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ORIGINAL RESEARCH

Pulmonary Hypertension Is Associated With Systemic Arterial Hypertension Among Patients With Normal Left Ventricular Diastolic Function

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BACKGROUND: The association of pulmonary and systemic arterial hypertension is believed to be mediated through hypertensive left heart disease. The purpose of the current study was to investigate whether pulmonary hypertension (PHT) is associated with systemic arterial hypertension among patients with apparently normal left ventricular diastolic function.

METHODS AND RESULTS: Consecutive patients who had echocardiographic evaluation between 2007 and 2019 were enrolled. Patients with disease states that are known to be associated with PHT, including diastolic dysfunction, were excluded from the analysis. Estimated right ventricular systolic pressure was extracted for all patients from the echocardiographic reports. PHT was defined as estimated right ventricular systolic pressure >40 mm Hg. Multivariate logistic regression models were applied. Final study population included 25 916 patients with a median age of 59 (interquartile range, 44–69) years, of whom 12 501 (48%) were men and 13 265 (51%) had systemic arterial hypertension. Compared with normotensive patients, hypertensive patients were 3.2 times more likely to have PHT (95% CI, 2.91–3.53; $P<0.001$). A multivariate model adjusted for clinical and echocardiographic parameters that are known to be associated with PHT demonstrated that hypertensive patients are almost 3 times more likely to have PHT (95% CI, 2.45–3.15; $P<0.001$). The association was significant in multiple subgroups but was more significant among women compared with men (odds ratio, 3.1 versus 2.4; P for interaction <0.001).

CONCLUSIONS: PHT is associated with systemic arterial hypertension irrespective of left heart disease. The association is more pronounced among women.

Key Words: diastolic dysfunction ■ pulmonary hypertension ■ systemic arterial hypertension

Systemic arterial hypertension is one of the leading causes of cardiovascular disease in adults.[1] Several mechanisms contribute to the increase in arterial blood pressure (BP), including intravascular volume overload and excessive activation of the sympathetic nervous system and the renin-angiotensin-aldosterone system (RAAS). Other possible mechanisms include endothelial dysfunction, systemic inflammation, activation of the immune system, and increased oxidative stress.[2]

Pulmonary hypertension (PHT) is classified as pulmonary arterial hypertension (PAH), PHT attributable to left heart disease, PHT attributable to lung disease or hypoxemia, PHT attributable to pulmonary artery obstruction, or PHT with unclear and/or multifactorial mechanisms. Although arterial hypertension can induce hypertensive left heart disease and diastolic dysfunction, it is not listed as a possible cause for PHT in contemporary guidelines and consensus documents.[3] Therefore, the purpose of the current study was to

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CLINICAL PERSPECTIVE

What Is New?

- The association of pulmonary and systemic arterial hypertension is believed to be mediated through hypertensive left heart disease.
- This study showed in a large cohort of patients that pulmonary hypertension was associated with systemic arterial hypertension irrespective of left heart disease.

What Are the Clinical Implications?

- Systemic hypertension is not currently listed in the guidelines as a possible sole cause of pulmonary hypertension.
- We believe that systemic hypertension should be incorporated into future guidelines as a possible cause of pulmonary hypertension.

Nonstandard Abbreviations and Acronyms

IVC	inferior vena cava
PAH	pulmonary arterial hypertension
PHT	pulmonary hypertension
RAAS	renin-angiotensin-aldosterone system
RVSP	right ventricular systolic pressure

investigate whether PHT is associated with systemic arterial hypertension among patients with apparently normal left ventricular diastolic function.

METHODS

Study Population

This is a retrospective cohort study of all adult patients (aged >18 years) evaluated at the Sheba Medical Center between 2007 and 2019, who completed an echocardiographic evaluation. It is based on the SHEBAHEART big data registry. Sheba Medical Center is the largest hospital in Israel, with 115 000 admissions per year, and 22 000 echocardiographic tests per year. The echocardiographic reports together with the electronic medical records of all patients are the source for this study. Subjects with echocardiographic evidence of diastolic dysfunction, clinical congestive heart failure, chronic obstructive pulmonary disease, atrial fibrillation, enlarged left atrium (LA), significant left-sided valvular disease, decreased left ventricular ejection fraction (<50%), or malignancy before the date of the index echocardiographic examination were excluded from the analysis (Figure). Also excluded were patients whose right ventricular systolic pressure (RVSP) was not measurable and those with missing clinical data (Figure).

The Institutional Review Board of the Sheba Medical Center approved this study based on strict maintenance of participants' anonymity during database analyses. No individual consent was obtained. The data that support the findings of this study are available from the corresponding author on reasonable request.

Arterial Hypertension and Diastolic Dysfunction Definition

Patients were considered to have arterial hypertension if the diagnosis was documented in their electronic medical records, if they were on long-term antihypertensive drug therapy, or if they had 2 separate measurements of either a systolic BP >140 mm Hg and/or a diastolic BP >90 mm Hg. Diastolic dysfunction was defined according to contemporary guidelines[4] when at least 2 of the following were recorded: (1) septal tissue Doppler E wave velocity was <7 cm/s or lateral tissue Doppler E wave velocity was <10 cm/s, (2) average of lateral and septal E/e′ ratio was >14, (3) enlarged LA (LA anterior-posterior diameter >3.9 or volume index >34), or (4) tricuspid regurgiation (TR) velocity >2.8 m/s.

Standard Echocardiographic and Doppler Measurements

Two-dimensional transthoracic echocardiographic and Doppler studies were obtained with clinical ultrasound machines equipped with 3.5-MHz transducers using standard views. The studies were digitally stored (McKesson's Horizon Cardiology Medical Software, Tel Aviv, Israel). Valvular heart disease was estimated according to the American Society of Echocardiography guidelines. Diastolic function was defined according to contemporary guidelines.[5] The left ventricular ejection fraction was estimated by the expert echocardiographist. Right atrial pressure was estimated by visualizing the inferior vena cava (IVC) and its response to respiration. Right atrial pressure was estimated as 5 mm Hg if the IVC was <2.0 cm in diameter at the junction of the right atrium with inspiratory collapse; 10 mm Hg if the IVC was <2.0 cm in diameter with only partial inspiratory collapse; 15 mm Hg if the IVC was dilated and partially collapsed with inspiration; and 20 mm Hg if the IVC was dilated and did not collapse with respiration. Estimated pulmonary artery systolic pressure was calculated as the sum of tricuspid jet gradient and estimated right atrial pressure.[6]

Clinical Data and Study End Point

Patients' baseline demographic and clinical data were retrieved from the patients' computerized records.

