Avaliação do ventrículo direito nos pacientes com hipertensão pulmonar

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Corrélation entre les donnés de l`imagerie par résonance magnetique (IRM) cardiaque et le cathétérisme droit dans l`hypertension artérielle pulmonaire (HTAP).

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Orientador: Prof. Dr. Rogério de Souza

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Sumário

Lista de Unidades

m^2.....Metros quadrados

kg.....Quilogramas

cm.....Centímetros

mg/dl.....Miligrama por decilitro

bpm.....Batimentos por minuto

mmHg.....Milímetros de mercúrio

L/min.....Litros por minuto

$L/min/m^2$.....Litros por minuto por metro quadrado

UW.....Unidades Wood

mL.....Mililitro

mm.....Milímetro

mL/m^2.....Mililitro por metro quadrado

cm/m^2..... Centímetro por metro quadrado

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Resumo

Hoette, S. Avaliação do ventrículo direito em pacientes com hipertensão pulmonar (tese). São Paulo: Faculdade de Medicina da Universidade de São Paulo (2012).

Introdução: A fração de ejeção do ventrículo direito (FEVD) é um importante fator prognóstico em pacientes com hipertensão pulmonar (HP), porém a sua medida é complicada e demorada devido à complexidade anatômica do ventrículo direito (VD). O TAPSE (*Tricuspid Annular Plane Systolic* Excursion) é um bom índice da FEVD, mas ele avalia apenas o componente longitudinal da contração ventricular direita. A RVFAC (*Right Ventricular Fractional Area Change*) parece ser um melhor índice da FEVD por incluir os componentes longitudinal e transversal da contração ventricular direita. O objetivo deste estudo foi avaliar a performance da RVFAC de acordo com a gravidade do acometimento hemodinâmico em dois grupos distintos de pacientes portadores de HP pré-capilar: hipertensão arterial pulmonar (HAP) e tromboembolismo pulmonar crônico hipertensivo (TEPCH).

Métodos: 62 pacientes realizaram cateterismo cardíaco direito e ressonância magnética cardíaca em ±72h. As áreas sistóica e diastólica finais do ventrículo direito (ASFVD, ADFVD), a área diastólica final do ventrículo esquerdo (ADFVE)

e o TAPSE foram medidos nas imagens de quatro cavidades. A RVFAC (ADFVD-ASFVD/ADFVD) e a relação entre as áreas diastólica finais ventriculares (ADFVD/ADFVE) foram calculadas. Os diâmetros entre as paredes livre e septal (dL-S) e antero-posterior (dA-P) do ventículo esquerdo (VE) foram medidos nas imagens em eixo curto e o índice de excentricidade do VE (IE) foi calculado (=dA-P/dL-S). A FEVD foi calculada a partir de imagens consecutivas de 6mm no eixo curto.

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Resultados: A população tinha 58 anos em média, a maioria era do sexo feminino e estava em classe funcional III, 23 tinham HAP e 39 TEPCH. A FEVD apresentou correlações fracas com as medidas hemodinâmicas de sobrecarga e de função do VD. A RVFAC apresentou melhor correlação (R^2=0,65, p < 0,001) do que o TAPSE (R^2=0,35, p<0,001) com a FEVD e melhor capacidade para estimar FEVD<35% do que o TAPSE (TAPSE: AUC 0,73 e RVFAC: AUC 0,93, p=0,0065). Dividimos a população pela mediana da resistência vascular pulmonar (RVP) e observamos que no grupo com maior gravidade hemodinâmica essa diferença se acentuou: no grupo com RVP<8,5UW (RVFAC: R^2=0,66, p<0,001 e TAPSE: R^2=0,30, e p=0,002) e no grupo com RVP>8,5UW (RVFAC: R^2=0,51, p<0,001 e TAPSE: R^2=0,14, e p=0,041). O grupo com RVP>8,5UW apresentou maior ADFVD/ADFVE e maior IE. As correlações da RVFAC e TAPSE com FEVD foram semelhantes entre os grupos HAP e TEPCH.

Conclusão: A RVFAC se correlacionou melhor com a FEVD do que o TAPSE tanto no grupo com menor como no grupo com maior gravidade hemodinâmica. No grupo com maior gravidade as correlações com a FEVD foram ainda mais significativas, não havendo diferenças na performance da RVFAC entre os pacientes com HAP e TEPCH. A RVFAC foi um melhor índice da FEVD talvez por incluir o movimento transversal da contração ventricular.

Descritores: disfunção ventricular direita, hipertensão pulmonar, ventrículos cardíacos, hemodinâmica.

Summary

Hoette, S. Right ventricle evaluation in pulmonary hypertension (tese). São Paulo: Faculdade de Medicina da Universidade de São Paulo (2012).

Introduction: The right ventricular ejection fraction (RVEF) is a surrogate marker in pulmonary hypertension (PH), but its measurement is complicated and time consuming. The TAPSE (Tricuspid Annular Plane Systolic Excursion) is a good index of RVEF, though it measures only the longitudinal component of right ventricular contraction. The RVFAC (Right Ventricular Fractional Area Change) seems to be a better index of RVEF because it takes into account the longitudinal and the transversal components of right ventricular contraction. The aim of our study was to evaluate the RVFAC performance according to hemodynamic severity in two groups of patients with PH: pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH).

Methos: Sixty-two patients with PAH and CTEPH underwent right heart catheterization and cardiac MR in a 72-hour delay. The right and left ventricle end diastolic areas (RVEDA, LVEDA), the right ventricle end systolic area (RVESA) and TAPSE were measured in the four chamber view. The RVFAC (= RVEDA – RVESA/RVEDA) and the RVEDA/LVEDA relationship were calculated. The diameter between the left ventricle (LV) free wall and the septum (dL-S) and

the diameter between the anterior and posterior walls (dA-P) were measured and the LV eccentricity index (EI) was calculated (=dA-P/dL-S). The RVEF was calculated by using 6 mm RV short axis cines.

Results: The population had mean age of 58 years with female majority, most of the patients were in functional class III, 23 had pulmonary arterial hypertension (PAH) and 39 had chronic thromboembolic pulmonary hypertension (CTEPH). The RVEF was weakly correlated to the hemodynamic variables of RV afterload and function. The RVFAC was more strongly correlated to RVEF (R^2=0.65, p<0.001) than TAPSE (R^2=0.35, p<0.001). RVEF<35% was better predicted by RVFAC than TAPSE (TAPSE: AUC 0.73 and RVFAC: AUC 0.93, p=0.0065). We divided the population by the median of the pulmonary vascular resistance (PVR) and we observed that in the group with worse hemodynamic severity this difference increased: in the group with PVR<8,5WU (RVFAC: R^2=0.66, p<0.001 and TAPSE: R^2=0.30, p=0.002) and in the group with PVR>8,5 WU (RVFAC: R^2=0.51, p<0.001 and TAPSE: R^2=0.14, p=0.041). The group with PVR>8,5WU had an increased RVEDA/LVEDA and an increased EI. There was no differences in the RVEF relationships between the groups of PAH and CETPH.

Conclusion: The RVFAC was better correlated to RVEF than TAPSE in the groups with less severe and more severe hemodynamics. In patients with increased hemodynamic severity, with no difference in the performance in the

HAP or CTEPH groups. RVFAC was a better index of RVEF possibly because it takes into account the transversal component of right ventricular function.

Descriptors: right ventricular dysfunction, pulmonary hypertension, cardiac ventricles, hemodynamics.

INTRODUÇÃO

A importância do ventrículo direito (VD) foi subestimada até recentemente. Trabalhos experimentais em modelo de cães com pericárdio aberto mostravam que não havia redução do débito cardíaco ou aumento da pressão venosa sistêmica quando VD era cauterizado e perdia sua função contrátil[1]. Assim, durante mais de quatro décadas, o VD foi considerado como tendo uma função de condução passiva com insignificante relevância circulatória. Na década de 80, estudos em modelos de cães com tórax fechado mostraram comprometimento hemodinâmico significativo no infarto de VD[2]. Nesta época, estudos clínicos começaram a mostrar também o maior risco de morte, arritmia e choque cardiogênico em pacientes com infarto de VD[3].

O papel do VD passou a ser então reconsiderado, levantando a hipótese de que os modelos iniciais não encontravam alterações com a exclusão do VD porque não levavam em conta a interdependência ventricular, uma vez que esses eram baseados em modelos com pericárdio aberto[1]. A partir de então, a função do VD começou a ganhar importância e em 2006 o Instituto Nacional de Coração, Pulmão e Sangue nos Estados Unidos identificou a fisiologia do ventrículo direito como prioridade na pesquisa cardiovascular[1,4].

1.1. Particularidades do ventrículo direito

Em condições normais, o VD, ao contrario do ventrículo esquerdo (VE), está acostumado a um regime de baixa pressão porque a circulação pulmonar tem características bastante diferentes da circulação sistêmica. A principal característica da circulação pulmonar é a capacidade de acomodar grandes aumentos de volume sanguíneo sem elevação da pressão do circuito. Isso é possível pela distensibilidade dos vasos pulmonares e pelo recrutamento de capilares[5]. Essa elevada complacência da circulação pulmonar associada a uma baixa resistência vascular pulmonar (RVP) (cerca de um sexto da resistência vascular sistêmica) faz com que o lado direito do coração trabalhe com pressões bastante inferiores do que o lado esquerdo[6,7]. As características anatômicas do VD diferem muito das do VE; o VD tem paredes finas e bastante trabeculadas e possui formato semilunar ou em crescente. Já o VE tem formato concêntrico e paredes bem mais espessas (a massa miocárdica do VD é aproximadamente um quarto da massa do VE).

A perfusão sanguínea também se dá de forma diferente entre o VD e o VE. O fluxo na artéria coronária descendente anterior tem padrão bifásico, sendo praticamente nulo durante a sístole, e significativo apenas durante a diástole, estando assim a perfusão miocárdica do VE limitada à diástole. Já o fluxo da artéria coronária direita tem padrão monofásico permanecendo

praticamente inalterado durante a sístole e a diástole, garantindo perfusão miocárdica ao VD durante todo o ciclo cardíaco[4].

Estas diferenças anatômicas proporcionam ao VD uma complacência muito maior do que a do VE e o levam a responder de forma diferente aos insultos. O VD responde de formas diferentes quando ocorre aumento de pressão ou de volume e também dependendo da rapidez com que o insulto se instala, seja de forma aguda ou crônica; tendendo a tolerar melhor sobrecarga de volume do que de pressão. Quando ocorre aumento súbito da pós-carga o VD dilata significativamente e o volume sistólico diminui quase que linearmente com o aumento da pós-carga. Assim, um VD normal é incapaz de gerar pressões de artéria pulmonar maiores que 40mmHg quando ocorre aumento abrupto na pós-carga. Em contrapartida, o VD consegue lidar bem com aumentos significativos de volume, mesmo que de forma abrupta. Aumentos súbitos em fluxo, como ocorre no exercício físico, não levam a aumentos significativos da pressão arterial pulmonar[5].

Uma causa importante de sobrecarga ventricular direita é a hipertensão pulmonar (HP). A HP é definida pelo achado de elevação da pressão pulmonar média (PAPm ≥ 25 mmHg) no cateterismo cardíaco direito e a sua classificação diagnóstica engloba achados hemodinâmica e fisiopatológicos[8]. Quando a pressão da artéria pulmonar ocluída (PAPo) é > 15 mmHg a HP é pós-capilar e classificada no grupo 2 da classificação diagnóstica que consiste na HP causada por doença do coração esquerdo.

Os outros 4 grupos da classificação diagnóstica envolvem a HP com PAPo ≤ 15 mmHg, chamada HP pré-capilar. O grupo 1 é denominado hipertensão arterial pulmonar (HAP) e engloba HAP classificadas como: idiopática, hereditária, induzida por drogas ou toxinas, hipertensão persistente do recém-nascido, doença pulmonar veno-oclusiva e/ou hemangiomatose capilar pulmonar e HAP associadas a doença do tecido conjuntivo, infecção pelo vírus da imunodeficiência humana, hipertensão portal, cardiopatia congênita, esquistossomose e anemia hemolítica crônica. A HP causada por doença pulmonar e/ou hipoxemia pertence ao grupo 3 e o grupo 4 consiste no tromboembolismo pulmonar crônico hipertensivo (TEPCH). No grupo 5 são classificados os casos de HP com mecanismos multifatoriais não esclarecidos[9].

1.2. Resposta do ventrículo direito ao aumento da pós-carga

Quando ocorre aumento da pós-carga o VD precisa se adaptar. Ocorre dilatação da cavidade ventricular, o que modifica sua forma inicial semilunar, deixando-o mais parecido com o VE, ou seja, mais concêntrico. O septo interventricular fica retificado podendo haver abaulamento e compressão da cavidade ventricular esquerda. A hipertrofia da parede muscular é outra importante alteração que ajuda o VD a vencer o aumento da RVP. Estudos experimentais mostram hipertrofia ventricular direita em apenas 96 horas de sobrecarga e aumento significativo da massa muscular do VD em 7 dias de hipóxia, sendo esse aumento progressivo, caso o estímulo seja mantido[5,10].

A maior massa muscular do VD leva ao aumento da demanda de oxigênio; porém, a oferta de oxigênio está associada à perfusão coronária do VD e esta se encontra alterada conforme a massa muscular do VD aumenta. Em pacientes com HP e hipertrofia do VD, o fluxo na artéria coronária direita muda de padrão; passa do padrão monofásico para o padrão bifásico, como o apresentado pela artéria coronária descendente anterior. O VD passa então a ser perfundido somente durante a diástole, como o VE. Essa mudança no fluxo coronariano é diretamente proporcional aos aumentos da pressão sistólica do VD e de sua massa muscular[4].

A resposta do VD ao incremento da pós-carga varia mesmo dentro de subgrupos da HP, podendo a disfunção ventricular direita estar presente de forma mais precoce em alguns grupos, mesmo que o padrão hemodinâmico seja similar[2]. Existe diferença na contratilidade cardíaca entre pacientes com HAP idiopática e associada à esclerose sistêmica, apesar dessas duas patologias estarem classificadas no mesmo grupo na classificação diagnóstica da HP. Overbeek et al.[11] mostraram que os pacientes com esclerose sistêmica apresentavam menor contratilidade ventricular direita que os pacientes com HAP apesar da mecânica vascular semelhante nos dois grupos; não havia diferença significativa na RVP nem na complacência vascular pulmonar. Essa diferença na contratilidade ventricular estaria associada à variação do acometimento do miocárdio entre essas duas patologias, como a presença de fibrose miocárdica e o envolvimento de vasos coronários intramiocárdicos.

Desta forma, acredita-se que o aumento da pós-carga induz alterações na morfologia, na massa muscular e na perfusão do VD, sendo que a dilatação do VD pode ainda levar a alterações na complacência do VE, pelo abaulamento septal. Todos estes fatores associados contribuem para a redução do débito cardíaco, que leva à diminuição da pressão de perfusão coronária. O aumento da massa miocárdica associado às mudanças na perfusão coronária podem causar isquemia relativa, piorando ainda mais a performance do VD, gerando assim um ciclo vicioso, com auto-agravamento[12].

Define-se, portanto, como disfunção do VD, o conjunto de alterações estruturais ou funcionais que levam ao comprometimento do enchimento ou da contração ventricular direita. Já a falência do VD se refere à síndrome clínica complexa que resulta destas alterações[12]. As principais manifestações clínicas desta síndrome são: retenção hídrica, que pode levar a edema periférico, ascite e anasarca; redução da reserva sistólica e baixo débito cardíaco, que pode levar a intolerância ao exercício físico e fadiga; e arritmias atrial e ventricular.

A capacidade funcional do VD é o principal determinante do prognóstico na HP. Enquanto o VD consegue manter o débito cardíaco (DC), apesar de aumentos na pós-carga, o paciente permanece pouco sintomático[2]. A função ventricular direita é, portanto, fundamental nos pacientes com HP.

1.3. O papel prognóstico da função ventricular direita na hipertensão pulmonar

Estudos têm comprovado que a função do VD é um importante fator prognóstico na HP[2]. As medidas do índice cardíaco e do volume sistólico do VD já foram estabelecidos como marcadores de sobrevida nesta doença[13,14]. van de Veerdonk et al.[15] mostraram que pacientes com HP e disfunção grave de VD, definida por uma fração de ejeção (FEVD) menor do que 35%, tiveram sobrevida pior independente da RVP apresentada na avaliação inicial. No seguimento desses pacientes, a diminuição da FEVD foi marcador de pior prognóstico enquanto o aumento da RVP não teve papel prognóstico. Ou seja, independente do comprometimento hemodinâmico, o fator prognóstico mais importante foi a maneira como o VD conseguiu lidar com esse aumento de pós-carga.

Em um estudo mais recente também em pacientes com HP, o mesmo grupo comparou pacientes com sobrevida maior do que cinco anos (grupo dos sobreviventes) com pacientes que morreram entre 1 e cinco anos (grupo dos não sobreviventes) da avaliação inicial[16]. O grupo dos não sobreviventes apresentava FEVD significativamente menor no momento da inclusão no estudo do que o grupo dos sobreviventes. A FEVD permaneceu estável entre a avaliação inicial e após um ano de tratamento no grupo dos sobreviventes, porém apresentou redução progressiva no grupo dos não

sobreviventes, reforçando a importância da FEVD como fator prognóstico nos pacientes com HP.

A sobrevida dos pacientes com HP varia não só entre os diferentes grupos, mas também dentro de cada um dos grupos existentes da classificação diagnóstica. A sobrevida dos pacientes com HAP associada à doença do colágeno é inferior a de pacientes com HAP idiopática que por sua vez é inferior a de pacientes com HAP associada à cardiopatia congênita[13]. Recentemente, Fernandes et al.[17] mostraram que os pacientes com HAP associada à esquistossomose apresentaram sobrevida maior do que pacientes com HAP idiopática. Se a função ventricular direita varia entre as patologias associadas a HP[11], talvez o acometimento miocárdico distinto seja um fator que contribua para essa diferença de sobrevida.

1.4. Avaliação não invasiva da função ventricular direita

A fração de ejeção é considerada o método padrão para se avaliar a função ventricular de forma não invasiva. Para o cálculo da fração de ejeção é necessário que sejam medidos os volumes sistólico e diastólico finais. A medida dos volumes é realizada pelo contorno da borda endocárdica no final da sístole e da diástole em diversos cortes paralelos, da base ao ápice dos ventrículos. Este processo é trabalhoso e demorado[18]. A avaliação da FEVD é ainda mais complicada do que do VE pela complexidade anatômica do VD. A parede mais trabeculada do VD dificulta a definição da borda endocárdica e o formato semilunar dificulta o desenvolvimento de modelos geométricos para o cálculo da sua função de forma automatizada[19]. A posição retroesternal ainda atrapalha a aquisição de boas imagens do VD pela ecocardiografia, já que a janela acústica é prejudicada pela interposição do esterno[20].

Pelas dificuldades técnicas que existem para a determinação da função do VD, formas para estimar a sua função que dispensam o cálculo da FEVD começaram a gerar interesse[21]. Para tal foi necessário compreender melhor a forma como se dá a contração do mesmo.

Estudos da década de 50 já mostravam o interesse em entender como ocorria a contração cardíaca. Rushmer et al.[22] fizeram um dos primeiros estudos que mostrou diferença na contração do VD e do VE em

cães. Eles suturaram pequenos pedaços de fio de metal na parede do VD e do VE e depois fizeram imagens com cinefluorografia. A análise das imagens permitiu identificar o principal eixo de aproximação desses pedaços de metal, definindo assim qual era o principal eixo de encurtamento das fibras musculares nas cavidades cardíacas. O VD se caracterizou principalmente pela aproximação das peças no sentido longitudinal, ou seja, o movimento da base em direção ao ápice do coração[22].

Recentemente, o uso de uma técnica mais moderna com a inserção cristais microtransdutores ultrassônicos possibilitou uma análise mais detalhada da contração cardíaca. Leather et al.[23] associaram essa técnica com monitorização hemodinâmica e infudiram volume ou garrotearam a artéria pulmnar para avaliar a resposta a mudanças na pré e pós-carga do VD. O estudo mostrou que a variação no volume sistólico apresentou correlação forte com a variação dos microtransdutores no eixo longitudinal e fraca com a variação no eixo transversal. As variações na pré e pós-carga também se correlacionaram melhor com a variação no eixo longitudinal do que no eixo transversal. Os autores concluíram então que a contratilidade regional longitudinal refletia melhor a contratilidade global do VD do que a transversal.

Com base nesses achados, a avaliação da contratilidade longitudinal parecia ser a melhor forma de estimar a função global e assim a medida da movimentação do anel tricúspide foi estudada como forma de estimar a

FEVD já que refletia o movimento longitudinal, ou seja, o movimento da base em direção ao ápice cardíaco[24].

Uma maneira de se aplicar esse conceito clinicamente é a avaliação do padrão de movimentação da válvula tricúspide. A medida do TAPSE (*Tricuspid Annular Plane Systolic Excursion*) é rápida e fácil de ser obtida, não requer o delineamento da borda interna do miocárdio e ainda é altamente reprodutível[25]. Ueti et al.[26] compararam a medida do TAPSE realizadas por ecocardiografia com a medida da fração de ejeção pela angiografia de radionuclídeos e encontraram forte correlação entre as duas medidas. A medida do TAPSE ainda apresentou boa capacidade em discriminar pacientes com boa função daqueles com disfunção de VD. Estudos com acompanhamento de longo prazo mostraram que o TAPSE é também um bom marcador prognóstico nas cardiopatias[27].

Na HP, esse índice também se mostrou útil. Forfia et al.[24] estudaram o TAPSE em 63 pacientes com HP. O TAPSE apresentou alta sensibilidade e especificidade como indicador de volume sistólico reduzido. Pacientes com TAPSE menor que 1.8 cm apresentaram menor índice cardíaco e menor trabalho sistólico de VD, ou seja, disfunção ventricular direita mais avançada. A sobrevida foi significativamente menor nos pacientes com TAPSE menor que 1,8 cm do que nos paciente com mais de 1,8 cm. Quando o TAPSE inicial era menor que 1,5 cm os pacientes apresentaram

mortalidade ainda maior. Assim, a medida do TAPSE mostrou ser também marcador de prognóstico em HP.

Brown S et al.[28] analisaram as áreas diastólica e sistólica finais do VD para avaliar os componentes longitudinal e transversal da contração ventricular. Em relação à área total reduzida entre a diástole e a sístole, o maior percentual de redução de área aconteceu no eixo longitudinal (77%). Quando analisaram o grupo com HP o achado foi semelhante: o principal componente na contração do VD continuou sendo o encurtamento longitudinal. Mas o interessante foi que quando comparado ao grupo controle, a importância do componente transversal foi significativamente mais importante no grupo HP (componente transversal representou 37% da redução total da área no grupo HP contra 23% no grupo controle). Quando um subgrupo de pacientes com HP foi analisado antes e após tratamento, a melhora na função ventricular direita esteve associada a ganho principalmente no componente longitudinal. Os autores concluem que o principal componente da contração do VD é o longitudinal em sujeitos normais e nos pacientes com HP e que a resposta à redução na pós-carga se reflete também no componente longitudinal.

Entretanto, os dados desse estudo[28] mostram que nos pacientes com HP o componente transversal é proporcionalmente mais importante do que nos controles, levantando a hipótese que neste grupo de pacientes o componente transversal não deve ser desprezado. Essa hipótese é

reforçada por outros estudos que não encontraram relação tão significativa do TAPSE com a função ventricular direita. Anevkar et al.[29] encontrou correlação fraca entre a medida do TAPSE pelo ecocardiograma e a FEVD medida por ressonância nuclear magnética cardíaca (RMC). Em pacientes com HP, o TAPSE apresentou correlação também apenas fraca com a FEVD quando ambos foram medidos pela RMC[30] e moderada quando ambos foram medidos pelo ecocardiograma tri-dimensional[31].

A RMC vem ganhando importância no estudo do VD e na HP. Os avanços nas técnicas de aquisição e processamento das imagens de RMC representaram um grande avanço na avaliação do VD, pois a RMC é um método não invasivo e com elevada resolução espacial que permite a avaliação do VD de forma tridimensional[20]. Este exame promove visualização tomográfica detalhada da morfologia do VD além de oferecer definição nítida entre o miocárdio e o sangue intracavitário. Estudos já validaram as medidas dos volumes, massa muscular e FEVD por RMC. A RMC é considerada hoje o padrão ouro para a avaliação não invasiva do VD[12,19].

Estudos utilizando RMC mostraram que pacientes com HP, quando comparados a grupo controle, apresentam aumento significativo dos volumes sistólico e diastólico finais e da massa muscular do VD, assim como redução significativa da FEVD[32]. Essas diferenças tiveram papel prognóstico na HP. Em pacientes com HP que tiveram RMC realizada no início do

acompanhamento e um ano após, a redução no volume sistólico, o aumento do volume diastólico final do VD e a diminuição do volume diastólico final do VE foram fatores fortemente preditores de falência de tratamento e mortalidade[14].

