction in the this study. Thus, some of the participants might belong in the category of stage B cardiovascular status, corresponding to a criterion of diastolic dysfunction with preserved systolic function.[6] Fourth, this study recruited the study population from highly selected group of patients, which might somewhat limit its generalizability. Finally, despite the importance of crackles for diagnosing acute heart failure decompensation,[2,6] there is often considerable disagreement among physicians about the actual presence of crackles in individual patients.[20] In our population (n = 65), there was 83% agreement on interpretation of the presence or absence of crackles.

Implications for Clinicians

The recognition of age-related crackles is important because such clinically unimportant crackles are so common among elderly patients that, without knowledge of this phenomenon, their existence might interfere with the physician's management of patients with suspected heart failure or presumable pulmonary disease.

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