

# Pulmonary Arterial Hypertension in Hyperthyroidism: Age, Ethnic, and Gender Disparities

Alan Sacerdote<sup>1,\*</sup>, Paulomi Dave<sup>2</sup>, Taiga Inoue<sup>3</sup>, Gul Bahtiyar<sup>2</sup>, Heidi Peynado<sup>4</sup>, Victor Navarro<sup>5</sup>, Ronny Cohen<sup>6</sup>, Mark L'Eplattancier<sup>7</sup> and Gabriel Fenteany<sup>8,9,\*</sup>

<sup>1</sup>Brooklyn, NY, USA, Formerly at SUNY Downstate Medical Center, Brooklyn, NY, USA

<sup>2</sup>Division of Endocrinology, Grossman School of Medicine, NYU Langone Health, New York, NY, USA

<sup>3</sup>P3 Health Partners, Tucson, AZ, USA

<sup>4</sup>Benefis Health System, Great Falls, MT, USA

<sup>5</sup>Division of Cardiology, Grossman School of Medicine, NYU Langone Health, New York, NY, USA

<sup>6</sup>Division of Cardiology, NYC Health+Hospitals/Woodhull, New York, NY, USA

<sup>7</sup>Hofstra University, Hempstead, NY, USA

<sup>8</sup>Department of Medical Chemistry, University of Szeged, Hungary

<sup>9</sup>ELKH-SZTE Biomimetic Systems Research Group, Eötvös Loránd Research Network, Szeged, Hungary

**Abstract:** *Objective:* Pulmonary arterial hypertension (PAH) affects 2.6% of adults and 36% of people with chronic obstructive pulmonary disease (COPD). Several case reports and small case series suggested a hyperthyroidism-PAH association.

*Design:* Retrospective chart review.

*Methods:* We undertook a retrospective chart review (1982–2018) to assess PAH prevalence in a multi-ethnic convenience sample of hyperthyroid adults with multiple etiologies. We calculated associations of pulmonary artery maximum systolic pressure (PSAPmax) with subject age, and maximum serum triiodothyronine (T3) and thyroxine (T4), free T3, and T4, minimum serum thyroid-stimulating hormone (TSH), and thyroid antibody titers, comparing PAH prevalence and the odds of being undiagnosed as to hyperthyroidism etiology by gender and ethnicity/race.

*Results:* We found a high prevalence of PAH in hyperthyroid people, like that reported for people with COPD. We found no significant association between PSAPmax and any thyroid function test or thyroid antibody titer. As reported more recently in the general population, PSAPmax significantly correlated with age in hyperthyroid people. There was no significant disparity in the prevalence of PAH among White, non-Hispanic Black, and Latinx hyperthyroid people or between genders. The percentage of patients whose hyperthyroidism etiology was undiagnosed was high with significant disparity only between non-Hispanic Black and White people and between men and women. PAH was common in hyperthyroid subjects with any hyperthyroidism etiology.

*Conclusions:* 2D-echocardiography should be performed in all hyperthyroid people because PAH is common, especially in older people because of their co-morbidities and poorer prognoses. Further research is needed regarding demographic disparities in being undiagnosed as to hyperthyroidism etiology.

*Principal Verdicts/Significance Statement:* We reconfirmed the high PAH incidence in hyperthyroidism, previously reported, but profoundly under-recognized by physicians, to patients' detriment. Further, we found that the shift in the general PAH population from younger to older individuals is mirrored in hyperthyroid people with PAH. This is concerning because older people have more co-morbidities and worse prognoses, necessitating early, effective intervention. PAH was present with diverse hyperthyroidism etiologies, suggesting that it is multicausal, resulting from autoimmunity, thyroid hormone excess, and goitrous upper airway obstruction and should be considered, regardless of etiology. Our observations that many subjects had no established hyperthyroidism etiology and that males and Blacks were likelier to be undiagnosed are concerning, warranting further study.