Kind T et al.[30] usaram as imagens de RMC no corte de quatro cavidades e estudaram a variação entre sístole e diástole dos componentes longitudinal e transversal. Para avaliar o componente transversal, eles traçaram segmentos entre a parede livre e septo e, para avaliar o componente longitudinal, segmentos do anel tricúspide ao ápice cardíaco. Esse estudo mostrou que o a redução no componente transversal teve melhor correlação com a FEVD do que a redução no sentido longitudinal em pacientes com HP. Eles ainda mostraram que quando comparados a um grupo controle, os pacientes com HP apresentam diferença no padrão de contração. A contração no eixo transversal apresenta maior redução nos segmentos apicais em indivíduos normais. Nos pacientes com HP essa diferença ocorre principalmente nos segmentos próximos a base do coração. O estudo conclui que o movimento transversal nos pacientes com HP se correlaciona melhor com a medida da função global do VD do que a medida do movimento longitudinal, pela RMC. Os autores acreditam que esse achado está associado ao fato do movimento transversal incluir o movimento septal. Quando a pós-carga aumenta e o VD dilata, o septo acaba sendo empurrado em direção ao VE e esse abaulamento septal não é levado em conta quando apenas o componente longitudinal é medido.

Assim outras formas de se estimar a FEVD continuaram a ser pesquisadas, entre elas a RVFAC (*Right Ventricular Fractional Area Change*). A RVFAC expressa o percentual de variação entre as áreas diastólica e sistólica finais do VD (ADFVD e ASFVD, respectivamente). As imagens são obtidas no corte de quatro-cavidades no eixo longitudinal e apenas duas imagens, a diastólica final e a sistólica final, são usadas. Para a determinação da RVFAC, ainda é necessário fazer o contorno da borda endocárdica, porém, como esse contorno é feito em apenas duas imagens, sua medida se torna muito mais rápida do que a da FEVD, que requer contorno em diversos cortes. O processo para o cálculo da RVFAC pode ser de 8 a 12 vezes mais rápido do que a determinação da FEVD[16]. A RVFAC, por ser uma medida bidimensional, engloba os componentes longitudinal e transversal da contração ventricular, incluindo a movimentação septal. Os estudos mostraram que ela tem boa correlação com a função ventricular direita medida pela RMC e ainda se mostrou ser um fator prognóstico em cardiopatias[29,33]. Essa ferramenta começou então a ser estudada em pacientes com HP.

O estudo já mencionado de Kind et al.[30] mostrou forte correlação deste índice com a FEVD (R^2 = 0,76, p < 0,001) e o estudo de Mauritz et al.[16] mostrou o valor prognóstico da RVFAC em pacientes com HP. A RVFAC parece ser melhor do que o TAPSE como índice da FEVD em pacientes com HP por incluir o movimento transversal enquanto que o

TAPSE avalia apenas o movimento longitudinal. No entanto, não se sabe qual o comportamento dessa medida em grupos com diferente comprometimento hemodinâmica e como ela se comporta nas diferentes etiologias de HP.

OBJETIVOS

2.1. Objetivo principal

Avaliar a performance da RVFAC de acordo com a gravidade do acometimento hemodinâmico em dois grupos distintos de pacientes portadores de hipertensão pulmonar pré-capilar: HAP e TEPCH.

2.2. Objetivo secundário

Comparar a performance da RVFAC com a do TAPSE como índices da FEVD.

MÉTODOS

3.1. População do estudo

A população estudada consistiu nos pacientes encaminhados para avaliar possível doença vascular pulmonar no Centro de Referência Francês para HP, o Hospital Antoine Béclère, em Clamart, na França, vinculado à Universidade de Paris XI. Todos os pacientes que eram avaliados pela primeira vez neste centro e que tinham indicação de cateterismo cardíaco direito foram entrevistados para realização de RMC. Pacientes que concordavam em participar do estudo realizavam então a ressonância cardíaca.

Os critérios de inclusão foram: idade maior que 18 anos, HP pré-capilar ao cateterismo cardíaco direito (caracterizada pela presença de PAPm ≥ 25 mmHg e pressão da artéria pulmonar ocluída ≤ 15 mmHg), RMC realizada em até 72 horas da realização do cateterismo cardíaco.

Os critérios de exclusão foram: gravidez, as contra-indicações para realização de ressonância cardíaca (claustrofobia conhecida, marcapasso ou desfibrilador implantável, clip de aneurisma cerebral, fragmento metálico ocular e implante coclear, obesidade mórbida), presença de hipertensão pulmonar associada a doenças pulmonares crônicas ou com componente multifatorial ou incerto.

3.2. Avaliação hemodinâmica

Todos os pacientes incluídos na análise final foram submetidos a cateterismo cardíaco direito. O cateterismo era realizado no laboratório de hemodinâmica do próprio centro por pneumologistas especialistas em HP. Os pacientes ficavam em posição supina e o cateter da artéria pulmonar era inserido através de punção venosa do membro superior direito ou da veia jugular interna direita. A medida da PAPo era realizada com o balão insuflado na artéria pulmonar após confirmação por radioscopia de que o cateter estava adequadamente posicionado. O débito cardíaco foi medido pelo método de termodiluição e a média de três medidas foi considerada. Eram registradas as pressões de átrio direito, ventrículo direito e da artéria pulmonar (PAP), assim como a freqüência cardíaca. Amostra de sangue venoso misto, ou seja, da artéria pulmonar, foi coletado em 57 pacientes. A RVP foi calculada: RVP=(PAPm–PAPo)/DC. O volume sistólico foi calculado de acordo com a fórmula: VS=DC/FC. A complacência vascular pulmonar foi calculada pela divisão do volume sistólico pela pressão de pulso (PAP sistólica – PAP diastólica).

3.3. Ressonância magnética cardíaca

Os exames foram realizados em equipamento de 1,5 Tesla de campo principal (Magnetom Avanto, Siemens Medical Solutions, Germany) com sincronização eletrocardiográfica e em pausa inspiratória. As imagens cardíacas foram adquiridas no eixo curto e no eixo longo do VE através da técnica de SSFP (*balanced steady-state free procession pulse sequence*). Uma seqüência de imagens em eixo curto foi adquirida da base ao ápice do VE com intervalos de aproximadamente 5 mm, totalizando em média 10 cortes para cobrir todo o VE. Para análise do VD, outra seqüência de imagens cortes de 6 mm de espessura, contíguos, ou seja, sem intervalos, foi adquirida em paralelo ao plano da valva tricúspide, da base ao ápice do VD. As imagens em quatro cavidades foram adquiridas no eixo longo que foi realizado perpendicularmente ao eixo curto. Imagens de cine-ressonância da artéria pulmonar foram também adquiridas.

3.4. Análise das imagens da ressonância cardíaca

Todas as imagens foram analisadas por um radiologista que desconhecia os resultados do cateterismo cardíaco e os diagnósticos dos pacientes.

A ASFVD e a ADFVD foram determinadas através do delineamento manual da borda endocárdica do VD nas imagens em quatro-cavidades (Figura 1). A RVFAC foi calculada: RVFAC= 100x(ADFVD-ASFVD)/ADFVD. A área diastólica final do VE (ADFVE) também foi determinada pelo delineamento manual da borda endocárdica nas imagens em quatro cavidades e a relação ADFVD/ADFVE determinada (Figura 2). A medida do TAPSE foi realizada também no corte de quatro-cavidades e a distância percorrida pelo anel da válvula tricúspide foi medida entre a sístole e a diástole máximas do VD (Figura 3). O diâmetro entre as paredes anterior e posterior (dA-P) e entre as paredes livre e septal (dL-S) do VE foram medidos nas imagens em eixo curto na sístole máxima e na diástole máxima do VE. O índice de excentricidade (IE) do VE foi calculado: IE=dA-P/dL-S (Figura 4).

Para o cálculo da fração de ejeção, as áreas sistólicas e diastólicas finais do VE e VD foram delineadas nas imagens em eixo curto, possibilitando a determinação dos volumes sistólico e diastólicos finais dos

mesmos. O software ARGUS (versão VA 50C, Siemens Medical Solucions, Erlangen, Germany) foi utilizado para cálculo das frações de ejeção ventricular.

O diâmetro do tronco da artéria pulmonar foi medido e as áreas máximas e mínimas da artéria pulmonar (AmaxAP e AminAP, respectivamente) foram determinadas para o cálculo da pulsatilidade da artéria pulmonar (Pulsat AP=100 x (AmaxAP – AminAP) / AminAP).

Figura 1. Áreas diastólica e sistólica finais do ventrículo direito.

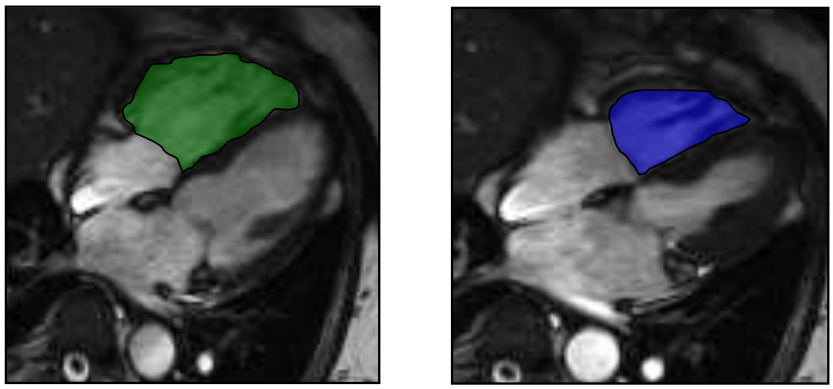


Imagem em corte de quatro cavidades: à esquerda, a área diastólica final (em verde) na diástole máxima e à direita, a área sistólica final (em azul) na sístole máxima do VD.

Figura 2. Áreas diastólica finais dos ventrículos direito e esquerdo.

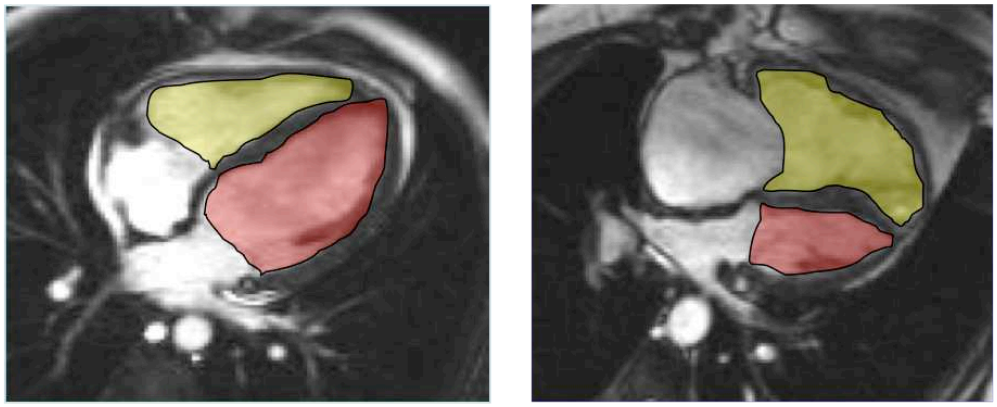


Imagem em corte de quatro cavidades mostrando as áreas diastólica final do VD (em amarelo) e diastólica final do VE (em vermelho). À esquerda: ADFVD/ADFVE = 0,59 em paciente sem HP (PAPm = 10 mmHg). À direita: ADFVD/ADFVE = 2,28 em paciente com HP (PAPm = 51 mmHg).

Figura 3. TAPSE.

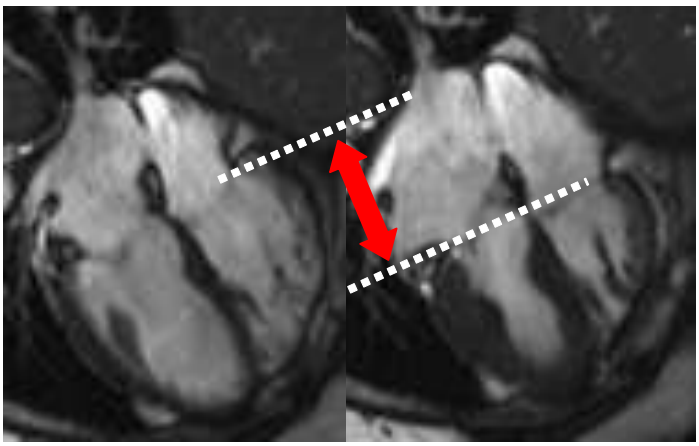


Imagem em corte de quatro cavidades: à esquerda na diástole máxima e à direita na sístole máxima do VD. A seta em vermelho indica a distância percorrida pelo anel da válvula tricúspide da base em direção ao ápice cardíaco.

Figura 4. Índice de excentricidade do ventrículo esquerdo.

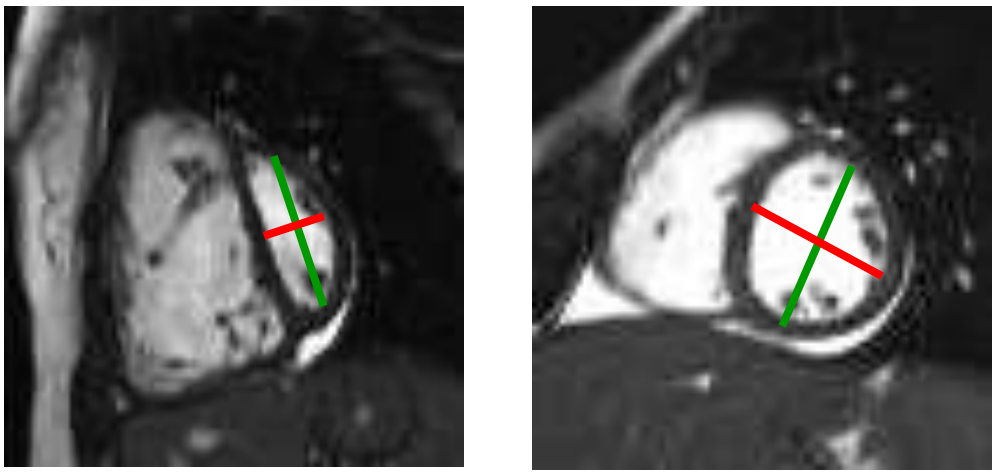


Imagem no corte em eixo curto na diástole máxima do VE. Em verde o diâmetro entre as paredes anterior e posterior (dA-P) e em vermelho o diâmetro entre as paredes septal e livre (dL-S) do VE. À esquerda paciente com HP (índice de excentricidade = 2,4 e PAPm = 53 mmHg) e a à direita paciente sem HP (índice de excentricidade = 0,9 e PAPm = 10 mmHg).

3.5. Análise estatística

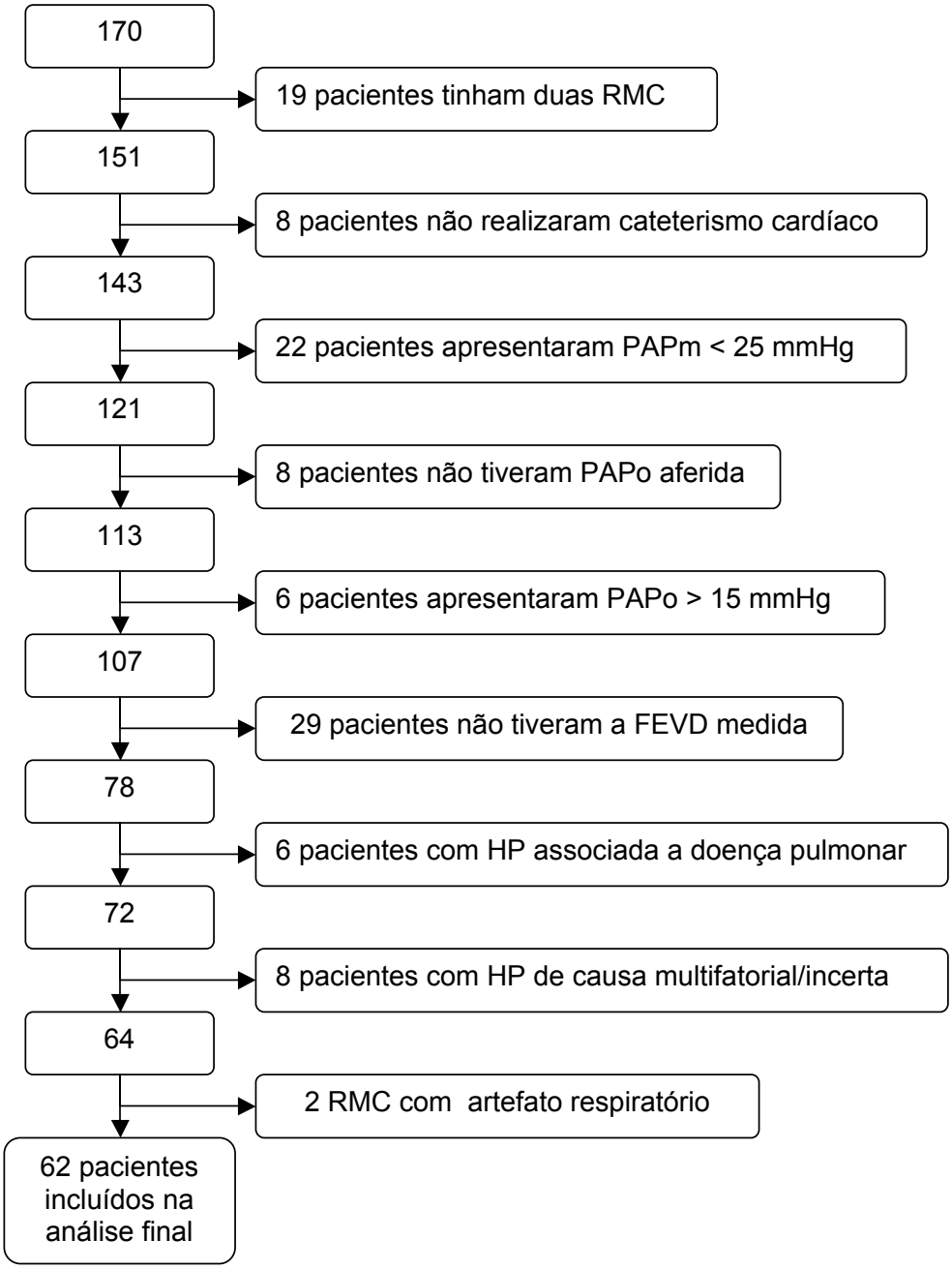
Os valores estão apresentados em média ± desvio padrão. Para comparação entre as médias utilizamos o Teste T de Student. As correlações foram testadas através de regressão linear, usando o método de média dos mínimos quadrados. Curvas ROC (*Receiver Operating Characteristic*) foram construídas para testar a capacidade da RVFAC e do TAPSE em detectar FEVD < 35%. O valor de $p < 0,05$ foi considerado estatisticamente significante. Para comparação das variáveis categóricas utilizou-se o teste do Chi-quadrado ou o teste exato de Fisher, conforme apropriado. As análises estatísticas foram realizadas no Software Medcalc®, versão 12.2.1.0 (Mariakerke, Belgium).

RESULTADOS

4.1. População do estudo

No período de Maio de 2009 a Fevereiro de 2011, 170 pacientes realizaram RMC. Foram incluídos para análise 62 pacientes com diagnóstico final de HAP e TEPCH (Figura 5).

Figura 5 – Fluxograma da seleção da população incluída para análise.



RMC: ressonância magnética cardíaca, PAPm: pressão da artéria pulmonar média, PAPo: pressão da artéria pulmonar ocluída, HP: hipertensão pulmonar, FEVD: fração de ejeção do ventrículo direito.

4.2. Dados clínicos e hemodinâmicos

As características clínicas e hemodinâmicas da população estão expostas nas tabelas 1 e 2 respectivamente. Quando dividimos a população conforme a classificação diagnóstica, obtivemos 23 pacientes no grupo 1 (HAP) e 39 no grupo 4 (TEPCH).

A população apresentava em média 58 anos, com maioria do sexo feminino e em classe funcional III pela NYHA (*New York Heart Association*). No grupo de HAP, o principal diagnóstico foi HAP idiopática com 12 casos. Os demais diagnósticos foram HAP associadas: à doença veno-oclusiva (2 pacientes), ao uso de anorexígenos (1 paciente), à doença do tecido conectivo (2 pacientes), à comunicação interatrial (3 pacientes), à hipertensão portal (2 pacientes) e à anemia falciforme (1 paciente).

Quando comparamos os grupos HAP e TEPCH encontramos apenas diferença significativa na idade e peso. Em relação aos pacientes com HAP, os pacientes com TEPCH eram mais velhos e tinham peso discretamente maior, conseqüentemente um índice de massa corpórea também maior.

Tabela 1. Características clínicas da população.

	População total n = 62	HAP n = 23	TEPCH n = 39	P valor
Idade, anos	58,3 ± 17,2	47,5 ± 17,6	64,6 ± 13,5	< 0,001
SC, m^2	1,75 ± 0,21	1,69 ± 0,19	1,79 ± 0,21	0,062
Peso, Kg	67,9 ± 14,6	62,7 ± 13,9	71,0 ± 14,3	0,029
Altura, cm	166,5 ± 9,1	166,1 ± 8,2	166,9 ± 9,7	0,735
IMC	24,3 ± 4,2	22,7 ± 4,6	25,3 ± 3,7	0,015
Sexo	34 F / 28 M	13 F / 10 M	21 F / 18 M	0,30
Classe funcional I e II / III e IV	11 / 51	6 / 17	5 / 34	1,0
TC6M, m (n=59)	379,4 ± 113,4	365,8 ± 114,3	387,5 ± 113,6	0,48
SvO_2 , % (n=57)	62,0 ± 8,9	63,6 ± 9,6	61,2 ± 8,6	0,336
Hb, mg/dL	14,6 ± 1,7	14,4 ± 1,7	14,8 ± 1,7	0,352

SC: superfície corpórea; IMC: índice de massa corpórea; TC6M: teste de caminhada de seis minutos; SvO_2: saturação venosa mista; Hb: hemoglobina.

Em relação às medidas hemodinâmicas houve diferença significativa entre os dois grupos diagnósticos. A pressão de pulso da artéria pulmonar foi maior e conseqüentemente a complacência vascular pulmonar foi menor no grupo TEPCH quando comparado com o grupo HAP (Tabela 2).

Tabela 2. Características hemodinâmicas da população.

	População Total n = 62	HAP n = 23	TEPCH n = 39	P valor
FC, bpm	80,8 ± 12,6	83,7 ± 14,4	79,2 ± 11,3	0,191
PAD, mmHg	6,39 ± 4,6	6,17 ± 4,14	6,52 ± 4,91	0,775
PAPm, mmHg	46,7 ± 12,3	47,6 ± 15,3	46,2 ± 10,3	0,683
PAPo, mmHg	7,4 ± 3,1	7,1 ± 2,9	7,6 ± 3,2	0,565
DC, L/min	4,76 ± 1,48	4,89 ± 1,79	4,67 ± 1,22	0,575
IC, L/min/m^2	2,70 ± 0,74	2,89 ± 0,95	2,59 ± 0,58	0,132
RVP, UW	9,2 ± 4,2	9,3 ± 4,6	9,1 ± 4,0	0,832
VS, mL	60,4 ± 19,9	60,1 ± 20,9	60,5 ± 19,5	0,939
PP, mmHg	52,2 ± 15,1	44,8 ± 12,7	56,6 ± 14,8	0,002
CVP, ml/mmHg	1,29 ± 0,63	1,56 ± 0,75	1,16 ± 0,51	0,016

FC: freqüência cardíaca; PAD: pressão de átrio direito; PAPm: pressão da artéria pulmonar média; PAPo: pressão da artéria pulmonar ocluída; DC: débito cardíaco; IC: índice cardíaco; RVP: resistência vascular pulmonar; VS: volume sistólico; PP: pressão de pulso; CVP: complacência vascular pulmonar.

4.3. Dados da ressonância cardíaca

Em relação às medidas realizadas pela RMC, houve diferença apenas na área diastólica final do VD; o grupo HAP apresentou VD mais dilatado do que o grupo de TEP crônico (Tabela 3).

A freqüência cardíaca medida durante a realização do cateterismo cardíaco direito e durante a RMC não apresentou variação significativa. (80,7 ± 12,7 e 81,5 ± 13,6 respectivamente, p = 0,722).

Tabela 3. Dados da ressonância magnética cardíaca.

