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Value of Orthopnea, Paroxysmal Nocturnal Dyspnea, and Medications in Prospective Population Studies of Incident Heart Failure

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Abstract

Prospective population studies of incident heart failure (HF) are often limited by difficulties in assembling a HF-free cohort. We used public-use copies of the Cardiovascular Health Study (CHS) datasets to determine sensitivity, specificity, and positive and negative predictive values (PPV and NPV) of orthopnea and paroxysmal nocturnal dyspnea (PND), with and without the use of medications used in CHS HF criteria (diuretics plus digoxin *or* vasodilators) in the diagnosis of prevalent HF and in the assembly of a relatively HF-free population. Of the 5771 community-dwelling older adults ≥ 65 years, 803 had orthopnea, 660 had PND, 1075 had either symptom, 388 had both symptoms, 547 were using HF medications, and 4315 had neither symptom nor were using HF medications. Definite HF was centrally adjudicated in 272 participants. The sensitivity, specificity, PPV and NPV (95% confidence intervals) for either orthopnea or PND were 52% (46%–58%), 83% (82%–84%), 13% (11%–15%) and 97% (97%–98%) respectively, and those for either orthopnea or PND or use of HF medications were 77% (72%–82%), 77% (76%–79%), 14% (13%–16%) and 99% (98%–99%) respectively. In conclusion, only <20% of those with either orthopnea or PND had definite HF, which limits their usefulness in the diagnosis of prevalent HF in the community. However, nearly 99% (NPV) of those with neither symptom nor using HF medications also did not have HF, which may be useful as a simple and inexpensive tool in assembling a relatively HF-free cohort for prospective population studies of incident HF.

Keywords

Orthopnea; paroxysmal nocturnal dyspnea; medications; heart failure; diagnosis; population studies

Heart failure (HF) is often difficult to diagnose in population studies.^{1, 2} This complicates population studies of incident HF as participants should ideally be free of prevalent HF at baseline. In clinical settings, orthopnea and paroxysmal nocturnal dyspnea (PND) are often considered specific symptoms of HF.^{1, 3} HF medications have also been used to diagnose HF

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in population settings. Although data on these symptoms and HF medications may be collected in population studies, their role in the diagnosis of prevalent HF in this setting is relatively unknown. The objective of this study was to determine the usefulness of orthopnea and PND, with and without HF medications, in assembling a cohort relatively free of prevalent HF using public-use copies of the Cardiovascular Health Study (CHS) datasets obtained from the National Heart, Lung, and Blood Institute (NHLBI).

Methods

CHS is an ongoing, prospective epidemiologic study of cardiovascular risk factors funded by the NHLBI. A total of 5888 community-dwelling older adults ≥ 65 years were recruited from a random sample of Medicare-eligible residents from the four study sites: Sacramento County, California; Washington County, Maryland; Forsyth County, North Carolina; and Allegheny County, Pennsylvania.⁴ An original cohort of 5201 participants was recruited between 1989 and 1990 and a second cohort of 687 African-Americans was recruited between 1992 and 1993. We used public-use copies of the CHS datasets obtained from the NHLBI, which contained data from 5795 participants, as some participants did not consent to be included in the de-identified public-use copy of the data. Of the 5795 participants, 5771 had data on baseline orthopnea or PND and were used in the current analysis.

Data on orthopnea and PND were collected during baseline home interviews using a CHS questionnaire. For orthopnea, participants were asked “*Have you ever had to sleep on two or more pillows to help you breathe*” and for PND, the question was “*Have you ever been awakened at night by trouble breathing*.” Data on use of prescription medications during the preceding two weeks were collected directly from prescription bottles, and data on the use of nonprescription medications such as aspirin, sleeping pills and antihistamines were collected using questionnaires.⁴ Medications used in the criteria for the diagnosis of HF included the use of any diuretics, and either digoxin or a vasodilator including an angiotensin-converting enzyme (ACE) inhibitor.