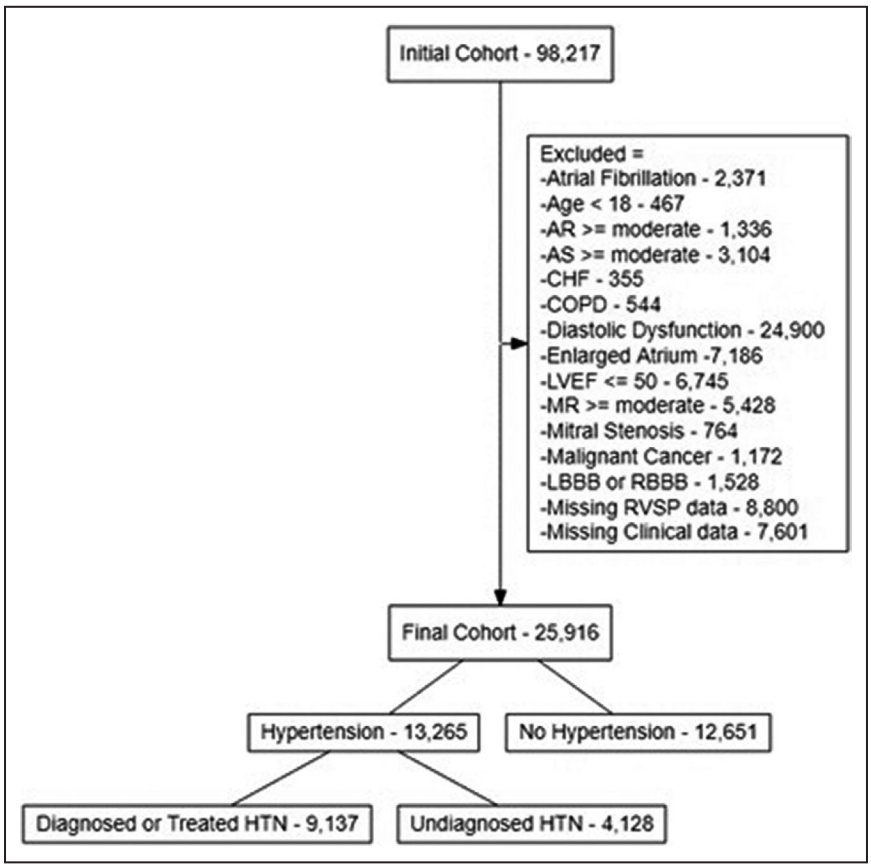

Figure. Study population.
AR indicates aortic regurgitation; AS, aortic stenosis; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; HTN, hypertension; LBBB, left bundle-branch block; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; RBBB, right bundle-branch block; and RVSP, right ventricular systolic pressure.

Diagnoses were based on computerized hospitalization records (*International Classification of Diseases, Ninth Revision* [*ICD-9*] codes), laboratory tests, medications, physiological signals (eg, ECGs), radiological images (eg, echocardiograms and angiograms), and procedures' reports. Diagnoses were validated by multiple sensitivity analyses, by performing logic tests and by reviewing selected cases. The Israel National Cancer Registry was used to collect information on cancer diagnosis at baseline and during follow-up. The Israel National Cancer Registry is a national population-based passive registry that receives reports on newly diagnosed cancer cases from all health care providers throughout the country.[7]

Statistical Analysis

Continuous variables were expressed as mean±SD if normally distributed or median with interquartile range if skewed. Categorical variables were presented as frequency (percentage). Continuous data were compared with the Student *t* test, and categorical data were compared with the use of the χ^2 test or Fisher exact test. Binary general logistic regression modeling was used to determine the unadjusted odds ratio (OR) for having PHT, as defined by RVSP >40 mm Hg. Parameters that were found to be significant in the univariate model or that are known to be significant in the development of PHT were then incorporated into the multivariate model; these were age, sex, obesity, left ventricular ejection fraction, LA anterior-posterior diameter, E/e′, and ischemic heart disease. Subsequently, subgroup analysis of specific populations was also performed using the variables in the multivariate model. All analyses were performed by using R software (R Foundation for Statistical Computing). An association was considered statistically significant for a 2-sided *P* value of <0.05.

RESULTS

Final study population included 25 916 patients. Median age of the study population was 59 (interquartile range, 44–69) years, of whom 12 501 (48%) were men and 13 265 (51%) had hypertension.

Hypertension diagnosis was based on documented *ICD-9* diagnosis or long-term drug therapy in 9137 (35%) patients and on direct BP measurements in 4128 (16%) patients. Compared with normotensive patients, hypertensive patients were older, were more likely to be men, had higher rates of obesity, and had higher rates of significant comorbidities, including diabetes and ischemic heart disease (Tables 1 and 2; $P<0.001$ for all). On echocardiography, hypertensive patients had higher LA diameter, higher lateral and medial E/e′ ratios, and higher estimated RVSP than normotensive subjects. When examining patients with hypertension only, the subpopulation of patients with PHT was older, consisted of mostly women, and had a higher prevalence of diabetes. The LA anterior-posterior diameter was higher, and they showed higher rates of elevated E/e′ ratio (Table 3). PHT was recorded in 1810 (14%) patients with hypertension and in only 595 (5%) normotensive subjects (unadjusted OR, 3.20; 95% CI, 2.91–3.53; $P<0.001$). Old age, female sex, obesity, diabetes, ischemic heart disease, LA size, diastolic E-wave velocity, and E/e′ ratio were all associated with higher likelihood of PHT in a univariate model ($P<0.001$ for all).

