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REVIEW ARTICLE

Drug-Induced Pulmonary Arterial Hypertension: Mechanisms and Clinical Management

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Abstract

Pulmonary arterial hypertension is a rare disease, with drug-induced causes even more uncommon, accounting for only 10% of cases in large registry series. Predisposing factors for drug-induced PAH have not been completely defined. This review summarizes drugs with definite, possible, or likely association to pulmonary hypertension and possible mechanisms involved in the occurrence of pulmonary hypertension. Controversies on mechanisms and on their role in pathophysiology were also shown. The possible synergism between drug abuse and HIV was discussed and the possible interactions of antiretroviral therapy in HIV subjects were analyzed. Furthermore, we reported clinical findings and possible management, specific for each class of drugs, in case of drug-induced PAH. Finally, we summarized into a unified algorithm possible management of drug-induced PAH.

Keywords Drug-induced pulmonary hypertension · Pulmonary arterial hypertension · Pulmonary hypertension

Introduction

Pulmonary arterial hypertension (PAH) is a rare disorder characterized by progressive obliteration of the pulmonary microvasculature and resulting in elevated pulmonary vascular resistance, hence in right heart failure, and finally premature death [1]. Anorexigens (aminorex, fenfluramine, benfluorex, phenylpropanolamine, and dexfenfluramine) were the first class of medications identified as possible cause of PAH [2]. Despite the great increase in knowledge and a more clear understanding of pathophysiology, drug-induced PAH (D-PAH) is an even more uncommon disease, accounting for only 10% of cases in large registry series [3]; the prognosis is comparable with other forms of PAH [4]. Predisposing factors for D-PAH, however, have not been completely elucidated.

According to clinical classification of PH, clinical group 1 (PAH) includes different forms (idiopathic,

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heritable, or associated with different conditions, including connective tissue disease, congenital heart disease, HIV infection, portal hypertension, and also exposure to toxins/drugs) that share a similar clinical picture and virtually identical pathological changes of the lung microcirculation [1]. The 6th World Symposia on PH (Nice 2018) proposed a new classification of D-PAH in two categories [5]. "*Definite association*" includes drugs with data based on outbreaks, epidemiological case–control studies, or large multicenter series; "*possible association*" is suggested by multiple case series or cases with drugs with similar mechanisms of action. Based on recent data, the association of PAH with two drugs (amphetamines, methamphetamines) and toxins (dasatinib) is now considered definite (Table 1).

This review therefore summarizes principal evidence on drugs associated with PH and possible mechanisms involved. Finally, we report clinical findings and possible management based on previous clinical experiences, specific for each class of drugs, in case of D-PAH.

Mechanisms

To date, more than 18 different compounds (Table 1) have been linked to the risk of developing D-PAH. Recently, these were divided in two levels of onset, definite and possible [4, 6]. These drugs may be grouped into seven pharmacological classes (Table 2) with specific mechanisms (Table 3). In the discussion, we will consider all drugs included in such classes with any report where these drugs were associated to development of D-PAH, even though not yet considered as a potential risk factor for PAH in the ERS/ESC guidelines (2015) [1] and the most recent world symposium on PH (2018) [5].

Table 1 Updated classification of drugs and toxins associated with PAH

Definite	Possible
Aminorex	Cocaine
Fenfluramine	Phenylpropanolamine
Dexfenfluramine	L-Tryptophan
Benfluorex	St. John's wort
Methamphetamines	Amphetamines
Dasatinib	Interferon-α and -β
Toxic rapeseed oil	Alkylating agents
	Bosutinib
	Direct-acting antiviral agents against HCV
	Leflunomide
	Indirubin (Chinese herb Qing-Dai)

Agents Affecting Serotonin Metabolism and Related Anorexigens

Serotonin (5-HT) is a vasoconstrictor and a potent mitogen for pulmonary smooth muscle cells (PASMCs), an effect which depends upon activity of both the 5-HT transporter (5-HTT) and the 5-HT receptors. Among several subtypes of serotonin receptors, the 5-HT_{1B} receptor could be more important for vasoconstriction and proliferation of PASMCs in cooperation with the 5-HTT [7]. Serotonin may induce vasoconstriction from 5-HTT pathways, by activation RhoA/Roh kinasi (ROCK) or by activation reactive oxygen species, ROS; 5-HT_{1B} receptor, instead, is responsible for the phosphorylation of ERK1/2 (Fig. 1). Serotonin may increase superoxide and hydrogen peroxide production in PASMCs and it may increase oxidized protein tyrosine phosphatases and decrease Nrf-2. 5-HT_{1B} receptors may contribute to PH by inducing lung ROS production [8]. There is also evidence that serotonin may interact with the bone morphogenetic receptor type II (BMPRII) to provide a "second hit" risk factor for PAH [9].

Pulmonary endothelial serotonin synthesis via tryptophan hydroxlase 1 (TPH1) is increased in patients with PAH and serotonin can act in a paracrine way on underlying PASMC [7, 10]. An increased expression of 5-HTT and an enhanced proliferative growth response of isolated PASMC to 5-HT were demonstrated in PAH patients. Furthermore, 5-HTT-overexpressing mice may develop PH [11]. In patients with chronic lung disease, a close association has been found between a 5-HTT gene polymorphism and the severity of PH [12].