Of the 5771 participants, 272 (4.7%) had definite baseline HF as centrally adjudicated by a committee and constituted “gold standard” cases for these analyses. The CHS criteria for HF assessment are well-described in the literature and have been shown to be more stringent than the Framingham criteria for HF.^{4–10} Briefly, a panel of experts adjudicated prevalent HF by reviewing all relevant data including history, physical examination, chest x-ray and medications from medical records related to hospitalizations or outpatient visits. The process began with self-reports of physician-diagnosed HF, which was then adjudicated by a central CHS committee of physicians based on the receipt of medical therapy for HF (defined as current use of a diuretic and either digitalis or a vasodilator, namely, ACE inhibitor, nitroglycerin, or hydralazine).⁵ For those with self-reported, physician-diagnosed HF who did not meet the medication criteria, a definite diagnosis of HF was made after medical record review for symptoms (shortness of breath, fatigue, orthopnea, PND), signs (edema, pulmonary râles, gallop rhythm, displaced left ventricular apical impulse), and tests (chest radiography).⁵ When self-reported, physician-diagnosed HF could not be confirmed using the above approaches, CHS field centers sought confirmation from treating physicians by questionnaires or from hospitals by discharge summaries which were then reviewed for symptoms, signs, and chest x-ray findings suggestive of HF. However, some cases of prevalent HF at baseline were retrospectively confirmed through surveillance during follow-up.⁵ All information was reviewed centrally at the CHS coordinating center for consistency of classification among the four centers.

Considering the clinical relevance of the symptoms of orthopnea and PND, we at first sought to understand the characteristics of participants who had either orthopnea or PND at baseline

compared to those who had neither. As such, we categorized participants into two groups based on the presence or absence of either of these two symptoms and compared them using Pearson's chi-square and Student's t-tests as appropriate. We estimated sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) along with 95% confidence intervals (CI) of baseline presence of orthopnea or PND for committee-adjudicated definite HF.^{11, 12} We then repeated our analysis adding HF medications into the criteria (orthopnea or PND or the use of HF medications). Data were analyzed using SPSS for Windows release 15 (Chicago, IL, 2008).

Results

Participants (n=5771) had a mean age of 73 (± 6.0) years, 57% were women and 16% were African Americans. At baseline, orthopnea and PND was reported by 803 (13.9%) and 660 (11.4%) participants, respectively, 1075 (18.6%) of participants reported *either* symptom, and 547 (9.5%) were using HF medications. Patients with *either* orthopnea or PND were more likely to be women, nonwhites, unmarried, living alone, have higher mean body mass index, higher comorbidity burden and report fair to poor health (Table 1). Only 388 (6.7%) participants had *both* symptoms. A total of 1456 (25.2%) participants had *either* orthopnea or PND, or received HF medications, and 4315 had neither symptom nor were using HF medications.

The sensitivity, specificity, PPV and NPV for either orthopnea or PND at baseline were respectively 51.8%, 83.0%, 13.1% and 97.2% (Table 2). The values for individual symptoms of orthopnea and PND, and combination thereof, are displayed in Table 2. The sensitivity, specificity, PPV and NPV for either orthopnea or PND or the use of HF medications at baseline were respectively 77.2%, 77.3%, 14.4% and 98.6% (Table 2 and Figure 1). The sensitivity, specificity, PPV and NPV for either orthopnea or PND or the use of HF medications at baseline for subgroups of participants are displayed in Table 3.

Discussion

The findings of our study demonstrate that the prevalence of symptoms of orthopnea or PND was relatively common among community-dwelling older adults. Over 97% of CHS participants who did not report either orthopnea or PND (NPV), also did not have HF. However, when CHS criteria for HF medications was added, nearly 99% of those who reported neither orthopnea nor PND or used HF medications, also did not have HF, suggesting that these criteria can be used to identify a cohort relatively free of prevalent HF. These findings are important as they provide simple and clear evidence for the use of an inexpensive tool to exclude prevalent HF patients in community cohorts, an important requirement for prospective population studies of incident HF.

Orthopnea and PND are considered major Framingham criteria for the diagnosis of HF.¹³ The presence of two major Framingham criteria confirms a diagnosis of HF, and as such, CHS participants with both orthopnea and PND met the Framingham criteria for the diagnosis of HF. However, only 20% (PPV) of CHS participants who reported both orthopnea and PND had HF. The low prevalence of HF among CHS participants may in part explain the low PPV of these two symptoms, as PPV is directly related to prevalence. However, the 4.7% prevalence of HF in the CHS is likely to be one of the highest in a community setting as the prevalence of HF increases with age and the CHS participants were ≥ 65 years. Another possible explanation for the low PPV of these two symptoms is that they may also be manifestations of other conditions such as chronic obstructive pulmonary disease or sleep apnea, the prevalence of which increases with age. Thus, the low PPV of these two symptoms makes them unsuitable for the diagnosis of HF in the community setting.