Multivariate Analysis

Multivariate binary logistic regression model, adjusted for clinical, demographic, and echocardiographic parameters, demonstrated that hypertensive patients were 77% more likely to have PHT (95% CI, 1.55–2.03; $P<0.001$). The same model demonstrated a 42% increased likelihood of PHT for every 10 years increase of age, and that women were 42% more likely to have PHT compared with men. Diabetes and LA diameter were not significant in the multivariate model (Table 4). An alternative model with dichotomized variables yielded consistent results, such that hypertensive patients were almost 3 times more likely to have PHT (Table 5). This model also demonstrated a significant and independent correlation with echocardiographic parameters: patients with E/e′ >14 were 5 times more likely to have PHT (95% CI, 2.5–9.81; $P<0.001$).

Subgroup Analysis

The independent association of PHT with systemic arterial hypertension was confirmed in multiple subgroups. PHT was similarly associated with hypertension among obese and nonobese patients (OR, 2.73 versus 2.77), among octogenarians and nonoctogenarians (OR, 2.01 versus 2.87), among patients older and younger than the age of 60 years (1.7 versus 2.15), among patients with and without diabetes (OR, 3.55 versus 2.65), and among patients with and without ischemic heart disease (OR, 2.06 versus 2.85; *P* for interaction not significant for all). Moreover, PHT was similarly associated with hypertension among patients with and without LA enlargement (OR, 5.29 versus 2.68) and among patients with normal or abnormal diastolic E-wave velocity (OR, 3.93 versus 1.91; *P* for interaction not significant for all). Interestingly, the association between PHT and systemic arterial hypertension was sex dependent, such that among women hypertension was associated with 3.07 increased likelihood of PHT (95% CI, 2.62–3.61; $P<0.001$) versus 2.38 increased likelihood among men (95% CI, 1.95–2.91; $P<0.001$; *P* for interaction 0.036). In addition, the association of other clinical and echocardiographic parameters was different among women versus men. Specifically, obesity was associated with increased likelihood of PHT among women but not among men, and elevated E/e′ was associated with increased likelihood of PHT among men but not among women. All subgroup models are available in Tables S1 through S20.

Sensitivity Analyses

A sensitivity analysis was performed where TR velocity criteria were removed to address a possible bias that might arise from using shared criteria for the calculation of pulmonary pressure and assessing diastolic dysfunction. In this analysis, diastolic dysfunction was defined as having at least 1 of the other 3 remaining criteria. The results of that analysis demonstrate consistent findings, such that hypertensive patients without any diastolic dysfunction criteria were 3 times more likely to have PHT in the multivariate model (OR,

Table 1. Demographic and Clinical Features of All Patients

Feature	Overall	No hypertension	Hypertension	Missing
No.	25 916	12 651	13 265	
Age, median (IQR), y	59 (44–69)	49 (35–62)	65 (56–75)	0
Male sex, N (%)	12 501 (48)	5734 (45)	6767 (51)	0
BMI, median (IQR), kg/m²	25.4 (22.8–28.6)	24.44 (21.88–27.47)	26.1 (23.5–29.4)	18.1
Diabetes, N (%)	3331 (13)	451 (4)	2880 (22)	0
Ischemic heart disease, N (%)	3001 (12)	606 (5)	2395 (18)	0
Systolic blood pressure, median (IQR), mm Hg	125 (113–140)	120 (108–130)	133 (120–148)	16.2
Diastolic blood pressure, median (IQR), mm Hg	73 (65–80)	70 (63–80)	75 (67–83)	16.3

$P<0.001$ for all comparisons. BMI indicates body mass index; and IQR, interquartile range.

Table 2. Echocardiographic Features of All Patients

Feature	Overall	No hypertension	Hypertension	*P* value	Missing
No.	25 916	12 651	13 265		
RVSP, median (IQR), mm Hg	29 (25–34)	28 (25–32)	31 (27–36)	<0.001	0
RVSP >40 mm Hg, N (%)	2405 (9)	595 (5)	1810 (14)	<0.001	0
LVEF, median (IQR), %	60 (60–60)	60 (60–60)	60 (60–63)	<0.001	17.2
LVEDD, median (IQR), cm	4.44 (4.12–4.75)	4.5 (4.2–4.8)	4.4 (4.1–4.7)	<0.001	17.2
LVESD, median (IQR), cm	2.7 (2.4–3)	2.72 (2.48–3)	2.66 (2.4–2.97)	<0.001	17.3
Left ventricle interventricular septum thickness, median (IQR), cm	1 (0.86–1.1)	0.9 (0.8–1)	1.01 (0.9–1.14)	<0.001	0.7
Left ventricle estimated mass, median (IQR), g	137 (113–164)	129 (106–156)	144 (119–173)	<0.001	2
Left ventricle estimated mass index, median (IQR), g/m^2	75 (64–88)	72 (61–83)	79 (67–93)	<0.001	8.4
Left atrium AP diameter, median (IQR), cm	3.5 (3.2–3.7)	3.4 (3.1–3.67)	3.5 (3.24–3.75)	<0.001	1.6
Enlarged left atrium, N (%)	684 (3)	196 (2)	488 (4)	<0.001	1.6
Mitral inflow peak E wave, median (IQR), cm/s	73.2 (61.6–86)	76 (64–88.4)	70.6 (59.6–83.5)	<0.001	6.4
Mitral inflow E/A ratio, median (IQR)	1.03 (0.78–1.36)	1.21 (0.92–1.56)	0.88 (0.71–1.15)	<0.001	8
Mitral inflow peak A wave, median (IQR), cm/s	70 (56.3–85.7)	62.4 (50.4–76)	78 (64.2–92.8)	<0.001	8
Mitral inflow deceleration time, median (IQR), ms	205 (174–246)	198 (169–232)	213 (179–256)	<0.001	10.2
Tissue Doppler S velocity septal, median (IQR), cm/s	7.72 (6.78–8.9)	8 (7–9)	7.31 (6.39–8.5)	<0.001	13.7
Tissue Doppler E velocity septal, median (IQR), cm/s	7.88 (6–9.83)	8.92 (7–11)	7 (5.8–8.3)	<0.001	12.4
Tissue Doppler E/E ratio septal, median (IQR)	9.44 (7.64–11.56)	8.6 (7.09–10.45)	10.3 (8.41–12.42)	<0.001	13.3
Tissue Doppler S velocity lateral, median (IQR), cm/s	9 (7.33–10.5)	9 (7.9–11)	8.39 (7–10)	<0.001	13.8
Tissue Doppler E velocity lateral, median (IQR), cm/s	10 (8–13)	11.6 (9–14.5)	9 (7.02–11)	<0.001	12.7
Tissue Doppler E/E ratio lateral, median (IQR)	7.2 (5.73–9.07)	6.48 (5.29–8.07)	7.96 (6.42–9.82)	<0.001	13.6
Elevated E/e′, N (%)	49 (0.2)	11 (0.1)	38 (0.3)	<0.001	14.4

