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Pulmonary arterial hypertension in congenital heart disease: An epidemiologic perspective from a Dutch registry

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Abstract

Background: Pulmonary arterial hypertension (PAH) associated with congenital heart disease is usually the result of a large systemic-to-pulmonary shunt, and often leads to right ventricular failure and early death. The purpose of this study was to determine the prevalence of PAH among adult patients included in a national registry of congenital heart disease and to assess the relation between patient characteristics and PAH.

Methods: Patients with PAH associated with a septal defect were identified from the registry. Gender, age, underlying diagnosis, previous closure, age at repair and NYHA classification were recorded. PAH was defined as a systolic pulmonary arterial pressure (sPAP) greater than 40 mm Hg, estimated by means of echocardiographical evaluation.

Results: The prevalence of PAH among all 5970 registered adult patients with congenital heart disease was 4.2%. Of 1824 patients with a septal defect in the registry, 112 patients (6.1%) had PAH. Median age of these patients was 38 years (range 18–81 years) and 40% were male. Of these patients, 58% had the Eisenmenger syndrome. Among the patients with a previously closed septal defect, 30 had PAH (3%). Ventricular septal defect (VSD) was the most frequent underlying defect (42%) among patients with PAH and a septal defect. Female sex (Odds ratio=1.5, $p=0.001$) and sPAP (Odds ratio=0.04, $p<0.001$) were independently associated with a decreased functional class.

Conclusion: PAH is common in adult patients with congenital heart disease. In our registry the prevalence of PAH in septal defects is around 6%. More than half of these patients have the Eisenmenger syndrome, which accounts for 1% of the total population in the CONCOR registry. Whether the prevalence of PAH will decrease in the future as a result of early detection and intervention remains to be awaited.

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1. Introduction

Pulmonary arterial hypertension (PAH) may lead to a decreased functional capacity, and right ventricular failure, and is often associated with early death [1]. The prevalence

of PAH in patients with congenital heart disease is not known. It has been suggested that 10% of all adult patients with congenital heart disease sooner or later develop PAH [2,3]. In the context of congenital heart disease, PAH may develop as a consequence of a systemic-to-pulmonary shunt. Due to systemic-to-pulmonary shunting, pulmonary blood flow increases. This leads to increased pressure in the pulmonary arteries, endothelial dysfunction and an increased vascular resistance. These changes may ultimately lead to a reversal of the systemic-to-pulmonary shunt accompanied by

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cyanosis [4], the so-called Eisenmenger syndrome. Eisenmenger syndrome is at the severe end of the spectrum of PAH and involves probably about 1–2% of patients with congenital heart disease [3].

Once the Eisenmenger syndrome exists, repair of the underlying defect is contraindicated. The right ventricle will be unable to generate enough pressure to overcome the high pulmonary vascular resistance and decompensate. Surgical correction of the congenital heart defect, during childhood, before the characteristic changes in the pulmonary arteries have started to appear, will mostly prevent the development of PAH [5–7].

A few studies have been devoted to the clinical course of the Eisenmenger syndrome, but little is known about the prevalence and clinical impact of PAH among patients with congenital heart defects. Various congenital heart defects may lead to PAH, such as univentricular heart, truncus arteriosus, patent ductus arteriosus and septal defects, but PAH may also develop as a result of surgical shunts (Potts, Waterston, Blalock–Taussig). Although PAH may occur in the context of a wide range of different defects, by far the largest proportion of patients with PAH have a septal defect as underlying defect. For that reason, in this study we focused in particular on ventricular septal defect (VSD), primum or secundum atrial septal defect (ASD I or ASD II, respectively) or complete atrioventricular septal defect (AVSD). As early surgery of the defect will mostly prevent the development of PAH, it is especially important to be informed on the risk of PAH in these patients. What is the prevalence of PAH in this category of patients, and what are the clinical characteristics of adult patients with PAH? To answer these questions, we analyzed data from the CONCOR (CONgenital COR vitia) registry, a nationwide registry of adult patients with congenital heart defects in the Netherlands. This registry was set up as a basis for studying the epidemiology of congenital heart defects and includes patients with structural congenital heart defects or Marfan syndrome. In the registry are not included, patients with cardiomyopathies (i.e. arrhythmogenic right ventricular dysplasia, hypertrophic cardiomyopathy and dilated cardiomyopathy) or inherited diseases leading to genetically determined cardiac arrhythmias and sudden death (i.e. long QT syndrome, Brugada syndrome) [8]. Consistent input of data by dedicated nurses travelling along the participating hospitals may guarantee a rather high consistency of data input and a rather low amount of missing data.