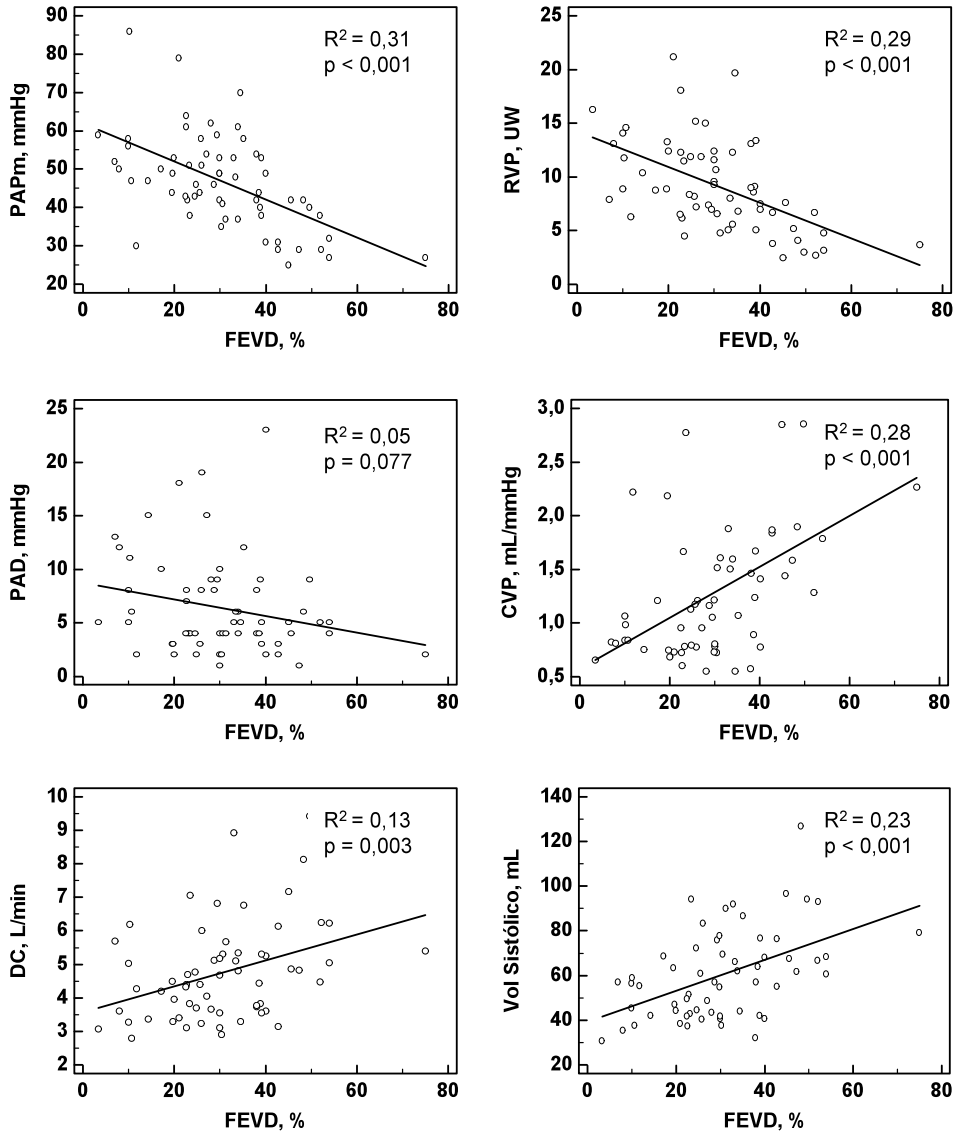
	População total n = 62	HAP n = 23	TEPCH n = 39	P valor
FEVE, %	61,6 ± 13,3	57,9 ± 16,9	63,6 ± 10,5	0,110
Tronco AP, mm	33,8 ± 4,8	34,6 ± 5,3	33,4 ± 4,5	0,375
Pulsat AP, %	17,5 ± 12,8	17,9 ± 12,8	17,3 ± 12,9	0,875
FEVD, %	30,6 ± 13,8	30,6 ± 15,5	30,6 ± 12,9	0,991
VDFVDi, mL/m^2	109,8 ± 37,1	116,4 ± 38,7	105,9 ± 36,0	0,282
VSFVDi, mL/m^2	78,7 ± 35,9	83,6 ± 39,8	75,8 ± 33,8	0,414
VSVDi, mL/m^2	31,1 ± 14,4	32,8 ± 16,0	30,1 ± 13,4	0,466
ADFVDi, cm^2/m^2	18,8 ± 4,6	20,5 ± 5,1	17,8 ± 4,1	0,026
ASFVDi, cm^2/m^2	14,2 ± 4,8	15,4 ± 5,5	13,5 ± 4,2	0,133
ASFVEi, cm^2/m^2	15,0 ± 3,3	15,3 ± 3,4	14,9 ± 3,2	0,642
TAPSE, mm	13,7 ± 4,6	14,4 ± 5,2	13,2 ± 4,3	0,359
RVFAC, %	25,7 ± 11,4	26,3 ± 12,8	25,3 ± 10,7	0,749

FEVE: fração de ejeção do ventrículo esquerdo; Tronco AP: tronco da artéria pulmonar; Pulsat AP: pulsatilidade da artéria pulmonar; FEVD: fração de ejeção do ventrículo direito; VDFVDi: volume diastólico final indexado do ventrículo direito; VSFVDi: volume sistólico final indexado do ventrículo direito; VSVDi: volume sistólico indexado do ventrículo direito; ADFVDi: área diastólica final indexada do ventrículo direito; ASFVDi: área sistólica final indexada do ventrículo direito; ADFVEi: área diastólica final do ventrículo esquerdo; TAPSE: *Tricuspid Annular Plane Systolic Excursio*n; RVFAC: *Right Ventricular Fractional Area Change*.

4.4. Correlações da FEVD com as variáveis hemodinâmicas

A FEVD apresentou correlação fraca tanto com as medidas hemodinâmicas que refletem o aumento da pós-carga do VD (PAPm, RVP, pressão de átrio direito e complacência vascular pulmonar) como com as medidas de função do VD (DC e volume sistólico) (Figura 6).

Figura 6. Correlações da FEVD com as variáveis hemodinâmicas.

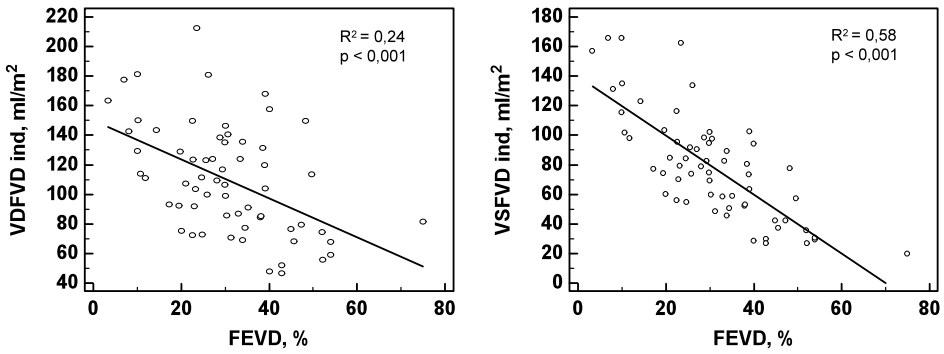


PAPm: pressão da artéria pulmonar média; RVP: resitência vascular pulmonar; PAD: pressão de átrio direito; CVP: complacência vascular pulmonar; DC: débito cardíaco; Vol Sistólico: volume sistólico; FEVD: fração de ejeção do ventrículo direito.

4.5. Correlações da FEVD com os volume do ventrículo direito

A FEVD apresentou correlação mais forte com a medida do volume sistólico final do que com a medida do volume diastólico final do VD (Figura 7).

Figura 7. Correlações da FEVD com os volumes do ventrículo direito.

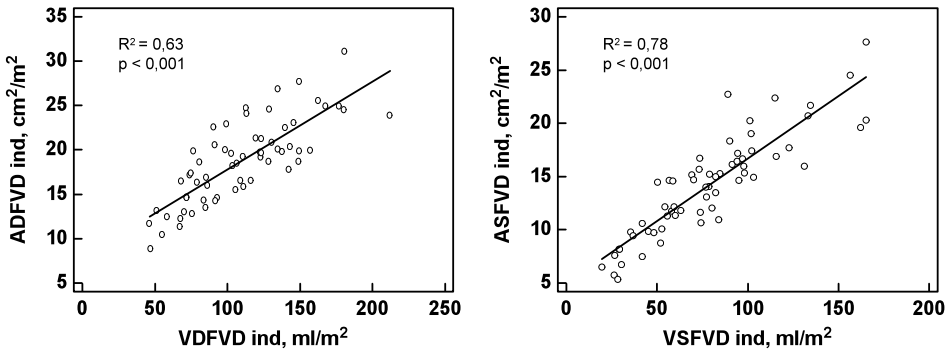


VDFVD ind: volume diastólico final indexado do ventrículo direito; VSFVD ind: volume sistólico indexado final do ventrículo direito; FEVD: fração de ejeção do ventrículo direito.

4.6. Correlações entre as áreas e os volumes do ventrículo direito

Apesar das medidas das áreas diastólica e sistólica finais serem medidas bidimensionais, elas apresentaram uma forte correlação com as medidas dos volumes diastólico e sistólico finais do VD (Figura 8).

Figura 8. Correlações entre as áreas e os volumes do ventrículo direito.

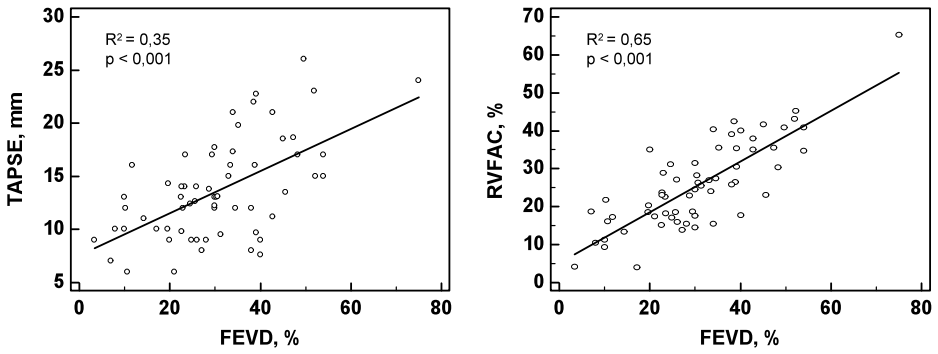


ADFVD ind: área diastólica final indexada do ventrículo direito; VDFVD ind: volume diastólico final indexado do ventrículo direito; ASFVD ind: área sistólica final indexada do ventrículo direito; VSFVD ind: volume sistólico final indexado do ventrículo direito.

4.7. Correlações entre FEVD , RVFAC e TAPSE

Quando analisamos a população total, a FEVD apresentou associação mais forte com a RVFAC (R^2 = 0,65, p < 0,001) do que com o TAPSE (R^2 = 0,35, p < 0,001) (Figura 9).

Figura 9. Correlações entre FEVD, RVFAC e TAPSE.



TAPSE: *Tricuspid Annular Plane Systolic Excursion*; RVFAC: *Right Ventricular Fractional Area Change*; FEVD: fração de ejeção do ventrículo direito.

4.8. Dados da ressonância cardíaca nos grupos com menor e maior gravidade hemodinâmica

Para avaliar o comportamento da função ventricular direita em relação à gravidade hemodinâmica, dividimos a população pela mediana da resistência vascular pulmonar (8,5 UW) (Tabela 4).

Tabela 4. Comparação dos dados da ressonância magnética cardíaca entre o grupo com menor e maior gravidade hemodinâmica.

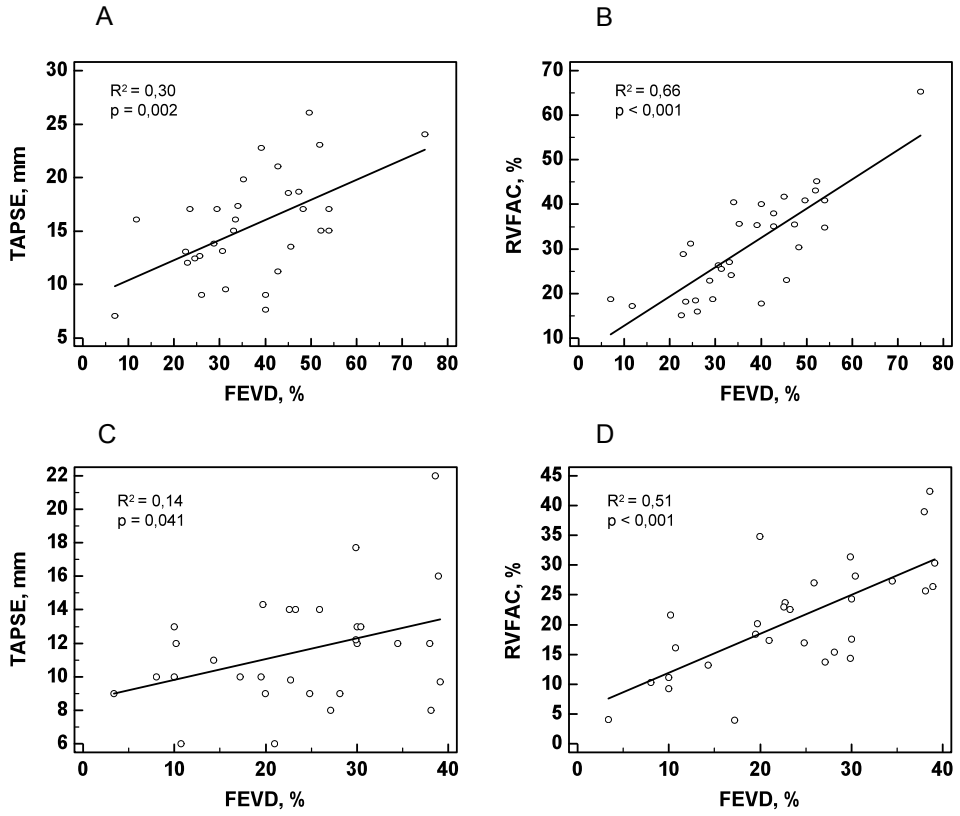
	População total	RVP < 8,5 n = 21	RVP > 8,5 n = 25	P valor
FEVE, %	61,6 ± 13,3	64,1 ± 11,7	58,9 ± 14,5	0,131
Tronco da AP, mm	33,8 ± 4,8	33,6 ± 5,0	34,1 ± 4,6	0,734
Pulsat AP, %	17,5 ± 12,8	24,2 ± 12,2	10,9 ± 9,5	< 0,001
FEVD, %	30,6 ± 13,8	37,0 ± 13,9	24,2 ± 10,2	< 0,001
VDFVDi, mL/m^2	109,8 ± 37,1	103,7 ± 43,0	115,8 ± 29,9	0,205
VSFVDi, mL/m^2	78,7 ± 35,9	68,6 ± 39,1	88,7 ± 29,8	0,414
VSVDi, mL/m^2	31,1 ± 14,4	35,2 ± 14,4	20,8 ± 9,3	0,001
TAPSE, mm	13,7 ± 4,6	15,5 ± 4,8	11,8 ± 3,7	0,001
RVFAC, %	25,7 ± 11,4	30,6 ± 11,3	20,8 ± 9,3	< 0,001

FEVE: fração de ejeção do ventrículo esquerdo; Tronco AP: tronco da artéria pulmonar; Pulsat AP: pulsatilidade da artéria pulmonar; FEVD: fração de ejeção do ventrículo direito; VDFVDi: volume diastólico final indexado do ventrículo direito; VSFVDi: volume sistólico final indexado do ventrículo direito; VSVDi: volume sistólico indexado do ventrículo direito; TAPSE: *Tricuspid Annular Plane Systolic Excursion*; RVFAC: *Right Ventricular Fractional Area Change*.

4.9. Correlações entre a FEVD, RVFAC e TAPSE nos grupos com menor e maior gravidade hemodinâmica

A RVFAC se relaciona melhor com a FEVD do que o TAPSE nos dois grupos (menor e maior gravidade hemodinâmica). No grupo com maior gravidade hemodinâmica essa diferença se acentuou, a RVFAC mostrou correlação mais de três vezes maior com a FEVD do que o TAPSE (Figura 10).

Figura 10. Correlações entre FEVD, TAPSE e RVFAC nos grupos com menor e maior gravidade hemodinâmica.



A e B: grupo com menor gravidade hemodinâmica (RVP < 8,5 UW); C e D: grupo com maior gravidade hemodinâmica (RVP > 8,5 UW). RVP: resistência vascular pulmonar, TAPSE: *Tricuspid Annular Plane Systolic excursion*; RVFAC: *Right Ventricular Fractional Area Change*; FEVD: fração de ejeção do ventrículo direito.

4.10. Medidas de interdependênca ventricular nos grupos com menor e maior gravidade hemodinâmica

Em um subgrupo de 46 pacientes, medidas de interdependência ventricular foram analisadas. A relação entre as áreas diastólica finais do VD e VE (ADFVD/ADFVE) esteve significativamente aumentada no grupo com maior gravidade hemodinâmica. Os índices de excentricidade do VE na sístole e na diástole foram significativamente maiores também no grupo com maior gravidade hemodinâmica (Tabela 5).

Tabela 5. Medidas de interdependência ventricular nos grupos com maior e menor gravidade hemodinâmica.

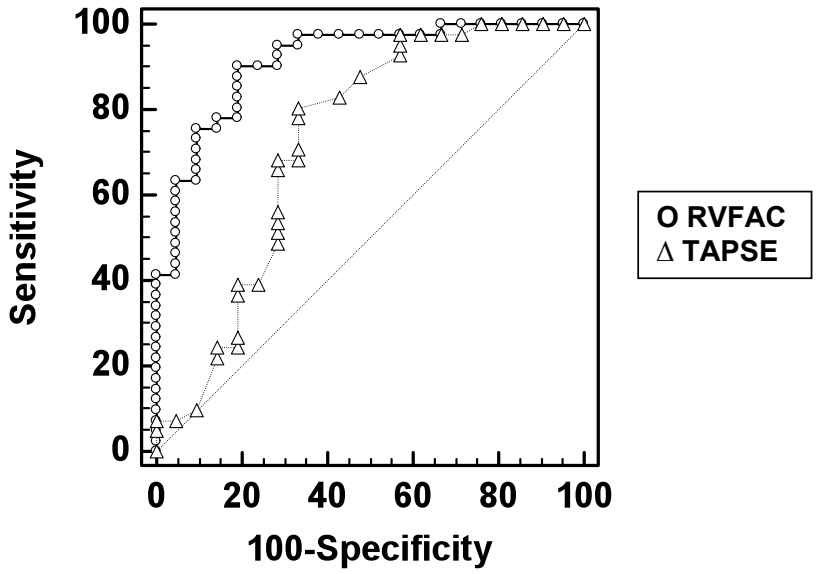
	n = 46	**RVP < 8,5 n = 21**	**RVP > 8,5 n = 25**	**P valor**
ADFVD, mm^2	32,2 ± 7,2	31,1 ± 7,4	33,1 ± 7,1	0,352
ADFVE, mm^2	25,5 ± 5,9	29,1 ± 4,8	22,5 ± 5,1	0,001
ADFVD/ADFVE	1,32 ± 0,41	1,09 ± 0,32	1,52 ± 0,38	0,001
IE diástole	1,37 ± 0,25	1,23 ± 0,14	1,49 ± 0,26	< 0,001
IE sístole	1,39 ± 0,33	1,23 ± 0,19	1,54 ± 0,36	0,001

ADFVD: área diastólica final do ventrículo direito; ADFVE: área diastólica final do ventrículo esquerdo; IE: índice de excentricidade do VE.

4.11. Comparação entre as curvas ROC para a capacidade da RVFAC e do TAPSE em diagnosticar disfunção grave de ventrículo direito

A comparação entre a capacidade desses dois índices em prever disfunção grave de VD (FEVD < 35%) através da comparação de curvas ROC mostrou que a RVFAC tem melhor performance. (TAPSE: AUC 0,73 e RVFAC: AUC 0,93, p = 0,0065) (Figura 11).

Figura 11. Comparação das curvas ROC para a capacidade da RVFAC e do TAPSE em diagnosticar disfunção grave do VD.



TAPSE: *Tricuspid Annular Plane systolic excursion*; RVFAC: *Right Ventricular Fractional Area Change*; FEVD: fração de ejeção do ventrículo direito.

4.12. Correlações entre FEVD, RVFAC e TAPSE em HAP e TEPCH

Analisamos as relações do TAPSE e RVFAC com a FEVD em cada um dos grupos diagnósticos (HAP e TEP crônico) separadamente.

No grupo com HAP, a correlação da FEVD com a RVFAC (R^2 = 0,80, p < 0,001) também foi melhores do que com o TAPSE (R^2 = 0,37, p=0,002) e no grupo com TEP crônico, os resultados se mantiveram semelhantes (TAPSE R^2 = 0,34 e RVFAC R^2 = 0,54, com p<0,001 para as duas medidas).

DISCUSSÃO

Nosso estudo mostrou que a RVFAC é um bom índice para estimar a FEVD em pacientes com HP. Nos pacientes com maior gravidade hemodinâmica, a RVFAC se correlacionou ainda melhor com a FEVD do que o TAPSE e esse achado parece ser relacionado à inclusão do componente transversal da contração ventricular na sua medida. A performance da RVFAC foi similar nos dois grupos de HP estudados: HAP e TEPCH.

Com o objetivo de entender melhor as determinantes da FEVD, analisamos as correlações da FEVD com as diferentes variáveis hemodinâmicas. Observamos que a FEVD apresentou associação apenas fraca, tanto com as determinantes de pós-carga (PAPm, RVP, pressão de átrio direito e complacência vascular pulmonar) como com as medidas de função (volume sistólico e débito cardíaco) do VD. Outro dado interessante foi que a FEVD apresentou associação mais forte com o volume sistólico final que com o volume diastólico final do VD. Esses achados mostram que não é apenas a sobrecarga do VD que determina a FEVD; o componente de contração miocárdica tem também papel importante na sua determinação[34]. Em outro estudo preliminar, nosso grupo havia mostrado que esses índices clássicos da pós-carga ventricular direita explicavam menos de 40% da variabilidade da FEVD[35]. Desta forma, a FEVD reflete além da sobrecarga ventricular, a forma como o VD responde à sobrecarga imposta pela HP, ou seja, a forma como ele remodela.

Dada a importância do componente miocárdico na determinação da FEVD, a melhor compreensão do remodelamento ventricular se faz necessária[36]. Além do estímulo pela sobrecarga volumétrica e de pressão, substâncias como a noradrenalina, a endotelina e a angiotensina (que estão envolvidas na fisiopatologia da HP) estimulam a hipertrofia miocárdica e interferem na apoptose celular. Na hipertrofia, os miócitos apresentam alterações no aparato de contração ventricular (mudança no padrão das proteínas contráteis), na eficiência energética (redução na síntese de adenosina e na absorção de glicose) e aumento do colágeno extracelular[37]. Existe assim, um comprometimento miocárdico independente do comprometimento vascular na HP. O fato de a FEVD incluir esse comprometimento miocárdico na sua determinação corrobora com o achado dela ser um fator prognóstico na HP independente do comprometimento hemodinâmico[38]. Os achados do nosso estudo reforçam o papel do comprometimento miocárdico na determinação da FEVD e reforçam o achado da FEVD como fator independente do acometimento hemodinâmico, como demonstrado por van de Veerdonk M et al.[15]. O reconhecimento do comprometimento miocárdico se torna importante na HP para que novas modalidades terapêuticas sejam testadas, já que os tratamentos específicos para HP visam apenas a ação nos vasos pulmonares[39]. Estudos com beta-bloqueadores, espirinolactona e inibidores da enzima conversora de angiotensina vêm sendo realizados em pacientes com HP[40-43] e talvez o tratamento direcionado ao acometimento cardíaco possa trazer novas perspectivas, já que o remodelamento miocárdico pode ser reversível com o

tratamento. Reesink et al.[44] mostraram que os pacientes com TEPCH apresentam redução significativa da massa muscular do VD e do abaulamento septal após tromboendarterectomia.

A necessidade de um índice para se estimar a FEVD existe porque o seu cálculo é trabalhoso e demorado devido à complexidade anatômica do VD[45]. O TAPSE e a RVFAC são índices classicamente usados na ecocardiografia para estimar a função ventricular direita[33]. Em indivíduos livres de sobrecarga do VD, o TAPSE apresenta boa correlação com a FEVD o que se justifica pelos achados que o principal componente da contração ventricular direita é o encurtamento longitudinal[46]. Em pacientes com HP, o aumento da pós-carga leva à dilatação importante do VD e estudos têm mostrado que o componente transversal ganha importância nesses casos e que a RVFAC seria um melhor índice da FEVD nesses pacientes[16,33]. Nosso estudo confirma os achados da Mauritz et al.[16] e Kind et al.[30] ao mostrar uma melhor correlação da RVFAC com a FEVD e uma melhor capacidade da mesma em diagnosticar disfunção grave do VD do que o TAPSE, potencialmente por englobar o componente transversal que se torna mais importante na medida em que a disfunção de VD progride.