AP indicates anterior-posterior; A wave, peak velocity flow in late diastole caused by atrial contraction; E wave, peak velocity flow peak velocity blood flow from left ventricular relaxation in early diastole caused by left ventricular relaxation; E/e`, the ratio between early mitral inflow velocity and mitral annular early diastolic velocity; IQR, interquartile range; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic dimension; and RVSP, right ventricular systolic pressure.

2.3; 95% CI, 1.86–2.85 in a model with continuous covariates; and OR, 3.6; 95% CI, 3.07–4.24 in a model with dichotomized covariates; *P*<0.001 for both). Full results for this are available in Tables S1 through S20.

Sensitivity analysis, excluding patients with any criteria for diastolic dysfunction, patients with ischemic heart disease, and octogenarians, was performed. In this group of 12 114 patients, in a multivariate model controlling for sex and obesity, hypertension was similarly associated with increased likelihood of PHT, with an OR of 3.92 (95% CI, 3.34–4.62; *P*<0.001).

Another sensitivity analysis, excluding patients with documented diagnosis of hypertension or long-term antihypertensive treatment, was performed. This analysis included a total of 16 779 patients, of whom 4128 (24%) were hypertensive based on 2 separate BP measurements documented in their medical record. Compared with normotensive patients, undiagnosed hypertensive patients were 2.68 times more likely to have PHT (95% CI, 2.37–3.04; *P*<0.001) in the univariate model. The same model demonstrated that each 10–mm Hg increase in arterial systolic BP of >130 mm Hg was associated with a significant increased likelihood of PHT (Figure S1). The multivariate model yielded consistent results such that untreated and underdiagnosed hypertensive patients were 2.44 times more likely to have PHT (95% CI, 2.08–2.85; *P*<0.001).

Table 3. Demographic, Clinical, and Echocardiographic Features of Only Patients With Hypertension

Feature	Overall	RVSP ≤40 mm Hg	RVSP >40 mm Hg	*P* value	Missing
No.	13 265	11 455	1810		
Age, median (IQR), y	65 (56–75)	65 (55–73)	73 (63–81)	<0.001	0
Male sex, N (%)	6767 (51)	6046 (53)	721 (40)	<0.001	0
BMI, median (IQR), kg/m²	26.1 (23.5–29.4)	26.1 (23.6–29.4)	26.1 (23.1–30.1)	0.6	13.8
Diabetes, N (%)	2880 (22)	2419 (21)	461 (26)	<0.001	0
Ischemic heart disease, N (%)	2395 (18)	2105 (18)	290 (16)	0.017	0
Systolic blood pressure, median (IQR), mm Hg	133 (120–148)	132 (120–147)	135 (120–151)	<0.001	13.3
Diastolic blood pressure, median (IQR), mm Hg	75 (67–83)	76 (67–84)	74 (64–82)	<0.001	13.4
RVSP, median (IQR), mm Hg	31 (27–36)	30 (26–34)	46 (43–53)	<0.001	0
RVSP >40 mm Hg, N (%)	1810 (14)	0 (0)	1810 (100)	<0.001	0
LVEF %, median (IQR)	60 (60–63)	60 (60–60)	60 (60–65)	<0.001	13.8
LVEDD, median (IQR), cm	4.4 (4.1–4.7)	4.4 (4.1–4.71)	4.3 (4–4.68)	<0.001	13.8
LVESD, median (IQR), cm	2.66 (2.4–2.97)	2.68 (2.4–2.99)	2.6 (2.3–2.9)	<0.001	14
Left ventricle interventricular septum thickness, median (IQR), cm	1.01 (0.9–1.14)	1 (0.9–1.13)	1.05 (0.92–1.2)	<0.001	1
Left ventricle estimated mass, median (IQR), g	144 (119–173)	144 (119–173)	144 (119–175)	1	2.2
Left ventricle estimated mass index, median (IQR), g/m²	79 (67–93)	78 (67–92)	82 (68–97)	<0.001	9.5
Left atrium AP diameter, median (IQR), cm	3.5 (3.24–3.75)	3.5 (3.22–3.7)	3.6 (3.3–3.8)	0.003	2.1
Enlarged left atrium, N (%)	488 (4)	416 (4)	72 (4.2)	0.3	2.1
Mitral inflow peak E wave, median (IQR), cm/s	70.6 (59.6–83.5)	70 (59–82.4)	77 (63.1–94)	<0.001	6.9
Mitral inflow E/A ratio, median (IQR)	0.88 (0.71–1.15)	0.88 (0.71–1.15)	0.87 (0.7–1.16)	0.6	9
Mitral inflow peak A wave, median (IQR), cm/s	78 (64.2–92.8)	77 (63.9–91.3)	85 (69.2–101)	<0.001	9
Mitral inflow deceleration time, median (IQR), ms	213 (179–256)	215 (180–256)	201 (166–249)	<0.001	10
Tissue Doppler S velocity septal, median (IQR), cm/s	7.31 (6.39–8.5)	7.33 (6.42–8.48)	7.2 (6.08–8.97)	0.7	13.8
Tissue Doppler E velocity septal, median (IQR), cm/s	7 (5.8–8.3)	7 (5.77–8.27)	7 (6–8.7)	0.08	12.9
Tissue Doppler E/E ratio septal, median (IQR)	10.3 (8.41–12.42)	10.2 (8.36–12.3)	11.14 (8.92–13.29)	<0.001	14
Tissue Doppler S velocity lateral, median (IQR), cm/s	8.39 (7–10)	8.38 (7–10)	8.49 (7–10)	0.8	13.9
Tissue Doppler E velocity lateral, median (IQR), cm/s	9 (7.02–11)	9 (7.02–11)	9 (7.1–11)	0.7	13.3
Tissue Doppler E/E ratio lateral, median (IQR)	7.96 (6.42–9.82)	7.86 (6.36–9.67)	8.68 (6.98–10.65)	<0.001	14.4
Elevated E/e′, N (%)	38 (0.3)	21 (0.2)	17 (1.2)	<0.001	15.2