2. Patients and methods

2.1. Patient population

In November 2005, the CONCOR registry contained diagnoses and clinical events of 5970 adult patients with congenital heart disease from 86 tertiary and regional hospitals [8]. Our assessment of the prevalence of PAH consisted of two parts. In a first, global, analysis, we estimated the prevalence of

PAH among all patients at risk for developing PAH. Thus, we defined a total “population at risk”, which included all patients in the registry who had as primary diagnosis a defect that may lead to PAH, i.e. one of the following defects: ASD I or II, VSD, AVSD (septal defects), patent ductus arteriosus, double inlet left ventricle, double outlet right ventricle, ductus arteriosus, or a surgical shunt (Potts, Waterston, Blalock–Taussig) in combination with another defect. We excluded defects that may lead to pulmonary hypertension in which the pathophysiology is congestion in the venous part of the pulmonary circulation. Next, for each of these patients we noted whether or not their record in the registry mentioned the diagnosis of PAH [8]. The diagnosis of PAH is entered in the registry when mentioned in the patients record by the treating cardiologist. We then determined the prevalence of PAH by dividing the number of cases with PAH by the population at risk (times 100).

In a second assessment, for reasons explained above, we focused on the patients with a septal defect. For these patients, we performed a more extensive review of the medical records. The reasons for going back to the patient files were two-fold. Firstly, we further evaluated cases with missing values in the registry. When values of measurements of sPAP could still not be found in this additional search, we assumed that the patient did not have PAH. Secondly, we wanted to obtain all available sPAP values to be able to perform analyses using quantitative sPAP values. sPAP was assessed on the basis of echocardiographic evaluation (tricuspid regurgitation jet velocity measurements) because invasive data were generally not available. The latest recorded PAP value was used. In this study, PAH was defined as a sPAP above 40 mm Hg [9,10]. Patients with a documented right ventricular outflow tract obstruction, or left sided cardiac valvular disease were excluded, because in the first case the right ventricular systolic pressure does not represent pressure in the pulmonary artery, and in the second case, left sided cardiac valvular disease may contribute to pulmonary venous hypertension.

Patients with a septal defect were classified into 2 groups: patients with the Eisenmenger syndrome and patients without Eisenmenger syndrome but with PAH (the “non-Eisenmenger” group). For each patient, apart from sPAP, the following data were collected: gender, age, underlying diagnosis, whether or not the underlying defect had been closed, age at repair and NYHA classification.

2.2. Statistical analysis

Continuous data were presented as mean with standard deviation when distributed normally and as median with range otherwise. Discrete data were given as counts, or as percentages. Differences between groups were assessed using the chi-square, *T*-test or Mann–Whitney *U*-test: Pearson correlation coefficients were calculated to investigate the relationship of sPAP with NYHA class. Ordinal multivariate regression analysis was used to identify

Table 1
Prevalence of pulmonary arterial hypertension in the population at risk

Defect	N	PAH	%
Atrial septal defect II	717	55	8
Atrial septal defect I	201	15	7
Ventricular septal defect	799	85	11
Atrioventricular septal defect	95	39	41
Patent ductus arteriosus	71	2	3
Truncus arteriosus	17	1	6
Aortopulmonary window	2	2	100
Double inlet left ventricle	28	2	7
Double outlet right ventricle	47	8	17
Univentricular heart	55	6	11
Other+surgical shunt	357	33	9
Total	2389	248	10

independent predictors for NYHA class. Logistic regression analysis was used to identify independent predictors for PAH. For each of the analyses, $p < 0.05$ was considered statistically significant.

3. Results

3.1. Population

Of the total population included in the CONCOR registry (5970 patients) from 86 hospitals, the population at risk existed of 2389 patients (see Table 1), having one of the defects mentioned in the methods section. Of those, 248 (10%) had PAH. In total, the prevalence of PAH among congenital heart disease patients was 4.2%. Further, 1824 patients (31%) were identified as having a septal defect; in 899 of these patients the

septal defect had been closed. Of the 1824 patients with a septal defect, 112 (6.1%) patients had PAH.