**Keywords:** PAH, hyperthyroidism, autoimmune, disparity, pathophysiology, Graves' disease, multinodular, goiter.

## INTRODUCTION

We became interested in pulmonary arterial hypertension (PAH) while consulting on our index patient, a 41-year-old Swedish woman, for severe

hyperthyroid Graves' Disease (GD). In her electronic medical record (EMR), we noted that echocardiography (for dyspnea, palpitations, and a 1/6 systolic murmur) showed severe PAH (pulmonary systolic arterial pressure (PSAP) = 60 mm Hg) and patent foramen ovale (PFO) [1]. Treatment included methimazole 10 mg/day, later 20 mg/day and propranolol 10 mg 3x/day. After 8 weeks, she had symptomatically improved with near normalization of thyroid function tests (TFTs),

\*Address correspondence to this author at the Brooklyn, NY, USA, Formerly at SUNY Downstate Medical Center, Brooklyn, NY, USA; E-mail: walrusa@netscape.net

PSAP reduction to 39 mm Hg, and PFO closure. She was advised to continue her current treatment and given a case summary for her endocrinologist in Sweden. We searched the then scant literature regarding PAH in hyperthyroidism. The articles cited below suggested that PAH incidence was increased in hyperthyroidism and, in one case series, in which all participants had GD, the authors suggested that PAH in their cohort was likely due to autoimmune angiopathy.

Suk reported the prevalence of PAH in 64 people with new-onset GD before and after treatment [2]. 44% had baseline PAH. PAH was associated with systemic hypertension, and pulmonary venous hypertension was perhaps still more closely associated with systemic hypertension. People with GD and PAH had reduced right ventricular function, indicated by higher right ventricular performance index without significant difference in pulmonary vascular resistance, increased right ventricular wall thickness, and peak systolic velocity of the free wall adjoining the tricuspid annulus. Follow-up echocardiography in 20/28 people with GD and PAH showed PAH reversal with anti-thyroid treatment in 19/20, suggesting that PAH in GD is more related to hyperthyroidism-enhanced pulmonary circulation than to autoimmunity. It is broadly accepted that thionamides have a mild anti-autoimmune effect as well as a potent anti-thyroid effect, however, patients whose TFTs were improved by radioiodine or surgery had similar reductions in pulmonary arterial pressure.

Badesch reported on 7 people (5 female) from their center enrolled in a multi-center continuous prostacyclin trial for severe PAH. 4/5 of the women had (autoimmune) hypothyroidism, suggesting an autoimmune/PAH link [3].

Curnock conducted a retrospective EMR review of 40 people with primary PAH (1991–1997) [4]. 22.5% were hypothyroid; much higher than reported in the similarly aged general population. (7.5% in women, 2.8% in men,  $p = 0.00294$ ), concluding that hypothyroidism is prevalent in primary PAH and should be routinely screened for.

Chu screened 63 consecutive people with PAH for autoimmune thyroid disease (AITD), finding that 49% had AITD, 18 newly diagnosed, with 9 requiring treatment [5]. No temporal association existed between the diagnoses/treatments of PAH and AITD. 25% had first degree relatives with AITD.

Nicolls noted in 2005 that an autoimmunity/PAH association had been known for 40 years; however, the

mechanisms by which autoimmune tissue injury could cause PAH had only been investigated in a clinical case-specific way or pre-clinically [6]. They asserted that it was becoming apparent that diverse illnesses from connective tissue disorders (CTDs) to some viral infections could have a common expression as indistinguishable pulmonary vascular pathology, regardless of etiology, due to a common pathophysiology. They suggested that explanations were discoverable in then recent data concerning the function of Treg cells in preventing maladaptive B-cell activation. Key similarities among diverse disorders associated with severe angioproliferative PAH are augmented autoantibody production and a CD4 T-cell defect. Endothelial cell autoantibodies promoted apoptosis, initiating PAH development. Finally, they focused on deciphering PAH autoimmune phenomena to discover if early loss of self-tolerance, followed by autoimmune-induced injury accelerates severe, angioproliferative PAH evolution.

We previously presented a small retrospective study involving 24 people with hyperthyroid GD and 3 people with toxic multinodular goiter (TMNG) [7]. 54.2% of those with GD had PAH while hyperthyroid vs. 100% of those with TMNG, suggesting that PAH is associated with hyperthyroidism and/or upper airway-obstructing goiter and not solely with autoimmunity. In the 3 people with follow-up echocardiograms when TFTs were sharply improved, mean PSAP showed great improvement, falling by 32%.

