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Prevalence and predictors of pulmonary hypertension in elderly patients with isolated diastolic heart failure

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Abstract

Background: Despite the growing recognition that pulmonary hypertension can develop in diastolic heart failure; its clinical significance remains poorly defined.

Aim: We sought to explore the prevalence and predictors of pulmonary hypertension in elderly patients with isolated diastolic heart failure.

Methods: We enrolled 100 consecutive elderly patients with isolated diastolic heart failure. All patients underwent transthoracic echocardiography to measure the pulmonary artery systolic pressure, diastolic function indices (mitral E peak deceleration time, isovolumetric relaxation time, early mitral annular diastolic velocity), left atrial diameter and left ventricular mass index. Pulmonary hypertension was defined as pulmonary artery systolic pressure ≥ 37 mm Hg. We classified patients into two groups: one with diastolic heart failure and concomitant pulmonary hypertension, and one with diastolic heart failure but without concomitant pulmonary hypertension.

Results: The mean age of the whole series was 65.4 ± 5.4 years, 49 (49%) being female. Patients with pulmonary hypertension (20% of the whole series) were more often females, hypertensive, more likely to have atrial fibrillation, pulmonary congestion symptoms, larger left atrial diameter, lower early mitral annular diastolic velocity, lower left ventricular ejection fraction, and more likely to have mitral regurgitation ($p < 0.05$ for all). Multivariate logistic regression analysis identified female gender, atrial fibrillation, and early mitral annular diastolic velocity (e’) as the independent predictors of the presence of pulmonary hypertension.

Conclusions: Pulmonary hypertension is fairly prevalent in elderly patients with diastolic heart failure. Female gender, atrial fibrillation, and early mitral annular diastolic velocity (e’) were the independent predictors of the presence of pulmonary hypertension in this patient group.

Key words: pulmonary hypertension, diastolic heart failure, prevalence

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INTRODUCTION

While pulmonary hypertension (PH) is a well-known sequel to heart failure with reduced left ventricular ejection fraction (LVEF) [1], several case reports and case series highlighted the importance of PH in heart failure with preserved LVEF or isolated diastolic heart failure (DHF) [2–6]. These patients usually have elevated left heart filling pressures. Classically, transmission of the high pressure to the pulmonary circulation leads to pulmonary venous hypertension and post-capillary PH. Yet a recent report emphasised also the contribution of a pre-capillary component to PH in these patients [7].

There is a growing belief that elderly patients are more susceptible to the development of PH [8], as age-related vascular stiffening has been consistently reported [9–12]. Inte-

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restingly, age-related increases in arterial stiffness are more pronounced in women than in men [9, 12–15].

Both PH and right ventricular (RV) function predict mortality in patients with systolic heart failure [16]. Despite the growing recognition that PH can develop in DHF, its clinical significance remains unclear. In a prospective study design, we tried to explore the prevalence and predictors of PH in elderly patients with DHF.

METHODS

Patient selection

We prospectively included 100 consecutive elderly patients referred to our echocardiography labs between May and November 2008 with the diagnosis of heart failure. Patients were considered eligible for inclusion if they were aged above 60, had symptoms and/or signs of heart failure as validated by the Framingham criteria, LVEF ≥ 50%, and early mitral annular (medial) diastolic velocity (e') ≤ 8 cm/s, as described later. We excluded patients in whom tricuspid regurgitation jets could not be analysed, those with pulmonary valve stenosis (defined as peak systolic pressure gradient > 5 mm Hg across the pulmonary valve), those with haemodynamically significant left-sided valve stenosis, those with chronic obstructive pulmonary disease or other potential causes of PH (for example, collagen vascular disease, history of pulmonary embolism, obstructive sleep apnea, chronic liver disease, etc.). Before inclusion, an informed written consent was obtained from each patient after full explanation of the study protocol. The study protocol was reviewed and approved by our local institutional human research committee to check that it conforms to the ethical guidelines of the 1975 Declaration of Helsinki, as revised in 2002.

Definition of risk factors

Hypertension was defined as systolic blood pressure ≥ 140 mm Hg and/or diastolic blood pressure ≥ 90 mm Hg, previously recorded by repeated non-invasive office measurements, which lead to lifestyle modification or antihypertensive drug therapy. Diabetes mellitus was defined as fasting plasma glucose ≥ 126 mg/dL, and/or two hour post glucose load ≥ 200 mg/dL, or specific anti-diabetic drug therapy.