AP indicates anterior-posterior; A wave, peak velocity flow in late diastole caused by atrial contraction; E wave, peak velocity flow peak velocity blood flow from left ventricular relaxation in early diastole caused by left ventricular relaxation; E/e`, the ratio between early mitral inflow velocity and mitral annular early diastolic velocity; IQR, interquartile range; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic dimension; and RVSP, right ventricular systolic pressure.

DISCUSSION

In the present study, we showed that, in patients with apparently normal left ventricular diastolic function, PHT is associated with systemic arterial hypertension. This association persisted after adjustment for relevant confounders and was consistent in each risk subset analyzed, suggesting an independent association between PHT and systemic arterial hypertension, irrespective of left heart disease. The association was more pronounced among women, suggesting that the mechanism is at least partially sex specific.

In this study, we tried to circumvent the mediation of the left heart using the power of big data analysis

Table 4. Multivariate Model for Continues Variables

Contentious multivariate model		
Variable	**OR (95% CI)**	***P* value**
Hypertension	1.77 (1.55–2.03)	<0.001
Age by 10 y	1.42 (1.36–1.47)	<0.001
Male sex	0.70 (0.62–0.78)	<0.001
Obese	1.28 (1.12–1.46)	<0.001
LVEF	1.03 (1.02–1.05)	<0.001
Left atrium AP diameter	1.04 (0.95–1.12)	0.3
E/e′	1.06 (1.04–1.08)	<0.001
IHD	0.72 (0.60–0.85)	<0.001

AP indicates anterior-posterior; E/e` the ratio between early mitral inflow velocity and mitral annular early diastolic velocity; IHD, ischemic heart disease; LVEF, left ventricular ejection fraction; and OR, odds ratio.

to explore the direct effect of hypertension on PHT, as determined by an echocardiographic elevated RVSP. We began with a cohort of 98 217 patients and systematically removed all patients with diastolic dysfunction per guidelines,[8] and patients with atrial fibrillation, congestive heart failure, reduced ejection fraction, valvular disorders, and chronic lung disease, to achieve a population free of possible known causes of PHT. A view of the distribution of RVSP in nonhypertensive patients versus hypertensive patients (Figure S2) showed the tendency toward higher RVSP in the hypertensive group, an assumption proven to be statistically significant (median RVSP, 31 versus 28 mm Hg, respectively; $P<0.001$). To our knowledge, the present study is the first to report the association between PHT and systemic arterial hypertension in patients with apparently normal left heart. The association between PHT and arterial hypertension can be explained by the effect of long-standing arterial hypertension on the left ventricle. Diastolic dysfunction and left ventricular failure lead to an increased backward pressure in the pulmonary vasculature and thereby cause pulmonary hypertension.[9] In the present study, we excluded all patients with apparent diastolic dysfunction, but it is still possible that

Table 5. Multivariate Model for Dichotomized Variables

Dichotomized multivariate model		
Variable	**OR (95% CI)**	***P* value**
Hypertension	2.78 (2.45–3.15)	<0.001
Octogenarian	2.78 (2.46–3.15)	<0.001
Male sex	0.64 (0.58–0.72)	<0.001
Obese	1.29 (1.14–1.47)	<0.001
Enlarged left atrium	1.10 (0.83–1.45)	0.5
Elevated E/e′	5.05 (2.51–9.84)	<0.001
IHD	0.77 (0.65–0.91)	0.003

E/e` the ratio between early mitral inflow velocity and mitral annular early diastolic velocity; IHD indicates ischemic heart disease; and OR, odds ratio.

hypertensive patients had subtle diastolic dysfunction that was not detected by the usual echocardiographic criteria. In our study, patients with hypertension were older and were more likely to be obese and to have diabetes and ischemic heart disease than normotensive subjects. These characteristics may increase the risk of diastolic dysfunction. Moreover, patients with hypertension had higher LA diameter than normotensive subjects, which may suggest subtle diastolic dysfunction. To exclude the possibility of subclinical diastolic dysfunction, we included E/e′ ratio and LA diameter in the multivariate analysis models. The multivariate models showed that patients with hypertension were 77% more likely to experience elevated RVSP. All subanalysis models that were constructed, including the most rigorous one that excluded older patients, patients with ischemic heart disease, and patients with any criteria for diastolic dysfunction per guidelines, consistently showed that hypertension was associated with an increased OR for elevated RVSP, ranging from a 2-fold to a 4-fold increase. Therefore, it is plausible that PHT and arterial hypertension may share similar pathogenic mechanisms that explain their association, irrespective of diastolic damage to the left ventricle. Such mechanisms may include endothelial dysfunction or the excessive activation of the RAAS.[10–12]