The anorexigenic drugs are 5-HTT substrates. 5-HTT substrates may be translocated into pulmonary cells where, depending on the degree of drug retention, intrinsic drug toxicity, and individual patient susceptibility, they may cause effects similar to or greater than those of serotonin [13]. 5-HTT substrates may also be mitogenic and promote 5-HTT-dependent hyperplasia of PASMCs [14].

The anorexigenic drugs act as indirect 5-HT receptor agonists and can inhibit 5-HT reuptake and cause the release of 5-HT from platelets. 5-HT activates both Gi- and Gq-linked receptors. Gq activation might amplify Gi-linked intracellular pathways to strengthen vasoconstrictor responses (this phenomenon is better known as pharmacological synergism, which occurs in the pulmonary circulation) [15]. Another mechanism by which anorexigens may promote pulmonary vascular remodeling is stimulation of 5-HTT expression. 5-HTT overexpression may represent a complementary mechanism promoting 5-HTT-dependent hyperplasia of PASMCs.

In particular, dexfenfluramine has direct effects on pulmonary vessels including inhibition of potassium channels, increased intracellular calcium, vasoconstriction, and proliferation. Dempsie et al. hypothesized that dexfenfluramine can

Table 2 Drug-induced PAH divided in pharmacological classes

Pharmacological classes	Drugs
Anoretic agent	Aminorex, Fenfluramine, Dexfenfluramine
Selective serotonin reuptake inhibitors (SSRIs)	Fluoxetine, Citalopram, Paroxetine, Sertraline
Amphetamine-, cocaine-, and amphetamine-derived	Amphetamine, Cocaine, Benfluorex, Methamphetamine
Sympathomimetic agents	Phenylpropanolamine
Interferon	Interferon α and β
Chemiotherapeutics agents	Bosutinib, Dasatinib, Mitomycin
Immune modulating drugs	Leflunomide
Direct-acting antiviral agents against hepatitis C virus	Sofusbuvir

also inhibit hypoxia-induced pulmonary vascular remodeling via 5-HTT activity and inhibition of hypoxia-induced p38 mitogen-activated protein kinase [16].

The selective serotonin reuptake inhibitors (SSRIs), like fluoxetine, citalopram, paroxetine, and sertraline, block the function of the 5-HTT by reducing intracellular reabsorption and increasing peripheral serotonin levels.

In a previous study [17], among all investigated tryptophan metabolites, kynurenine showed the strongest correlation with mean pulmonary arterial pressure (mPAP). Kynurenine may acutely decrease mPAP, increase both cAMP and cGMP in PASMC and, in synergy with NO, exert acute pulmonary vasodilatation on PASMC.

Amphetamine, Cocaine, and Amphetamine-Derived

Amphetamine and its chemical derivative methamphetamine are synthetic stimulants that increase catecholamine concentration in the central and peripheral nervous systems. The mechanism linking amphetamine to PAH was attributed to its pharmacologic similarity to serotonin. Amphetamine or methamphetamine have been reported to induce systemic DNA damages on pulmonary artery endothelial cells (PAECs) [18] through oxidative stress [19]. The amphetamine alone does not cause DNA damage in normoxic PAECs, but amplifies DNA damage in hypoxic PAECs.

Amphetamine also inhibits mitochondrial function, a major source of ROS [20]. Amphetamine and methamphetamine act more potently on norepinephrine and dopamine transporters. Serotonin and norepinephrine have vasoconstrictive effects on PASMCs, suggesting a possible involvement of AMPH or methamphetamine in the development of PAH [21, 22].

Cytochrome P450 2D6 (CYP2D6) and carboxylesterase 1 (CES1) are involved in the metabolism of METH and other amphetamine-like compounds. CES1 expression was significantly reduced in the endothelium of METH-PAH microvessels. Orcholski et al. [23] proposed that reduced CES1 expression could promote the development of METH-PAH by increasing pulmonary microvascular endothelial cells apoptosis.

Table 3 Drug-induced PAH: specific mechanism of action

Drug-induced PH	Mechanisms of action
Serotonin	Increased genic transcription
Anoretic agents	Inhibition of potassium channels;
	Increased intracellular calcium;
	Increased cell proliferation.
SSRIs	Block of serotonin transporters;
	Increased serotonin levels.
Amphetamine	Systemic DNA damage
Cocaine	Increased ET-1 levels
Benfluorex	Similar effect to anorexigens agents
Phenylpropanolamine	Unknown
Interferon-α and -β	Increased ET-1 and Interferon-gamma inducible protein 10 levels
Bosutinib and Dasatinib	Inhibition of ScrTK
Mitomycin C	Inhibition of DNA and protein synthesis.
Lenflunomide	Inhibition of PGE2 synthesis
Sofosbuvir	Reduction of Cox2 and PGE2 levels