Para demonstrar isso, optamos por avaliar esses dois índices em grupos com diferente gravidade hemodinâmica. Dividimos a população do estudo pela mediana da RVP. O grupo com RVP > 8,5 UW apresentou FEVD, pulsatilidade da artéria pulmonar e volume sistólico significativamente

menores do que o grupo com RVP < 8,5 UW. Esses índices são marcadores já estabelecidos de gravidade da HP, confirmando que o grupo com RVP > 8,5 UW engloba os pacientes mais graves[47-49]. No grupo com maior gravidade hemodinâmica, a associação da RVFAC com a FEVD foi três vezes mais forte do que a associação do TAPSE com a FEVD, enquanto no grupo com menor gravidade hemodinâmica essa diferença foi apenas duas vezes mais forte. Esse achado mostra que em pacientes com maior sobrecarga do VD a avaliação da função ventricular direita apenas pelo encurtamento longitudinal é insuficiente. Reforçando que o movimento transversal ganha importância quando existe aumento da sobrecarga ventricular direita. A RVFAC parece ser melhor do que o TAPSE porque ela é uma medida bidimensional enquanto o TAPSE é apenas uma medida unidimensional. A RVFAC engloba tanto o componente longitudinal quanto transversal da contração ventricular e o TAPSE reflete apenas o encurtamento longitudinal.

Um achado interessante do nosso estudo foi a forte correlação das medidas de área com as medidas de volume, apesar da medida de área ser bidimensional apenas e a medida volumétrica ser tridimensional. Esses achados justificam o fato da RVFAC apresentar boa correlação com a FEVD.

A RVFAC medida pela RMC mostrou que é um índice melhor do o TAPSE para estimar disfunção grave do VD. A comparação das curvas ROC para diagnóstico de FEVD menor do que 35% mostrou performance

bastante superior da RVFAC em relação ao TAPSE (TAPSE: AUC 0,73 e RVFAC: AUC 0,93, p = 0,0065). Esse achado foi semelhante aos achados dos estudos de Mauritz et al.[16] e Kind et al.[30], reforçando que em pacientes com HP a RVFAC é melhor índice da função ventricular direita do que o TAPSE quando medida pela RMC.

O nosso estudo acrescentou uma nova informação ao avaliar esses índices nos dois grupos de HP (HAP e TEP crônico) separadamente. Quando comparamos as relações de RVFAC e TAPSE com a FEVD nos dois grupos observamos que as relações se mantêm semelhantes às relações encontradas na população total do estudo. Esse dado mostra que a RVFAC é um melhor índice do que o TAPSE independente da causa da HP. A análise preliminar do nosso estudo, com 23 pacientes em cada grupo diagnóstico, já havia demonstrado não havia diferença significativa nos dados da RMC entre esses dois grupos de HP[50]. Nosso resultado final só reforça que não há diferença nos dados de RMC entre os grupos de HAP e TEPCH.

Por considerar o componente transversal, a RVFAC inclui o movimento septal, que tem importância fundamental na avaliação da função ventricular direita. Mauritz et al.[16] mostraram que os pacientes com sobrevida menor do que cinco anos evoluíam, no primeiro ano de seguimento, com importante redução no movimento transversal. O interessante foi que ao analisar os componentes do movimento transversal,

a movimentação da parede livre não apresentou diferença significativa. A redução no encurtamento transversal se dava pela redução da movimentação do septo em direção a parede livre do VD, ou seja, o abaulamento do septo em direção ao VE. O septo parece ser a região cardíaca que está sujeita a maior estresse mecânico quando ocorre aumento da pós-carga. Estudos mostraram que os pontos de inserção do VD no septo e a parede septal são os pontos em que existem sinais de fibrose miocárdica nos pacientes com HP, por apresentaram realce tardio na RMC[51,52]. Nessas regiões também foram descritas áreas de fibrose em estudos anatomopatológicos[53] e, em estudos experimentais, estas são as áreas que são submetidas a estresse máximo numa contração ventricular normal e também são estas áreas as primeiras a produzir peptídeo natriurético do tipo A em modelos de HP[10]. Estudos experimentais em cães já haviam demonstrado a interferência do abaulamento septal na função ventricular[54]. Dong et al.[55] estudaram o gradiente transseptal (diferença entre a pressão do VE e a pressão do VD) e o diâmetro entre o septo e a parede livre do VE pela monitorização com ecocardiografia, em cães submetidos a garroteamento da artéria pulmonar. Eles mostraram que conforme o gradiente transseptal diminuía, o diâmetro do VE reduzia linearmente, mostrando que existia relação direta entre o gradiente transseptal e posição do septo. Esse estudo avaliou ainda a orientação da contração septal usando cristais microtransdutores ultrassônicos e mostrou que o abaulamento septal estava associado ao comprometimento da contração do mesmo. A mudança na posição do septo e conseqüente mudança na

orientação das fibras miocárdicas septais parece comprometer a contração septal. Outros estudos realizados também em cães compararam a pressão gerada pelo VD antes e após a inativação do septo (por eletrocoagulação septal[56] ou ligadura da artéria septal[57]). A inativação septal levou à redução significativa na pressão gerada pelo VD[56]. O volume sistólico do VD permanecia inalterado apesar da inativação do septo em condições normais de pós-carga do VD, mas em condições de aumento do volume do VD o volume sistólico apresentou redução significativa[57]. Estes achados sugerem que o VD consegue manter sua função apesar da inativação do septo se não existe sobrecarga do VD, mas em situações de sobrecarga a contração septal se torna fundamental para a função ventricular direita.

O comprometimento da função septal associado ao seu abaulamento pode ser um dos motivos pelo qual o encurtamento no eixo longitudinal se torna proporcionalmente menos importante em pacientes com sobrecarga ventricular direita. A orientação anatômica principal das fibras miocárdicas do VD é transversal, assim como a contração da parede livre do VD tem também como principal componente a contração no sentido transversal. Porém, ao analisar a contração global do VD, a resultante final é o encurtamento no eixo longitudinal. O encurtamento no eixo longitudinal está associado à presença de feixes de fibra miocárdicas, que tem orientação longitudinal no infundíbulo do VD, e também à contração septal. O septo tem sua contração principalmente em espiral como o VE com a resultante de

contração no sentido longitudinal[6]. O abaulamento septal e sua conseqüente disfunção comprometeriam a contração ventricular direita[58].

Em pacientes com HP, estudos mostraram que esses pacientes apresentam abaulamento septal levando a redução significativa das medidas do diâmetro entre parede septal e a parede livre do VE[59-61]. Nosso grupo já havia demonstrado que a medida o ângulo entre a parede septal e a parede livre do VE, que reflete o abaulamento septal, apresentava correlação significativa com a PAPm e RVP[62]. Quanto maior a PAPm e a RVP menor o angulo, ou seja, maior a compressão do VE. Nós demonstramos também, que a RVP esteve mais fortemente associada à redução da área diastólica final do VE do que ao aumento da área diastólica final do VD. Nesse estudo mostramos ainda a forte correlação da relação ADFVD/ADFVE com a RVP[63]. Quanto maior era a RVP maior a relação ADFVD/ADFVE, refletindo mais uma vez a dilatação do VD e compressão do VE. Marcus et al.[63] mostraram também que o abaulamento septal está relacionado à redução significativa do volume diastólico do VE e à disfunção diastólica do mesmo.

Nosso estudo, portanto, reforça o papel do comprometimento septal para a avaliação do VD. As medidas que refletem interação interventricular foram comparadas entre o grupo com maior e menor gravidade hemodinâmica. No grupo com maior gravidade hemodinâmica, a relação entre as áreas diastólicas finais do VD e VE foi maior, refletindo dilatação do VD e compressão do VE. Os dados mostram ainda que essa relação

aumentou às custas da compressão do VE, já que não houve diferença significativa entre os grupos com relação à área diastólica final do VD e tendo sido a área diastólica final do VE significativamente menor no grupo com maior gravidade hemodinâmica. A análise das medidas do VE com o índice de excentricidade do VE confirma esse achado. O índice de excentricidade esteve significativamente aumentado no grupo com maior gravidade. Isso significa que no grupo com maior gravidade o septo esteve mais deslocado, comprimindo o VE.

Nosso estudo apresenta limitações que precisam ser mencionadas. O estudo foi conduzido em centro único, o que pode trazer um viés de seleção da população estudada. Porém o Hospital Antoine Béclère é o centro nacional francês de referência para o tratamento de HP, assim sendo, este centro recebe pacientes de todas as regiões da França, tornando a população bastante representativa dessa doença neste país. O cateterismo cardíaco direito e a ressonância magnética cardíaca não foram realizados ao mesmo tempo por questões técnicas. Entretanto, os dois exames foram realizados no máximo com três dias de diferença e sem mudanças no tratamento nesse período. Nós mostramos que a freqüência cardiaca medida durante a realização do cateterismo não apresentou diferença significativa em relação à freqüência cardíaca medida durante a realização da RMC, reforçando que os pacientes estavam em condições basais semelhantes durante a realização dos dois exames. Outra limitação é que incluímos apenas pacientes com HAP e TEP crônico, excluindo da análise

uma proporção significativa de pacientes com HP associada a outras condições, não sendo possível, portanto, extrapolar nossos achados para todos os pacientes com HP. Uma limitação importante do estudo é que não foi medida a massa ventricular direita. A medida da massa miocárdica depende do contorno das bordas endocárdica e epicárdica do ventrículo. Como VD tem a parede fina e muito trabeculada este processo se torna complexo e demorado e por isso optamos por não mensurá-la.

Apesar das limitações, acreditamos que estudamos uma população homogênea e representativa de pacientes com HP. Mostramos que a RVFAC é um bom índice de avaliação da função ventricular direita e que ela teve melhor capacidade para estimar a disfunção grave do VD do que o TAPSE medido pela RMC. Conseguimos demonstrar ainda que está medida tem melhor capacidade para avaliar a função ventricular em pacientes com maior gravidade hemodinâmica e que pode ser utilizada para pacientes com HAP e TEP crônico.

CONCLUSÃO

A RVFAC se correlacionou melhor com a FEVD do que o TAPSE tanto no grupo com menor como no grupo com maior gravidade hemodinâmica, porém de forma ainda mais significativa em pacientes com maior gravidade hemodinâmica, não havendo diferenças na performance da RVFAC entre os pacientes com HAP e TEPCH.

A RVFAC se correlacionou melhor com a FEVD do que o TAPSE na população total do estudo. De forma análoga, a capacidade da RVFAC para diagnosticar disfunção grave do VD (FEVD < 35%) também foi maior que a do TAPSE. A RVFAC foi um melhor índice da FEVD talvez por incluir o movimento transversal da contração ventricular.

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Apport de l'IRM dans l'hypertension artérielle pulmonaire précapillaire

Contribution of MRI to precapillary pulmonary arterial hypertension

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Le diagnostic d'hypertension artérielle pulmonaire (HTAP) précapillaire repose sur le cathétérisme cardiaque droit montrant une pression artérielle pulmonaire moyenne de repos ≥ 25 mmHg, associée à une pression artérielle occluse ≤ 15 mmHg. Dans l'HTAP, la postcharge du ventricule droit est chroniquement augmentée, ce qui entraîne une dilatation et une hypertrophie des cavités droites. Cela conduit à une défaillance ventriculaire droite progressive, responsable des signes fonctionnels d'effort et principale cause de mortalité chez les patients qui en sont atteints *(1, 2)*. La valeur pronostique de la fonction droite dans l'HTAP justifie son évaluation systématique et son suivi régulier sous traitement. La morphologie complexe du ventricule droit (forme en croissant, trabéculations) et sa position rétrosternale rendent difficile son exploration par les techniques classiques comme l'échocardiographie.

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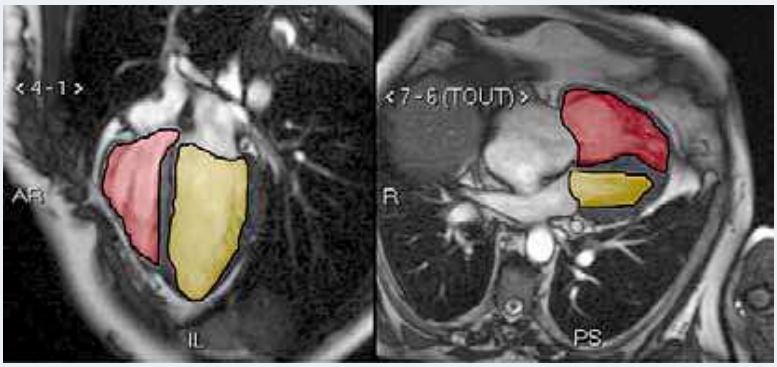

Figure 1. Surfaces télédiastoliques des ventricules droit (rouge) et gauche (jaune) en coupe 4 cavités.
À gauche : patient sans HTAP (PAPm à 21 mmHg) avec un rapport STDVD/STDVG à 0,66.
À droite : patient avec HTAP (PAPm à 58 mmHg) avec un rapport STDVD/STDVG à 1,90.

Pour de multiples raisons, l'imagerie par résonance magnétique (IRM) cardiaque (MRI, ou CMRI pour *Cardiac Magnetic Resonance Imaging*) s'est imposée ces dernières années comme la technique de référence pour l'évaluation non invasive morphologique et fonctionnelle du cœur *(3-6)* : fenêtre d'exploration optimale en raison de l'excellent contraste entre la graisse médiastinale, le myocarde et le sang contenu dans les cavités cardiaques ; bonne visualisation du cœur dans les 3 plans de coupe usuels ; très bonne reproductibilité inter- et intraobservateur ; caractère non irradiant de la technique. L'IRM est réalisée avec *gating* cardiaque et nécessite des apnées courtes (environ 20 secondes), bien tolérées par le patient.

Les séquences ciné-IRM dans les 3 plans du ventricule droit (petit axe, 4 cavités, long axe) permettent l'étude morphologique (volume et masse) et fonctionnelle (fraction d'éjection) du ventricule droit (VD). Les séquences en contraste de phase (sans injection) centrées sur l'artère pulmonaire (AP) permettent l'étude des flux.

L'injection de gadolinium est parfois réalisée pour étudier le rehaussement tardif du myocarde – qui visualise les zones avec œdème ou fibrose – et pour opacifier les artères pulmonaires lorsqu'on recherche du matériel endoluminal chez les patients suspects d'emboles.

Les recommandations internationales font à ce jour une place très modeste à l'IRM dans l'HTAP *(1, 2)*, mais cette technique nous semble particulièrement utile et prometteuse dans cette pathologie. Les récentes données morphologiques et hémodynamiques obtenues en IRM cardiaque et ayant fait l'objet de publications dans l'HTAP précapillaire seront détaillées ici.

Points forts ++

» 5. L'IRM cardiaque devrait s'imposer à l'avenir dans l'évaluation initiale de la fonction ventriculaire droite et de l'hémodynamique artérielle pulmonaire dans l'HTAP ; elle pourrait également améliorer le suivi non invasif de ces patients.

» La valeur pronostique de la fonction du ventricule droit (VD) nécessite son évaluation systématique et son suivi régulier sous traitement dans l'hypertension artérielle pulmonaire (HTAP).

» L'imagerie par résonance magnétique (IRM) cardiaque s'est imposée ces dernières années comme la technique de référence pour l'évaluation non invasive morphologique et fonctionnelle du VD ; l'IRM est également prometteuse dans l'évaluation de l'hémodynamique artérielle pulmonaire.

» Parmi les variables cardiaques reliées à la sévérité de l'HTAP et à un mauvais pronostic, citons la diminution de la fraction d'éjection ventriculaire droite (FEVD), la cinétique septale paradoxale et la diminution des dimensions du ventricule gauche par rapport à celles du ventricule droit.

» Parmi les variables artérielles pulmonaires reliées à la sévérité de l'HTAP et à un mauvais pronostic, citons la diminution de la compliance et de la vitesse moyenne du flux.

Mots-clés

IRM
Hypertension artérielle pulmonaire
Ventricule droit
Hémodynamique
Artère pulmonaire

Le ventricule droit en IRM

Les valeurs normales de volumes, masse et fraction d'éjection ont récemment été définies sur de larges populations en IRM pour le ventricule droit. Elles sont principalement fonction de la surface corporelle, de l'âge et du sexe *(6)*.

Volume ventriculaire droit

Dans l'HTAP précapillaire, l'augmentation des pressions pulmonaires est responsable d'une dilatation du ventricule droit, quantifiée en IRM par une augmentation des volumes, de la surface ou des diamètres mesurés en télédiastole ***(figure 1)***. De nombreux travaux ont suggéré qu'un volume télédiastolique du ventricule droit (VTDvd) supérieur à 100 ml/m² témoignait d'une dilatation VD *(3, 6)*, mais des seuils plus élevés ont été rapportés *(5)*. L'anatomie complexe du ventricule droit (VD) contribue probablement à ces discordances, et cela doit inciter à la prudence dans l'application pratique de ces seuils. L'augmentation du VTDvd est un facteur de mauvais pronostic en termes de survie *(7)*. Sous traitement, la diminution du VTDvd a également été rapportée *(8-10)*. Il est généralement admis qu'un volume d'éjection systolique diminué est de mauvais pronostic *(7, 11)*, mais ce n'est pas systématique *(12)*. La dilatation ventriculaire droite est également responsable d'une sphérisation du ventricule droit expliquant l'apparition d'une insuffisance tricuspide fonctionnelle, bien visualisée en IRM *(13)*.

Fonction ventriculaire droite

Elle est généralement appréciée par le calcul de la fraction d'éjection ventriculaire droite (FEVD) en coupe petit axe, en utilisant la règle de Simpson modifiée. Une FEVD inférieure à 45 % est considérée comme pathologique ; l'âge et le sexe doivent être pris en compte dans l'interprétation des valeurs de FEVD comprises entre 45 et 60 % *(14)*. Une FEVD inférieure à 35 % signe une défaillance droite sévère, dont le rôle pronostique a été démontré dans l'HTAP précapillaire et semble prédominer sur celui de l'augmentation des résistances vasculaires pulmonaires *(15, 16)*.

La fonction ventriculaire droite peut également être estimée à l'aide d'autres indices. Les travaux en échocardiographie ont popularisé la mesure de TAPSE (*Tricuspid Annulus Plane Systolic Excursion*), indice lié à la fonction ventriculaire droite et à la survie, et qui peut également être mesuré en IRM, avec une moindre précision *(17)*. De même, comme en échocardiographie, le pourcentage de raccourcissement surfacique du ventricule droit mesuré en 4 cavités, ou RVFAC (*Right Ventricular Fractional Area Change*), peut être obtenu en IRM pour apprécier la fonction droite, une valeur de RVFAC inférieure à 30 % étant associée à une FEVD inférieure à 35 % *(18, 19)*.

Septum interventriculaire et volumes du ventricule gauche

Dans l'HTAP, la surcharge barométrique et volumétrique du ventricule droit est responsable d'un bombement du septum interventriculaire dans le ventricule gauche, entraînant une compression ventriculaire gauche. Le niveau de pression moyenne dans l'artère pulmonaire et la surcharge ventriculaire droite conditionnent l'importance de ce bombement *(20-22)*. Il est possible d'apprécier ce signe de façon qualitative : septum plat dans les HTAP modérées ; bombement septal intraventriculaire gauche plus ou moins prononcé dans les HTAP sévères ***(figure 2)***. Il est aussi possible d'apprécier ce bombement septal de façon quantitative ("C-ratio"), mais les mesures sont alors plus complexes *(20-22)*, et donc plus rarement utilisées. Les zones de fibrose myocardique peuvent être visualisées par l'étude du rehaussement tardif du myocarde 10 minutes après injection de gadolinium. Chez les patients souffrant d'HTAP, ces images de rehaussement tardif ont été retrouvées au niveau de la jonction (insertion) de la paroi libre du ventricule droit sur le septum interventriculaire, et cela d'autant plus que l'HTAP est sévère *(23-25)*.

Toujours par analogie avec l'échocardiographie, l'association d'une dilatation ventriculaire droite et d'une diminution du volume ventriculaire gauche secondaire au déplacement paradoxal du septum est

Highlights

» Right ventricular (RV) function carries prognostic implications in patients with pulmonary hypertension (PH), and this explains why RV function must be systematically evaluated at baseline and during follow-up.

» Cardiac Magnetic Resonance imaging (CMR) is nowadays considered as the gold standard technique for non-invasively evaluating RV morphology and function. Pulmonary hemodynamics may be also successfully studied by CMR.

» The main CMR-derived cardiac variables related to the severity and prognosis of PH are a lowered RV ejection fraction, paradoxical septal motion and decreased left ventricular dimension relative to RV.

» The main CMR-derived pulmonary artery variables related to the severity and prognosis of PH are a decreased compliance and decreased mean flow velocity.

» CMR plays a key role in the non-invasive evaluation of RV function and pulmonary hemodynamics of PH patients. It is likely that CMR will improve the rationale evaluation and survey of these patients in the near future.

Keywords

MRI
Pulmonary hypertension
Right ventricle
Hemodynamics
Pulmonary artery.

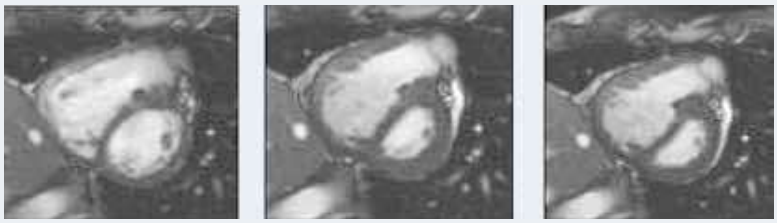

Figure 2. Septum paradoxal.
De gauche à droite : septum en position normale, septum aplati et septum bombant dans le ventricule droit.

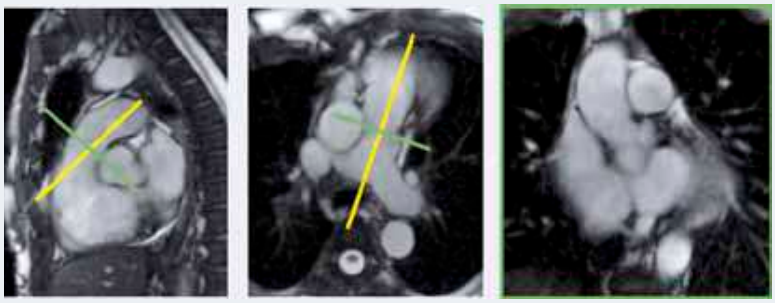

Figure 3. Repérage du plan de coupe perpendiculaire à l'axe valve/bifurcation de l'artère pulmonaire déterminé sur une coupe sagittale (image de gauche) et coronale oblique (image du milieu) en utilisant le principe de double obliquité. À noter : l'aspect parfaitement circulaire de l'artère pulmonaire sur la coupe obtenue ainsi (image de droite).

quantifiable par la mesure du rapport des surfaces télédiastoliques ventriculaire droite/ventriculaire gauche en coupe 4 cavités ***(figure 1)***. L'augmentation de ce rapport est fortement liée à la sévérité de l'HTAP *(26, 27)*.

Masse ventriculaire droite

L'épaisseur normale de la paroi libre du VD est de 2 à 3 mm *(3)*. Ainsi, pour des raisons techniques (résolution, contourage imprécis du fait des trabéculations), la quantification précise et reproductible de la masse ventriculaire droite semble difficile, en particulier dans les HTAP modérées ou débutantes.
Comme le prédit la loi de Laplace, l'HTAP s'accompagne d'une hypertrophie compensatrice de la paroi ventriculaire droite par un mécanisme adaptatif visant à normaliser la contrainte ventriculaire droite, principal déterminant avec la fréquence cardiaque des besoins myocardiques en oxygène. L'index de masse ventriculaire (rapport de la masse ventriculaire droite divisée par la somme [masse ventriculaire gauche + septum]) est augmenté et significativement corrélé à la pression artérielle pulmonaire moyenne, mais cette relation est faible *(28)*. L'index de masse ventriculaire est également lié au pronostic *(7)*, et il peut diminuer sous traitement en cas de remodelage rapide du ventricule droit *(8-10)*.

Autres

Classiquement, l'épanchement péricardique est un facteur de mauvais pronostic, mais c'est un signe de gravité souvent tardif *(1, 2)*. Peu de données IRM sont disponibles sur la quantification de la dilatation de l'oreillette droite et sur son rôle pronostique dans l'HTAP (contrairement à l'échocardiographie). L'intérêt de l'évaluation IRM des dimensions et de la compliance des veines caves inférieure et supérieure a été initialement suggéré *(29)*, mais ces éléments sont difficiles à mesurer en pratique courante de manière fiable et reproductible.

Les artères pulmonaires

Aspects techniques

Chez les patients souffrant d'HTAP précapillaire, l'analyse de l'artère pulmonaire en IRM nécessite un plan d'étude perpendiculaire au tronc de l'AP, à mi-distance de la valve pulmonaire et de la bifurcation de l'AP. Ce plan est perpendiculaire à l'axe passant par la valve et la bifurcation pulmonaires, axe repéré sur 2 plans orthogonaux passant par l'artère pulmonaire ***(figure 3)***. La circularité de l'AP est vérifiée par l'égalité de 2 diamètres perpendiculaires. Deux séquences sont ensuite réalisées dans ce plan d'étude : une séquence ciné-IRM permettant d'obtenir la surface maximale et minimale de l'AP durant un cycle cardiaque (pour le calcul de la compliance), et une séquence de flux en contraste de phase permettant d'obtenir des données hémodynamiques (vitesse, flux, temps). Pour limiter les artéfacts de battement cardiaque, il a été proposé par certains auteurs de calculer la compliance sur l'AP droite, mais, dans notre expérience, les images obtenues dans le tronc de l'AP sont peu ou pas artéfactées malgré la faible distance par rapport au cœur.