The RAAS is well known and studied for its effect on systemic volume status and vascular contraction. Novel studies show that elements of the RAAS have a role in inflammatory lung disease,[13] acute lung injury, chronic obstructive pulmonary disease, idiopathic pulmonary fibrosis, and PAH.[12] This is mediated most likely via angiotensin-converting enzyme 2 action that cleaves angiotensin II into angiotensin 1–7, a heptapeptide that activates G-coupled MAS receptors, in turn reducing pulmonary inflammation and fibrosis.[14] The pathogenesis of PAH has been studied in animal models. One such model is the Ren-2 transgenic model of rats, which exhibits inhibition of angiotensin-converting enzyme gene expression and activity, angiotensin 1 inhibition, and suppression of angiotensin II, along with an increase in lung angiotensin-converting enzyme 2 gene expression and activity, angiotensin 1–7 concentrations, and MAS receptor gene expression. When these rats were subjected to chronic hypoxia, they showed attenuated levels of mean pulmonary arterial pressure compared with equivocally exposed controls.[15] These results emphasize the role of the RAAS in the pathogenesis of PAH. Another possible mechanism that may explain the association between pulmonary and systemic hypertension, unrelated to left ventricular failure, is activation of the sympathetic nervous system. In our previous study, we showed that hypertensive patients have enhanced activation of the sympathetic nervous system in response to stressors, thus causing increased vasoconstriction.[16]

Nootens et al[17] showed a correlation between plasma norepinephrine levels and pulmonary artery pressure. Another study[5] that used microneurography to assess muscle sympathetic nerve activity showed increased sympathetic nerve traffic in patients with PAH compared with healthy controls. Our results raise the question whether lowering systemic arterial BP may also lower pulmonary pressure and whether using RAAS blockers or β blockers may be more beneficial than other antihypertensive agents in lowering pulmonary pressure.

To conclude, our study shows that, even after accounting for left heart disorders, patients with systemic arterial hypertension are significantly more likely to have elevated pulmonary pressures. Thus, systemic arterial hypertension should be considered as cause for PHT, rending some cases of "idiopathic" PHT as secondary to systemic arterial hypertension.

Strengths and Limitations

Our database is contemporary and is the largest echocardiographic cohort investigating the association between PHT and systemic arterial hypertension to date. However, this study has several important limitations. First, invasive hemodynamics were not available and therefore pulmonary vascular resistance was not calculated and PHT was only an estimation based on echocardiographic measurements. Second, no ambulatory BP measurements were available, the diagnosis of hypertension was based on electronic health care records only, and the duration of hypertension was unknown for most patients. Third, this is a retrospective cohort based on electronic medical record data; thus, it is liable to classification bias that might arise from improper documentation. The study was made in the largest tertiary medical center in our country, and the center is subject to Joint Commission International quality control regulation; thus, we believe that errors in the medical record were minimal. Fourth, LA volume was not available for most patients, and the definition of LA enlargement was based solely on anterior-posterior diameter in many patients, thus resulting in some patients with enlarged anterior-posterior diameters to carry over the initial exclusion by LA volume index into the study group. This was controlled for in a secondary sensitivity analysis excluding those patients as well. Diastolic dysfunction is a challenging diagnosis. Diagnostic criteria have changed during the past decade. Provocation studies, including exercise echocardiography or invasive hemodynamics, have been shown to unmask diastolic dysfunction in specific subpopulations. Therefore, we cannot rule out that at least part of the observed association can be explained by underdiagnosed diastolic dysfunction. Last, right ventricular systolic pressure was estimated by echocardiography and not directly measured via pulmonary catheterization, which, although is by far the more common, is not the gold standard for diagnosis.

Clinical Implications

When evaluating patients with PHT, arterial hypertension should be taken into consideration irrespective of echocardiographic evidence of diastolic dysfunction. This is especially important among women subjects.

ARTICLE INFORMATION

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None.

Supplemental Material

Tables S1–S20
Figures S1–S2

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SUPPLEMENTAL MATERIAL

Table S1. Multivariate Model.

	exp(coef) [confint]	p
HTN	2.83 [2.48, 3.24]	<0.001
Octogenarian	2.88 [2.46, 3.36]	<0.001
Obese	1.28 [1.11, 1.48]	0.001
Enlarged Left Atrium	1.03 [0.75, 1.39]	0.9
High Ee	6.30 [3.04, 12.78]	<0.001
IHD	0.71 [0.59, 0.84]	<0.001

HTN – Hypertension; IHD – Ischemic Heart Disease

Undiagnosed

Table S2

Multivariate Model

	exp(coef) [confint]	p
HTN	2.44 [2.08, 2.85]	<0.001
Octogenarian	3.11 [2.38, 4.01]	<0.001
Obese	1.51 [1.25, 1.83]	<0.001
Enlarged Left Atrium	0.92 [0.55, 1.46]	0.7
High Ee	3.55 [0.78, 11.51]	0.056
IHD	0.65 [0.46, 0.89]	0.010

HTN – Hypertension; IHD – Ischemic Heart Disease

In Males

Table S3

Multivariate Model

	exp(coef) [confint]	p
HTN	2.38 [1.95, 2.91]	<0.001
Octogenarian	3.09 [2.43, 3.91]	<0.001
Obese	1.15 [0.92, 1.43]	0.2
Enlarged Left Atrium	1.30 [0.90, 1.83]	0.2
High Ee	11.47 [4.41, 29.69]	<0.001
IHD	0.69 [0.55, 0.87]	0.002

HTN – Hypertension; IHD – Ischemic Heart Disease

In Females

Table S4

Multivariate Model

	exp(coef) [confint]	p
HTN	3.08 [2.62, 3.62]	<0.001
Octogenarian	2.54 [2.13, 3.02]	<0.001
Obese	1.38 [1.18, 1.61]	<0.001
Enlarged Left Atrium	0.91 [0.57, 1.40]	0.7
High Ee	2.03 [0.64, 5.42]	0.2
IHD	0.92 [0.72, 1.18]	0.5

HTN – Hypertension; IHD – Ischemic Heart Disease

In patients with abnormal la diameter

Table S5

Multivariate Model

	exp(coef) [confint]	p
HTN	3.40 [1.67, 7.88]	0.002
Octogenarian	2.15 [1.10, 4.05]	0.021
male	0.66 [0.39, 1.12]	0.1
Obese	0.74 [0.43, 1.25]	0.3
IHD	0.97 [0.52, 1.73]	0.9