Doppler echocardiography

Doppler echocardiography was performed using a General Electric Vivid 7 Pro cardiac ultrasound machine (General Electric, Horten, Norway). A 2.5 MHz phased array probe was used to obtain standard 2-D, M-mode and Doppler images. Patients were examined in the left lateral recumbent position using standard parasternal and apical views. Measurements were averaged from three cardiac cycles. Left ventricular ejection fraction was estimated from 2-D-derived M-mode linear measurements, using the method described by Teichholz et al. [17]. Left ventricular mass index was calculated from linear LV dimensions as described by Devereux et al. [18] (validated with necropsy r = 0.90, p < 0.001).

Estimation of pulmonary artery systolic pressure

In the absence of pulmonary valve stenosis, pulmonary artery systolic pressure (PASP) equals RV systolic pressure which can be estimated by adding the systolic pressure gradient between the RV and right atrium, to an assumed value of right atrial pressure. Systolic pressure gradient between the RV and right atrium can be measured from the tricuspid regurgitation jet envelope (obtained by continuous-wave Doppler examination with a Doppler beam passing between the tips of the tricuspid valve leaflets) using the modified Bernoulli equation as $4v^2$, where v is the peak velocity of tricuspid regurgitation (m/s). We used an assumed value of 5 mm Hg for right atrial pressure, according to the most recent guidelines suggested by the Task Force of the European Society of Cardiology [19]. In accordance with these guidelines, we adopted the suggested definition of 'possible PH' as a PASP ≥ 37 mm Hg (class IIa, level of evidence C, for identification of possible PH with or without additional echocardiographic variables suggestive of PH) [19].

Evaluation of left ventricular diastolic function

Mitral E peak deceleration time was measured from the mitral inflow velocity envelope (obtained by pulsed-wave Doppler examination with a sample volume of 2.0 mm placed at the tips of the mitral valve leaflets). Isovolumetric relaxation time (defined as the time interval from the end of aortic systolic outflow to the onset of mitral inflow) was estimated by placing the sample volume in the LV outflow tract close to the anterior mitral leaflet, in order to record both inflow and outflow signals simultaneously. Doppler tissue imaging was performed using the same cardiac ultrasound machine (General Electric, Horten, Norway). The Doppler sample volume was placed at the medial mitral annulus and the early mitral annular (medial) diastolic velocity (e') was measured (cm/s).

Patient groups

According to the above definition of PH, we classified patients into two groups: one with DHF and concomitant PH and one with DHF but without concomitant PH.

Statistical analysis

All continuous variables are presented as mean ± standard deviation, if they are normally distributed. Data were tested for normal distribution using the Kolmogorov-Smirnov test. Categorical variables are described with absolute and relative (percentage) frequencies. Pearson χ^2 test and unpaired t-test were used to compare the distribution of categorical and continuous variables, respectively, between the two study groups. Pearson's correlation coefficient test was performed to

Table 1. Baseline clinical characteristics of the whole series and the two individual study groups

	Whole series (n = 100)	DHF with PH (n = 20)	DHF without PH (n = 80)	P
Age [years]	65.4 ± 5.4	65.2 ± 4.7	65.5 ± 5.5	NS
Female gender	49 (49%)	15 (75%)	34 (42.5%)	< 0.01
Smoking	38 (38%)	8 (40%)	30 (37.5%)	NS
Diabetes	41 (41%)	8 (40%)	33 (41.25%)	NS
Duration of diabetes [years]	7.6 ± 8.3	7.8 ± 6.6	7.6 ± 8.7	NS
Hypertension	59 (59%)	16 (80%)	43 (53.75%)	< 0.05
Duration of hypertension [years]	10.4 ± 9.9	10.0 ± 6.6	6.2 ± 9.9	NS
Atrial fibrillation	24 (24%)	12 (60%)	12 (15%)	< 0.001
Dyspnea (NYHA class > 1)	77 (77%)	18 (90%)	59 (73.75%)	NS
Pulmonary rales	5 (5%)	4 (20%)	1 (1.25%)	< 0.001

DHF — diastolic heart failure; PH — pulmonary hypertension; NYHA — New York Heart Association

Table 2. Echocardiographic characteristics of the whole series and the two individual study groups