Surface et diamètre de l'artère pulmonaire

Une dilatation du tronc de l'AP est observée dans l'HTAP précapillaire, avec augmentation de son

diamètre et de sa surface *(30-32)*. Certains ont proposé de calculer le rapport entre le diamètre du tronc de l'AP et celui du tronc de l'aorte pour s'affranchir des différences interindividuelles, principalement liées au sexe, à la surface corporelle ou à la pathologie (maladies fibrosantes, par exemple). Il a été montré récemment qu'un rapport supérieur à 1,1 avait une sensibilité de 80 % et une spécificité de 94 % pour identifier les patients avec HTAP précapillaire *(33)*. Comme pour les cavités droites cependant, cette dilatation n'est pas proportionnelle à la sévérité de l'HTAP *(observation personnelle)*.

Compliance de l'artère pulmonaire

Chez les patients souffrant d'HTAP précapillaire, la compliance de l'AP est diminuée, sa rigidité étant augmentée *(30-32, 34-36)*, et ce signe pourrait constituer l'une des anomalies hémodynamiques les plus précoces de l'affection *(34, 37)*. La compliance artérielle peut être indirectement reflétée par la pulsatilité de l'AP (%), calculée comme suit : 100 × (surface maximale – surface minimale)/surface minimale *(30, 34, 36)* ***[figure 4]***. Une pulsatilité de l'AP inférieure à 40 % identifie les patients souffrant d'HTAP précapillaire avec une grande sensibilité (93 %). Une valeur inférieure à 24 % a une grande spécificité (95 %) *[34]*. Une valeur inférieure à 16 % est associée à un mauvais pronostic *(36)*. Il est possible de calculer plus précisément la compliance de l'AP (exprimée en mm^2/mmHg) en couplant les données de l'IRM et la pression artérielle pulmonaire pulsée obtenue par cathétérisme (PP = pression systolique – diastolique). Pour cela, on emploie la formule : compliance = (surface maximale – surface minimale)/PP *(34)*, avec des résultats essentiellement similaires à ceux de la pulsatilité.

Étude des flux, des vitesses et des temps en IRM

La vitesse maximale et la vitesse moyenne dans l'AP peuvent être calculées à partir de la séquence en contraste de phase perpendiculaire au tronc de l'AP ***(figure 5)***. Sur cette séquence, on obtient également une courbe de flux moyen permettant de déterminer le temps d'accélération et la durée d'éjection. Pour les vitesses de flux, dans l'HTAP, on observe une diminution de la vitesse maximale et surtout de la vitesse moyenne *(30, 32, 38)*, cette dernière étant plus reproductible. La vitesse moyenne, supérieure à 15 cm/s chez le sujet normal, est ramenée à une valeur comprise entre 14 et 4 cm/s selon la sévérité de l'HTAP *(32)*. Il est par ailleurs possible de déterminer le flux (débit) moyen passant par l'AP durant un cycle cardiaque, qui semble bien corrélé au débit cardiaque obtenu par cathétérisme *(32, 39)*. La mesure du flux moyen en IRM s'affranchit des causes d'erreurs liées à la présence d'une insuffisance tricuspide importante ou d'un shunt intracardiaque, contrairement aux renseignements fournis par le cathétérisme standard. Cet avantage pourrait être d'une grande utilité dans la surveillance et l'évaluation du pronostic des HTAP, et il fait actuellement l'objet d'études.

Les différents temps sont déterminés sur la courbe de flux. Le temps séparant le début de l'éjection du pic de flux est appelé temps d'accélération (AT [*Acceleration Time*]) *[30, 34, 39]* ***(figure 6)***. Dans l'HTAP, le pic de flux survient plus tôt à mesure que la pression AP moyenne augmente, et, en conséquence, l'AT est raccourci. Ce raccourcissement d'AT est généralement attribué au retour précoce de l'onde de pression réfléchie, responsable de l'interruption précoce du flux systolique (*Midsystolic Notching*).

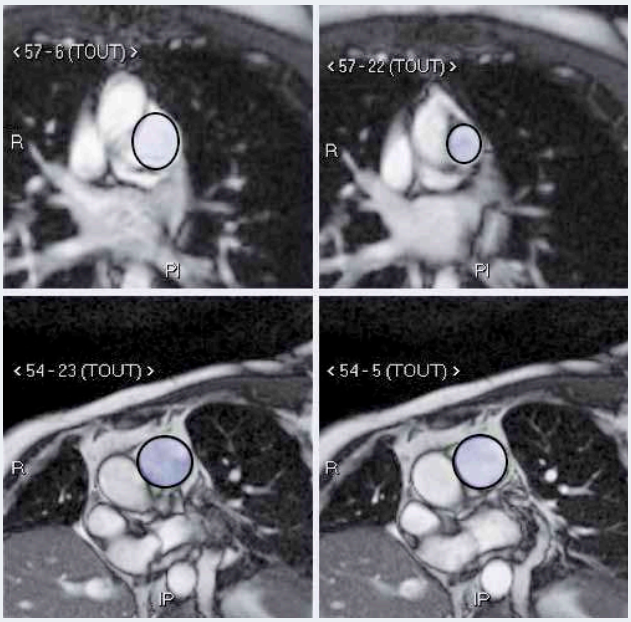

Figure 4. Estimation de la compliance de l'artère pulmonaire par la détermination de la surface maximale (à gauche) et minimale (à droite) du tronc de l'artère pulmonaire durant un cycle cardiaque en séquence ciné-IRM. En haut : patient sans HTAP (PAPm à 21 mmHg) avec une compliance estimée à 36 %. En bas : patient avec HTAP (PAPm à 58 mmHg) avec une compliance estimée à 7 %.

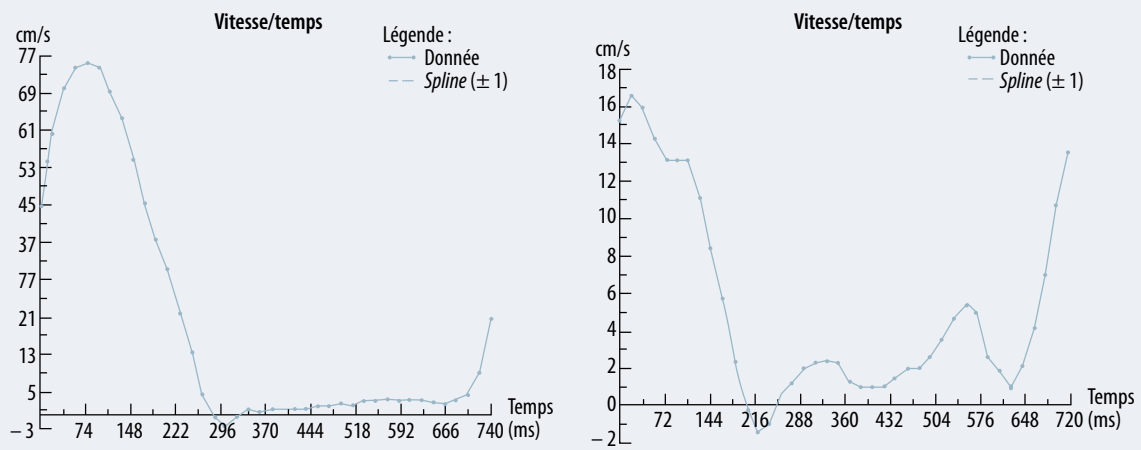

Figure 5. Courbes de vitesse dans le tronc de l'artère pulmonaire permettant d'estimer la vitesse moyenne (Vmoy) au cours d'un cycle cardiaque (séquences en contraste de phase perpendiculaire au tronc de l'artère pulmonaire). À gauche : patient sans HTAP (PAPm à 21 mmHg) avec une Vmoy à 22,9 cm/s. À droite : patient avec HTAP (PAPm à 58 mmHg) avec une Vmoy à 5,2 cm/s.

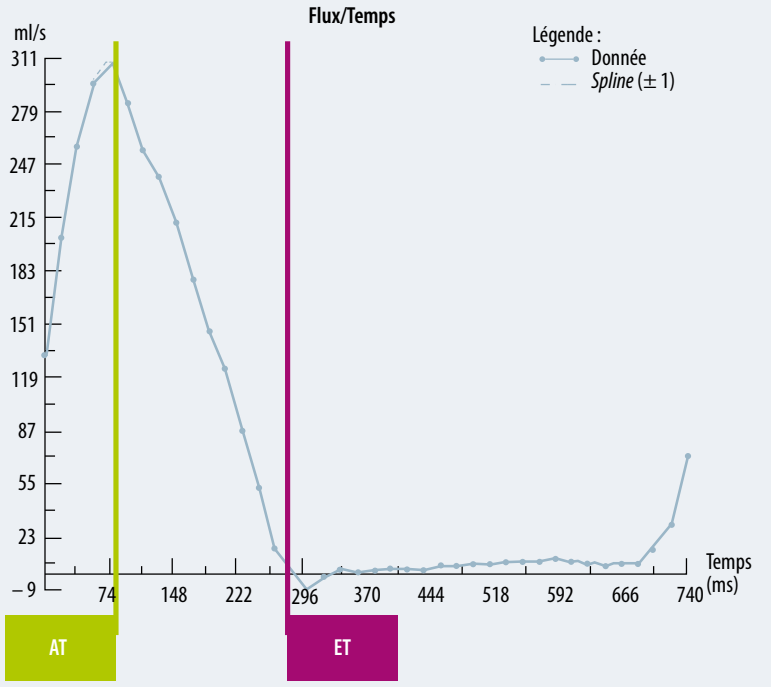

Figure 6. Courbe de flux obtenue à partir de la séquence en contraste de phase perpendiculaire au tronc de l'artère pulmonaire permettant de déterminer le temps d'accélération (AT) et le temps d'éjection (ET).

Les données concernant les variations du temps d'éjection (*Ejection Time* [ET]) dans l'HTAP ne sont pas univoques.

Phénomènes de vortex

En cas d'HTAP sévère, on observe souvent un flux rétrograde *(38-40)* contribuant à une image évocatrice à type de tourbillons dans le tronc de l'AP : c'est le vortex *(40)*. Cette hétérogénéité de flux peut être expliquée : par la baisse de compliance limitant la distension radiaire de l'AP ; par la difficulté de progression du flux vers la distalité, du fait de l'obstruction anatomique ou fonctionnelle (avec augmentation des pressions AP moyennes et des résistances) ; et par le retour précoce de l'onde de pression réfléchie. L'augmentation du pourcentage du volume rétrograde (fraction de régurgitation), calculé à partir des courbes de vélocité *(30, 35, 39)*, pourrait permettre de quantifier indirectement le vortex dans l'HTAP.

Sévérité de l'HTAP en IRM : vers une hiérarchie des critères ?

La diminution de la FEVD, l'augmentation du rapport des surfaces télédiastoliques ventriculaire droite/ventriculaire gauche en coupe 4 cavités, la diminution de la vitesse moyenne et la diminution de la compliance du tronc de l'AP représentent, dans notre expérience, les critères les plus liés à la sévérité de l'HTAP, et ce sont également les plus reproductibles (analyse en inter- et intraobservateur).

Suivi des patients en IRM

Chez les patients souffrant d'HTAP précapillaire et bénéficiant d'un traitement médical par époprostenol *(8)* ou bosentan *(10)*, la distance parcourue lors du test de marche de 6 minutes – qui sert à quantifier précisément l'amélioration fonctionnelle – est corrélée à l'augmentation de la fraction d'éjection VD et du volume d'éjection systolique VD, ainsi qu'à la diminution du VTDvd en IRM. L'IRM permet de visualiser une normalisation des volumes ventriculaires, de la masse ventriculaire droite et de la courbure septale (C-ratio) après thromboendartériectomie chirurgicale, témoignant du caractère réversible des phénomènes de remodeling VD *(9)*.

Perspectives

Elles sont nombreuses, et de nouvelles techniques IRM sont actuellement en développement *(40-43)*, qui reposent par exemple sur l'injection de produit de contraste et permettent l'opacification des AP (recherche de thrombus) ainsi que la quantification de la perfusion pulmonaire, dont la principale application sera l'HTAP postembolique.

Conclusion

La tolérance clinique à l'effort et le pronostic vital des patients souffrant d'une HTAP précapillaire sont très dépendants de la fonction VD. Des travaux IRM récents montrent de façon concordante que plusieurs variables cardiaques et artérielles pulmonaires sont liées à la sévérité de l'HTAP et à un mauvais pronostic *(4)*. Parmi les variables cardiaques, citons la diminution de la FEVD, la cinétique septale paradoxale et la diminution des dimensions du ventricule gauche (par rapport à celles du ventricule droit). Pour l'artère pulmonaire, citons la diminution de la compliance et de la vitesse moyenne du flux. Les recommandations internationales font à ce jour une place très modeste à l'IRM, mais cette technique de référence, non invasive et reproductible, devrait s'imposer à l'avenir dans l'évaluation initiale et dans la surveillance des HTAP. ■

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Diagnosis and treatment of pulmonary hypertension: an update*

Diagnóstico e tratamento da hipertensão pulmonar: uma atualização

Susana Hoette, Carlos Jardim, Rogério de Souza

Abstract

Over the last five years, knowledge in the field of pulmonary hypertension has grown consistently and significantly. On the basis of various clinical studies showing the usefulness of new diagnostic tools, as well as the efficacy of new medications and drug combinations, new diagnostic and treatment algorithms have been developed. Likewise, in order to simplify the clinical management of patients, the classification of pulmonary hypertension has been changed in an attempt to group the various forms of pulmonary hypertension in which the diagnostic and therapeutic approaches are similar. The objective of this review was to discuss these modifications, based on the 2005 Brazilian guidelines for the management of pulmonary hypertension, emphasizing what has been added to the international guidelines.

Keywords: Hypertension, pulmonary/diagnosis; Hypertension, pulmonary/therapy; Clinical protocols.

Resumo

Ao longo dos últimos cinco anos, o conhecimento na área de hipertensão pulmonar evoluiu de forma consistente e significativa. Novos algoritmos diagnósticos e de tratamento foram desenvolvidos com base no resultado de diversos estudos clínicos que evidenciaram a utilidade de novas ferramentas, assim como a eficácia de novos medicamentos e de combinações. Da mesma forma, a classificação da hipertensão pulmonar evoluiu, na tentativa de agrupar as diferentes formas de hipertensão pulmonar que apresentam abordagens diagnósticas e terapêuticas semelhantes a fim de facilitar a condução clínica dos pacientes. Esta revisão visa discutir cada uma dessas modificações, tendo por base as diretrizes brasileiras para manejo da hipertensão pulmonar de 2005, ressaltando aquilo que foi acrescentado às diretrizes internacionais.

Descritores: Hipertensão pulmonar/diagnóstico; Hipertensão pulmonar/terapia; Protocolos clínicos.

Introduction

Since the latest pulmonary hypertension (PH) guidelines were published in this Journal in 2005, a new meeting of PH specialists was held in Dana Point, California, USA, in 2008, and various articles in the field PH have been published. Therefore, an update of certain aspects of PH diagnosis and treatment is necessary. In this article, we review what has changed in the diagnosis and treatment of PH in recent years.[1,2]

Screening

Patients with complaints of dyspnea on exertion and chest pain, with or without dizziness, syncope, and signs of right heart failure of unknown cause, should be screened for PH. Various tests, which present a broad spectrum of sensitivity and specificity, can be used for the initial evaluation of patients suspected of having PH. Chest X-rays and electrocardiography (ECG), for instance, are tests that have low accuracy for the diagnosis of PH. Nevertheless, due to

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their broad availability and low cost, they can be employed in PH screening programs.

ECG

In patients with PH, ECG can show increased P wave amplitude (≥ 2.5 mm in the DII derivation), signs of right ventricular hypertrophy, right bundle branch block, right QRS axis deviation, and repolarization changes (right ventricular strain). Although a deviation greater than 100° has been shown to correlate well with hemodynamic measurements, its specificity for the diagnosis of PH has been shown to be low. Up to 13% of the patients with a diagnosis of PH confirmed by right heart catheterization (RHC) can initially present with normal ECG results (Figure 1).[3]

Chest X-ray

A chest X-ray reveals hilar enlargement that reflects pulmonary artery (PA) dilation and cardiomegaly. Chest X-rays also play an important role in the diagnosis of other diseases, such as those that impair the lung parenchyma and can cause dyspnea (Figure 2a).

Chest CT

Computed angiotomography of the chest plays a significant role in the diagnostic evaluation of PH. The diameter of the PA trunk is significantly larger in patients with PH than in normal individuals and correlates well with PA pressure measurements.[4] Studies have shown that the diameter of the PA ranges from 32.6 mm to 33.2 mm in normal individuals. One group of authors found that a PA diameter > 33.2 mm has a 95% specificity for the diagnosis of PH (Figure 2b).[5]

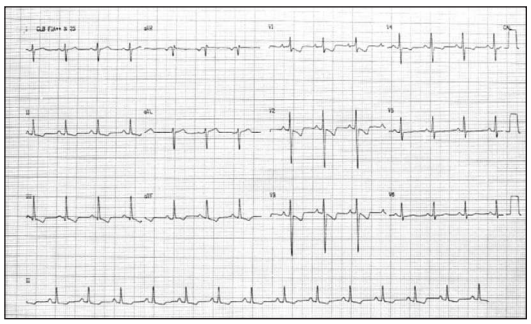

Figure 1 - Electrocardiogram of a 24-year-old patient with idiopathic pulmonary arterial hypertension. Note signs of right ventricular hypertrophy, right QRS axis deviation, and repolarization.

Echocardiography

Echocardiography is the principal screening tool for PH. However, echocardiography is a test that has significant limitations, such as the fact that it is highly examiner-dependent and that a significant proportion of patients present with a poor acoustic window. Another limitation of echocardiography is that the estimation of PA systolic pressure (PASP) depends on the tricuspid regurgitant jet and right atrial pressure (RAP). In up to 10% of cases, it is impossible to measure the tricuspid regurgitant jet velocity and, consequently, to estimate PASP. Although some studies have shown a significant correlation between echocardiography findings and RHC values, one group of authors recently reported that the RAP and PASP values estimated by echocardiography differ significantly from those measured by RHC.[6] In that study, 65 patients referred for PH diagnosis or follow-up treatment underwent echocardiography and RHC one hour apart, meaning that the basal conditions of patients varied minimally. It was also shown that cardiac output (Qt) as measured by echocardiography is not useful and that echocardiography typically overestimates pressures. Therefore, PASP values as estimated by echocardiography should be used to screen for PH, rather than to diagnose it. In addition to PASP estimates, dilation and right ventricular dysfunction should be considered to constitute indirect signs of PH. Despite its limitations, echocardiography continues to be the principal screening tool for PH because it is a noninvasive and readily available test, as well as being useful in identifying left heart malformations and diseases.

Because right ventricular function plays a significant role in the prognosis of patients with PH, it is necessary to measure right ventricular function appropriately. The characteristics of the right ventricle (RV) are quite different from those of the left ventricle (LV). Unlike the LV, which has thick, cone-shaped walls, the RV has thin, semilunar or crescent-shaped walls, and the myocardial mass of the RV is significantly lower and more trabecular than is that of the LV. The contraction pattern is also different; in the

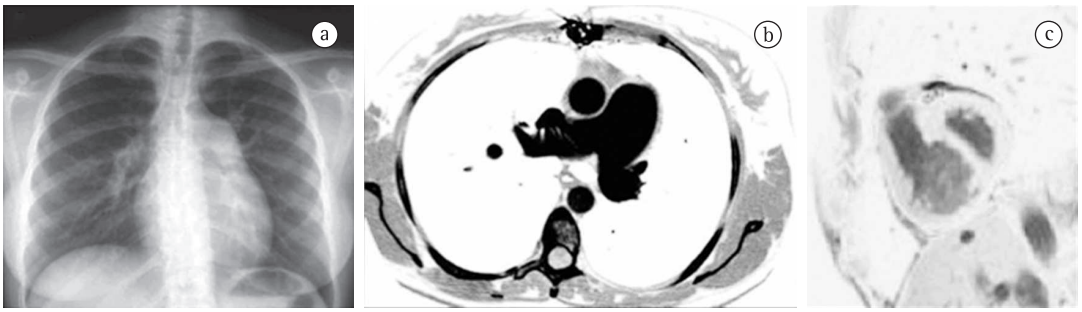

Figure 2 - In a), chest X-ray of a 30-year-old patient with idiopathic pulmonary arterial hypertension showing hilar enlargement. In b), CT scan of the chest of a patient with pulmonary arterial hypertension showing a severely dilated pulmonary artery trunk (39 mm). In c), cardiac magnetic resonance imaging of a patient with pulmonary hypertension. Image without short-axis contrast showing the right ventricle (on the left) and the left ventricle (on the right). Note ventricular septal bowing leading to compression of the left ventricle.

RV, longitudinal contraction of the myocardial fibers predominates, whereas, in the LV, spiral movement predominates. Therefore, it does not seem sufficient or appropriate to evaluate right ventricular function with the same tools used to evaluate left ventricular function.

New techniques for a better estimation of right ventricular function have been studied. The determination of tricuspid annular plane systolic excursion (TAPSE) has been shown to be a useful tool. This technique calculates the degree to which the pulmonary valve ring is shifted, in relation to the right ventricular apex during systole. A study comparing TAPSE and RHC measurements for the evaluation of right ventricular function showed that the measurements correlated well. The authors found that a TAPSE < 1.8 cm showed good accuracy in detecting right ventricular dysfunction and designated it a prognostic marker, because survival rates were lower in patients with a TAPSE < 1.8 cm than in those with a TAPSE ≥ 1.8 cm.[7]

Other techniques for the evaluation of right ventricular function, such as the comparison between the right ventricular area at systole and that at diastole—designated right ventricular fractional area change—and the comparison between the right ventricular end-diastolic area and the left ventricular end-diastolic area, have been studied and might prove useful in patients with PH.

Magnetic resonance imaging

Advances in the techniques for acquiring and processing magnetic resonance imaging of the heart have allowed three-dimensional evaluation of the RV and detailed tomographic visualization of its morphology. Cardiac magnetic resonance imaging (CMRI) creates a clear distinction between the myocardium and intracavitary blood, presenting well-defined myocardial and endocardial borders.[8] Because the RV presents the aforementioned particularities and CMRI allows a more detailed visualization of the RV, CMRI is currently considered the gold standard for a noninvasive evaluation of the RV.[9,10] Studies in which CMRI was used to evaluate patients with PH showed that, when compared with control group patients, PH patients presented with a significant increase in end-systolic and end-diastolic volumes, as well as in right ventricular muscle mass, together with a significant reduction in right ventricular ejection fraction. Other studies have shown ventricular septal bowing, together with a reduction in the LV volume in early diastole, revealing impaired left ventricular function associated with right ventricular dysfunction.[11] One group of authors demonstrated that the position of the septum, as determined by calculating its shift toward the LV, was accurate in predicting right ventricular systolic pressure.[12] Even without the use of contrast enhancement, CMRI allows excellent visualization of the PA, and it is possible to assess PA compliance and flow by means of the phase-contrast technique. In patients with PH, PA compliance values are significantly lower.[13] One study showed that measurements of pulsatility (which is related to compliance) can also correlate with the response to the NO test.[14] The measurement of PA velocity and the time it takes to reach the maximum velocity

Chart 1 - Hemodynamic definition of pulmonary hypertension.[a]

Definition	Characteristics	Clinical group
PH	MPAP ≥ 25 mmHg	All
Precapillary PH	MPAP ≥ 25 mmHg	1. PAH
	PAOP ≤ 15 mmHg	3. PH caused by lung disease
	Normal or reduced Qt	4. CTEPH
		5. PH with multifactorial mechanism, unknown mechanism, or both
Postcapillary PH	MPAP ≥ 25 mmHg	2. PH caused by left heart disease
	PAOP > 15 mmHg	
	Normal or reduced Qt	
Passive (proportional)	TPG ≤ 12 mmHg	
Reactive (disproportional)	TPG > 12 mmHg	

PH: pulmonary hypertension; MPAP: mean pulmonary artery pressure; PAOP: pulmonary artery occlusion pressure; Qt: cardiac output; PAH: pulmonary arterial hypertension; CTEPH: chronic thromboembolic pulmonary hypertension; and TPG: transpulmonary gradient. [a]Adapted from Badesh et al.[2]

(acceleration time) are reduced in patients with PH, and these measurements are related to systolic volume as measured by RHC.[15] In addition, CMRI plays a role in the follow-up of patients with PH. Two studies used CMRI before treatment initiation and 6-12 months after treatment initiation. In one of the studies, the patients received epoprostenol, and in the other, they received bosentan.[16,17] In both studies, improvement in the six-minute walk test (6MWT) was significantly related to improvement in right ventricular function parameters, as determined by CMRI. In another study, CMRI was used before and after pulmonary thromboendarterectomy.[18] The study showed a significant reduction in myocardial mass, right ventricular end-systolic volume, and right ventricular end-diastolic volume, as well as increased left ventricular volumes, reflecting the reversion of ventricular remodeling and septal deviation, hemodynamic improvement having been achieved with the surgical procedure (Figure 2c).