HTN – Hypertension; IHD – Ischemic Heart Disease

In patients with normal la diameter

Table S6

Multivariate Model

	exp(coef) [confint]	p
HTN	2.70 [2.41, 3.03]	<0.001
Octogenarian	2.79 [2.45, 3.17]	<0.001
male	0.64 [0.58, 0.71]	<0.001
Obese	1.35 [1.20, 1.51]	<0.001
IHD	0.84 [0.72, 0.98]	0.027

HTN – Hypertension; IHD – Ischemic Heart Disease

In patients with abnormal Ee' ratio

Table S7

Multivariate Model

	exp(coef) [confint]	p
HTN	2.13 [0.40, 13.68]	0.4
Octogenarian	2.29 [0.38, 15.96]	0.4
male	3.29 [0.76, 16.40]	0.1
Obese	1.61 [0.25, 10.00]	0.6
IHD	0.37 [0.04, 2.35]	0.3

HTN – Hypertension; IHD – Ischemic Heart Disease

In patients with normal Ee' ratio

Table S8

Multivariate Model

	exp(coef) [confint]	p
HTN	2.80 [2.48, 3.18]	<0.001
Octogenarian	2.72 [2.36, 3.13]	<0.001
male	0.65 [0.58, 0.72]	<0.001
Obese	1.30 [1.15, 1.47]	<0.001
IHD	0.80 [0.68, 0.94]	0.008

HTN – Hypertension; IHD – Ischemic Heart Disease

In patients with abnormal eVelocity

Table S9

Multivariate Model

	exp(coef) [confint]	p
HTN	1.91 [1.62, 2.26]	<0.001
Octogenarian	2.59 [2.22, 3.02]	<0.001
male	0.65 [0.57, 0.74]	<0.001
Obese	1.24 [1.06, 1.45]	0.006
Enlarged Left Atrium	1.08 [0.78, 1.48]	0.6
High Ee	NA [NA, NA]	0.008
IHD	0.77 [0.64, 0.93]	<0.001

HTN – Hypertension; IHD – Ischemic Heart Disease

In patients with normal eVelocity

Table S10

Multivariate Model

	exp(coef) [confint]	p
HTN	3.93 [3.24, 4.78]	<0.001
Octogenarian	4.35 [2.88, 6.48]	<0.001
male	0.61 [0.51, 0.74]	<0.001
Obese	1.32 [1.06, 1.65]	0.013
Enlarged Left Atrium	1.12 [0.60, 1.93]	0.7
High Ee	4.42 [2.11, 8.97]	<0.001
IHD	0.77 [0.54, 1.07]	0.1

HTN – Hypertension; IHD – Ischemic Heart Disease

In patients with Diabetes Mellitus

Table S11

Multivariate Model

	exp(coef) [confint]	p
HTN	3.55 [2.08, 6.63]	<0.001
Octogenarian	1.97 [1.45, 2.67]	<0.001
male	0.52 [0.40, 0.66]	<0.001
Obese	1.25 [0.95, 1.62]	0.1
Enlarged Left Atrium	0.65 [0.33, 1.18]	0.2
High Ee	7.00 [2.26, 22.36]	0.001
IHD	0.98 [0.73, 1.30]	0.9

HTN – Hypertension; IHD – Ischemic Heart Disease

In patients without Diabetes Mellitus

Table S12

Multivariate Model

	exp(coef) [confint]	p
HTN	2.65 [2.32, 3.02]	<0.001
Octogenarian	3.01 [2.57, 3.53]	<0.001
male	0.68 [0.60, 0.76]	<0.001
Obese	1.27 [1.09, 1.47]	0.001
Enlarged Left Atrium	1.30 [0.94, 1.76]	0.1
High Ee	4.00 [1.58, 9.32]	0.002
IHD	0.67 [0.54, 0.83]	<0.001

HTN – Hypertension; IHD – Ischemic Heart Disease

In octogenarians

Table S13

Multivariate Model

	exp(coef) [confint]	p
HTN	2.02 [1.31, 3.25]	0.002
male	0.68 [0.52, 0.89]	0.005
Obese	1.16 [0.82, 1.61]	0.4
Enlarged Left Atrium	0.90 [0.45, 1.68]	0.8
High Ee	3.33 [0.91, 12.18]	0.062
IHD	1.19 [0.86, 1.63]	0.3

HTN – Hypertension; IHD – Ischemic Heart Disease

In non-octogenarians

Table S14

Multivariate Model

	exp(coef) [confint]	p
HTN	2.87 [2.53, 3.28]	<0.001
male	0.64 [0.56, 0.72]	<0.001
Obese	1.32 [1.15, 1.51]	<0.001
Enlarged Left Atrium	1.15 [0.83, 1.55]	0.4
High Ee	5.71 [2.49, 12.34]	<0.001
IHD	0.66 [0.54, 0.81]	<0.001

HTN – Hypertension; IHD – Ischemic Heart Disease

In obese patients

Table S15

Multivariate Model

	exp(coef) [confint]	p
HTN	2.75 [2.08, 3.69]	<0.001
Octogenarian	2.31 [1.65, 3.20]	<0.001
male	0.55 [0.43, 0.70]	<0.001
Enlarged Left Atrium	0.76 [0.47, 1.19]	0.3
High Ee	4.24 [0.86, 17.09]	0.049
IHD	0.71 [0.49, 0.99]	0.052

HTN – Hypertension; IHD – Ischemic Heart Disease

In non-obese patients

Table S16

Multivariate Model

	exp(coef) [confint]	p
HTN	2.77 [2.42, 3.19]	<0.001
Octogenarian	2.85 [2.43, 3.32]	<0.001
male	0.67 [0.59, 0.75]	<0.001
Enlarged Left Atrium	1.44 [1.00, 2.02]	0.040
High Ee	5.30 [2.39, 11.39]	<0.001
IHD	0.79 [0.65, 0.95]	0.014