This is in contrast to the usefulness of these symptoms in the clinical setting where follow-up questions may clarify their presence or absence, which may also be assessed in the context of other symptoms, signs, and other medical conditions, such as coronary artery disease or hypertension, which are underlying etiologic factor for most HF. Furthermore, the prevalence of HF in the clinical setting is expected to be higher, which is also likely to improve the PPV of these symptoms. Among patients presenting with dyspnea in the emergency department in whom the prevalence of HF is estimated to be as high as 50%, the PPV of orthopnea and PND is estimated to be 68% and 72% respectively.^{3, 14} The sensitivity and specificity of orthopnea and PND observed in our study among community-dwelling older adults were similar to those of patients with acute dyspnea.³ This suggests that these two symptoms alone may not be very reliable in the diagnosis of HF even in the clinical setting, and that coordination with other clinical information is necessary.

The absence of either orthopnea or PND, on the other hand, may be useful in identifying those without HF. Over 97% (NPV) of CHS participants without either symptom did not have HF. Yet, it may not be suitable to assemble a cohort free of HF, as the 3% of the participants with HF (false negative) would include nearly half of all prevalent HF patients. However, when HF medications were added into the criteria, nearly 99% of those with neither symptom nor receiving HF medications were free of HF. Importantly, the addition of HF medication increased the NPV from 97.2% to 98.6%, with 95% confidence intervals (98.2% to 98.9%) that did not include the NPV for orthopnea or PND (97.2%), thus highlighting the statistical significance of the improvement in NPV with the addition of HF medications. Although the remaining 1% of participants with HF includes about one fifth of all HF patients, they are asymptomatic and thus likely to be stable and may have better prognoses. Therefore, by collecting data on orthopnea, PND, and HF medications used in the CHS criteria for the diagnosis of HF, one can assemble a cohort that may include about 1% of asymptomatic stable HF patients, which may be suitable for long-term follow up of incident HF and HF hospitalization. The NPV is inversely related to prevalence. However, the effect of the prevalence of HF on NPV is likely to be minimal as the prevalence of HF in the community can only vary within a narrow range (between 1% and 8%).¹⁵ The 4.7% prevalence of HF in CHS would be considered high as the prevalence of HF increases with age and would likely be lower in cohorts younger than 65 years, thus yielding higher NPV.

The relevance or lack thereof of the sensitivity and specificity of a screening tool to assemble a HF-free cohort in the community setting deserves further discussion. In the clinical setting, sensitivity and specificity of diagnostic tests are determined in studies using gold standard diagnostic tests and those probabilities are used on individual patients, and are not meant to assemble cohorts. A diagnostic test should have high sensitivity (ability to detect a true positive) if the cost of missing cases (false negative) is too high to be acceptable. For example, if phenylketonuria is not detected early after birth, it may cause irreversible brain damage.^{11, 16} On the other hand, a test should have high specificity if the cost of wrong diagnoses (false positive) is too high to be acceptable. For example, a wrong diagnosis of prostate cancer may lead to anxiety, insurance consequences and potentially invasive diagnostic and therapeutic interventions. HF is a clinical syndrome, which unlike phenylketonuria or prostate cancer, is unlikely to be asymptomatic on initial presentation. Therefore, a high false negative rate (low sensitivity) may delay the diagnosis of HF and initiation of HF therapy, but is not likely to be life-threatening in those without the typical HF symptoms of orthopnea and/or PND. On the other hand, a high false positive rate (low specificity) may lead to false diagnosis of HF which in turn may lead to prescription of HF medications or even hospitalization. Therefore, a high specificity may be more desirable for HF screening in the clinical setting.