Baseline characteristics of patients with a septal defect and PAH are summarized in Table 2. Of the 112 patients with PAH, 65 (58%) patients had the Eisenmenger syndrome. This accounts for 1.1% of all patients (5970) registered in the CONCOR registry. Mean sPAP in patients with Eisenmenger syndrome was 89 mm Hg, and in non-Eisenmenger patients 53 mm Hg. Among the patients with a septal defect, the proportion of patients treated at a tertiary referral hospital was different between the patients with and without PAH: 85% of patients with PAH vs. 69% of patients without PAH ($p < 0.001$).

3.2. Underlying defect

VSD was the most frequent underlying defect among all patients with PAH (42%) in the septal defect group. Most of the VSD's ($n = 39$; 83%) had not been closed. Of all patients with a VSD and PAH, 31 (79%) patients had Eisenmenger syndrome. Of the eight (21%) patients without Eisenmenger syndrome, one had refused operation, four had borderline PAH, one was on the waiting list for VSD closure and in two cases operative risk was deemed too high (co-morbidity). Mean sPAP in these non-closed VSD patients without Eisenmenger syndrome was not significantly higher compared to patients with a closed VSD (54 ± 13 mm Hg vs. 59 ± 17 mm Hg, respectively; $p = 0.50$).

In the non-Eisenmenger patients with PAH, ASD II was the most frequent underlying diagnosis ($n = 20$, 38%). Most of the ASD II's had not been closed ($n = 16$; 57%). Of all patients with an ASD II and PAH, eight (29%) patients had Eisenmenger syndrome. Of the eight (29%) patients without Eisenmenger syndrome, one had refused operation, five were on the waiting list for ASD closure, in one case risk of closure was deemed too high (co-morbidity) and in one patient it was unknown why the defect had not been closed. It should be noted, that 12 of the 426 patients (3%) with a closed ASD II developed PAH.

The proportions of patients with PAH is shown, for each septal defect, in Fig. 1. The prevalence of PAH was 11% among 799 patients with VSD, 8% among 717 patients with

Table 2
Baseline characteristics of patients with a septal defect and PAH

	Eisenmenger syndrome ($n = 65$)	Non-Eisenmenger		Total ($n = 112$)
		Not closed ($n = 17$)	Closed defect ($n = 30$)	
Male	40%	41%	40%	40%
Median age, years (range)	36 (18–70)	57 (23–80)	37 (21–81)	38 (18–81)
Underlying diagnosis (%)				
VSD	31 (48)	8 (47)	8 (27)	47 (42)
ASD II	8 (12)	8 (47)	12 (40)	28 (25)
ASD I	3 (5)	1 (6)	5 (17)	9 (8)
AVSD	23 (35)	0 (0)	5 (17)	28 (25)
Mean PAP, mm Hg (\pm SD)	89 (\pm 21)	58 (\pm 19)	49 (\pm 12)	71 (\pm 26)
NYHA classification (%)				
I	6 (12)	4 (29)	13 (48)	23 (25)
II	15 (29)	8 (57)	8 (30)	31 (33)
III	28 (54)	0 (0)	6 (22)	34 (37)
IV	3 (6)	2 (14)	0 (0)	5 (5)

VSD=ventricular septal defect, ASD II=secundum atrial septal defect, ASD I=primum atrial septal defect, AVSD=atrioventricular septal defect, PAP=pulmonary arterial hypertension.

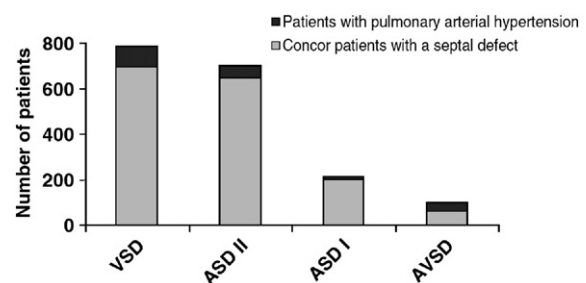


Fig. 1. Total number of patients ($n = 1824$) per type of septal defect in the CONCOR registry. PAH: pulmonary arterial hypertension; VSD: ventricular septal defect; ASD II: atrial septal defect secundum; ASD I: atrial septal defect primum; AVSD: complete atrioventricular septal defect.