We undertook this study to:

- a) Ascertain PAH incidence in a larger, urban, ethnically diverse hyperthyroid population seen in our hospital and/or its clinics.
- b) Ascertain whether PAH occurred with varied hyperthyroidism etiologies.
- c) Determine whether there were significant disparities among different ethnic/racial groups and between genders regarding PAH incidence in hyperthyroidism and/or prevalence of an undiagnosed hyperthyroidism etiology.
- d) Ascertain if there was significant correlation between PSAPmax and various thyroid function tests (TFTs) and/or thyroid antibody titers.
- e) Possibly determine whether there was a significant negative association between PSAPmax and improving TFTs/antibody titers in GD and Marine-Lenhart Syndrome (MLS).

## MATERIALS AND METHODS

The protocol was approved by the NYU-Langone Human Research Committee, waiving individual informed consent requirements. We requested a search for EMRs from our Medical Records Department for those containing ICDM codes for hyperthyroidism, thyroid storm, GD, TMNG, toxic uninodular goiter (TUG), subacute thyroiditis (ST), iatrogenic hyperthyroidism, and MLS.

Initial EMR review eliminated those with unverified hyperthyroidism, those without echocardiogram, and duplicates.

For each qualifying EMR, we recorded the following, when available: PSAPmax, maximum-serum T3 and T4, free T3 and T4, calculated free thyroxine index, minimum serum thyroid-stimulating immunoglobulin (TSIG), TSH, thyroid peroxidase (TPO) and thyroglobulin (Tg) antibody titers, transthoracic 2-dimensional (2D)-echocardiograms, and thyroid imaging (thyroid sonogram and/or thyroid nuclear scan).

Subjects were considered to have GD without elevated TSIG if they were hyperthyroid concomitantly with elevated TPO and/or Tg antibodies, were not post-partum, had a normal sedimentation rate, or homogeneous, diffusely increased 24-hour radioiodine uptake.

PSAPmax was estimated echocardiographically with PSAPmax > 25 mm Hg defining PAH. Serum T4 was measured by paramagnetic particle chemiluminescence and competitive-binding enzyme immunoassay; serum T3, free T3 and T4, TSH, TPO, and Tg antibodies by immunoassay; serum thyroid hormone binding capacity by T3 resin uptake; and TSIG by *in vitro* bioassay.

### Statistical Analysis

Linear regression analysis was performed to assess associations between PSAPmax and age, key TFTs, and their logs. Since TSIG methodology and reference ranges had changed, we did separate linear regression analyses for each TSIG group. Two-tailed unpaired Student's *t*-tests were performed to evaluate mean intergroup differences for PSAPmax. The odds ratio (OR) values for intergroup differences in categorical variables were calculated. Excel and socscistatistics.com were used for *t*-tests, calculator.net was used for linear regression analysis,

and <https://gigacalculator.com/calculators/odds-ratio-calculator.php> was used for OR calculations and intergroup comparisons (with  $p < 0.05$  defining statistical significance).

## RESULTS

The Medical Records Department provided a list of 789 EMRs. Additionally, 46 EMRs were reviewed when subjects presented to Endocrine Clinic or for inpatient consultation. After eliminating non-qualifying EMRs, there remained 244 at least partially analyzable EMRs. The subject age range was 25–101 years (mean = 59.8 and SD = 17.0, with 27% being male). Nobody identified as gender non-binary. 36% self-identified as non-Hispanic Black, 35% as Hispanic, 16% as White, and 13% as Asian (including South, East, and Southeast Asian).

Echocardiogram reports usually omitted PSAP for pressures < 25 mm Hg. Where PSAP was omitted, we assigned a value of 15 mm Hg, to enable statistical analysis.

PSAPmax was significantly associated with age;  $r = 0.229$ ;  $p = 0.000665$ .

Mean PSAPmax did not differ significantly between Whites = 33.961 (mean)  $\pm$  19.491 (SD) mm Hg and

Blacks = 33.105 (mean)  $\pm$  19.191 (SD);  $p = 0.8233$  (NS).

Mean PSAPmax did not differ significantly between Whites = 33.961 (mean)  $\pm$  19.491 (SD) and

Hispanics = 28.435 (mean)  $\pm$  1.864 (SD);  $p = 0.0636$  (NS), but possibly trended toward significance.

Hyperthyroid Blacks, Hispanics, and Whites all had mean PSAPmax above the reference range.

OR males/females for PAH = 1.26; 95% CI = 0.67–2.375;  $p = 0.236$  (NS).