The modest 77% specificity for orthopnea or PND or HF medication use in the community in our study is comparable to the 76% specificity of brain natriuretic peptide (BNP) using a cutoff

of 100 pg/ml observed in patients with dyspnea in the emergency department.¹⁷ In that study, the highest BNP cutoff of 150 pg/ml yielded a specificity of 83%. Of note, when we used either orthopnea alone, or PND alone, or the presence of both orthopnea and PND, we obtained much higher specificities (88%, 90% and 94% respectively). However in the clinical setting, a diagnosis of HF is complex and requires assessment of a set of clinical and laboratory findings, which may not be feasible in the community setting. Although there is no data on the usefulness of BNP in the diagnosis of HF in the community, BNP was not useful for community screening for left ventricular hypertrophy and systolic dysfunction in the Framingham Heart Study.¹⁸ Therefore, the criteria used in our study provide an inexpensive yet efficient tool for HF screening in the community for population studies of incident HF.

One of the limitations of our study is that the participants were older adults. Because the prevalence of HF may be lower in a younger population, the findings of this study may not be generalizable to a younger population. However, over 80% of HF patients are ≥ 65 years, and data from our subgroup analyses suggest that the NPV was similar regardless of age. Also, unlike PPV, which is reduced with lower prevalence, the NPV increases with the decrease in prevalence, therefore the findings of this study may be more useful in assembling a younger HF-free population.¹⁹ Another limitation was that we had no data on angiotensin receptor blockers or beta blockers currently recommended for use in HF. None of the CHS participants were receiving angiotensin receptor blockers. Data on beta blockers were also collected but were not included in the CHS HF medication list. Beta blockers were considered harmful and contraindicated in HF during the period when CHS participants were being enrolled. The results of the major randomized trials of beta blockers in HF that are currently recommended for use in HF (carvedilol, metoprolol succinate extended release and bisoprolol) were published after CHS enrollment. Future studies need to examine if the inclusion of these drugs would improve the CHS HF criteria. In conclusion, when used in conjunction with HF medications, orthopnea and PND can identify nearly 99% of those without HF in the community, and thus this simple, efficient and inexpensive tool can be useful in assembling relatively HF-free cohorts for prospective studies of incident HF.

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		Baseline definite heart failure confirmed by Cardiovascular Health Study criteria		Total	
		Yes	No		
Baseline orthopnea <i>or</i> paroxysmal nocturnal dyspnea <i>or</i> heart failure medications	Yes	210 (a) True positive	1246 (b) False positive	1456 (a + b)	PVP (95% CI) = a / (a + b) = 210 / 1456 = 14.4% (12.6–16.2 %)
	No	62 (c) False negative	4253 (d) True negative	4315 (c + d)	
Total		272 (a + c)	5499 (b + d)	5771 (a + b + c + d)	
		Sensitivity (95% CI) = a / (a + c) = 210 / 272 = 77.2% (72.2– 82.2%)	Specificity (95% CI) = d / (b + d) = 4253 / 5499 = 77.3% (76.2–78.5%)	Prevalence (pre-test likelihood of disease) = (a + c) / (a + b + c + d) = 272 / 5771 = 4.7%	

Figure 1.

Two by two table demonstrating sensitivity, specificity, and predictive values of symptoms of orthopnea or paroxysmal nocturnal dyspnea and HF medications in the Cardiovascular Health Study. (CI = confidence interval; PPV = positive predictive value or post-test likelihood of disease; NPV = negative predictive value or post-test likelihood of *no* disease).

Table 1

Baseline characteristics by either orthopnea or paroxysmal nocturnal dyspnea (PND)