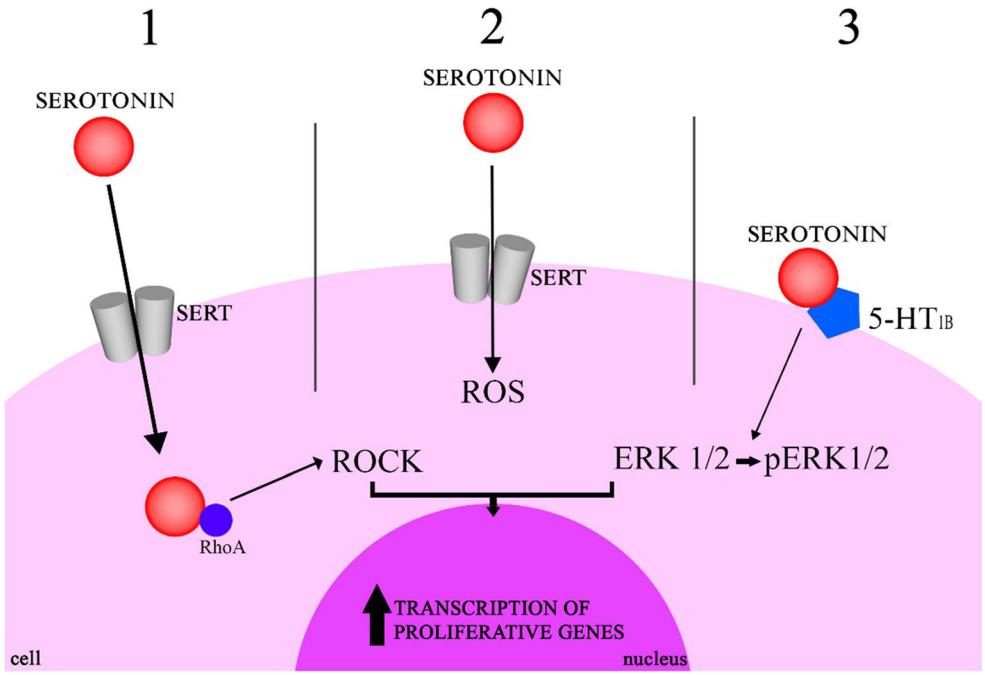

Fig. 1 Mechanism of action of serotonin

Benfluorex is a benzoate ester that shares similar structural and pharmacological characteristics with fenfluramine derivatives. The active and common metabolite of each of these molecules is norfenfluramine, which itself has a chemical structure similar to that of amphetamines [24] and the same effect as that of anorectic agents [25].

Principal mechanism by which cocaine, amphetamines, and related compounds are considered "possible" causes of PAH is thought their vasoconstrictive effect. Cocaine can directly stimulate endothelial cells to release endothelin-1 and increase the expression of ETA receptor, resulting in vasoconstriction [26, 27]. It decreased both eNOS protein expression and NO production in a concentration- and time-dependent manner[20]. Microembolization of foreign particles to the lung and obstruction of the pulmonary arteries have been described in IV cocaine abusers [28, 29]. Even blockage of the reuptake of norepinephrine, dopamine and serotonin at the synaptic junctions, resulting in increased vascular tone, could be responsible for PH.

The effects of cocaine on lung and left heart function could partly justify why it is not considered as "definite" cause of PAH; in fact, cocaine could lead to an increase in pulmonary pressure with a pathophysiology different from that of PAH, secondary to its effects on lung and left heart function and on others organs. It may cause irreversible structural changes on the brain, heart, lung, and other organs such as liver and kidney with different mechanisms involved in the genesis of these changes. Cocaine is a powerful stimulant of the sympathetic nervous system by inhibiting catecholamine reuptake, stimulating central sympathetic outflow, and increasing the sensitivity of adrenergic nerve endings to norepinephrine and some effects are determined by the overstimulation of the adrenergic system. Most of the direct toxic effects are mediated by oxidative stress and by mitochondrial dysfunction, produced during the metabolism of noradrenaline or during the metabolism of norcocaine, as in cocaine-induced hepathotoxicity.

A variety of respiratory problems temporally associated with crack inhalation have been reported. Smoked cocaine (crack cocaine) causes several forms of injury to the respiratory tract, including asthma exacerbations, lung edema and hemorrhage, and nasal mucosal alterations [30]. Cocaine may also cause changes in the respiratory tract according to its method of administration (smoking, sniffing, injecting), or its alteration of central nervous system neuroregulation of pulmonary function [31].

Chronic cocaine use is associated with myocarditis, ventricular hypertrophy, dilated cardiomyopathy, and heart failure. Regarding the effects of cocaine on the LV function, in an animal model, ejection-phase indexes of LV function were reduced by cocaine, but effects were attributable to increased wall stress rather than to reduced myocardial contractility [32]. In dogs, large doses of intravenous cocaine cause a profound deterioration of LV systolic function and an increase in LV end-diastolic pressure; in humans, the intracoronary infusion of cocaine may cause a deterioration of LV systolic and diastolic performance [33].

One established risk factor for developing PAH is HIV infection [34-37]. HIV-PAH does not seem to be due to direct HIV infection of pulmonary vascular cells; in fact, HIV-1 RNA or DNA were not found in the pulmonary vascular cells of human lungs [38]. Several possible mechanisms might be

relevant in HIV-PAH. HIV viral proteins, Gp-120 and TAT-protein, may induce the production of reactive oxygen species (ROS) and consequent endothelial cell dysfunction and vascular injury; 10 polymorphisms in NEF protein were identified by Almodovar [39]. Inflammation and immune activation induced by HIV may lead to increased secretion of proinflammatory cytokines and growth factors. Risk factors common in the HIV-infected population are implicated as a possible risk factor in the development of PAH [40]; the majority of HIV-PAH cases occur in individuals with a history of intravenous drug use, mainly opioids and/or cocaine.