ASD II, 7% among 201 patients with ASD I, and 41% among 95 patients with AVSD. So, PAH was most prevalent in patients with AVSD. Nineteen (70%) of these AVSD patients had Down syndrome. Of these, 17 had Eisenmenger syndrome and 2 had closed defects.

3.3. Age distribution

In Fig. 2A, the age distribution of all patients (1824) with a septal defect in the CONCOR registry is shown. The majority of patients with a septal defect were between 20 and

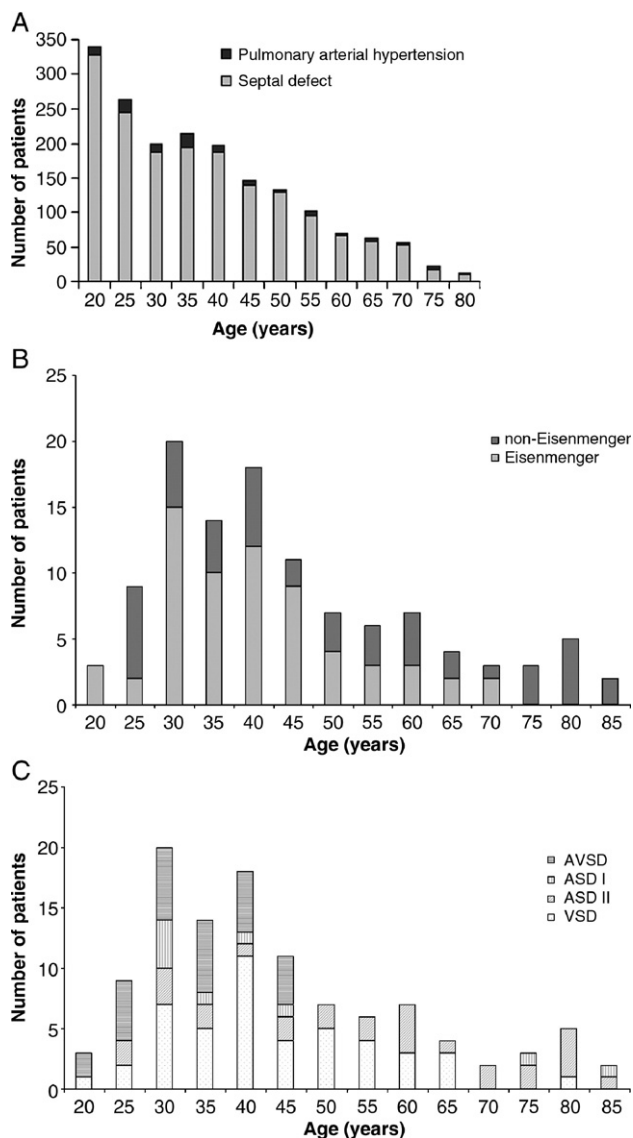


Fig. 2. A, B, C. Panel A shows the age distribution of 1824 patients with one of the following septal defects: atrial septal defect type I or II, ventricular septal defect, or complete atrioventricular septal defect. Panel B shows the age distribution of the patients ($n=112$) with pulmonary arterial hypertension among the patients with a septal defect (see Fig. 2A). “Non-Eisenmenger” refers to patients without Eisenmenger syndrome but with pulmonary arterial hypertension. Panel C shows the age distribution per underlying septal defect of the patients ($n=112$) with pulmonary arterial hypertension.

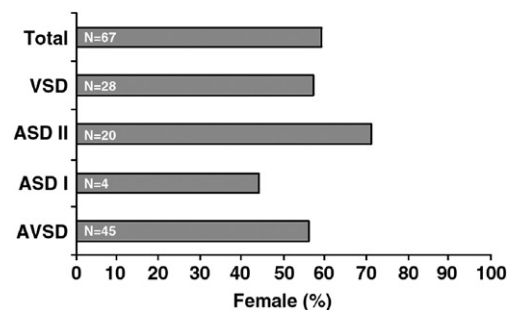


Fig. 3. Percentage of females among the patients with pulmonary arterial hypertension and a septal defect. The numbers in the bars represent the absolute numbers of females. VSD: ventricular septal defect; ASD II: atrial septal defect secundum; ASD I: atrial septal defect primum; AVSD: complete atrioventricular septal defect.