Variable	No orthopnea or PND (n = 4696)	Orthopnea or PND (n = 1075)	P value
Age (years)	73 (±6)	73 (±5)	0.610
Female	2641 (56%)	672 (63%)	<0.0001
African American	718 (15%)	216 (20%)	<0.0001
Married	3165 (67%)	640 (60%)	<0.0001
Live alone	567 (12%)	177 (17%)	<0.0001
Education college or higher	2031 (43%)	434 (40%)	0.085
Income ≥25k	1734 (37%)	326 (30%)	<0.0001
Current smoker	569 (12%)	128 (12%)	0.849
Alcohol (units per week)	2.5 (±6.4)	2.0 (±5.9)	0.019
Body mass index (kg/m ²)	26 (±4)	27 (±5)	<0.0001
Self-reported general health fair to poor	987 (21%)	478 (45%)	<0.0001
Heart failure	131 (3%)	141 (13%)	<0.0001
Myocardial infarction	481 (10%)	121 (11%)	0.327
Current angina pectoris	627 (13%)	314 (29%)	<0.0001
Bypass surgery	173 (4%)	71 (7%)	<0.0001
Transient ischemic attack	126 (3%)	38 (4%)	0.130
Stroke	188 (4%)	59 (6%)	0.030
Carotid endarterectomy	71 (2%)	21 (2%)	0.297
Claudication	110 (2%)	39 (4%)	0.017
Deep vein thrombosis	216 (5%)	90 (8%)	<0.0001
Hypertension	2173 (58%)	676 (63%)	0.002
Dizzy/light headed on standing up	843 (18%)	349 (33%)	<0.0001
Diabetes mellitus	732 (16%)	206 (19%)	0.004
Chronic kidney disease	1010 (22%)	234 (22%)	0.852
Chronic obstructive pulmonary disease	412 (9%)	327 (30%)	<0.0001
Asthma	165 (4%)	189 (18%)	<0.0001
Sleep apnea	302 (6%)	105 (10%)	<0.0001
Arthritis	2303 (49%)	665 (62%)	<0.0001
Cancer	642 (14%)	180 (17%)	0.009
Atrial fibrillation (by ECG)	110 (2%)	44 (4%)	0.001
Left ventricular hypertrophy (by ECG)	211 (5%)	68 (6%)	0.012
Ankle arm index ratio	1.1 (±0.2)	1.1 (±0.2)	0.160
Bundle branch block	403 (9%)	131 (12%)	<0.0001
Medications			
ACE inhibitors	318 (7%)	111 (10%)	<0.0001
Other vasodilators	356 (8%)	83 (8%)	0.876
Beta blockers	586 (13%)	155 (14%)	0.086
Calcium channel blockers	537 (11%)	241 (22%)	<0.0001
Aspirin	132 (3%)	58 (5%)	<0.0001
Statins	106 (2%)	21 (2%)	0.540
Non steroidal anti-inflammatory drugs	548 (12%)	184 (17%)	<0.0001
Nitrates	322 (7%)	199 (19%)	<0.0001
Potassium supplement	292 (6%)	125 (12%)	<0.0001
Insulin	118 (3%)	33 (3%)	0.302
Oral hypoglycemic drugs	282 (6%)	85 (8%)	0.021
Digitalis	332 (7%)	155 (14%)	<0.0001
Loop diuretics	245 (5%)	162 (15%)	<0.0001
Thiazide diuretics	519 (11%)	127 (12%)	0.475
Potassium sparing diuretics	38 (1%)	12 (1%)	0.327
Pulse rate (beats/minute)	68 (±11)	69 (±12)	0.002
Blood pressure (mm Hg)			
Systolic	137 (±22)	136 (±22)	0.674
Diastolic	71 (±11)	71 (±11)	0.630
Plasma glucose (mg/dL)	111 (±37)	113 (±38)	0.051
Serum creatinine (mg/dL)	0.96 (±0.38)	0.97 (±0.49)	0.476
Serum potassium (mEq/L)	4.17 (±0.38)	4.14 (±0.39)	0.005
Total cholesterol (mg/dL)	211 (±39)	210 (±39)	0.566
Low-density lipoprotein (mg/dL)	130 (±35)	129 (±35)	0.357
High-density lipoprotein (mg/dL)	54 (±15)	54 (±17)	0.842
Triglyceride (mg/dL)	139 (±77)	141 (±79)	0.421
Albumin (g/dL)	3.99 (±0.29)	3.99 (±0.30)	0.459
Fibrinogen (mg/dL)	323 (±67)	330 (±67)	0.001
Interleukin-6 (pg/mL)	2.2 (±1.8)	2.4 (±1.9)	<0.0001
Serum insulin (mcU/mL)	17 (±25)	20 (±33)	0.001
Coagulant factor 7 (IU/dL)	123 (±29)	123 (±30)	0.717
C reactive protein (mg/dL)	4.5 (±7.3)	6.1 (±11.5)	<0.0001
Hemoglobin (g/dL)	14.0 (±1.3)	14.0 (±1.4)	0.001
White blood cell (10 ³ /μL)	6.2 (±2.0)	6.6 (±2.3)	<0.0001
Platelet (10 ³ /μL)	249 (±74)	254 (±76)	0.081