Although CMRI is not widely available and its cost is still high, the role of CMRI in the diagnosis and follow-up of patients with PH is promising, because the test allows a better evaluation of right ventricular function, PA flow, and PA behavior.

Diagnosis

If a patient suspected of having PH has been screened and signs consistent with increased pressure levels in the pulmonary circulation have been detected in the initial tests, the need to perform RHC to confirm the diagnosis of PH should be evaluated, because a definitive diagnosis of PH can only be established by invasive pressure measurements (Figure 3).

Since the last Brazilian consensus, there have been changes in the definition of PH. Before the meeting in Dana Point, CA, PH was defined as mean PA pressure (MPAP) ≥ 25 mmHg at rest or ≥ 30 mmHg during exercise, with pulmonary capillary pressure ≤ 15 mmHg. The group of specialists who reviewed the data that had been published up until the time of the meeting concluded that the data collected during exercise were extremely heterogeneous regarding the load used, the duration of the exercise, and the position of the patient during exercise, factors that might influence PA pressure measurements. Due to this lack of standardization, a decision was made to remove exercise-induced PH from the definition of PH. This does not mean that exercise-induced PH does not exist; it only means that the data collected to date are not sufficiently robust to provide a definition of exercise-induced PH values. This underscores the importance of conducting new studies in this field in order to provide an appropriate definition of exercise-induced PH.[2]

A review of 47 studies evaluating PA pressure in healthy volunteers showed that the MPAP at rest was 14.0 ± 3.3 mmHg. When individuals from different age brackets were compared, there was only a slight, less than significant, variation in the MPAP at rest.[19] Normal MPAP at rest was then defined as < 20 mmHg. The

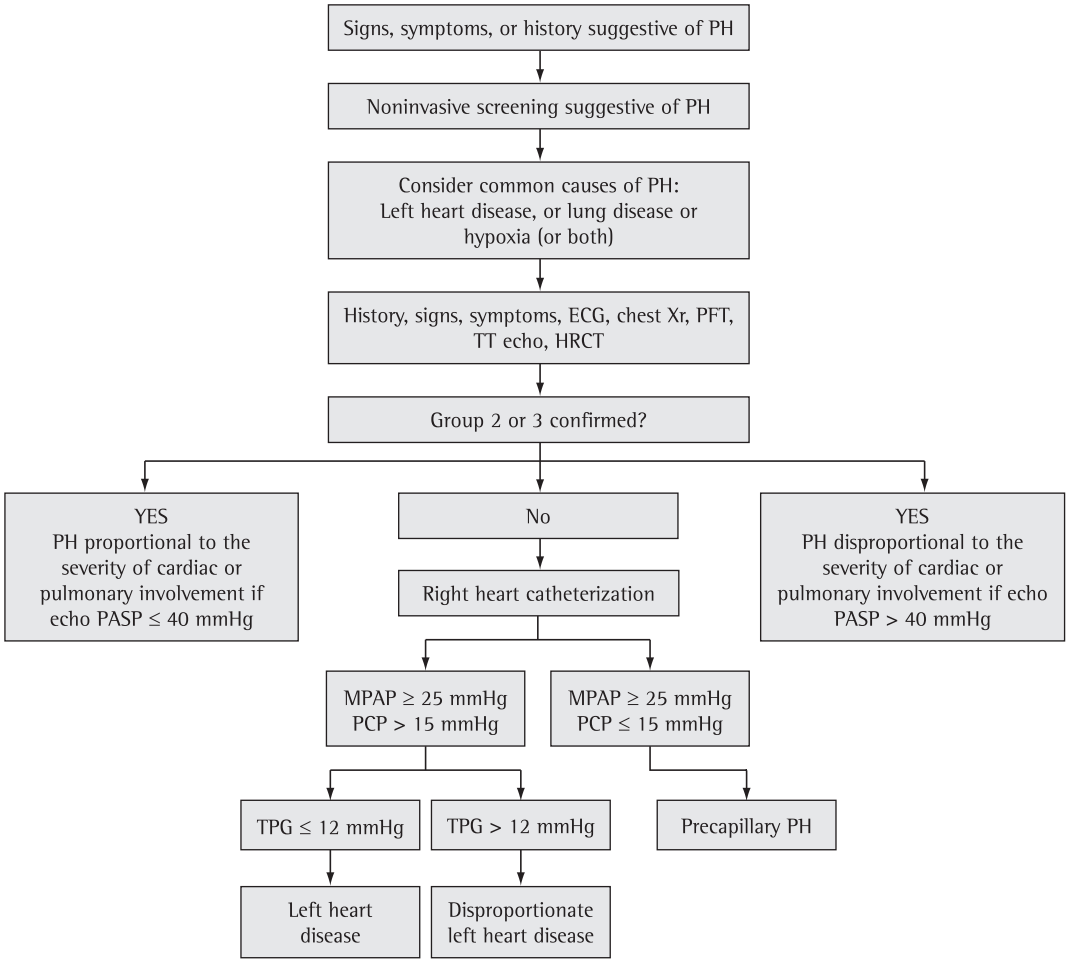

Figure 3 - Flowchart for the diagnosis of pulmonary hypertension (PH). ECG: electrocardiography; Xr: X-ray; PFT: pulmonary function test; echo: echocardiogram; TT: transthoracic; PASP: pulmonary artery systolic pressure; MPAP: mean pulmonary artery pressure; PCP: pulmonary capillary pressure; and TPG: transpulmonary gradient. Adapted from Galiè et al.[27]

significance of a finding of pressure levels ranging from 20 mmHg to 25 mmHg remains unclear. Studies involving patients with COPD and pulmonary fibrosis showed that patients with MPAP > 17 mmHg had a worse prognosis than did those with MPAP < 17 mmHg and drew attention to the fact that MPAP < 25 mmHg might have clinical significance.[20] Values of MPAP at rest ≥ 25 mmHg are currently used to establish a diagnosis of PH.

Patients with MPAP ≥ 25 mmHg are diagnosed with PH, and, after the diagnosis has been established, it must be determined whether the PH is precapillary or postcapillary. If the PA occlusion pressure (PAOP) is ≤ 15 mmHg, the PH is classified as precapillary. If the PAOP is > 15 mmHg, the transpulmonary gradient (TPG) must be determined. The TPG is calculated be the difference between the MPAP and the PAOP. When this difference is ≤ 12 mmHg, the increase in the MPAP is considered passive, which means that the increase in the MPAP is caused exclusively by cardiac involvement. If the TPG is > 12 mmHg, the increase in the MPAP is disproportionate to the increase in left ventricular pressure, indicating that there is pulmonary vascular remodeling or another associated cause of increased MPAP (Chart 1 and Figure 3).

The acute test with a vasodilator should be performed during the initial hemodynamic evaluation in patients with precapillary PH. The test can be performed with NO, prostacyclin, or adenosine. The result is considered positive when there is a reduction in the MPAP of ≥ 10 mmHg

and when values ≤ 40 mmHg are observed. A positive acute test result predicts the clinical and hemodynamic response to calcium channel blockers.[21,22]

After the presence of PH and its correct hemodynamic classification are confirmed by RHC, various tests should be performed in order to determine the specific etiology of PH. It should be highlighted that idiopathic PH is a differential diagnosis, and it is fundamental to follow an appropriate flowchart to facilitate the diagnostic investigation (Figure 4).

Classification

There have been various changes in the clinical classification of PH. Although the basic structure of the 2003 Venice classification—five principal groups and their respective subgroups—was maintained, pathologies have been moved from one group or subgroup to another. In addition, some new groups or subgroups have been created, whereas others have been eliminated. These changes are described below. The former and current classifications are compared in Chart 2.[23]

The first group is still designated "pulmonary arterial hypertension" (PAH) and is divided into two subgroups: "idiopathic" and "heritable" (formerly "familial"). There have been no changes in subgroup 1.1, idiopathic PAH (IPAH), which still comprises the sporadic cases in which no risk factors for PAH are detected or in which

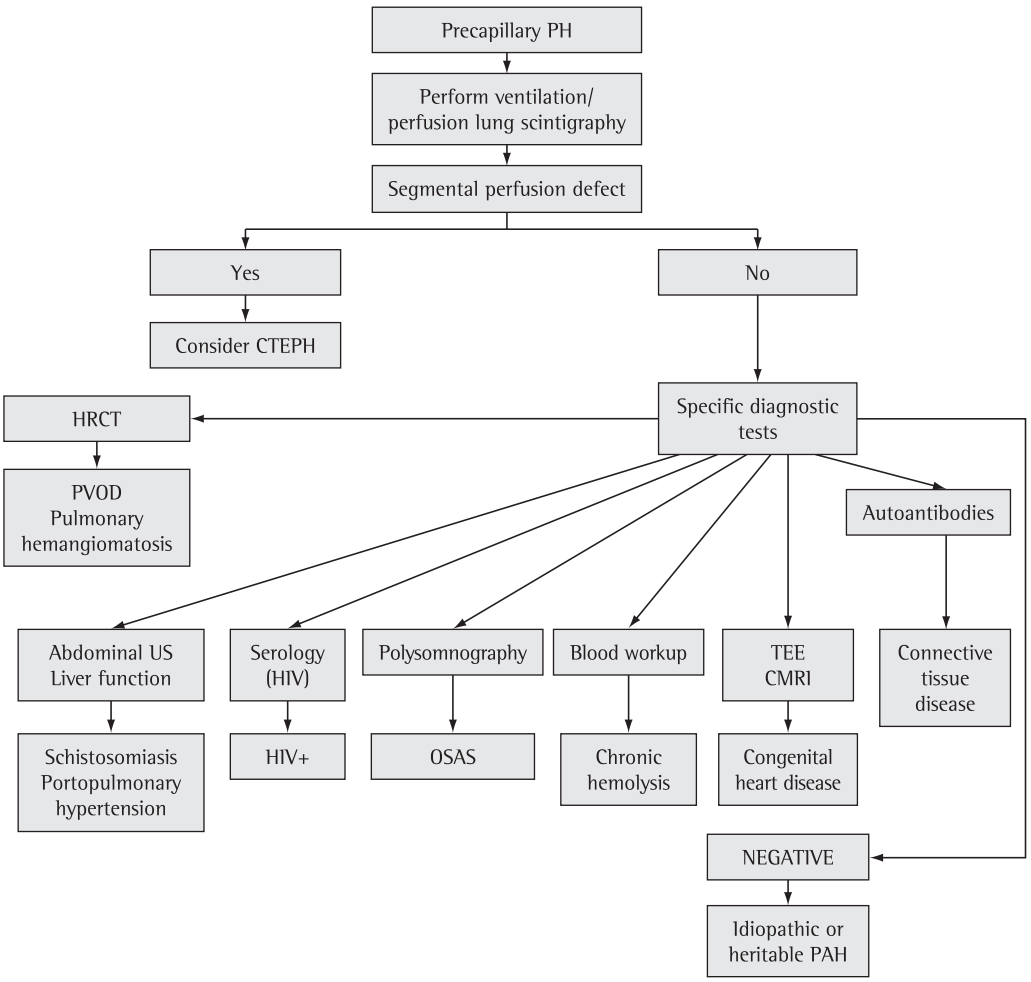

Figure 4 - Flowchart for the diagnosis of the etiology of pulmonary hypertension. CTEPH: chronic thromboembolic pulmonary hypertension; PVOD: pulmonary veno-occlusive disease; US: ultrasound; TEE: transesophageal echocardiogram; CMRI: cardiac magnetic resonance imaging; and OSAS: obstructive sleep apnea syndrome. Adapted from Galiè et al.[27]

Chart 2 - Clinical classification of pulmonary hypertension established in Venice, Italy, in 2003, and the current classification, established in Dana Point, CA, USA, in 2008.[a]

Venice, 2003	Dana Point, 2008
1. Pulmonary arterial hypertension	1. Pulmonary arterial hypertension
1.1. Idiopathic	1.1. Idiopathic
1.2. Familial	1.2. Heritable
1.3. Associated with:	1.2.1. BMPR2
1.3.1. Collagen vascular diseases	1.2.2. ALK-1, endoglin (with or without hereditary hemorrhagic telangiectasia)
1.3.2. Congenital systemic-pulmonary shunts	1.2.3. Unknown
1.3.3. Portal hypertension	1.3. Drug- and toxin-induced
1.3.4. Infection with the human immunodeficiency virus	1.4. Associated with
1.3.5. Drugs/toxins	1.4.1. Connective tissue diseases
1.3.6. Others (thyroid diseases, hereditary hemorrhagic telangiectasia, hemoglobinopathies, Gaucher's disease, myeloproliferative disorders, and splenectomy)	1.4.2. Human immunodeficiency virus infection
1.4. Associated with significant capillary or venous involvement	1.4.3. Portal hypertension
1.4.1. Pulmonary veno-occlusive disease	1.4.4. Congenital heart diseases
1.4.2. Pulmonary capillary hemangiomatosis	1.4.5. Schistosomiasis
1.5. Persistent pulmonary hypertension of the newborn	1.4.6. Chronic hemolytic anemia
	1.5. Persistent pulmonary hypertension of the newborn
	1'. Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis
2. Pulmonary venous hypertension	2. Pulmonary hypertension owing to left heart disease
2.1. Left ventricular or left atrial heart disease	2.1. Systolic dysfunction
2.2. Left valvular heart disease	2.2. Diastolic dysfunction
	2.3. Valvular disease
3. Pulmonary hypertension associated with lung disease, hypoxemia, or both	3. Pulmonary hypertension owing to lung diseases and/or hypoxia
3.1. COPD	3.1. COPD
3.2. Interstitial lung disease	3.2. Interstitial lung disease
3.3. Sleep-disordered breathing	3.3. Other lung diseases with mixed restrictive and obstructive pattern
3.4. Alveolar hypoventilation	3.4. Sleep-disordered breathing
3.5. Chronic exposure to high altitudes	3.5. Alveolar hypoventilation disorders
3.6. Developmental abnormalities	3.6. Chronic exposure to high altitude
	3.7. Developmental abnormalities
4. Pulmonary hypertension due to embolic disease, chronic thrombotic disease, or both	4. Chronic thromboembolic pulmonary hypertension
4.1. Thromboembolic obstruction of proximal pulmonary arteries	
4.2. Obstruction of distal pulmonary arteries	
4.3. Nonthrombotic pulmonary embolism (tumor, parasites, foreign body)	
5. Miscellaneous	5. Pulmonary hypertension with unclear multifactorial mechanisms
Sarcoidosis, histiocytosis X, lymphangioleiomyomatosis, compression of pulmonary vessels (adenopathy, tumor, and fibrosing mediastinitis)	5.1. Hematologic disorders: myeloproliferative disorders, splenectomy
	5.2. Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis: lymphangioleiomyomatosis, neurofibromatosis, vasculitis
	5.3. Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
	5.4. Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure on dialysis

BMPR2: bone morphogenetic protein receptor, type 2; and ALK-1: activin receptor-like kinase-1.[a]Adapted from Simonneau et al.[23]

there is no family history of PAH. Subgroup 1.2, heritable PAH, is subdivided as follows: 1.2.1—due to mutations in bone morphogenetic protein receptor, type 2 (BMPR2); 1.2.2—due to mutations in activin receptor-like kinase-1 or endoglin; and 1.2.3—of unknown cause. This new subdivision was necessary due to the importance of new genes associated with PH and of the description of mutations in the BMPR2 gene in 11-40% of the cases of IPAH; these cases, even without a family history of PAH, now characterize a subpopulation with hereditary disease, which makes the term "familial" inappropriate.

Subgroup 1.3 is now designated "drug- and toxin-induced" PAH. This change resulted from recent studies demonstrating the role of certain drugs in inducing PAH without changing its clinical course, as demonstrated for fenfluramine.[24] According to the new classification, subgroup 1.4 comprises conditions associated with the pathogenesis of PAH. Subgroup 1.4 subdivisions underwent small changes, HIV infection, portal hypertension, and persistent PH of the newborn remaining as subdivisions of this subgroup. The subgroup formerly known as "collagen vascular disease" is now designated "connective tissue diseases". The subgroup formerly known as "congenital systemic-pulmonary shunts" is now designated "congenital heart diseases". The subgroup designated "other" was eliminated from the current classification, and two new subgroups were created: subgroup 1.4.5, which now comprises patients with schistosomiasis; and subgroup 1.4.6, which comprises chronic hemolytic anemia, because the association between these pathologies and PAH has been shown to be important. Patients with schistosomiasis used to be allocated to the group of embolic diseases—group 4, in the previous classification—because it was believed that the mechanism that led to PH in this pathology was associated with the mechanic obstruction of pulmonary vessels by eggs of the parasite. Anatomic pathology studies have demonstrated that the pulmonary involvement in schistosomiasis is similar to that found in IPAH, being accompanied by the development of plexiform lesions and hypertrophy of the tunica intima and tunica media, regardless of the obstruction by the parasite. Studies conducted in Brazil have also contributed to this change in the classification. One of these studies demonstrated that the clinical characteristics of patients with schistosomiasis and PH are similar to those of patients with IPAH.[25] The other study demonstrated that 7.7% of the patients with hepatosplenic schistosomiasis who were being treated at the University of São Paulo School of Medicine *Hospital das Clínicas*, located in the city of São Paulo, Brazil, had PH (4.6% of whom had precapillary PH).[26] Given the number of patients worldwide, schistosomiasis might become the leading cause of PH. Therefore, this change in the classification has a significant impact on Brazil and on all countries in which schistosomiasis is endemic. Concluding the changes in group 1, subgroup 1' (read "one prime") was created. This subgroup comprises pulmonary veno-occlusive disease and pulmonary capillary hemangiomatosis, because the histopathological features of these two entities have been shown to overlap. It is currently believed that they can represent different phases of the evolution of the same pathology. A decision was made to maintain the two entities in the group related to primarily arterial involvement, due to their degree of clinical response to the treatment with PAH-specific drugs, among other reasons.

Group 2 is designated "[PH] owing to left heart disease", in order to highlight the causal relationship between cardiac involvement and the development of PH, because this is potentially the most common cause of PH. This group was subdivided into three subgroups: 2.1—systolic dysfunction; 2.2—diastolic dysfunction; and 2.3—valvular disease.

In group 3, the term "associated with" was changed to "owing to", reinforcing the causal importance of pulmonary involvement. Therefore, group 3 is now designated "[PH] owing to lung disease and/or hypoxia", and its subgroups are as follows: COPD; interstitial lung disease; sleep-disordered breathing; alveolar hypoventilation disorders; chronic exposure to high altitude; developmental abnormalities; and a new subgroup, designated "other pulmonary diseases with mixed restrictive and obstructive pattern". The last subgroup comprises chronic bronchiectasis, cystic fibrosis, and a recently recognized syndrome in which fibrosis predominates in the lung bases and emphysema predominates in the lung apices. The prevalence of PH in patients with this syndrome is nearly

50%, and it is therefore necessary to emphasize this entity in the new classification.

Group 4, formerly known as "[PH] due to embolic disease, chronic thrombotic disease, or both", is now designated "chronic thromboembolic pulmonary hypertension" (CTEPH). The subdivision of obstruction into distal obstruction and proximal obstruction was removed from the classification, because the definitions of "proximal" and "distal" are difficult to standardize and vary among centers, making a definitive classification imprecise. This change should result in patients diagnosed with PH due to CTEPH being immediately referred to tertiary-care centers at which there are professionals with experience in performing thromboendarterectomy, so that operability can be determined by a multidisciplinary team.

Group 5 was changed from "miscellaneous" to "[PH] with unclear multifactorial mechanisms" and is now divided into four subgroups: "hematologic disorders"; "systemic disorders"; "metabolic disorders"; and a subgroup designated "others", which comprises a variety of conditions associated with PH.

Treatment

After the diagnosis of PH has been established by RHC and the disease has been clinically classified, PH treatment can be discussed, because the definition of the clinical group determines the treatment to be given. The general measures and the supportive therapy should be evaluated for any patient with PH; however, the largest amount of evidence, even regarding the general measures, is based on studies of patients with PAH, that is, group 1 patients.

General measures and supportive therapy

All patients diagnosed with PH should receive some general instructions. The patients should be instructed not to do heavy physical exercise and to limit physical activity when experiencing mild dyspnea. They should receive influenza vaccination and pneumococcal vaccination because infection is a major cause of morbidity and mortality in these patients. Female patients of childbearing age should be instructed to use contraceptive methods, because pregnancy significantly increases mortality in patients with PH. Although there is no consensus regarding the ideal type of contraception for patients with PH, it should be borne in mind that concomitant use of bosentan and oral contraceptives can reduce the effect of the latter. Patients in functional class III or IV, as well as those with hypoxemia (PaO_2 < 60 mmHg), should use supplemental oxygen if flying or visiting areas at altitudes above 1,500-2,000 m.[27]

Supplemental oxygen therapy is indicated for patients with hypoxemia (PaO_2 < 60 mmHg) and can be considered for patients who present symptomatic benefit from the correction of hypoxemia during physical exertion. The use of diuretics is indicated for all patients who present with signs of hypervolemia.[27]

The use of anticoagulants in patients with PH is controversial, because there have been no randomized controlled studies evaluating the effects of anticoagulation in these patients. The rationale for the indication of anticoagulation for these patients originates from the histopathological findings of microvascular thrombosis, activation of the coagulation system, and platelet dysfunction in patients with IPAH, which have led to the assumption that these patients present with a prothrombotic state. In a meta-analysis of the theme, conducted in 2006, the authors concluded that anticoagulation should be indicated, given that 5 of the 7 studies analyzed demonstrated that anticoagulation was beneficial. In the absence of any contraindications, the use of oral anticoagulants is indicated for patients with PH, with the objective of maintaining an international normalized ratio of 1.5-2.5. Attention should be given to patients with liver disease and scleroderma, because these patients might be at a higher risk for bleeding; likewise, attention should be given to the interaction between anticoagulants and the PAH-specific treatment. Some studies, for instance, have suggested that concomitant use of anticoagulants and sitaxsentan can increase the risk of bleeding.[28]

Group 1

Most of the studies of PH treatment were conducted in patients with PAH; therefore, PH-specific treatment is, for the time being, restricted to group 1 patients. However, there has been no confirmation that all subgroups of patients with PAH respond to the specific drugs that are currently available. In general, the

evidence discussed here is restricted to patients with IPAH, heritable PAH, drug-induced PAH, PAH associated with connective tissue diseases, or PAH associated with congenital heart diseases. There is also some evidence for patients with HIV infection. However, for patients with portopulmonary hypertension, schistosomiasis, or hemolytic anemia, it is still impossible to indicate the use of the same drugs, and clinical studies specifically designed to investigate those indications are needed.

If the patient presents pulmonary vasoreactivity, as assessed by the acute test, treatment with a calcium channel blocker should be initiated, and, if there is a sustained clinical response, the drug should be maintained, together with supportive treatment. The survival rates in patients who respond to the use of a calcium channel blocker are significantly higher than in those who do not respond well to the drug.[22] However, the use of calcium channel blockers in patients who do not present pulmonary vasoreactivity, as assessed by the acute test, can lead to a reduction in Qt and systemic vascular resistance without a reduction in the MPAP or pulmonary vascular resistance (PVR). Therefore, the use of a calcium channel blocker is contraindicated for patients who do not present pulmonary vasoreactivity or those who have not undergone the acute test, due to the risk of clinical deterioration. The calcium channel blocker to be used can be nifedipine, diltiazem, or amlodipine. However, in patients with high heart rates, diltiazem is the drug of choice. The treatment should be initiated with low doses, which should be progressively increased in accordance with the tolerance limit of the patient.

The classes of specific drugs that are approved for use in PAH patients, that is, in group 1 patients, are as follows: prostacyclin analogues; phosphodiesterase-5 inhibitors; and endothelin receptor antagonists.

Prostacyclin analogues

Prostacyclin analogues constitute the first class of drugs to be approved for PH-specific treatment. Prostacyclin analogues can be administered intravenously, subcutaneously, orally, or by inhalation.

Epoprostenol

In an open randomized study conducted in 1996, clinical and hemodynamic improvements, as well as increased survival, were described in PAH patients who used epoprostenol in combination with conventional therapy (anticoagulation, diuretics, and oxygen therapy), when compared with those who used the conventional therapy in isolation.[29] Although other studies have shown functional and hemodynamic improvements, the improvement in survival described in the aforementioned study has not been described elsewhere. Epoprostenol should be administered intravenously, through a tunneled catheter, and continuously, through a portable infusion pump, due to its short half-life. The most common side effects are jaw pain, flushing, diarrhea, nausea, and vomiting. Catheter-related complications, such as infection and thrombosis, as well as those related to the functioning of the equipment, have often been reported. Although epoprostenol is unavailable for use in Brazil, it is the only drug for functional class IV patients that has a grade of recommendation of A.