OR Blacks/Hispanics for PAH = 1.15359; 95% CI = 0.59–2.076;  $p = 0.3653$  (NS).

OR Hispanics/Whites for PAH = 0.643720; 95% CI = 0.285–1.453;  $p = 0.1449$  (NS).

OR Blacks/Whites for PAH = 0.717929; 95% CI = 0.321–1.606;  $p = 0.2099$  (NS).

39% of Hispanics, 28% of Whites and 46% of Blacks had an unknown hyperthyroidism etiology. ORs

**Table 1: Significant Disparities in Percentages of Subjects with Undiagnosed Etiology of Hyperthyroidism**

Comparator group	% with undiagnosed hyperthyroidism etiology	Odds ratio	95% confidence interval	p value
Black	46%			
White	28%	2.238	1.006–4.980	0.0241
Male	56%			
Female	26%	2.169	1.294–2.637	0.0033

for having an undiagnosed hyperthyroidism etiology differed significantly between Blacks and Whites; OR Blacks/Whites = 2.238; 95% CI = 1.006–4.980;  $p = 0.0241$ ; not differing significantly in other ethnic/racial comparisons. Males (56%) were more likely to have an undiagnosed hyperthyroidism etiology than females (26%); OR = 2.169; 95% CI = 1.294–3.637;  $p = 0.033$  (Table 1). Since there was only one statistically significant correlation found and no significant intergroup differences in mean PSAPmax, for the sake of reader clarity we have only presented significant intergroup OR comparisons in table form, rather than presenting a distracting mass of mostly negative data as a table.

As the number of Asian subjects was very small and quite heterogeneous, their data were excluded from only inter-ethnic/racial statistical comparisons.

26% of females had a PSAPmax > 40, 30% > 35, 45% > 30, and 51% > 25 mm Hg.

26% of males had a PSAPmax > 40, 36% > 35, 42% > 30, and 48% > 25 mm Hg.

81% of Whites emigrated from Poland or the former Soviet Union post-Chernobyl event.

44% of subjects had GD, 12% TMNG, < 1% TUNG, 6% MLS, 1% ST, and 35% an unknown hyperthyroidism etiology.

PAH was common regardless of hyperthyroidism etiology.

## DISCUSSION

Like us, Marvisi reported that PAH was common in hyperthyroidism; especially in older people with TMNG, describing recent data suggesting several influences of T3 on pulmonary artery pressure, including increased catecholamine sensitivity augmenting pulmonary vascular vasoconstriction, accelerated degradation of endogenous pulmonary vasodilators (e.g. endothelial nitric oxide and prostacyclin), and slowed

vasoconstrictor catabolism involving endothelin-1, thromboxane, and serotonin [8]. These T3 effects offer one additional explanation for PAH in hyperthyroid people.

As highlighted by Bilezikian, increased  $\beta$ -adrenergic sensitivity is widely appreciated by clinicians treating hyperthyroidism, exemplified by the frequent use of  $\beta$ -blockers in treatment [9]. However, increased  $\alpha$ -adrenergic sensitivity is largely unknown. Hyperthyroidism increases catecholamine sensitization by increasing receptor number and enhancing post-receptor effects, offering yet another mechanism for PAH in hyperthyroid people.

Marvisi searched the Medline database 1972–2003 and found approximately 35% of hyperthyroid people in the largest series had PAH, which is somewhat lower than our incidence: women 51%; men 48% [10].

Our higher PAH incidence could be multicausal:

1. Our study was retrospective, not cross-sectional, allowing us to look for PAH occurring throughout hyperthyroid subjects' clinical course.
2. We diagnosed PAH at PSAPmax > 25 mm Hg, while some reviewed studies possibly required higher PSAPmax.
3. Exclusion of subjects without echocardiograms possibly introduced selection bias.

PAH prevalence in the general population reported by Hoepfer and Simon was 0.001%–0.005%, much lower than what we and others found in hyperthyroid patients [11]. Group 1 PAH is subdivided by etiology and includes: idiopathic, hereditary (mutational), toxin/drug-, CTD-, schistosomiasis-, congenital heart disease-, and HIV-associated forms. Establishing etiology is essential for prognosis and precision treatment.