	Whole series (n = 100)	Group 1 (n = 20)	Group 2 (n = 80)	P
LVESD [mm]	31.8 ± 5.6	32.5 ± 5.9	31.7 ± 5.6	NS
LVEDD [mm]	49.5 ± 6.5	49.3 ± 7.8	49.6 ± 6.2	NS
IVST [mm]	10.7 ± 2.1	11.1 ± 1.9	10.6 ± 2.1	NS
PWT [mm]	10.5 ± 2.6	11.1 ± 2.2	10.4 ± 2.3	NS
Ejection fraction [%]	63 ± 8	60.2 ± 6.7	64.5 ± 7.6	< 0.05
LV mass [g]	200 ± 74	210 ± 74	198 ± 74	NS
LV mass index [g/m^2]	108 ± 40	112 ± 40	108 ± 40	NS
LAD [mm]	40.1 ± 7.7	46.6 ± 8.8	38.5 ± 6.5	< 0.001
Mitral E peak DT [ms]	130 ± 89	163 ± 40	169 ± 44	NS
IVRT [ms]	69 ± 47	84 ± 30	90 ± 32	NS
Mitral annular velocity e' [cm/s]	5.5 ± 1.6	4.7 ± 0.9	5.7 ± 0.9	< 0.001
Mitral regurgitation	42 (42%)	13 (65%)	29 (36.25%)	< 0.05

LV — left ventricular; ESD — end-systolic diameter; EDD — end-diastolic diameter; IVST — inter-ventricular septal thickness; PWT — posterior wall thickness; LAD — left atrial diameter; DT — deceleration time; IVRT — iso-volumetric relaxation time

study the correlation between PH and diastolic function indices (mitral E peak deceleration time, isovolumetric relaxation time, and early mitral annular [medial] diastolic velocity [e']). Finally, multivariate logistic regression analysis was performed to identify the independent predictors of the presence of PH. All tests were two-sided and a p value < 0.05 was considered statistically significant. Analyses were performed with SPSS version 12.0 statistical package (SPSS Inc., Chicago, Illinois, USA).

RESULTS

A total of 100 elderly patients with DHF were enrolled in the current study. Twenty (20%) patients had concomitant PH, whereas 80 (80%) did not. The mean PASP in the whole series was 43.4 ± 13.6 mm Hg. The prevalence of PH was 9.8% (5 out of 51) among males as compared to 30.6% (15 out of 49) in females ($p < 0.05$).

Clinical characteristics

Table 1 shows the baseline clinical characteristics of the whole series, as well as the two individual study groups. The mean age of the whole study group was 65.4 ± 5.4 years, of whom 49 (49%) were females. Comparison of the baseline clinical characteristics between the two individual study groups revealed that patients with PH were more often female (75% *vs* 42.5%, $p < 0.01$), hypertensive (80% *vs* 53.75%, $p < 0.05$), more likely to have atrial fibrillation (AF; 60% *vs* 15%, $p < 0.001$) and pulmonary rales (20% *vs* 1.25%, $p < 0.001$). All other baseline characteristics were similar between the two study groups.

Echocardiographic characteristics

Table 2 shows the echocardiographic characteristics of the whole series, as well as the two individual study groups. Comparisons of the echocardiographic characteristics between the

Table 3. Multivariate regression analysis to identify independent predictors of pulmonary hypertension in patients with isolated diastolic heart failure

Variable	B	P	Odds ratio	95.0% confidence interval for odds ratio	
				Lower	Upper
Female gender	–2.085	0.012	0.124	0.024	0.632
Hypertension	1.338	0.117	3.811	0.717	20.272
Rales	1.741	0.411	5.702	0.090	363.160
Atrial fibrillation	1.763	0.037	5.829	1.114	30.488
Ejection fraction	–0.103	0.080	0.902	0.803	1.012
Left atrial dilatation	0.051	0.260	1.052	0.963	1.150
Mitral annular velocity (e')	–0.978	0.025	0.376	0.160	0.885

two individual study groups revealed that patients with PH had a larger left atrial diameter (46.6 ± 8.8 *vs* 38.5 ± 6.5 mm, $p < 0.001$), a lower early mitral annular diastolic velocity (e') (4.7 ± 0.9 *vs* 5.7 ± 0.9 cm/s, $p < 0.001$), a lower LVEF (60.2 ± ± 6.7% *vs* 64.5 ± 7.6%, $p < 0.05$), and were more likely to have mitral regurgitation (65% *vs* 36.25%, $p < 0.05$).