HTN – Hypertension; IHD – Ischemic Heart Disease

In patients with IHD

Table S17

Multivariate Model

	exp(coef) [confint]	p
HTN	2.06 [1.24, 3.65]	0.008
Octogenarian	4.40 [3.10, 6.22]	<0.001
male	0.50 [0.36, 0.69]	<0.001
Obese	1.16 [0.79, 1.68]	0.5
Enlarged Left Atrium	1.61 [0.86, 2.81]	0.1
High Ee	1.51 [0.21, 7.47]	0.6

HTN – Hypertension; IHD – Ischemic Heart Disease

In patients without IHD

Table S18

Multivariate Model

	exp(coef) [confint]	p
HTN	2.85 [2.51, 3.25]	<0.001
Octogenarian	2.51 [2.15, 2.93]	<0.001
male	0.67 [0.59, 0.75]	<0.001
Obese	1.32 [1.15, 1.51]	<0.001
Enlarged Left Atrium	0.99 [0.71, 1.36]	1
High Ee	6.46 [2.99, 13.56]	<0.001

HTN – Hypertension

Sensitivity analysis - Healthy Patients

Table S18

Multivariate Model

	exp(coef) [confint]	p
HTN	3.92 [3.34, 4.62]	<0.001
Male	0.69 [0.59, 0.81]	<0.001
Obese	1.33 [1.10, 1.61]	0.003

HTN – Hypertension

Sensitivity analysis - Undiagnosed vs diagnosed.

Table S19

Multivariate Model

	exp(coef) [confint]	p
HTN	2.43 [2.08, 2.85]	<0.001
Octogenarian	3.01 [2.31, 3.89]	<0.001
male	0.73 [0.62, 0.85]	<0.001
Obese	1.48 [1.22, 1.78]	<0.001
Enlarged Left Atrium	0.96 [0.57, 1.52]	0.9
High Ee	3.60 [0.80, 11.71]	0.053

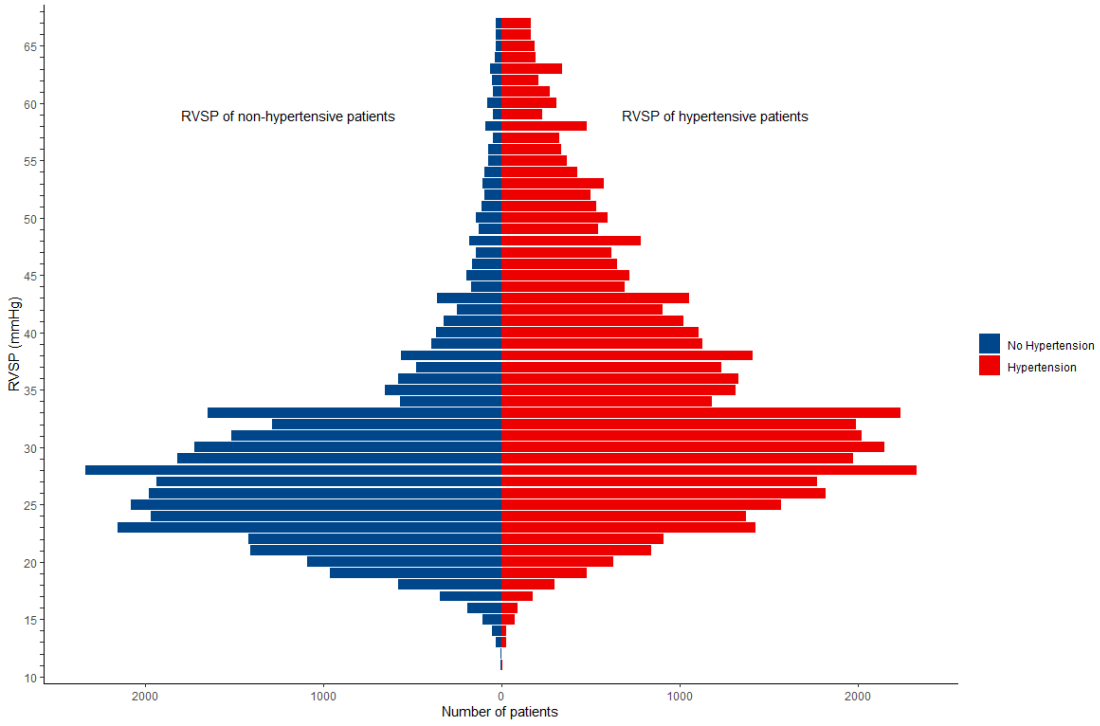
HTN - Hypertension

Sensitivity analysis – diastolic dysfunction defined by 3 variables only without TR velocity

Table S20

Contentious multivariate model			**Dichotomized multivariate model**		
	OR (CI)	p		OR (CI)	p
Hypertension	2.30 (1.86-2.85)	<0.001	Hypertension	3.60 (3.07-4.24)	<0.001
Age by 10	1.46 (1.37-1.56)	<0.001	Octogenarian	3.81 (2.98-4.86)	<0.001
Male	0.63 (0.52-0.77)	<0.001	Male	0.62 (0.53-0.72)	<0.001
Obese	1.17 (0.92 -1.48)	0.2	Obese	1.35 (1.12-1.61)	0.001
LVEF	1.03 (1.00 -1.06)	0.085			
Left Atrium AP Diameter	1.07 (0.87-1.23)	0.4	Enlarged Left Atrium	1.35 (0.84-2.07)	0.2
Ee’	1.23 (1.17-1.29)	<0.001	IHD	1.03 (0.80-1.31)	0.8
IHD	0.65 (0.45-0.91)	0.016			

Figure S1. The odds ratio and confidence intervals for suffering from pulmonary hypertension based on systolic blood pressure on admission.



Odds ratio for elevated Right Ventricular Systolic Pressure (RVSP) per 10 mmHg increase in systolic blood pressure.

Figure S2. Distribution of Right Ventricular Systolic Pressure (RVSP) in population, grouped by hypertension status.