Recent data from several PAH registries they summarized suggest evolving PAH demographics. In

the US National Institutes of Health registry from the 1980s, idiopathic PAH was mostly diagnosed in young adults; more recent data indicates a change toward older people, which is consistent with our data in hyperthyroid people in whom PSAPmax correlated significantly with age. This is concerning because older people often have more advanced PAH and more comorbidities. Between 1982-2006, the proportion of diagnoses of idiopathic and heritable PAH has decreased and CTD-associated PAH has increased.

We found no other study reporting incidence of PAH by race/ethnicity; however, Al-Naamani found differences in presentation, severity, and access to newer treatments among different groups (Hispanics and African-Americans were more likely than Whites to present with PAH associated with conditions like congenital heart disease and CTD and less likely to receive newer drugs) [12].

Li retrospectively studied (for the period 1992–2006) the prevalence of thyroid disease defined as abnormal TSH level, being on thyroid replacement, or having elevated TPO antibody titer in 356 people with PAH and 698 controls [13]. In those with PAH 24% had thyroid disease vs 15% in controls. The increased prevalence of thyroid disease in PAH was clearest when confirmed with right heart catheterization; OR vs. controls = 2.53; 95% CI 1.55–4.08,  $p < 0.001$ . Among subjects with thyroid disease, most had mild disease and were hypothyroid (unlike our subjects). Only 16% of those with thyroid disease had no prior history.

In a preclinical study by Al Hussein investigating PAH pathogenesis in hyperthyroidism he reported that arterial lumen narrowing due to endothelial cell proliferation is a major feature of this disorder and that T3 is known to be angiogenic (in a rodent model of angioproliferative PAH induced with vascular endothelial growth factor (VEGF) antagonists and hypoxia); induction of hypothyroidism prevented PAH, while propylthiouracil reversed PAH [14]. T4 replacement re-established the PAH phenotype. PAH prevention via thyroidectomy was accompanied by a lower cell turnover rate, a slower phosphorylation rate of extracellular signal-regulated protein kinases 1 and 2, and reduced expression of integrin  $\alpha$ - $\beta$ , fibroblast growth factor-2, and their receptors.

In people with autoimmune thyroid disorders (e.g. GD, HT, MLS, and some with ST), autoimmune endothelial damage possibly plays a contributory role.

Naiboglu reported that PAH is inducible by upper airway obstruction in children with enlarged tonsils and

adenoids and resolved by their removal [15]. It seems likely that other causes of upper airway obstruction, such as goiter, which is present in most hyperthyroid people, could cause PAH. Chadha reported that epoprostenol PAH treatment can cause goiter and TSHG-negative hyperthyroidism [16]. None of our subjects, however, used epoprostenol.

Men in our study had an OR for PAH of 1.26 vs. women (NS). This differs from findings of Batton, who reported a female predominance of 2–4/1 in reviewing worldwide PAH registries [17]. They found that genetic predisposition accounts for 1–5% of PAH, while infections and autoimmune disorders are closely associated with PAH in a large proportion of affected people. People with “idiopathic” PAH frequently have autoantibodies. As of 2018, the two largest PAH registries reporting gender ratios for autoimmune-associated PAH found a female/male ratio of 9:1. Female-predominant autoimmune-disorders associated with PAH include rheumatoid arthritis, lupus, Sjögren’s syndrome, HT, and GD. Male-predominant autoimmune PAH-associated disorders include myocarditis, itself HIV-associated, suggesting that sex hormones and chronic inflammation contribute to PAH pathogenesis. Future studies in transgender people may clarify the roles of sex hormones and chromosomal sex in PAH pathogenesis.

We found no reports regarding racial/ethnic disparities in the prevalence of hyperthyroidism with undiagnosed etiology, while we found that Blacks were significantly more likely to have an unknown hyperthyroidism etiology than Whites. The cause(s) of this disparity is (are) unknown. We found no reports of gender disparity in establishing hyperthyroidism etiology; however, a review by Samulowitz reported that women were less likely to receive an accurate diagnosis for a chronic pain complaint [18]. Weyand reported underdiagnosis and delayed diagnosis of bleeding disorders in women [19]. Liu reported that bipolar disorder was significantly underdiagnosed in male subscribers to a private insurance plan [20]. Among our subjects hyperthyroidism etiology was significantly underdiagnosed in men. Possible explanations for this disparity are unconfirmed.