In particular, Dhillon et al. [41] demonstrated that cocaine use contributes to enhanced HIV-related pulmonary vascular remodeling. Cocaine and some HIV protein, such us TAT, induce production of ROS that are involved in the activation of secondary signaling pathways like RAS-Raf-Erk, resulting in a disruption of tight junction protein-1 and leading to pulmonary endothelial dysfunction [42]. Moreover, cocaine induces downregulation of the BMPR axis resulting in enhanced activity of PDGF signaling pathway [43].

Furthermore, Dhillon et al.[41] support an additive effect of cocaine on HIV infection in the development of pulmonary arteriopathy, through the enhancement of endothelial dysfunction and proliferation of PSMCs. Dalvi et al. postulated an additive effect of cocaine and HIV [44] on smooth muscle dysfunction, resulting in enhanced pulmonary vascular remodeling and associated elevation of mean PAP and right ventricle systolic pressure in HIV rats exposed to cocaine.

Excessive pulmonary vascular remodeling with increased apoptosis followed by increased proliferation of pulmonary endothelial cells on simultaneous exposure to both opioids and HIV proteins was reported [45]. Dalvi et al. demonstrated that morphine in combination with viral proteins could cause the induction of autophagy in pulmonary endothelial cells; this may lead to an increase in severity of angio-proliferative remodeling of the pulmonary vasculature on simian and HIV infection in the presence of opioids [46]. This could prove that there is a synergism between drug abuse and HIV in the mechanism of the action.

The intravenous use of buprenorphine could lead to an increase in pulmonary arterial resistances [47, 48], in the absence of other PAH-related factors like HIV coinfection [49].

Sympathomimetic Agents

Phenylpropanolamine is a psychoactive drug of the phenethylamine and amphetamine chemical classes which is used as a stimulant, decongestant, and anorectic agent. It acts as a nonselective adrenergic receptor agonist and norepinephrine reuptake inhibitor. Its most important toxic effect is hypertension, which may result in hypertensive encephalopathy or intracerebral hemorrhage. The therapeutic index of phenylpropanolamine is low, and severe hypertension may occur after ingestion of less than three times the therapeutic dose. As an adrenergic vasoconstrictor, it may affect the vascular tone of pulmonary arterioles. We have data from the Surveillance of Pulmonary Hypertension in America (SOPHIA) [50] study, where an increased risk of developing PAH after exposure to phenylpropanolamine was found. Furthermore, a case of fatal PAH was reported in a child heavily treated with cold remedies containing phenylpropanolamine [51]. However, this remains a controversial area, with the lack of definite data and the need of large multicentric studies in order to clarify the role of phenylpropanolamine as a risk factor for PAH.

Interferon-α and -β

Conditions characterized by chronically elevated endogenous interferon (IFN) levels, such as systemic sclerosis, are strongly associated with PAH [52–54]. IFN therapy has an important role in the treatment of multiple sclerosis and chronic hepatitis C infection. The thromboxane, a mediator of inflammation cascade, is directly involved in the effect of IFN on the lungs and may be a mediator of PAH [55]. IFN-α and IFN-β stimulation can activate pulmonary vascular cells to release endotelin-1 [56] and INF-γ-inducible protein 10 [57–59]. IFN-β induced much higher chemokine production than IFN-α. Type I IFN-induced chemokines may be involved in the pathophysiology of pulmonary vascular diseases. In fact, type I IFN-induced higher CX3CL1 (fractalkine) mRNA expression and protein secretion in pulmonary arterial vascular endothelial cells (VEC) and type I IFN also induced CCL5 production in VEC [60]. Moreover, Type I IFN, via an action of IFNAR1 (type I IFN receptor), mediates PAH [36]. Patients with elevated levels of TNF-α have a greater risk of developing PAH induced by increased levels of endotelin-1 stimulated by IFN [56 61].

Tyrosine Kinase Inhibitors

Imatinib, nilotinib, dasatinib, bosutinib, ponatinib, carfilzomib, and ruxolitinib are potent tyrosine kinase inhibitors (TKIs) used in the treatment of chronic myeloid leukemia (CML) and acute lymphoblastic leukemia [62, 63]. PAH have been reported in patients treated with TKIs [64–66], more frequently observed with dasatinib use. Treatment with bosutinib, imatinib and nilotinib, can also be associated with subclinical PH. Two cases suggested overlapping pulmonary toxicity of bosutinib and dasatinib. A low pulmonary vascular tone is maintained

by Src tyrosine kinase (SrcTK) family and inhibition of SrcTK will lead to vasoconstriction of pulmonary arteries and thus to an increase in PH [67]. The activation of Src appears to play a critical role in the proliferation of PASMCs. PASMCs proliferation requires the coordinated interaction of several growth factors, including the platelet-derived growth factor (PDGF) with TK receptor. An increased expression of PDGF ligands and receptors (PDGFR) in pulmonary arteries of idiopathic PAH lungs was demonstrated. Dasatinib is the most potent inhibitor of PDGF signaling compared to imatinib and nilotinib [68, 69]. Imatinib has demonstrated anti-vasoproliferative properties and has been investigated as a potential treatment for PAH.