ACE=angiotensin-converting enzyme; ECG=electrocardiography

Table 2

Sensitivity, specificity, positive predictive values, and negative predictive values, along with 95% confidence interval (CI) of orthopnea and paroxysmal nocturnal dyspnea, with and without heart failure (HF) medications for the diagnosis of HF in the Cardiovascular Health Study (CHS)

Variable	N	Sensitivity % (95% CI)	Specificity % (95% CI)	Positive predictive values % (95% CI)	Negative predictive values % (95% CI)
Orthopnea	803	42.8 (36.9–48.7)	87.5 (86.8–88.4)	14.5 (12.0–16.9)	96.9 (96.4–97.4)
Paroxysmal nocturnal dyspnea	660	37.6 (31.8–43.3)	89.8 (90.0–90.6)	15.3 (12.6–18.1)	96.7 (96.2–97.2)
Orthopnea <i>or</i> paroxysmal nocturnal dyspnea	1075	51.8 (45.9–57.8)	83.0 (82.0–84.0)	13.1 (11.1–15.1)	97.2 (96.7–97.7)
Orthopnea <i>and</i> paroxysmal nocturnal dyspnea	388	27.9 (22.6–33.3)	94.3 (93.7–94.9)	19.6 (15.6–23.5)	96.4 (95.9–96.9)
Orthopnea <i>or</i> paroxysmal nocturnal dyspnea <i>or</i> CHS heart failure medications*	1456	77.2 (72.2–82.2)	77.3 (76.2–78.5)	14.4 (12.6–16.2)	98.6 (98.2–98.9)

* CHS heart failure medications include a diuretic *and* either digitalis *or* a vasodilator

Table 3

Sensitivity, specificity, positive predictive values, and negative predictive values, along with 95% confidence intervals (CI) of *either* orthopnea *or* paroxysmal nocturnal dyspnea *or* heart failure medications for the diagnosis of Cardiovascular Health Study participants

Subgroups	N	Sensitivity (95% CI)	Specificity (95% CI)	Positive predictive values % (95% CI)	Negative predictive values % (95% CI)
All patients	5771	77.2 (72.2–82.2)	77.3 (76.2–78.5)	14.4 (12.6–16.2)	98.6 (98.2–98.9)
Age <72 yrs	2442	78.7 (69.4–87.9)	77.9 (76.2–79.5)	10.1 (7.7–12.6)	99.1 (98.7–99.6)
Age ≥72 yrs	3329	76.7 (70.7–82.6)	77.0 (75.5–78.4)	17.3 (14.8–19.8)	98.1 (97.6–98.7)
Men	2458	72.0 (64.3–79.6)	80.8 (79.2–82.4)	17.5 (14.3–20.7)	98.1 (97.5–98.7)
Women	3313	82.1 (75.8–88.5)	74.8 (73.3–76.3)	12.6 (10.4–14.7)	99.0 (98.6–99.4)
White	4837	75.1 (69.3–81.0)	78.2 (77.0–79.4)	13.5 (11.5–15.4)	98.6 (98.2–99.0)
African-American	896	83.1 (73.5–92.6)	73.0 (70.0–76.0)	17.8 (13.3–23.3)	98.4 (97.4–99.4)
Coronary artery disease	1130	78.5 (72.4–84.6)	66.4 (63.4–69.4)	29.5 (25.4–33.7)	94.5 (92.8–96.2)
No coronary artery disease	4641	75.0 (66.5–83.5)	79.7 (78.5–80.8)	7.5 (5.9–9.1)	99.3 (99.1–99.6)
Chronic obstructive pulmonary disease	739	83.0 (72.9–93.1)	52.0 (48.3–55.8)	11.8 (8.5–15.1)	97.5 (96.0–99.1)
No chronic obstructive pulmonary disease	4828	75.5 (69.6–81.4)	81.2 (80.1–82.3)	15.1 (12.9–17.3)	98.7 (98.3–99.1)