40 years of age. This is also shown in Fig. 2B for the PAH group. Eisenmenger patients and non-Eisenmenger patients were equally distributed over all age groups until the age of 70 (Fig. 2B). Patients with Eisenmenger syndrome were younger compared to non-Eisenmenger patients with an open defect and PAH (respectively 36 vs. 57 years, $p<0.01$) (Table 2). The oldest patient among the Eisenmenger patients was 69 years old (ASD II) compared with a patient aged 81 years in the non-Eisenmenger group (ASD I). In Fig. 2C, the age distribution per septal defect of the patients with PAH is shown. No difference was found in age distribution among the septal defects and among the three subgroups Eisenmenger syndrome, non-Eisenmenger with an unclosed defect and PAH with a closed defect.

3.4. Gender distribution

In the CONCOR registry, among the patients with a septal defect there were relatively more females (59%) compared to patients without a septal defect (45%; $p<0.001$). This is mostly due to the large proportion of ASD II (46%) among patients with a septal defect of whom 64% were female. The prevalence of PAH among male and female patients with a septal defect was similar, both overall and per defect (7.8 vs.

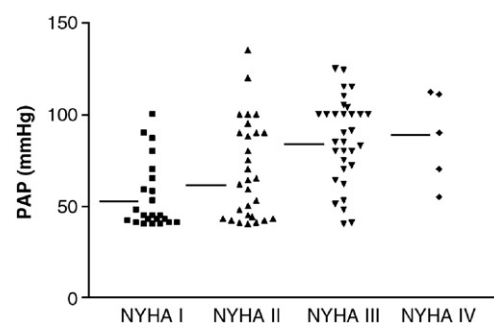


Fig. 4. Relation between systolic pulmonary arterial pressure and NYHA functional class. The horizontal bars represent mean systolic pulmonary arterial pressure for each class.

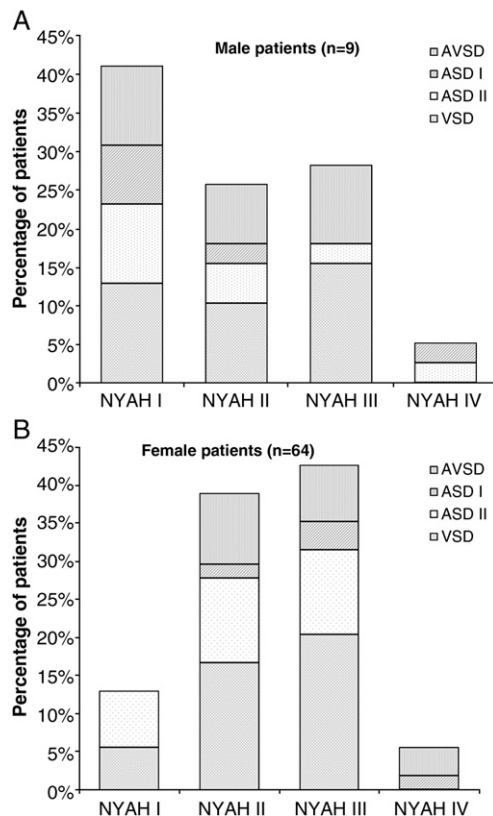


Fig. 5. A, B. Panel A shows the percentage of male patients with pulmonary arterial hypertension per NYHA classification. Panel B shows the percentage of female patients with pulmonary arterial hypertension per NYHA classification. In both panels, Bars represented percentages. The whole bars sum to 100%. Subdivisions of the bars represent the proportions taken up by the individual defects within each NYHA class.

7.6%, $p=n.s.$). As a consequence, there were more females than males with PAH. Apart from ASD II, gender distribution among PAH patients was similar in the different underlying diagnoses (Fig. 3). Similarly, no difference was found in the gender distribution between Eisenmenger and non-Eisenmenger patients (60 and 59%, resp.).