Independent predictors of PH

Multivariate logistic regression analysis identified female gender, AF, and early mitral annular diastolic velocity (e') as the independent predictors of the presence of PH ($p < 0.05$; Table 3).

DISCUSSION

Prevalence and severity of PH

The current study demonstrated that PH is fairly prevalent among elderly patients with DHF (20%), and occurs much more frequently among females as compared to males (75% *vs* 42.5%, respectively). Age-associated advancement in arterial stiffness was consistently reported to be more pronounced in women than in men with matched baseline criteria [9, 12–15]. We have deliberately adopted the definition of 'possible PH' suggested by the Task Force of the European Society of Cardiology (PASP ≥ 37 mm Hg) rather than definition of 'likely PH' (PASP > 50 mm Hg) suggested by the same Task Force. This was so that we could include milder levels of elevation of PASP in patients with isolated DHF that would, otherwise, be missed as 'normal pulmonary pressure'. The mean PASP in the our series (43.4 ± 13.6 mm Hg) is in line with that reported in former series of patients with DHF [4, 6, 7]. However, the prevalence of PH in our series was much lower than that in population-based data (83% of the symptomatic group) reported by Lam et al. [7]. This divergent result might be attributable to the markedly higher prevalence of systemic hypertension in their series (97% and 91% in those with and without PH, respectively) as compared to our series (59%). A recent population-based study showed that advanced age is an independent predictor of elevated PASP ($r = 0.31$, $p < 0.001$) [20]. The more advanced age in the series by Lam et al. (79 ± 12 and 74 ± 11 years in those with and without PH, respectively) as compared to ours, may provide another explanation [7].

Predictors of PH in patients with DHF

The prevalence of systemic hypertension was higher in patients with PH compared to those without PH ($p < 0.05$). The higher the systemic blood pressure, the more elevated the left heart filling pressures, which would eventually translate into a higher PASP.

Atrial fibrillation reduces forward pulmonary venous flow as assessed by echocardiography [21], and hence can lead to higher pulmonary venous pressures, something that would help explain the higher prevalence of AF in patients with, as compared to those without, PH. Signs of pulmonary venous congestion were more prevalent in patients with PH, reflecting higher left filling pressures in these patients.

Early mitral annular diastolic velocity (e') was significantly reduced in patients with PH compared to those without PH. Meanwhile, the other diastolic function indices (mitral E peak deceleration time, isovolumetric relaxation time) did not differ significantly between the two groups. Clearly, measurement of the early mitral annular diastolic velocity (e') eliminates the effect of loading conditions (in contrast to the other diastolic function indices), adding to the reliability of diastolic function assessment. Again, this would reflect a higher left filling pressure, a more impaired diastolic compliance, and a more advanced stage of DHF in patients who developed PH.

Among the traditional indices of cardiac remodelling, left atrial size was significantly larger in patients with PH than in those without PH, while LV mass index was not. Left atrial size increases, and left atrial emptying decreases, in elderly patients with either systolic or diastolic heart failure [22]. Moreover, left atrial volume index is an independent predictor of exercise capacity in patients with isolated diastolic dysfunction [23]. Reduced exercise capacity in these patients might be ascribed, at least in part, to elevated pulmonary circulation pressures.

Mitral regurgitation was significantly more frequent in patients with PH compared to those without PH. Increased pulmonary capillary wedge pressure was shown as an independent predictor of PASP in patients with heart failure with and without mitral regurgitation [24]. By further increasing left heart filling pressures, mitral regurgitation would account for increased PASP in patients with DHF.

Clinical implications

Being prevalent in elderly patients with DHF (especially females), and being strongly associated with mortality in these patients [7], PH may represent an attractive therapeutic target. It is reasonable that afterload reducing agents for mitral regurgitation would serve to reduce the ensuing rise of PASP. Immediate cardioversion and subsequent prevention of recurrence of AF would attenuate the progressive elevation of left filling pressures, and hence the resultant PH. Furthermore, adequate control of systemic hypertension is essential to abort subsequent cardiac remodelling and haemodynamic deterioration. Finally, there is no proven therapeutic option, to date, for isolated DHF. Therapeutic recommendations delineated in heart failure guidelines are largely empirical and obviously need to be updated. The demonstrated fact that PH entails the contribution of a pre-capillary component [7] makes pulmonary arterial vasodilators an appealing therapeutic tool. Recent studies employing phosphodiesterase-5 inhibitors in systolic heart failure demonstrated improvement of both exercise capacity and quality of life in patients with heart failure and secondary PH [25, 26].