In rats, both TKIs increased plasma nitric oxide (NO), did not induce PAH-related structural or molecular changes in PA or lungs, and did not alter hemodynamic lung function compared with positive controls. Similarly, in the pulmonary artery endothelial cells and SMC co-culture model, imatinib and dasatinib increased NO and decreased endothelin-1 protein and mRNA [70].

Unlike imatinib, dasatinib causes pulmonary vascular damage, induction of ER stress, and mitochondrial ROS production (independent of Src family kinases), which leads to increased susceptibility to PH development [71]. In fact, dasatinib may attenuate hypoxic pulmonary vasoconstriction responses and increase susceptibility to experimental PH in rats that was not observed with imatinib [69]. Dasatinib treatment induced pulmonary endothelial cell apoptosis in a dose-dependent manner, while imatinib did not. Dasatinib treatment mediated endothelial cell dysfunction via increased production of ROS [69]. Finally, elevations in markers of endothelial dysfunction and vascular damage in the serum of CML patients treated with dasatinib, compared with CML patients treated with imatinib, were observed [69]. Dasatinib alters pulmonary endothelial permeability in a ROS-dependent manner in vitro and in vivo leading to pleural effusion [72]. However, the complete mechanisms of dasatinib-induced PAH remain unclear [73]. The pathophysiology of PAH induced by TKIs remains unclear. To gain major knowledge into this topic, Cornet et al. [74] performed a study combining a pharmacovigilance approach and the pharmacodynamic properties of TKIs. The study highlights the potential role of the Src protein kinase family and TEC in PAH induced by TKIs; in this study, five non-receptor protein kinases significantly correlated with disproportional signals: c-Src, c-Yes, Lck, and Lyn (all belonging to the Src protein kinase family) and TEC. Bosutinib, used in case of intolerance or resistance to imatinib, nilotinib or dasatinib, is a potent inhibitor of fibroblast growth factor receptor and mitogen-activated protein kinases that are signaling pathways involved in EC survival [61].

Direct-Acting Antiviral Agents Against Hepatitis C Virus

Sofusbuvir is a selective nucleotide inhibitor of RNA-dependent polymerase and a direct antiviral agent approved for treatment of hepatitis C. The pathophysiological link between HCV infection and PAH and the mechanism of sofusbuvir-induced PAH is unclear [75, 76]. Suppression of HCV viral replication is achieved at the cost of acute decrease in vasodilators (COX-2 and PGE2) which may exacerbate stable PAH or preclinical PAH.

Drug-Induced PVOD/PCH (Alkylating Agents)

Pulmonary veno-occlusive disease (PVOD) is an uncommon form of PH characterized by the obstruction of small pulmonary veins and a poor prognosis. PVOD may be sporadic or heritable because of biallelic mutations of the EIF2AK4 gene coding for GCN2.

Mitomycin C (MMC) is an antineoplastic antibiotic that acts as an alkylating agent by inhibiting DNA and protein synthesis. It can inhibit cell division, protein synthesis, and fibroblast proliferation[77]. Mitomycin C–induced lung vascular injury is characterized by endothelial cell (EC) changes including perivascular edema, the presence of thrombi in pulmonary capillaries, intimal hyperplasia, and medial hypertrophy of small arteries. Mitomycin C is directly cytotoxic and causes significant DNA cross-linking [78].

In rats, intraperitoneal administration of MMC-induced PVOD and MMC administration was associated with dose-dependent depletion of pulmonary GCN2 content and decreased smad1/5/8 signaling. Several mechanisms have been described to cause MMC-induced lung toxicity. The covalent binding of MMC to DNA results in DNA synthesis inhibition [79, 80]. Recent research further shows that MMC inhibits vascular endothelial growth factor (VEGF) expression [81].

PVOD was significantly associated with occupational exposure to organic solvents, with trichloroethylene (a chlorinated solvent used widely for metal degreasing and dry cleaning) as the main agent implicated. In fact, job exposure matrix analysis independently confirmed the association between PVOD and trichloroethylene exposure [82].

Clinical Findings and Possible Management Based on Previous Clinical Experiences

Management of drug-induced PAH is actually based on 2 points:

1) withdrawal of the suspected drugs.

2) management of PAH as proposed in the current international guidelines [1].

A flowchart summarizing an algorithm for the management of D-PAH (Fig. 2) possibly useful in guiding clinical decisions has been provided. In this figure, once obtained definitive PH diagnosis derived by RHC (according to the 6th World Symposia on PH proceedings) [5], we suggest to suspend immediately the drug suspected for worsening PAH, and then, based on the NYHA class, start specific PAH therapy (NYHA functional class III/IV) or to reevaluate the patient at follow-up (NYHA functional class I/II).