3.5. Closure of defect

In patients with an open septal defect (925), 82 had PAH, of whom 65 had Eisenmenger syndrome. In patients with PAH and an open septal defect, mean sPAP tended to be higher compared to patients with a closed septal defect and PAH (58 vs. 49 mm Hg, respectively $p=0.06$). Among 899 patients with a closed septal defect, 30 (3%) patients had developed PAH in spite of previous closure. The prevalence of PAH was 4% among patients with a closed VSD and 3% among patients with a closed ASD II ($p=0.6$).

In ASD II, age at repair was independently associated with the development of PAH (Odds=1.1, $p=0.01$), after correction for age and gender. In the other septal defects this association did not reach statistical significance. In patients with VSD, median age at repair was comparable in patients with PAH (6.3 (3.9–11) years) and without PAH (7.0 (0–62)

years; $p=n.s.$). Median age at repair, among patients with PAH, was significantly different between patients with VSD and ASD II (7 (4–11) vs. 50 (1–76) years; $p=0.03$). The difference between mean sPAP among patients with either a closed VSD or ASD II was not significant (59 ± 17 vs. 46 ± 5 , $p=0.5$ respectively).

3.6. NYHA classification

The majority of the Eisenmenger patients were in NYHA class III (54%), whereas most non-Eisenmenger patients with PAH (81%) were in class I or II ($p<0.001$). Fig. 4 shows the relationship between sPAP and NYHA class. The increase of sPAP correlates with decreasing functional capacity ($r=0.49$, $p<0.001$). Fig. 5, panels A. and B. shows a significant difference in functional class according to gender: relatively more females than males were symptomatic; 41% of the males were in NYHA class I compared to 13% of the females. Most females (82%) were in NYHA functional class II and III. Mean sPAP was not different between males and females (72 vs. 71 mm Hg, $p=0.8$). Multivariate analyses adjusting for age showed that female sex (Odds ratio=1.5, $p=0.001$) and increased sPAP (Odds ratio=0.04, $p<0.001$) were both independently associated with a worse NYHA functional class.

4. Discussion

Our data show that the prevalence of PAH among patients with a septal defect is at least 6.1% among adult patients included in the CONCOR registry. The estimated prevalence of PAH among all patients included in the CONCOR registry as a whole is at least 4.2%. One percent of all patients (5970) registered in the CONCOR registry had the Eisenmenger syndrome. VSD was the most common underlying diagnosis among patients with PAH in the septal defect group. Female sex and increased sPAP were both independently associated with worse NYHA functional class.

4.1. Prevalence

To our knowledge, this is the first study reporting on the prevalence of PAH and Eisenmenger syndrome among adult patients with congenital heart disease. Our sample consisted of patients believed to be representative of the general population of adult patients with congenital heart disease. Although, at present, patients attending tertiary referral hospitals are still overrepresented, it is the aim of the CONCOR registry to detect all patients with congenital heart disease in the Netherlands. As always, there are disadvantages in using data collected as part of a registry. Moreover, this registry was not specifically designed to detect PAH. In particular, for many patients values of measurements of sPAP were lacking. When such patients were not registered as having PAH, we assumed that they, indeed, did not have PAH and counted them in the denominator but not in the

numerator. It is thus likely that our estimate of 4.2% is an underestimation of the true prevalence. Prevalence of PAH between 5–10% seems realistic [2,3]. Unfortunately, PAH may proceed gradually without causing overt symptoms and thus may remain undetected for a long period of time.

PAH may occur in the context of a wide range of different defects. Among such defects, by far the largest group of patients with congenital heart disease at risk for developing PAH consists of patients with septal defects. It is, therefore, especially important to be informed on the risk of PAH in these patients. Furthermore, in such patients the progress to severe PAH and Eisenmenger syndrome, is considered to be preventable. However, our data shows that 3% of the patients with a previously closed septal defect had developed PAH. So, closure of the septal defect apparently did not prevent the development of PAH. In retrospect, some of these patients might have been operated too late. In ASD II, age at repair was independently associated with the development of PAH. In the other septal defects this association did not reach statistical significance due to the small numbers of patients.