We found no significant racial/ethnic disparities in mean PSAPmax among our subjects; however, mean PSAPmax in Whites was higher compared to Hispanics;  $p = 0.0636$ , possibly indicating a trend.

As our study was retrospective, we did not find more than the three previously reported subjects who

had follow-up echocardiograms when hyperthyroidism was resolved or much improved [1,7]. Most echocardiograms were performed for non-PAH indications. As stated previously, these three subjects reduced their PSAPmax with improvement of their TFTs [1,7].

Gazzana prospectively studied the right ventricle of 32 hyperthyroid subjects echocardiographically at diagnosis and when they had normalized their free T4 levels [21]. His literature review found that 35–65% of hyperthyroid people have PAH. In their own hyperthyroid series, 43.8% of people had PAH. Our figures were similar with 51% of females and 48% of males having PAH. In most series, including ours, GD was the most common hyperthyroidism etiology (75% in Gazzana's series, 44% in ours). Despite the high incidence of PAH in hyperthyroidism and the high incidence of thyroid dysfunction in PAH, echocardiography is very underperformed in hyperthyroid people and then, rarely for PAH-related concerns. TFTs are woefully underperformed in those with PAH. In Gazzana's study cardiac chamber volumes and cardiac output were increased in people with PAH above the already increased cardiac output prevailing in hyperthyroidism. Right ventricular systolic function was abnormal in those with PAH. Free T4 and cardiac output were significantly associated with PSAP;  $p < 0.05$ , whereas we found no significant association between free T4 and PSAPmax. The fact that their study was prospective—with echocardiograms performed when hyperthyroidism was maximal and repeated when subjects were much improved “unmasked” this association. Co-morbidities and demographic differences possibly contributed to different observations. Chamber size, cardiac output, left ventricular ejection fraction, and PSAP were significantly lower when their subjects were euthyroid or nearly so. Right ventricular myocardial performance index and fractional area change also improved significantly as subjects neared/achieved euthyroidism. In our three previously reported hyperthyroid subjects with PAH, PSAP declined with treatment, including in our index patient, whose PFO closed concomitantly [1,7].

The observation that 81% of our White subjects were post-Chernobyl emigres from Poland and nearby portions of the former Soviet Union reflects the demographics of our clientele and suggests additional thyroid disorder risk from radiation, particularly radioiodine. Apropos, our index patient was from Sweden, the country that first announced a radiation

uptick following the disaster. We reported the spectrum of thyroid disorders in the first 12 post-Chernobyl Polish emigres followed in our Brooklyn, NY clinic in 1995 [22]. Subsequently, we saw many more such people, always with a lopsidedly female preponderance, possibly because women are predisposed to thyroid disorders (especially autoimmune) or due to some interaction between radioiodine thyroid damage and sex hormones, or both. In our original survey, no woman had thyroid cancer; however, GD, HT, and MNG were common, alone or in combination. Later, we encountered people from this demographic with thyroid cancers.

Jereczek-Fossa reported that radiotherapy-induced thyroid disorders are under-reported and include MNG, HT, ST, GD, and hypothyroidism [23].

Pacini reported differences in thyroid cancer between children from Ukraine, Belarus, and the Russian Federation developing post-Chernobyl vs age-matched “control” children from Italy and France [24]. Cancers in the Chernobyl region were much less influenced by gender, presented more aggressively, were nearly all papillary (both solid and follicular variants), and more often autoimmunity-associated. The RET receptor tyrosine kinase and less often Trk neurotrophin receptor are reported to be causative in some papillary cancers. RET activation occurs in almost 70% of Chernobyl-associated papillary thyroid cancers. Radiation-associated thyroid disease includes benign nodules, hypothyroidism, and euthyroid/hypothyroid HT. The same spectrum of thyroid disorders was reported in people with environmental radiation exposure and following atomic bomb blasts. Consistent with the short follow-up period in Pacini's study, a high prevalence of anti-thyroid antibodies without significant thyroid dysfunction was found. Nevertheless, he predicted that many of these children would later develop significant autoimmune thyroid disease (AITD). Interestingly, while our adult post-Chernobyl emigre subjects often had GD this was not true for any of the Chernobyl-exposed children when Pacini's data was collected. Irradiation timing may be a determinant of GD development.