Agents Affecting Serotonin Metabolism (and Related Anorexigens)

A positive association between SSRI use and PAH was shown [83] and the risk of persistent PH of the newborn seems to be increased for infants exposed to SSRIs in late pregnancy [84]. In a large population of patients with PAH enrolled in REVEAL Registry (Registry to Evaluate Early and Long-term PAH Disease Management), incident SSRI use was associated with

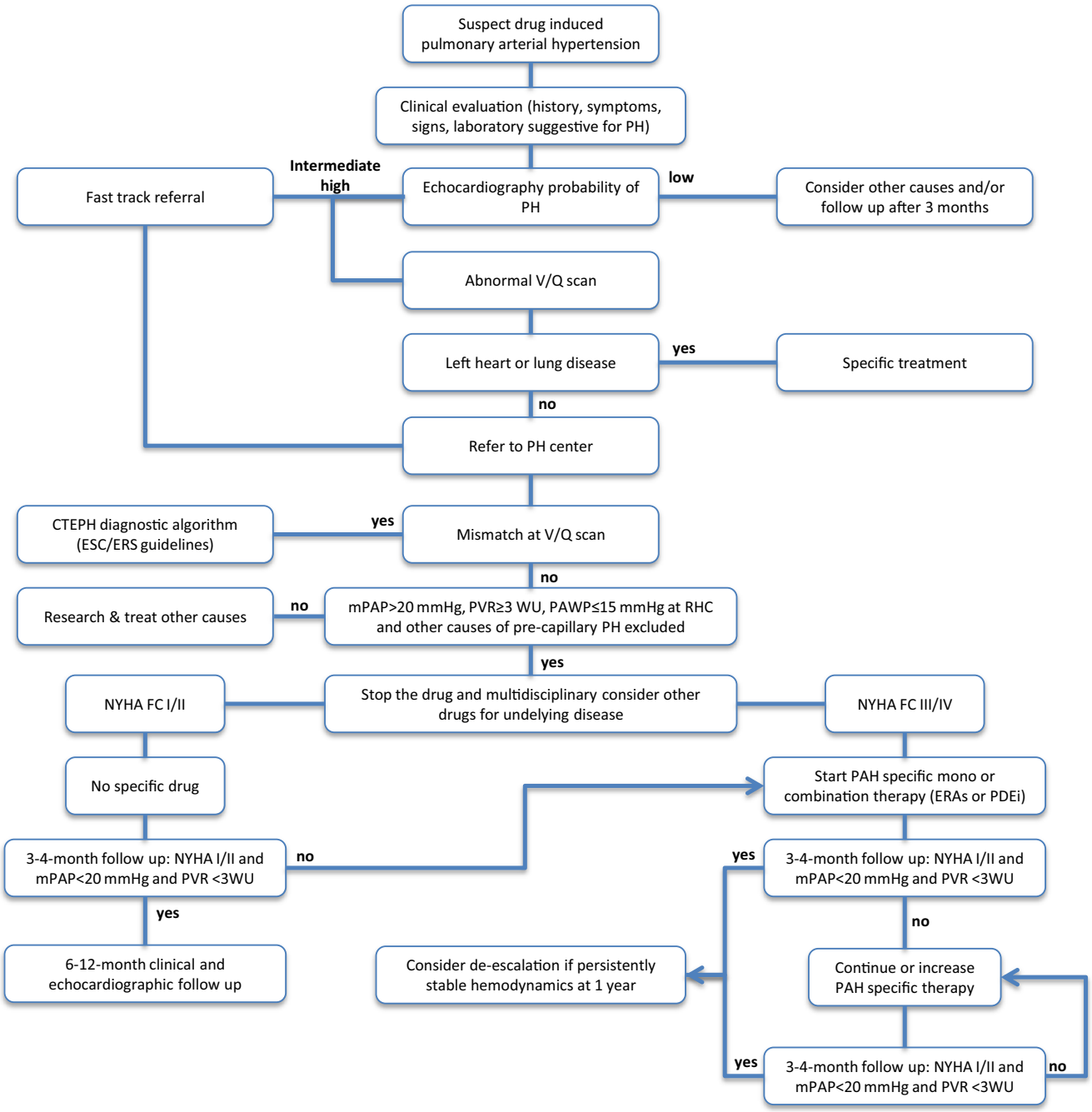

Fig. 2 Algorithm for the management of drug related pulmonary arterial hypertension

an increased mortality and a greater risk of clinical worsening [85]. Serotonin-associated PAH may be reversible with the interruption of drugs inhibiting its reuptake [86]. Instead, the fenfluramine exposure represents a potent trigger for PAH without influencing its clinical course [87].

Cases of heart valve replacement complicated by disproportionate PH with early death were reported in patients on treatment with benfluorex [88, 89].

Warfarin has a beneficial influence on the long-term prognosis in patients with Aminorex-induced PH [90].

Despite new specific PAH drugs available, anorexigen-associated PAH remains a progressive, fatal disease. Mortality is most closely associated with male gender, right ventricular hemodynamic function, and exercise limitation [91]. However, first-line therapy with epoprostenol, especially when combined with oral PAH treatment, was associated with a substantial improvement in clinical and hemodynamic status and favorable survival estimates in patients with severe anorexigen-associated PAH [92].

There are cases of PH due to long-term lithium therapy with hemodynamic normalization after lithium discontinuation [93].

Amphetamines and Methamphetamine

Unlike amphetamine-associated PAH, methamphetamine-associated PAH (Meth-APAH) has not been well described. In order to characterize these patients, recently, Zamanian et al. [94] showed that patients with Meth-APAH were less likely to be female, but they reported more advanced heart failure symptoms, significantly higher right atrial pressures, and lower stroke volume index; instead, considering event-free survival in Meth-APAH vs iPAH, Meth-APAH patients showed a more than twofold risk of clinical worsening or death, compared with iPAH. A 2.6-fold increase in risk of PAH diagnosis in hospitalized methamphetamine users has also been demonstrated. In the future, larger studies are needed to identify which susceptibility factors increase risk of PAH in methamphetamine users.