It is possible that the prevalence of PAH will decrease in the future as a result of improved early detection and timely intervention. In fact, our population reflects the treatment strategies of 20 years and more ago, since then management has changed in a few aspects, Down syndrome, for example is no longer considered a contraindication for operation. It can be expected that operation will contribute to the prevention of Eisenmenger syndrome in these patients. Further, an unclosed significant VSD may lead to substantial pathology later in life, in particular PAH and left ventricle overload [11]. Development of PAH has been reported to be rare after closure of a VSD in the first 2 years of life [7]. Therefore, with detection and closure of VSD at younger age, one might expect that future decrease in the prevalence of PAH is likely. However, sPAP increases with age in healthy adults [9]. Systolic PAP >40 mm Hg is present in 6% of otherwise normal individuals older than 50 years, and 5% in obese patients with a BMI >30 kg/m² [9,12]. More research is needed on the course of PAH after (non-) closure of the defect, to estimate the prevalence of PAH in the future.

4.2. Age, gender and underlying diagnosis

Patients with Eisenmenger syndrome in this study were relatively younger than non-Eisenmenger patients with an open defect and PAH. This is partly due to a decreased life expectancy of patients with Eisenmenger syndrome. In addition, among the patients with an open defect a greater proportion had an ASD II as an underlying defect. It is known that these patients often remain asymptomatic for a long period, and only come to medical attention when they develop symptoms later in life.

It has been suggested that there is a predisposition to PAH in females [13]. On the other hand, Wood [14] described that males and females develop PAH at a similar rate. In our data set, we indeed found a larger proportion of females.

However, the prevalence of PAH among males and females with a septal defect was similar. The larger proportion of females is a result of the gender distribution of patients with a septal defect in the CONCOR registry [13,15]. In particular, it is known also from other studies that among patients with secundum ASD's females predominate [14–18].

Overall, VSD was the most common underlying defect among patients with PAH in the septal defect group. This is consistent with previous studies, in which VSD was found to be the most common congenital heart defect among patients with PAH, accounting for 33–50% [2,13,19]. Of the unclosed VSD's, 79% had already developed Eisenmenger syndrome. It seems that, once patients with VSD develop PAH it soon leads to Eisenmenger syndrome. It is further remarkable that of patients with a previously closed ASD II, 3% had PAH. Apparently, closure of an ASD II is not always followed by reversal of the PAH. This could be due to the fact that these secundum ASDs have been closed too late [11]. On the other hand, individual genetic predisposition could be a risk factor for the development of advanced PAH [20].

4.3. Functional capacity

The majority of patients with PAH had severe functional limitations. Female sex and increased sPAP were independently associated with a worse NYHA class. Mean sPAP was not different between males and females in our study. Possibly, this worse NYHA class in females exists as a result of influences of specific hormonal factors [13]. It is as expected that functional class was worst in the Eisenmenger patients [21]. This could be due to higher sPAP.

4.4. Study limitations

This was a retrospective analysis of data collected as part of a national registry. As a consequence, due to lacking data, some of our estimates represent lower limits rather than estimates of true prevalence. However, the consistent input of data by two dedicated nurses travelling along the 86 participating hospitals may guarantee a rather high consistency of data input and a rather low amount of missing data. As for the septal defects, medical records were reviewed, which allows an even higher accuracy for this dataset. PAH is commonly defined as a mean PAP above 25 mm Hg in rest or above 30 mm Hg during exercise, measured by right heart catheterization [9,12]. However, data from right heart catheterization is seldom available in this registry. Therefore, in this study we used echo measurements. The criterion of PAH, detected by echocardiography, is not clearly defined, PAH is suggested when an echocardiography-derived estimate of sPAP exceeds 40 mm Hg at rest [10].

4.5. Conclusion

Our study reports on the prevalence and clinical characteristics of patients with PAH included in CONCOR, a national

registry of adult patients with congenital heart disease in The Netherlands. The prevalence of PAH among all patients in CONCOR is at least 4.2%. Among patients with a septal defect the prevalence of PAH is at least 6%. Fifty-eight percent of these patients presented with the Eisenmenger syndrome which accounts for 1% of the total population in the CONCOR registry. Among the closed septal defects 3% had still developed PAH. Female gender and increased sPAP were independently associated with decreased functional class. So far, it is uncertain whether the prevalence of PAH will decrease in the future as a result of systematic and early intervention. Periodic checkup of predisposed patients may detect progression and allow early therapy.