Treprostinil

Treprostinil is a prostacyclin analogue whose half-life is longer than is that of epoprostenol, which allows treprostinil to be administered subcutaneously. In a randomized, placebo-controlled study, there was improvement in the symptoms, as well as slight but significant functional and hemodynamic improvements. Treprostinil has the advantage of not requiring an indwelling catheter, which avoids catheter-related complications. However, subcutaneous administration of treprostinil has been associated with pain at the injection site in 85% of the patients receiving the drug, and discontinuation of the drug is necessary in 8% of the cases. The speed at which the dose of the drug was increased was the principal causative factor for this side effect. Therefore, the dose should be increased slowly and progressively, and the site of injection should be changed every three days, in order to reduce this problem. The other side effects associated with epoprostenol can also occur in patients treated with treprostinil.[30] In one study, sustained hemodynamic and symptomatic improvements were observed during a mean follow-up period of 26 months.

[27] Treprostinil is also currently unavailable for use in Brazil. The administration of the drug through inhalation and continuous intravenous administration is currently being evaluated.

Iloprost

Iloprost is the prostacyclin analogue that is administered through inhalation. This route of administration has the advantage of acting on the pulmonary arteries that are in contact with ventilated regions; however, the drug must be inhaled 6-9 times a day and is commonly associated with the development of dry cough. Other side effects observed are the same as those of other prostacyclin analogues. A randomized, placebo-controlled study involving patients with PAH and CTEPH showed significant clinical improvement in a combined outcome that included physical exercise capacity, functional class in accordance with the New York Heart Association, and clinical deterioration for the group of patients treated with iloprost, who also presented hemodynamic stability during the study period.[31] Although it has been registered for use in Brazil, iloprost is not yet commercially available in the country.

Beraprost

Beraprost is the only prostacyclin analogue that is available for oral administration. Although two studies have demonstrated an improvement in the six-minute walk distance (6MWD), this response was not sustained, and there was no hemodynamic response. The side effects of the drug are the same as those of other prostacyclin analogues.[28] In an open, uncontrolled study conducted in Japan, long-acting beraprost (a preparation designated TRK-100STP) was reported to produce clinical, functional, and hemodynamic improvement, its future use being therefore promising.[32] Beraprost is also currently unavailable for use in Brazil.

Phosphodiesterase-5 inhibitors

Increased phosphodiesterase-5 in pulmonary arterioles and right ventricular myocytes has been demonstrated in patients with PH. The inhibition of this enzyme leads to an increase in the concentration of cyclic guanosine monophosphate, which promotes vasodilation, inhibits pulmonary artery remodeling due to its antiproliferative and pro-apoptotic effects, and seems to have a positive inotropic effect on the RV.[33] Phosphodiesterase-5 inhibitors reduce PVR and lead to an increase in Qt, and the use of these drugs has been associated with clinical and functional improvement in patients with PH.[34,35] Two phosphodiesterase-5 inhibitors have been approved for use in patients with PH: sildenafil, approved in 2005; and tadalafil, approved in 2009. One study compared the use of increasing doses of sildenafil (20, 40, and 80 mg), administered three times a day, with the use of placebo. The study showed a significant but not dose-dependent increase in the 6MWD, as well as a significant, dose-dependent reduction in PVR.[36] The benefits of tadalafil have been demonstrated in another study, in which increasing doses of the drug were also compared with placebo. Only the 40-mg dose correlated with a significant increase in the 6MWD, an improvement in the markers of quality of life, and a slight increase in the time to clinical worsening.[37] Phosphodiesterase inhibitors are relatively safe and well tolerated. Tadalafil has the advantage of being administered only once daily. The major side effects of the drugs are headache, nasal congestion, dyspepsia, flushing, muscle pain, and epistaxis. Phosphodiesterase inhibitors are metabolized in the liver, and the use of protease inhibitors, such as ritonavir and saquinavir, can increase their bioavailability, and care should therefore be taken when prescribing this class of drugs to HIV-infected patients. Visual disorders, such as blurred vision, color changes, and photosensitivity, have been described, principally in patients with diabetic neuropathy or anterior ischemic optic neuropathy. Dilated eye examination is recommended before starting the treatment with this type of medication.[27]

Endothelin receptor antagonists

Endothelin-1 levels are elevated in the lung tissue and plasma of patients with PAH and scleroderma. Endothelin-1 acts by binding to endothelin receptors (ETA and ETB), promoting vasoconstriction and smooth muscle cell proliferation. Bosentan is a nonselective endothelin receptor antagonist, meaning that it blocks types A and B, and has been shown to be beneficial for patients with IPAH and for those with PAH associated with collagen disease, leading to an increase in exercise capacity and

in the time to clinical worsening.[38] Other studies have reinforced the beneficial effects of bosentan, as well as showing hemodynamic and functional improvements.[27,39] One study showed that the use of bosentan in functional class II patients is also beneficial.[40] The use of bosentan in these patients, who are less symptomatic, was shown to produce hemodynamic improvement and prevent clinical worsening.[40] The drug is generally well tolerated, and its principal side effect is an increase in hepatic enzyme levels, which requires that liver function be monitored throughout the treatment. The treatment should be initiated at a dose of 62.5 mg, twice daily, and, if the drug is well tolerated, the dose should be increased to 125 mg, twice daily. Monitoring through blood workup is also indicated, due to a report of anemia associated with the use of the drug.[27] Retrospective studies have also shown a reduction in the mortality associated with the use of endothelin receptor antagonists.

Another endothelin receptor antagonist is sitaxsentan, which is a specific inhibitor of the ETA receptor and has also been associated with better quality of life and functional capacity in patients with PH.[41] An open study comparing patients receiving sitaxsentan with those receiving bosentan demonstrated that the patients receiving sitaxsentan showed a trend toward reduced clinical worsening and better tolerance, with a lower increase in hepatic enzyme levels. A subgroup analysis has suggested that patients with PAH associated with connective tissue disease benefit significantly more from sitaxsentan than from bosentan.[42] The use of sitaxsentan significantly increases serum levels of dicumarol, requiring even closer monitoring of the coagulation profile during the treatment. This characteristic, together with case reports of complications related to the use of sitaxsentan, is what prevents this medication from being universally approved by the agencies that regulate the use of medications.

Yet another endothelin receptor antagonist is ambrisentan, which is also a selective ETA receptor antagonist and has been shown to produce a significant increase in the 6MWD and in the time to clinical worsening, as well as improving dyspnea and quality of life scores. It is of note that none of the patients who received treatment with ambrisentan presented with increased hepatic enzyme levels, and the drug also has the advantage of being administered only once daily. Another characteristic of the use of ambrisentan is the low interaction with other drugs, specifically with dicumarol and its derivatives, which allows safer concomitant use.[43]

However, it should be highlighted that there have been no controlled studies to determine which of the endothelin receptor antagonists, if any, is the most effective.

Combination therapy

Although the therapeutic armamentarium for the treatment of PH has expanded greatly in recent years, a significant proportion of patients show no improvement or present clinical worsening during monotherapy. Until recently, there had been no studies confirming that the clinical response to combination therapy was effective or reporting that such therapy was well tolerated, although the concept of targeting different pathophysiological pathways was deemed logical in theory. Case reports and uncontrolled studies showed clinical improvement with and tolerance to the use of combination therapy. Consequently, randomized, placebo-controlled studies were conducted. Concomitant use of sildenafil in patients receiving epoprostenol was found to provide greater functional and hemodynamic improvement, as well as greater improvement in quality of life, together with an increase in the time to clinical worsening.[44] Patients treated with the bosentan-epoprostenol combination showed a trend toward significant hemodynamic improvement, as well as good tolerance to the concomitant use of the two drugs. The lack of statistical significance is likely attributable to the small number of patients studied. The only symptom that was more common in the group of patients treated with combination therapy was edema of the lower limbs, which was not attributed to right ventricular dysfunction, because the combination therapy produced a reduction in RAP. It is of note that there was a reduction in the side effects secondary to epoprostenol in the group of patients who also received bosentan, possibly due to the inhibition of the activation of the sympathetic system, which is characteristic of the use of epoprostenol, by bosentan.[45] Concomitant use of iloprost was well tolerated in patients receiving bosentan, who showed a trend toward an increase in

the 6MWD, significantly improving functional parameters and increasing the time to clinical worsening.[46]

The use of combination therapy was therefore shown to be safe and effective. In cases in which the clinical response is inadequate or in which there is deterioration during monotherapy, concomitant use of another class of drugs should be indicated. Combination therapy can be initiated at the beginning of the treatment in cases in which the initial presentation is extremely severe. However, further studies are needed in order to confirm the true benefit of this approach.

Group 2

The treatment of patients with PH caused by left heart disease should focus on compensating for the underlying heart disease, and the use of PH-specific treatment is therefore contraindicated for these patients. Studies involving the use of bosentan and epoprostenol in this group of patients were terminated earlier than intended because the number of events observed in the groups of patients who received treatment was greater than was that observed in the placebo group. In addition, only one small-scale study has shown that the use of sildenafil is beneficial for the functional capacity of patients treated with the drug. These results therefore require corroboration from other studies, which might determine the true effectiveness and safety of the drugs that are currently available for this specific group of patients. Patients with a disproportionate increase in the MPAP, that is, those with TPG ≥ 12 mmHg, should be included in studies designed to that end.

Group 3

Patients with parenchymal disease or hypoxemia should be primarily treated with oxygen therapy, and the treatment of the underlying disease should be optimized. The effectiveness of PH-specific drugs in this group of patients has yet to be confirmed, and the use of such drugs is currently contraindicated for these patients. When the MPAP is disproportionately high, that is, when parenchymal or functional involvement does not explain the degree of dyspnea and the MPAP at rest is higher than 40-45 mmHg, patients should be referred to a tertiary-care center, and the inclusion of such patients in studies is encouraged. However, PH-specific treatment should not be prescribed. It should be borne in mind that a finding of diastolic left ventricular dysfunction is not uncommon in these patients and might constitute another factor related to the pathogenesis of PH.

Group 4

In all patients with PH, CTEPH should be ruled out. A ventilation/perfusion lung scintigraphy should always be performed, as seen in the diagnostic algorithm, and, if the result is normal, CTEPH can be ruled out. Angiotomography of the chest is useful for the evaluation of pulmonary circulation; however, it should not be used as an isolated tool for determining the operability of CTEPH. Patients with a diagnosis of CTEPH should receive anticoagulants and be referred

Chart 3 - Parameters for the evaluation of the clinical severity of pulmonary arterial hypertension, as well as prognosis of the disease.[a]

Better prognosis	Determinants	Worse prognosis
No	Clinical evidence of right ventricular failure	Yes
I or II	Functional class	IV
No	Syncope	Yes
Slow	Symptom progression speed	Rapid
> 500 m	6MWD	< 300 m
Normal or stable	BNP	High or increased
Without pericardial effusion	Echocardiography	With pericardial effusion
TAPSE > 15 mm		TAPSE < 15 mm
RAP < 8 mmHg	Hemodynamic function	RAP > 15 mmHg
CI ≥ 2.5 L/min/m^2		CI ≤ 2.0 L/min/m^2

6MWD: six-minute walk distance; BNP: brain natriuretic peptide; TAPSE: tricuspid annular plane systolic excursion; RAP: right atrial pressure; and CI: cardiac index. [a]Adapted from Galiè et al.[27]

to a tertiary-care center for the evaluation of the possibility of surgery. If the obstruction is operable, such patients should be referred for thromboendarterectomy. When a surgical intervention is contraindicated or cannot be performed, or when the patient presents with PH after thromboendarterectomy, the use of specific treatment seems beneficial.

A recent randomized controlled study demonstrated the hemodynamic benefit of the use of bosentan in patients with inoperable CTEPH, although the effect of the drug on functional capacity was not significant.[47] The use of sildenafil in patients with CTEPH for whom surgery is contraindicated has previously been described in a case series.[48] In addition, an open uncontrolled study conducted in 2007 and involving 104 patients showed good patient tolerance to the drug and a reduction in PVR, as well as improved function and 6MWD.[49] A small-scale but placebo-controlled study showed improved quality of life, as well as hemodynamic and functional improvement, in patients with residual PH after thromboendarterectomy or with distal CTEPH.[50] The decision to use specific medication in patients with CTEPH who cannot undergo surgery or who present with residual PH after surgical intervention should be made after an adequate evaluation of the case in a referral center, in order to rule out the hypothesis that these patients will benefit from the surgical approach. In addition, these patients should remain under close clinical monitoring.

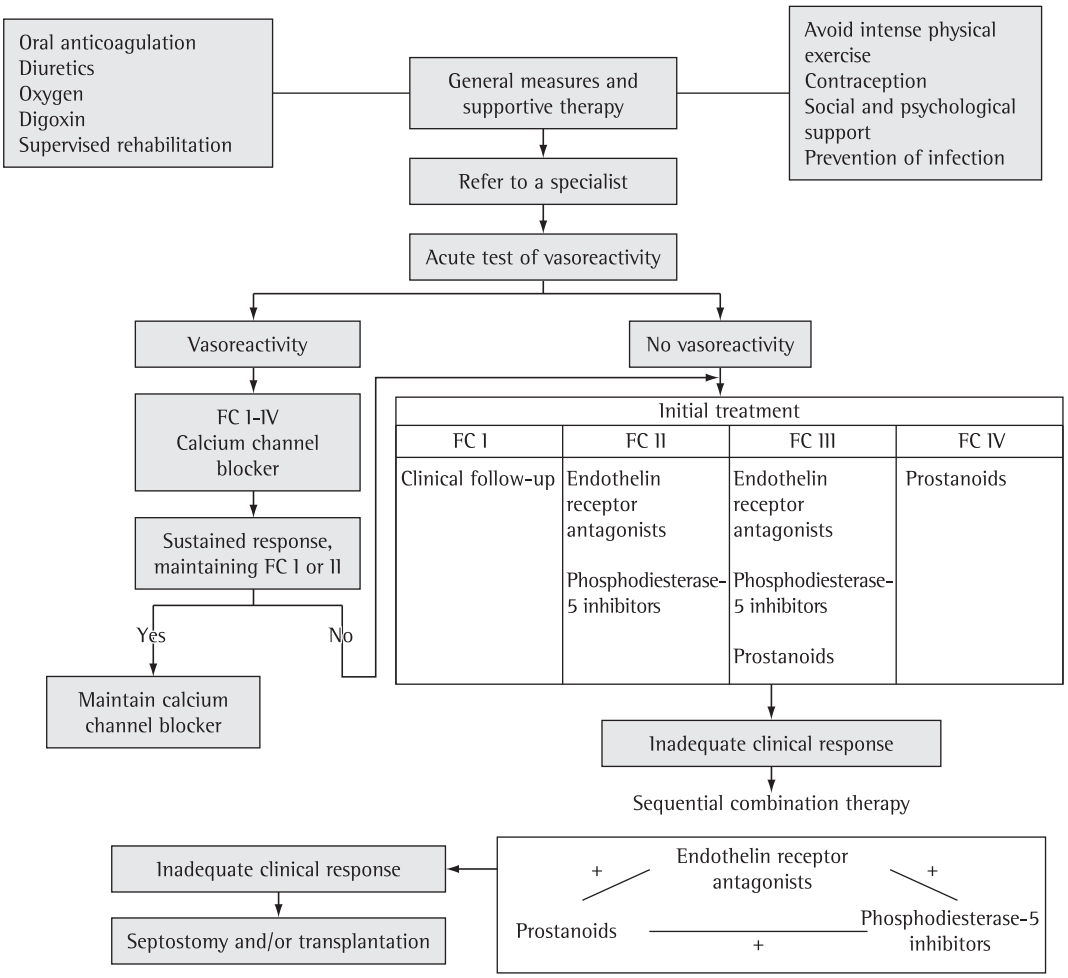

Figure 5 - Treatment algorithm. FC: functional class. Adapted from Barst et al.[55]

Treatment initiation and follow-up

After it has been decided whether patients should receive specific treatment, it is important to establish the clinical severity of the initial presentation of the disease. The fact that certain prognostic markers are major indicators of disease severity in patients with PH has been established in the literature. The following have been associated with a worse prognosis: functional classes III and IV; an increase in brain natriuretic peptide (BNP) or N-terminal-pro-BNP levels; 6MWD < 330 m; maximal oxygen uptake during the cardiopulmonary test < 12 mL/min/kg; and hemodynamic variables (RAP > 8 mmHg and cardiac index ≤ 2.0 L/min/m^2).[27,51-53] Patients with markers of severity should be considered candidates for intravenous therapy in countries where this treatment is available. In localities where intravenous therapy is unavailable, combination therapy can be given at the initiation of treatment. However, it should be highlighted that there have been no clinical studies validating this approach; nevertheless, this approach has been considered in the latest international algorithms (Chart 3).

After the initiation of treatment, patients should be reevaluated, generally every 3-4 months, through analysis of the symptoms, physical examination findings, 6MWD, and BNP levels, in order to assess the response to treatment and decide the course of action. In localities where the 6MWT cannot be performed in a corridor, functional evaluation can be performed by means of a treadmill 6MWT, a protocol that has previously been validated for use in patients with PH.[54] If patients present clinical improvement or stabilization, as well as improvement or stabilization of the aforementioned markers, the treatment should be maintained; otherwise, an investigation should be performed in order to find the cause of treatment failure and avoid clinical deterioration. Infection, dietary noncompliance (excessive ingestion of salt or fluids), or the inappropriate use of the drugs are common causes of decompensation. If an evident cause is not found, a new hemodynamic evaluation can be performed, and, if hemodynamic worsening is confirmed, the specific treatment should be optimized by increasing the dose or adding another class of drugs. Patients who present with progressive worsening despite the optimized clinical treatment should be referred for an evaluation for lung transplantation (Figure 5).[55]

Future perspectives

There have been significant advances in recent years, and existing concepts, the levels of evidence of which had not been sufficient to allow further extrapolations, have been consolidated, making it possible to construct new diagnostic and therapeutic algorithms. The prospect of effective therapeutic alternatives for the various PH groups is excellent, and new pathophysiological pathways with therapeutic potential have been discovered, providing the spark for the development of new classes of drugs that might be added to the existing therapeutic armamentarium. This development has always been based on research, of increasing quality, which generates increasingly robust evidence. In the coming years, the expectation is that this characteristic will be increasingly present in the field of PH.[56]

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The association between resting and mild-to-moderate exercise pulmonary artery pressure

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ABSTRACT: The mean pulmonary artery pressure ($\bar{P}$pa) achieved on mild-to-moderate exercise is age related and its haemodynamic correlates remain to be documented in patients free of pulmonary hypertension (PH).

Our retrospective study involved patients free of PH investigated in our centre for possible pulmonary vascular disease between January 1, 2007 and October 31, 2009 who underwent right heart catheterisation at rest and during supine exercise up to 60 W. The 38 out of 99 patients aged <50 yrs were included and a $\bar{P}$pa of 30 mmHg was considered the upper limit of normal on exercise.

The 24 subjects who developed $\bar{P}$pa>30 mmHg on exercise had higher resting $\bar{P}$pa (19±3 *versus* 15±4 mmHg) and indexed pulmonary vascular resistance (PVRi; 3.4±1.5 *versus* 2.2±1.1 WU·m^2; p<0.05) than the remaining 14 subjects. Resting $\bar{P}$pa >15 mmHg predicted exercise $\bar{P}$pa >30 mmHg with 88% sensitivity and 57% specificity. The eight patients with resting $\bar{P}$pa 22–24 mmHg all had exercise $\bar{P}$pa >30 mmHg.

In subjects aged <50 yrs investigated for possible pulmonary vascular disease and free of PH, patients with mild-to-moderate exercise $\bar{P}$pa >30 mmHg had higher resting PVRi and higher resting $\bar{P}$pa, although there was no resting $\bar{P}$pa threshold value that could predict normal response on mild-to-moderate exercise. The clinical relevance of such findings deserves further long-term follow-up studies.

KEYWORDS: Cardiac output, pulmonary hypertension, pulmonary vascular disease, right heart catheterisation

For the last 30 yrs, the diagnosis of pulmonary hypertension (PH) depended on either a resting mean pulmonary artery pressure ($\bar{P}$pa) of >25 mmHg or an increase in $\bar{P}$pa on exercise to >30 mmHg, with the pulmonary capillary wedge pressure ⩽15 mmHg in the subgroup of pre-capillary PH. Since the 4th World Conference on PH, new guidelines have recommended that the exercise criterion should be eliminated [1, 2], given both the marked age-dependency of ''normal'' $\bar{P}$pa threshold on exercise [3] and the paucity of robust data supporting its clinical relevance [1, 2]. The age-dependency of $\bar{P}$pa is much less at rest [3–7], such that a common 20.6 mmHg upper limit of normal (ULN) was suggested in supine healthy subjects [3]. Though a $\bar{P}$pa of ⩾21 mmHg is beyond the normal range (mean +2 standard deviations) and may be suspicious of pulmonary vascular disease, a small but significant proportion of apparently normal individuals will have a $\bar{P}$pa ⩾21 mmHg and they will outnumber the previously documented proportion of patients with PH [3]. As a result, new guidelines have defined pulmonary hypertension by a $\bar{P}$pa at rest ⩾25 mmHg (mean +3 standard deviations), and have also highlighted the fact that studies focusing on patients with resting $\bar{P}$pa of 21–24 mmHg are especially needed [1–3].

Numerous studies have documented the high percentage of patients at high risk for PH exhibiting elevation of $\bar{P}$pa on exercise >30 mmHg while their $\bar{P}$pa was normal at rest [8–16], and this may be considered as an early manifestation of pulmonary vasculopathy [12, 14, 17, 18]. Most of these studies

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had been carried out in middle-aged patients, at a time when normal $\bar{P}_{pa}$ values during exercise have not yet been defined. Recently, the review of the range of pulmonary haemodynamic responses to exercise in normal subjects by KOVACS *et al*. [3] was timely in alerting the community to the huge amount of available data supporting the ''classical'' definition of exercise induced PH in patients aged <50 yrs, while the ULN of 30 mmHg was not always supported by the available data in older patients. Thus, the precise relationship between resting $\bar{P}_{pa}$ and the age-related $\bar{P}_{pa}$ responses during mild-to-moderate exercise still deserve further studies in patients free of PH, and this may have implications for improving our understanding of PH pathophysiology.

The present study examined the range of haemodynamic responses in individuals aged <50 yrs with resting $\bar{P}_{pa}$ <25 mmHg being investigated for possible pulmonary vascular disease in our institution who underwent measurement of pulmonary haemodynamic responses to mild-to-moderate exercise while supine.

METHODS

This was a retrospective study. We extracted the catheter laboratory records of all patients who underwent diagnostic right heart catheterisation at the Centre National de Référence de l'Hypertension Pulmonaire Sévère, Hôpital Antoine Béclère, Assistance Publique Hôpitaux de Paris, Université Paris-Sud, Paris, France over a 34-month period (January 1, 2007–October 31, 2009).

We included patients with a $\bar{P}_{pa}$ at rest of <25 mmHg and a pulmonary artery occlusion pressure (P_{pao}) ⩽15 mmHg who underwent progressive supine exercise test during the right heart catheterisation procedure. Patients with unexplained exertional dyspnoea or an abnormal screening echocardiogram $\bar{P}_{pa}$ were included, as well as patients with a history of probable or possible pulmonary thromboembolic disease being investigated for chronic thromboembolic pulmonary hypertension. As our aim was to examine a ''real life'' patient population undergoing diagnostic right heart catheterisation, we did not exclude patients with significant comorbidities, including diseases known to carry a risk of PH [1, 2]. We also excluded patients in whom acceptable quality P_{pao} could not be obtained. On exercise, P_{pao} >20 mmHg was considered as abnormal but the corresponding patients were not excluded *a posteriori*. The 6-min walking distance and respiratory and biological tests were obtained according to our routine protocol. Our retrospective study was compliant with requirements of the French Commission Nationale de l'Informatique et des Libertés (CNIL), and right heart catheterisation with exercise is part of the usual care at our institute.

Amongst the 99 eligible patients, only patients aged <50 yrs (n=38) were included in our final analysis and 30 mmHg was considered the ULN on mild-to-moderate exercise [3]. Patients aged ⩾50 yrs were excluded, given that KOVACS *et al*. [3] have suggested that an upper limit of 30 mmHg could not be supported by the available data in such subjects. The main risk factors and comorbidities were a previous history of thromboembolic pulmonary disease (n=14, 37%), connective tissue disease (n=8, 21%; namely two lupus and six systemic sclerosis) and anorexigens intake (n=5, 13%) (table 1).