Tyrosin-Kinase Inhibitors

No specific patient attributes appear to be associated with an increased risk of developing PAH while receiving dasatinib [95]. TKIs should be avoided in those patients with a history of PH [96]. The US FDA issued a warning in 2011 regarding the cardiac and pulmonary risks of dasatinib [97]. Patients should be evaluated for signs and symptoms of cardiopulmonary disease before and during dasatinib treatment. Furthermore, due to the persistence of PAH in these patients, ongoing surveillance is important [52].

The dasatinib-induced PAH diagnosis is suspected based on clinical findings; pleural effusions, not related to PH, and not improving after drug dose reduction or thoracentesis are often present. The diagnosis is suggested by echocardiographic findings and confirmed by right heart catheterization [98]. The time occurrence of PAH after initiation of dasatinib is not predictable. In a French PH registry, the median time between initiation of dasatinib and diagnosis of PAH was 42 months [104]. Once PAH is diagnosed, potential causative or risk factors other than dasatinib should be also excluded. If dasatinib-induced PAH is confirmed or suspected, dasatinib should be immediately discontinued [99]; however, PAH persists in more than one-third of patients [100] and can reoccur when other TKIs are used. Dose reduction is often unsuccessful, and PAH may progress despite dasatinib dose reduction [101]. Patients may not respond to pulmonary vasodilators if dasatinib is continued [102]. Even if initially thought to be a largely reversible process, recent follow-up studies suggest persistence in a substantial number of cases, and it would seem reasonable to initiate pulmonary vasodilators just after dasatinib cessation, particularly in symptomatic patients, or in case of severe PAH and/or RV failure. Treatment with PAH-specific therapy is also recommended for patients with persistent PAH after discontinuation of the TKI or with right heart failure [103]. In case of partial reversibility after drug withdrawal, the upfront combination therapy may be a useful option for symptomatic patients [104]. If pulmonary arterial pressure and RV function return to normal, discontinuation and weaning of pulmonary vasodilators should be addressed by expert centers. Treatment algorithms on vasodilator use have been proposed [104]. Unfortunately, the algorithm for dasatinib-induced PAH was based on relatively few patients and should not be considered an official recommendation, as acknowledged by the same authors. The algorithm should also be updated to the 6th World Symposia on PH (Nice 2018) recommendations; a new PH hemodynamic definition was provided with different cut-off levels (mPAP >20 mmHg). An early vasodilatator therapy after dasatinib discontinuation could be also considered in a large number of patients in NYHA FC III; PH is a progressive condition and early treatment may be effective in slowing the progression of the disease. In the last ESC/ERS guidelines for PH [1], ERAs, PDEi or GCs, and calcium channel blockers are recommended in NYHA FC II with evidence IA or IB.

To the best of our knowledge, based on currently available data, no recommendations can be made regarding the choice of specific pulmonary vasodilators. In the majority of cases, the specific vasodilator utilized was sildenafil, bosentan is used in few cases, and calcium channel blocker even less. The role of the newer pulmonary vasodilators or initial combined vasodilator therapy is still not clearly defined. Standard PH guidelines approach is probably the best to evaluate specific therapy response and possible treatment adjustment.

In patients in treatment with nilotinib, after imatinib failure, pulmonary pressures returned to normal with discontinuation of nilotinib [105]. Ponatinib has been associated to PAH with partial response to cessation of ponatinib and specific PAH therapy [106].

Carfilzomib, a proteasome inhibitor used in the treatment of multiple myeloma, has been linked to both causes with an incidence of PAH of 3% [107] requiring treatment for PAH [108]. The relationship between carfilzomib and PH is controversial due to the fact that multiple myeloma is a form of group 5 PH [5]. Additional research is required to definitively establish the role of carfilzomib in PAH. One case series has demonstrated improvement in pulmonary hemodynamics in 66% of patients with PH secondary to myelofibrosis in treatment with Ruxolitinib, a JAK1/JAK2 inhibitor [109]. Conversely, in a patient receiving ruxolitinib for myelofibrosis, the drug was supposed as a potential cause of PAH [110].

Interferon-Induced PAH

In some cases, PH was reversible after cessation of INF exposure [111 112], especially in patients without concomitant risk factors for PH; some cases illustrate irreversible progressive PAH, while others demonstrate partially response to a combination therapy (sildenafil or tadalafil with bosentan or ambrisentan) [23, 113] with functional capacity and symptom improvement [114–116]. It is not still clear whether clinical improvement was due to cessation of IFN or upfront combination therapy.

Direct-Acting Antiviral Agent–Induced PAH

Sometimes, PAH is diagnosed in patients treated with sofosbuvir and with comorbidities (HIV coinfection and portal hypertension) [73]. In these cases, bosentan therapy was associated to incomplete clinical improvement and the patients should receive combination therapy (bosentan + epoprostenol or sildenafil + epoprostenol + bosentan). On the basis of severe and acute onset of PAH, authors hypothesized a causal link between HCV treatment and PAH that suppression of HCV replication may have promoted a decrease in vasodilatory inflammatory mediators, leading to worsening of underlying PAH.

In the cases of DAA-induced PAH monitored in the French referral center [117], PAH was reversible in the patients without portal hypertension after DAA withdrawal. PAH was dramatically improved by PAH-targeted therapy (bosentan plus sildenafil or tadalafil, for one patient). Clinicians should be warned of this potential risk of PAH exacerbation in patients receiving DAA against HCV. Further studies should establish the exact mechanisms and the appropriate management of DAA-induced PAH.