Limitations of the study

Our findings are based on a single centre study with a relatively small sample size of the cohort, a fact that makes it difficult to generalise our results to all patients with DHF. Multicentre studies using the same protocol and examining a larger number of patients are needed. Moreover, the study population was composed of symptomatic heart failure patients referred for evaluation by echocardiography. This referral bias makes it hard to extrapolate our data to patients with asymptomatic diastolic dysfunction. Although potential causes of secondary PH were excluded, hidden diagnoses may have been missed in some cases. An important limitation of our study was exclusion of patients with non-analysable tricuspid regurgitation jets, a fact that could have over- or underestimated the prevalence of PH. Furthermore, the potential drawback of PASP estimated by echocardiography is another possible limitation [27]. Notably, echocardiographic data needs to be prospectively validated against 'gold standard' invasive measurements. Finally, follow-up is needed both in the short and long terms, to exactly determine the influence of PH on the hard cardiovascular end-points.

CONCLUSIONS

PH is fairly prevalent among elderly patients with DHF, and is more frequent among females. Female gender, AF, and early mitral annular diastolic velocity (e') were the independent predictors of the presence of PH in this group of patients.

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Czynniki predykcyjne nadciśnienia płucnego u osób w podeszłym wieku z izolowaną rozkurczową niewydolnością serca

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Streszczenie

Wstęp: Mimo wzrostu świadomości, że nadciśnienie tętnicze może się przyczynić do rozwoju rozkurczowej niewydolności serca, jego znaczenie kliniczne nadal nie zostało ściśle określone.

Cel: Celem niniejszej pracy było zbadanie częstości występowania czynników predykcyjnych nadciśnienia płucnego u osób w podeszłym wieku z izolowaną rozkurczową niewydolnością serca.

Metody: Do badania włączono 100 kolejnych pacjentów w podeszłym wieku z izolowaną rozkurczową niewydolnością serca. U wszystkich chorych wykonano przezklatkowe badanie echokardiograficzne w celu określenia wartości ciśnienia skurczowego w tętnicy płucnej, wskaźników czynności rozkurczowej serca (czas deceleracji fali E, czas rozkurczu izowolumetrycznego, prędkość wczesnego napełniania lewej komory), wymiaru lewego przedsionka i wskaźnika masy lewej komory. Nadciśnienie płucne definiowano jako ciśnienie skurczowe w tętnicy płucnej ≥ 37 mm Hg. Pacjentów podzielono na 2 grupy: grupę z rozkurczową niewydolnością serca i współistniejącym nadciśnieniem płucnym oraz grupę z rozkurczową niewydolnością serca bez nadciśnienia płucnego.

Wyniki: Średni wiek badanych wynosił 65,4 ± 5,4 roku, 49% stanowili mężczyźni (n = 49). Nadciśnienie płucne (u 20% badanych) występowało częściej u kobiet i osób z nadciśnieniem tętniczym. U chorych z nadciśnieniem tętniczym częściej stwierdzano migotanie przedsionków, objawy zastoju płucnego, zwiększenie wymiaru lewego przedsionka, zmniejszenie prędkości wczesnego napełniania i frakcji wyrzutowej lewej komory oraz niewydolność zastawki mitralnej ($p < 0,05$ dla wszystkich porównań). W wieloczynnikowej analizie regresji wskazano, że płeć żeńska, migotanie przedsionków i prędkość wczesnego napełniania lewej komory (e') są niezależnymi czynnikami predykcyjnymi nadciśnienia płucnego.

Wnioski: Nadciśnienie płucne występuje stosunkowo często u osób w podeszłym wieku z rozkurczową niewydolnością serca. Płeć żeńska, migotanie przedsionków i zmniejszona prędkość wczesnego napełniania lewej komory (e') są niezależnymi czynnikami predykcyjnymi obecności nadciśnienia płucnego w tej grupie pacjentów.

Słowa kluczowe: nadciśnienie płucne, rozkurczowa niewydolność serca, chorobowość

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