References

- [1] D'Alto L, Somerville J, Presbitero P, et al. Eisenmenger syndrome. Factors relating to deterioration and death. *Eur Heart J* 1998;19:1845–55.
- [2] Vongpatanasin W, Brickner ME, Hillis LD, Lange RA. The Eisenmenger syndrome in adults. *Ann Intern Med* 1998;128:745–55.
- [3] Bouzas B, Gatzoulis MA. Pulmonary arterial hypertension in adults with congenital heart disease. *Rev Esp Cardiol* 2005;58:465–9.
- [4] Granton JT, Rabinovitch M. Pulmonary arterial hypertension in congenital heart disease. *Cardiol Clin* 2002;20:441–57 vii.
- [5] Berger RM. Possibilities and impossibilities in the evaluation of pulmonary vascular disease in congenital heart defects. *Eur Heart J* 2000;21:17–27.
- [6] Bando K, Turrentine MW, Sharp TG, et al. Pulmonary hypertension after operations for congenital heart disease: analysis of risk factors and management. *J Thorac Cardiovasc Surg* 1996;112:1600–7.
- [7] McLaughlin VV, Presberg KW, Doyle RL, et al. Prognosis of pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. *Chest* 2004;126:78S–92S.
- [8] Van der Velde ET, Vriend JW, Mannens MM, Uiterwaal CS, Brand R, Mulder BJ. CONCOR, an initiative towards a national registry and DNA-bank of patients with congenital heart disease in the Netherlands: rationale, design, and first results. *Eur J Epidemiol* 2005;20:549–57.
- [9] McQuillan BM, Picard MH, Leavitt M, Weyman AE. Clinical correlates and reference intervals for pulmonary artery systolic pressure among echocardiographically normal subjects. *Circulation* 2001;104:2797–802.
- [10] Rubin LJ, Badesch DB. Evaluation and management of the patient with pulmonary arterial hypertension. *Ann Intern Med* 2005;143:282–92.
- [11] Engelfriet P, Tijssen J, Kaemmerer H, et al. Adherence to guidelines in the clinical care for adults with congenital heart disease: the Euro Heart Survey on adult congenital heart disease. *Eur Heart J* 2006;27:737–45.
- [12] Barst RJ, McGoon M, Torbicki A, et al. Diagnosis and differential assessment of pulmonary arterial hypertension. *J Am Coll Cardiol* 2004;43:40S–7S.
- [13] Somerville J. The Denolin Lecture: the woman with congenital heart disease. *Eur Heart J* 1998;19:1766–75.
- [14] Wood. The Eisenmenger syndrome or pulmonary hypertension with reversed central shunt. *Br Med J* 1958;46:755–62.
- [15] Engelfriet P, Boersma E, Oechslin E, et al. The spectrum of adult congenital heart disease in Europe: morbidity and mortality in a 5 year follow-up period: The Euro Heart Survey on adult congenital heart disease. *Eur Heart J* 2005;26:2325–33.
- [16] Vogel M, Berger F, Kramer A, exi-Meshkishvili V, Lange PE. Incidence of secondary pulmonary hypertension in adults with atrial septal or sinus venosus defects. *Heart* 1999;82:30–3.
- [17] Steele PM, Fuster V, Cohen M, Ritter DG, McGoon DC. Isolated atrial septal defect with pulmonary vascular obstructive disease—long-term follow-up and prediction of outcome after surgical correction. *Circulation* 1987;76:1037–42.
- [18] Campbell M. Natural history of atrial septal defect. *Br Heart J* 1970;32:820–6.
- [19] Saha A, Balakrishnan KG, Jaiswal PK, et al. Prognosis for patients with Eisenmenger syndrome of various aetiology. *Int J Cardiol* 1994;45:199–207.
- [20] Roberts KE, McElroy JJ, Wong WP, et al. BMP2 mutations in pulmonary arterial hypertension with congenital heart disease. *Eur Respir J* 2004;24:371–4.
- [21] Diller GP, Dimopoulos K, Okonko D, et al. Exercise intolerance in adult congenital heart disease: comparative severity, correlates, and prognostic implication. *Circulation* 2005;112:828–35.