Opioids and Substance of Abuse

In long-term cocaine and heroin abusers with asymptomatic PH, it has not been proved whether the cessation of the chronic insult could result in the hemodynamic recovery or if the vascular damage remains permanent [118]. More studies are necessary to evaluate the role of specific PAH therapies in these patients [119]. Etorphine, a potent opioid agonist, causes PH and respiratory depression. In animal models, hypoxia following etorphine administration, the P(A-a)O2 gradient was positively correlated with the mean PAP, indicating that pulmonary pressure plays a significant role in altering pulmonary gas exchange [120].

It has been well documented that HIV patients who abuse illicit drugs such as opioids are more susceptible to develop PAH [121]. We can hypothesize a deleterious synergy between HIV infection and drug abuse in inducing the progression of PAH. Generally, HIV patients are not enrolled in RCTs for specific PAH treatments. The effect of highly active antiretroviral therapy (HAART) on HIV-PAH patients remains controversial. Study populations may be different for HIV stage, coinfections, comorbidities, and previous therapies, and often PAH is not confirmed at right heart catheterization. In a longitudinal analysis of a large population of HIV-PAH patients in the modern therapeutic era [122], long-term HAART without additional specific PAH is unable to improve hemodynamic parameters in most patients and unable to prevent the development of PAH in HIV-infected patients. However, in these patients treated by long-term HAART, the hemodynamics at baseline tended to be less impaired compared with previous studies, so we could speculate that HAART may help to delay the development of PAH in HIV-infected patients. Larger scale prospective studies should establish the efficiency of specific PH treatment in IV buprenorphine users.

Drug-Induced PVOD/PCH (Alkylating Agents)

Alkylating and alkylating-like agents, such as bleomycin, cyclophosphamide, and MMC, have increased the risk of pulmonary veno-occlusive disease (PVOD). MMC therapy is a potent inducer of PVOD in humans; seven cases of PVOD induced by MMC therapy were reported from the French Pulmonary Hypertension Registry. All patients displayed squamous anal cancer and were treated with MMC alone or MMC plus 5-fluoruracil [123].

Unlike PAH, treatment options for PVOD are usually quite limited. In literature, a few cases of favorable response to Bosentan (in one case in combination therapy with tadalafil [124] or in monotherapy [125]) in MMC-induced PVOD were reported. These patients should be referred to lung transplantation as treatment of choice, since PVOD has a poor rate of response to PAH therapy and there is the possibility of developing severe pulmonary edema with specific PAH therapy [126].

Miscellaneous Medications

Several cases of reversible PH related to thalidomide treatment in patients with multiple myeloma with a rapid decrease of pulmonary artery pressure after thalidomide discontinuation have been described [127].

Protamine, used after cardiopulmonary bypass in order to reverse the anticoagulant effects of heparin, appears to be able to cause acute, reversible PH. Prostacyclin was effective in the treatment of protamine-mediated PH [128]. In particular, after inhaled-nebulized prostacyclin administration, pulmonary artery pressures decreased with minimal systemic hypotensive effects [129]. In the case of severe pulmonary vasoconstriction induced by protamine in cardiac surgery, epoprostenol may be infused at dosage of 20 to 40 ng/kg min and the hemodynamic instability lasts for 40 to 65 min and generally, all the patients recover uneventfully [130].

In the case of severe precapillary PH, 4-aminopyridine, used to improve walking in individuals with multiple sclerosis, was immediately stopped and combination therapy with ambrisentan and tadalafil was started with clinical and hemodynamic improvement [131].

Withdrawal of the Suspected Drugs

In drug-induced PAH patients, there are few cases with hemodynamic normalization after drug withdrawal. Generally, hemodynamic normalization and clinical improvement after suspected drug withdrawal are more likely in patients without concomitant risk factors for PH or in the absence of interacting factors (HCV, HIV infection, or portal hypertension, for example). Serotonin-associated PAH may be reversible with the interruption of drugs inhibiting its reuptake [86]. There are cases of PH due to long-term lithium therapy with hemodynamic normalization after lithium discontinuation [93]. If dasatinib-induced PAH is confirmed or suspected, dasatinib should be immediately discontinued [99]; however, PAH persists in more than one-third of patients [100]. PH was reversible after cessation of INF exposure [111, 112], especially in patients without concomitant risk factors for PH. In DAA-induced PAH patients[117], PAH was reversible in patients without portal hypertension after DAA withdrawal. Several cases of reversible PH related to thalidomide treatment in patients with multiple myeloma with a rapid decrease of pulmonary artery pressure after thalidomide discontinuation have been described [127].

Conclusions

Further studies should be held to identify genetic, biological, and clinical factors that determine individual susceptibility to develop D-PAH. Careful cardiological monitoring may be proposed for patients with a prior diagnosis of PAH or with risk factors for PAH during the aforementioned therapies. Because of the potential severity of PAH in this clinical setting, patients with onset of D-PAH should be early referred to an expert center for diagnosis confirmation and specific PAH therapies. It remains still unclear whether clinical improvement is due rather to cessation of the drugs than to upfront combination therapy. More studies are needed to answer this question.

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