Kirkpatrick reviewed the increased PAH risk in people who had received radiotherapy for childhood cancer [25]. PAH is a widely appreciated cancer and treatment complication but is less well characterized in children. The pathophysiology of cancer promotes vascular remodeling and injury like that encountered in PAH unassociated with neoplasia. Their findings

underline the need for lifelong echocardiographic follow-up of cancer survivors.

Kramer reviewed reports that radiation induces pneumonitis and post-inflammatory fibrosis and described a patient who developed severe veno-occlusive disease (VOD) 6 years after mantle irradiation for Hodgkin's Disease with severe PAH and cor pulmonale [26]. Following left lung transplant, the resected lung showed severe VOD, suggesting that, without any alternative toxic or inflammatory insult, the severe VOD and resulting PAH were due to radiation damage to the venous endothelium, precipitating lumen narrowing and pulmonary vascular obliteration. Kramer cited several reports of radiation-associated VOD, chiefly after radiation in preparation for bone marrow transplant. Radiation-associated VOD plausibly contributed to the high incidence of PAH in our post-Chernobyl hyperthyroid subjects.

## CONCLUSIONS

PAH was at least as common in our hyperthyroid subjects as reported in those with COPD and much more common than in the general population, consistent with most other reports, suggesting that 2D-echocardiography should be part of the standard of care for hyperthyroid people.

We encountered PAH in people with disparate etiologies of hyperthyroidism including GD, TMNG, TUNG, MLS, and ST. This conclusion runs counter to those authors who attribute hyperthyroid PAH solely to autoimmune vasculitis and agrees with literature suggesting multifactorial predisposition to PAH in hyperthyroidism, with varied etiologies following a common final pathway.

PSAPmax was positively associated with age, contrasting with earlier case series, but consistent with more recent ones. This is concerning as older people generally have more co-morbidities, which may negatively affect outcomes.

The OR for PAH in our study did not differ significantly between genders (1.26:1:00), contrasting with data reported by Manes and associates indicating a female preponderance of PAH [27]. Their findings may reflect the higher prevalence of autoimmune disease in women, while our subjects were pre-selected by virtue of being hyperthyroid, such that gender differences in PAH incidence were largely eliminated and hyperthyroid men were slightly, albeit not significantly, more likely to have PAH.

Blacks were significantly more likely than Whites to have an undiagnosed hyperthyroidism etiology. This is concerning because hyperthyroidism etiology helps determine treatment. Future studies should confirm this finding and identify cause(s) of disparity.

Men were more likely than women to be undiagnosed regarding hyperthyroidism etiology. Similar concerns apply as with racial/ethnic disparities.

## STRENGTHS AND LIMITATIONS

Strengths of our study included its size: with 244 analyzable EMRs, this was a sizeable study.

Generalizability: There was significant female and male representation and there was sizeable representation of several racial/ethnic groups, enhancing generalizability.

Sensitivity: Our EMR review's retrospective design improved our chances of seeing if PAH occurred anytime in our subjects' clinical course; a cross-sectional design would only detect PAH at a given time point.

Limitations of our study included: Due to its retrospective, rather than prospective, interventional design, most hyperthyroid subjects had no echocardiograms, potentially introducing selection bias, in that possibly people who had echocardiograms were more likely to have PAH than the general hyperthyroid population. It should, however, be noted that few of the echocardiograms were performed for suspicion of PAH, due to general ignorance of this association. Possibly, some subjects had non-thyroid co-morbidities predisposing to PAH, however, there is no a priori reason to suppose that such co-morbidities are more or less common in hyperthyroid people than in the general population.

The retrospective design hindered our definitively answering one of the primary outcome questions, whether effective hyperthyroidism treatment ameliorated/resolved PAH, although PSAP was reduced in the three patients with echocardiograms corresponding closely to when they presented with hyperthyroidism and when thyroid function was normal/near normal.

Asian subjects were underrepresented and from diverse backgrounds, precluding their inclusion in analyses of inter-ethnic/racial disparities and limiting generalizability. Their data was, however, included in

whole group analyses and gender disparity analyses. There were no self-identified Native-American subjects in our study limiting generalizability.

Nobody identifying as sexually non-binary was in our study, limiting generalizability.

### APPROVAL FOR PUBLICATION

All the authors declare that they have reviewed the manuscript and approve its submission.

### AVAILABILITY OF DATA

The original data sheets are available.

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### CONFLICT OF INTEREST

None of the authors have any conflicts of interest to disclose.

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