TABLE 1 Characteristics of the study population

	Overall population	$\bar{P}_{pa,ex}$ ⩽30 mmHg	$\bar{P}_{pa,ex}$ >30 mmHg	p-value
Subjects n	38	14	24	
Demographic and clinical data				
Females	30 (80)	10 (71)	20 (83)	NS
Age yrs	40±8	40±8	40±8	NS
BSA m^2	1.72±0.22	1.86±0.22	1.63±0.18	<0.01
SAP mmHg	118±17	123±18	116±16	NS
DAP mmHg	76±10	77±9	75±10	NS
*f*C bpm	76±11	74±12	78±10	NS
Haemoglobin $g \cdot dL^{-1}$	13.3±2.0	13.7±1.7	13.2±2.1	NS
BNP $pg \cdot mL^{-1}$	31±21	30±8	32±24	NS
6MWD m	505±104	550±100	478±99	0.062
FEV_1 % pred	86±22	98±20	81±21	0.048
FVC % pred	85±21	94±19	80±21	0.110
$D_{L,CO}$ % pred	62±20	74±18	56±19	0.030
Risk factors and comorbidities n				
History of thromboembolic disease	14	6	8	
CTD	8	1	7	
Anorexigens	5	5	0	
Miscellaneous	7	1	6	
None	4	1	3	

Data are presented as n (%) or mean±SD, unless otherwise stated. $\bar{P}_{pa,ex}$: exercising mean pulmonary arterial pressure; BSA: body surface area. SAP: systolic arterial pressure. DAP: diastolic arterial pressure; *f*C: cardiac frequency; BNP: brain natriuretic peptide; 6MWD: 6-min walking distance; FEV_1: forced expiratory volume in 1 s; % pred: % predicted; FVC: forced vital capacity; $D_{L,CO}$: diffusing capacity of the lung for carbon monoxide; CTD: connective tissue diseases; NS: not significant.

Patients had baseline haemodynamic measurements showing resting $\bar{P}_{pa}$ <25 mmHg and P_{pao} ⩽15 mmHg. They then carried out supine bicycle exercise ergometry [19, 20], including baseline measurements with feet in the pedals but no dynamic exercise followed by a stepwise increase of load. The number of steps and the pattern of increase in load were determined for each individual by the operator's judgement based on the patient's age, comorbidities and clinical response to initial load. As we have concentrated on examining the haemodynamic response at mild-to-moderate exercise, we examined the data obtained <60 W [3]. As our standard protocol was developed before the new guidelines from the 4th World Conference on PH [1, 2], the exercise was terminated in cases where the $\bar{P}_{pa}$ was noted to be >30 mmHg. In patients whose exercise was terminated prior to 60 W, either due to symptoms or reaching a $\bar{P}_{pa}$ >30 mmHg, we analysed their response at their highest workload.

Statistics

Data are presented as mean±SD. Comparisons at baseline (rest) were performed by using one-way ANOVA followed by unpaired t-test. The haemodynamic effects of exercise were compared between patients with normal and abnormal $\bar{P}_{pa}$ on mild-to-moderate exercise by using a two-way ANOVA (group × time interaction). Correlations were tested by using the least squares method. Frequency distribution of both sex and $\bar{P}_{pa}$ responses between subgroups were compared using the Chi-squared test. Receiver operating characteristic (ROC) curves (with 95% confidence interval) were constructed for testing the ability of the resting $\bar{P}_{pa}$ to predict mild-to-moderate exercise $\bar{P}_{pa}$ >30 mmHg. A p-value <0.05 was considered statistically significant. The statistical analysis was performed using StatView 512 software (Abacus concepts, Berkeley, CA, USA), except for ROC curves analysis which was performed by using MedCalc8.1.0.0 software (Mariakerke, Belgium).

RESULTS

The study population (n=38) comprised 30 females and eight males (age=40±8 yrs); their clinical characteristics are listed in table 1. Median workload was 40 W (mean±SD 41±16 W). Overall, 24 out of 38 (63%) of patients developed $\bar{P}_{pa}$ >30 mmHg on mild-to-moderate exercise. As compared with the remaining 14 subjects, the 24 patients who developed $\bar{P}_{pa}$>30 mmHg on mild-to-moderate exercise had lower body surface area, lower forced expiratory volume in 1 s, and lower diffusing capacity of the lung for carbon monoxide (table 1). Differences in risk factors and comorbidities were also observed between the two groups (table 1). The two groups had similar sex ratio, age, systolic and diastolic arterial pressure, cardiac frequency and haemoglobin and brain natriuretic peptide blood content. The 6-min walking distance was 478±99 m in the 24 patients who developed $\bar{P}_{pa}$ >30 mmHg and 550±100 m in the remaining 14 patients (p=0.062) (table 1).

The haemodynamic characteristics of the study population are listed in table 2. Individual haemodynamic data are presented as online supplementary material. The 24 patients who developed $\bar{P}_{pa}$ >30 mmHg on mild-to-moderate exercise had higher resting $\bar{P}_{pa}$ (19±3 *versus* 15±4 mmHg; p<0.01) and higher indexed pulmonary vascular resistance (PVRi) at rest (3.4 ±1.5 *versus* 2.2 ±1.1 WU·m^{-2}; p<0.05) compared with the remaining 14 subjects, (table 2). They also had similar P_{pao} and cardiac index at rest (table 2), and similar right atrial pressure at rest (4±3 *versus* 5±3 mmHg; p=NS).

TABLE 2 Haemodynamics at rest and at mild-to-moderate exercise in the study population[#]

	Rest	Mild-to-moderate exercise[¶]
P_{ra} mmHg	4±3	Not recorded
$\bar{P}_{pa}$ mmHg	18±4	31±8
P_{pao} mmHg	8±3	12±5
TPG mmHg	10±5	19±7
CI L·min^{-1}·m^{-2}	3.49±0.54	6.34±1.13
PVRi WU·m^2	2.9±1.5	3.1±1.5[+]

Data are presented as mean±SD. P_{ra}: right atrial pressure; $\bar{P}_{pa}$: mean pulmonary arterial pressure; P_{pao}: pulmonary arterial occlusion pressure; TPG: transpulmonary pressure gradient; CI: cardiac index; PVRi: pulmonary vascular resistance index. [#]: n=38; [¶]: p<0.001 in each case except where indicated; [+]: not significant. n=38.

In the overall study population, there was a weak positive relationship between resting $\bar{P}_{pa}$ and mild-to-moderate exercise $\bar{P}_{pa}$ (r^2=0.44; p<0.001) (fig. 1). There was no relationship between age and either resting $\bar{P}_{pa}$ or mild-to-moderate exercise $\bar{P}_{pa}$.

Haemodynamic responses to mild-to-moderate exercise in the two subgroups are detailed in table 3 and individual $\bar{P}_{pa}$, P_{pao} and cardiac index values are presented as online supplementary material. Cardiac index increased in a similar way and PVRi remained unchanged in the two subgroups (table 3). Mild-to-moderate differences in P_{pao} changes (p=0.047) were documented between the two subgroups. On exercising, two patients had P_{pao}>20 mmHg (25 and 21 mmHg, see online supplementary material) with >12 mmHg transpulmonary pressure gradient (24 and 13 mmHg, respectively), and both had $\bar{P}_{pa}$ >30 mmHg.

Exercising $\bar{P}_{pa}$ exceeded 30 mmHg in 15 out of 27 (55%) of the patients with resting $\bar{P}_{pa}$ <21 mmHg and in nine out of 11 (82%) of the patients with resting $\bar{P}_{pa}$ between 21 and 24 mmHg (p=NS) (table 4). The eight patients with resting $\bar{P}_{pa}$ 22–24 mmHg all had

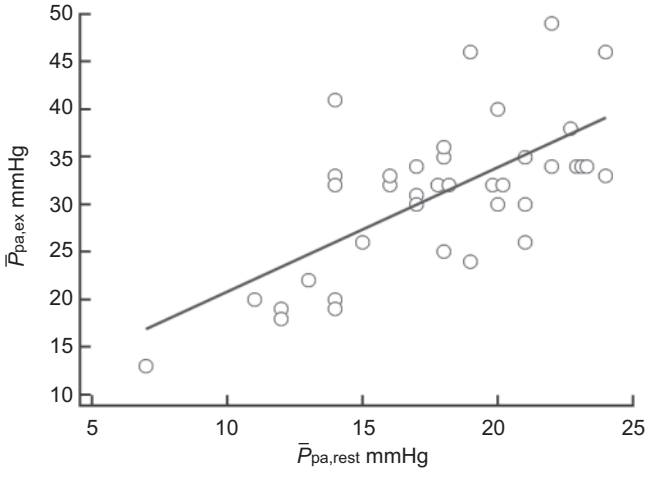

FIGURE 1. Linear relationship between mean pulmonary arterial pressure whilst exercising ($\bar{P}_{pa,ex}$) and at rest ($\bar{P}_{pa,rest}$). n=38; r^2=0.44; p<0.001.

TABLE 3 Haemodynamic data at rest and while exercising according to the normal/abnormal response of mean pulmonary arterial pressure on mild-to-moderate exercise ($\bar{P}$pa,ex)

	$\bar{P}$pa,ex ⩽30 mmHg		$\bar{P}$pa,ex >30 mmHg		Two-way ANOVA p-value
	Rest	Exercise	Rest	Exercise	
Subjects n	14		24		
$\bar{P}$pa mmHg	15±4	23±5	19±3**	36±5	0.0001
Ppao mmHg	8±4	10±4	8±3#	13±5	0.047
TPG mmHg	8±4	13±5	11±4*	22±6	0.0001
CI L·min^{-1}·m^{-2}	3.62±0.56	6.26±1.24	3.41±0.52#	6.38±1.09	0.30
PVRi WU·m^2	2.2±1.1	2.1±1.0	3.4±1.5*	3.7±1.5	0.25

Data are presented as mean±SD, unless otherwise stated. $\bar{P}$pa: mean pulmonary arterial pressure; Ppao: pulmonary arterial occlusion pressure; TPG: transpulmonary pressure gradient; CI: cardiac index; PVRi: pulmonary vascular resistance index. #: not significant. *: p<0.05; **: p<0.01 *versus* resting values in the $\bar{P}$pa,ex ⩽30 mmHg subgroup.

an exercising $\bar{P}$pa >30 mmHg. ROC curve analysis (fig. 2) indicated that a resting $\bar{P}$pa >15 mmHg predicted an exercising $\bar{P}$pa >30 mmHg with 88% sensitivity (95% CI 68–97%) and 57% specificity (95% CI 29–82%).

DISCUSSION

Our retrospective study was performed in 38 patients aged <50 yrs, free of PH (resting $\bar{P}$pa <25 mmHg), being investigated in our centre for possible vascular disease between January 1, 2007 and October 31, 2009. The main results were as follows: 1) patients with mild-to-moderate exercise $\bar{P}$pa >30 mmHg had higher resting PVRi and higher resting $\bar{P}$pa; 2) it was not possible to reliably set a lower limit of resting $\bar{P}$pa that guarantees normal $\bar{P}$pa at mild-to-moderate exercise loads; and 3) all eight patients with resting $\bar{P}$pa 22–24 mmHg had exercising $\bar{P}$pa >30 mmHg. The clinical relevance of such findings deserves further long-term follow-up studies.

The present study was undertaken following recent articles and editorials that stressed the necessity of further research in the area of haemodynamics in patients with pulmonary vascular diseases, with special focus on the potential link between resting and exercising pulmonary haemodynamics and on the significance of resting $\bar{P}$pa 21–24 mmHg [1–3, 12, 17, 18]. Numerous studies [8–16] have documented the so-called ''exercise-induced pulmonary hypertension'' [12, 13, 15, 17] frequently observed in various populations carrying a high risk of PH while their $\bar{P}$pa was normal at rest. To the best of our knowledge, our study is the first to take into account the recent recommendations made by KOVACS *et al*. [3], namely that the 30 mmHg ULN for the $\bar{P}$pa achieved on mild-to-moderate exercise fairly applies only in patients aged <50 yrs. Thus elderly patients (61 out of 99) were not included in our final analysis, given that an ULN of 30 mmHg could not be supported by the available data in such patients [3].

Our study focused on mild-to-moderate exercise only, and this was based on the following rationale. First, the literature review made it possible to define reliable ULN for $\bar{P}$pa during mild-to-moderate exercise [3, 5]. Secondly, reliable and consistent $\bar{P}$pa, Ppao and cardiac output data have been published during mild-to-moderate exercise [4, 5, 21], thus allowing pathophysiological interpretation of our data. Finally, light exercise may reflect the daily life physiological stress put on the pulmonary circulation and right ventricle more accurately than maximal exercise [1, 2].

In healthy subjects aged <50 yrs, the resting $\bar{P}$pa is ~14 mmHg on average [1–3], and the haemodynamic changes on mild-to-

TABLE 4 Summary of resting mean pulmonary arterial pressure ($\bar{P}$pa,rest) *versus* exercising $\bar{P}$pa ($\bar{P}$pa,ex) in the 38 patients

$\bar{P}$pa,ex	$\bar{P}$pa,rest <21 mmHg	$\bar{P}$pa,rest 21–24 mmHg	Total
⩽30 mmHg	12	2	14
>30 mmHg	15	9	24
Total	27	11	38

Data are presented as n.

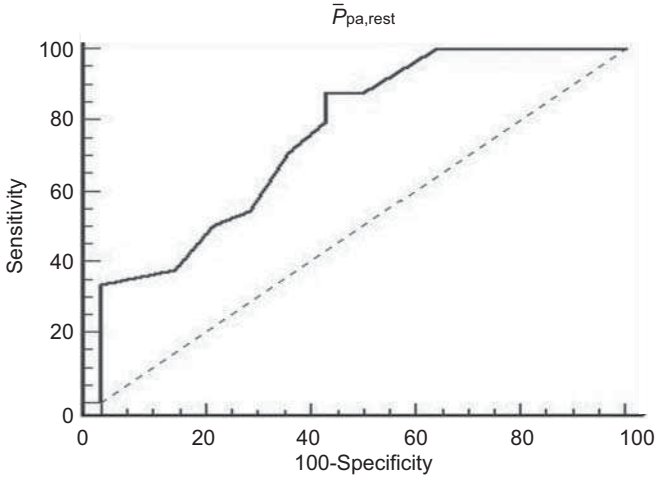

FIGURE 2. Receiver operating characteristic curve showing mean pulmonary arterial pressure at rest ($\bar{P}$pa,rest) >15 mmHg and predicted exercise $\bar{P}$pa >30 mmHg with 88% sensitivity (95% CI 68–97%) and 57% specificity (95% CI 29–82%).

moderate exercise while supine slightly differ according to the research team, with either unchanged PVR [5, 22], or slightly decreased PVR [23]. Pulmonary capillary pressure may increase slightly [3, 5, 6, 24], although other studies and reference textbooks often indicate unchanged pulmonary capillary pressure during exercise. The 18 mmHg resting $\bar{P}_{pa}$ value documented in our study (table 2) is consistent with that previously reported in populations similar to ours [12–15] and reflects the fact that patients were investigated in our centre for possible vascular disease. It has been suggested that age, sex and resting systolic blood pressure significantly influence $\bar{P}_{pa}$ responses to exercise, but all were similar in the two groups (table 1). The underlying risk factors and comorbidities (table 1) may contribute, at least in part, to explaining the high percentage (24 out of 38; 63%) of patients exhibiting abnormal $\bar{P}_{pa}$ responses [8–16].

The stress put on the right ventricle is minimal at rest and this may in part explain why resting pulmonary haemodynamics do not correlate highly with exercise pulmonary haemodynamics in patients with established PH [6, 8, 12, 19, 20, 25, 26]. In our patients at risk for PH and exhibiting normal $\bar{P}_{pa}$ at rest, ROC curve analysis indicated that resting $\bar{P}_{pa}$ >15 mmHg predicted exercise $\bar{P}_{pa}$ >30 mmHg with 88% sensitivity and 57% specificity. Interestingly, SAGGAR *et al*. [15] have suggested that resting $\bar{P}_{pa}$ $\geqslant$14 mmHg was associated with abnormal $\bar{P}_{pa}$ responses on exercise in patients with systemic sclerosis. However, in our study, it was not possible to reliably set a lower limit of resting $\bar{P}_{pa}$ that guarantees normal $\bar{P}_{pa}$ at mild-to-moderate exercise loads

As far as the upper limit that guarantees abnormal $\bar{P}_{pa}$ at mild-to-moderate exercise loads is concerned, it may be expected that the closer the resting $\bar{P}_{pa}$ lies to the ULN on exercise (30 mmHg) the more likely the exercise $\bar{P}_{pa}$ threshold is to be breached. Resting $\bar{P}_{pa}$ was consistently higher in the 24 patients who developed $\bar{P}_{pa}$ >30 mmHg on mild-to-moderate exercise, and this was explained by the 55% higher levels for resting PVRi as compared with the remaining 14 patients who did not develop $\bar{P}_{pa}$ >30 mmHg on mild-to-moderate exercise (table 3). This could also explain why exercise $\bar{P}_{pa}$ was >30 mmHg in 82% (nine out of 11) of the patients with resting $\bar{P}_{pa}$ 21–24 mmHg and in all eight patients with resting $\bar{P}_{pa}$ of 22–24 mmHg.

Significant differences in P_{pao} changes were also documented and contributed to explaining differences in exercising $\bar{P}_{pa}$ in the two subgroups (table 3). Amongst the 24 patients with $\bar{P}_{pa}$ >30 mmHg on exercise, two (8%) had an exercising P_{pao} of >20 mmHg (see online supplementary material), thus confirming that acute left ventricular dysfunction could also contribute to the rise in $\bar{P}_{pa}$, *e.g.* diastolic dysfunction [27, 28]. Conversely, similar cardiac output responses on exercise were documented in the two subgroups and gave similar PVRi responses (table 3). In summary, in patients aged <50 yrs and free of PH, the increased PVRi at rest resulting in higher resting $\bar{P}_{pa}$ was the main factor likely to explain abnormally high $\bar{P}_{pa}$ on mild-to-moderate exercise. Additionally, further exercise-related increases in capillary wedge pressure also played a role.

Our study did not involve healthy subjects, but patients with symptoms and a certain risk of PH. Accordingly, the results cannot be used to create novel thresholds of physiological changes during exercise and may not be compared with studies examining healthy individuals. The clinical heterogeneity of the study group reflects the current ''real-life'' experience of a reference PH centre. Other limitations include the retrospective study design and the lack of extensive assessment of left ventricular function at rest (*e.g.* detailed echocardiography to detect diastolic and/or systolic dysfunction). The intrinsic limitations related to the exercise protocol must also be discussed. We have examined $\bar{P}_{pa}$ responses on mild-to-moderate exercise as best as we could, with the understanding that we do not measure oxygen consumption during our right heart studies. We could not determine the slope and pressure axis intercept of the $\bar{P}_{pa}$–cardiac output relationship, as the number of data points and pattern of exercise varied between individuals. The determination of multipoint $\bar{P}_{pa}$–cardiac output plots provides a more accurate insight into the nature of PVR than the single-point PVR, as the intercept may be higher than pulmonary capillary pressure [6, 7, 19, 20, 29, 30]. Thus, the observed pattern of increased transpulmonary pressure gradient and increased cardiac output together with unchanged or decreased single-point PVR does not necessarily reflect unchanged or decreased resistive properties of the pulmonary circulation [7, 20, 29, 30]. Similarly, we cannot exclude the possibility that our results reflect averaging patients with various patterns of $\bar{P}_{pa}$–cardiac output relationship on exercise [20]. The two patients with exercise P_{pao} >20 mmHg were included in our final analysis as our aim was to study the relationship between resting and mild-to-moderate exercise $\bar{P}_{pa}$ in patients at risk of PH but free of PH at rest ($\bar{P}_{pa}$ <25 mmHg) and with normal filling pressure at rest (P_{pao} $\leqslant$15 mmHg). Finally, elderly subjects could not be studied for the above-mentioned reasons and further studies focusing on this population are thus needed.

The implications of our study must be carefully considered. First of all, we wish to emphasise the fact that our study did not intend to challenge the 4th World Conference proposal that exercise testing must be abandoned in the definition of PH [1, 2]. However, we remain concerned by the fact that the new consensus does sometimes leave clinicians faced with a patients that have symptoms suggestive of pulmonary vascular disease but with resting $\bar{P}_{pa}$ <25 mmHg [12, 14, 18]. Interestingly, our study pointed to a major redundancy between resting and mild-to-moderate exercise $\bar{P}_{pa}$ values in the subgroup of patients <50 yrs with a resting $\bar{P}_{pa}$ of 22–24 mmHg. The 22–24 mmHg range of resting $\bar{P}_{pa}$ may help clinicians to recognise patterns consistent with abnormal haemodynamic responses on mild-to-moderate exercise. Elsewhere, our study demonstrates a lack of tight correlation between resting and exercise haemodynamics in non-PH patients. In other words, our data would suggest that it is not possible to reliably set a lower limit of resting $\bar{P}_{pa}$ that guarantees that pulmonary haemodynamic responses to exercise will be normal at mild-to-moderate exercise loads in patients <50 yrs.

In conclusion, in subjects aged <50 yrs and free of PH, patients with mild-to-moderate exercise $\bar{P}_{pa}$ >30 mmHg had higher resting PVRi and higher resting $\bar{P}_{pa}$. Although all patients with resting $\bar{P}_{pa}$ 22–24 mmHg had an exercising $\bar{P}_{pa}$ >30 mmHg, there was no resting $\bar{P}_{pa}$ threshold value that could reasonably predict normal/abnormal response on mild-to-moderate exercise. The clinical relevance of such findings deserves further long-term follow-up studies.

STATEMENT OF INTEREST

Statements of interest for K. Whyte, S. Hoette, D. Montani, L. Savale, D.S. O'Callaghan, G. Garcia, O. Sitbon, G. Simonneau and M. Humbert can be found at www.erj.ersjournals.com/site/misc/statements.xhtml

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CHEST

Original Research

PULMONARY VASCULAR DISEASE

The Role of Target Therapies in Schistosomiasis-Associated Pulmonary Arterial Hypertension

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Background: **Schistosomiasis-associated pulmonary arterial hypertension (Sch-PAH) may be one of the most prevalent forms of pulmonary arterial hypertension (PAH) worldwide. However, the clinical and hemodynamical response to specific PAH therapy in Sch-PAH is not known.**
Methods: **We retrospectively analyzed the charts of all patients with Sch-PAH who initiated specific PAH treatment between June 2003 and June 2010 in a single PAH reference center in São Paulo, Brazil. Clinical and hemodynamical data were retrospectively collected and evaluated in two periods: baseline and posttreatment.**
Results: **The study population consisted of 12 patients with Sch-PAH. They were treated with phosphodiseterase-5 inhibitors (seven patients), endothelin receptor antagonists (four patients), or combination therapy (one patient). Mean treatment period was 34.9 ± 15.5 months. Patients with Sch-PAH presented significant improvements in terms of functional class, 6-min walk test distance (439 ± 85 to 492 ± 79 m, *P* = .032), cardiac index (2.66 ± 0.59 to 3.08 ± 0.68 L/min/m², *P* = .028), and indexed pulmonary vascular resistance (20.7 ± 11.6 to 15.9 ± 9 W/m², *P* = .038) with the introduction of specific PAH treatment.**
Conclusions: **We conclude that specific PAH therapy may be of benefit to patients with Sch-PAH, considering clinical, functional, and hemodynamic parameters.** ***CHEST 2012; 141(4):923–928***

Abbreviations: 6MWT = 6-min walk test; ERA = endothelin receptor antagonist; IPAH = idiopathic pulmonary arterial hypertension; NYAH = New York Heart Association; PAH = pulmonary arterial hypertension; PoPH = portopulmonary hypertension; Sch-PAH = schistosomiasis-associated pulmonary arterial hypertension

Pulmonary arterial hypertension (PAH) is a life-threatening disease that may occur either in idiopathic form or in the setting of different associated medical conditions. PAH is characterized by a marked and sustained elevation of pulmonary vascular resistance, leading to an increase in pulmonary artery pressure, right ventricular failure, and ultimately death.[1] Nevertheless, despite its severity, in the last 20 years advances in the therapeutic management of the disease have changed the natural history of PAH.[2,3] In modern days, patients with idiopathic pulmonary arterial hypertension (IPAH), connective tissue disease-associated PAH, or congenital heart disease-associated PAH benefit from prostanoids, endothelin receptor antagonists (ERAs), and phosphodiesterase-5 inhibitors, improving clinical and hemodynamic function as well as quality of life and even survival.[4,5] Other etiologies in group 1 of the pulmonary hypertension classification also have demonstrated some benefit with specific PAH treatment.[6-9] However, there is no evidence in medical literature about clinical efficacy of specific PAH treatment for one of the pivotal causes of PAH, the disease associated with schistosomiasis.

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In the setting of pulmonary hypertension, the relevance of schistosomiasis-associated PAH (Sch-PAH) has been better recognized in recent years. It is believed that approximately 5% of patients diagnosed with hepatosplenic *Schistosomiasis mansoni* may also present themselves with PAH,[10] suggesting that Sch-PAH is potentially the most prevalent cause of PAH worldwide. Its importance might be even greater in endemic regions for schistosomiasis. Indeed, it is estimated that up to 30% of all pulmonary hypertension patients followed at reference centers in Brazil have Sch-PAH.[11] In the updated classification of PAH,[12] following the better understanding of the mechanisms involved in Sch-PAH as well as its hemodynamic features, Sch-PAH has been reclassified within group 1 (PAH), the group that generates the biggest interest in the area, as well as the most researched of all five groups.

Mortality rates associated with Sch-PAH were recently described in a Brazilian cohort and may reach up to 15% in 3 years.[13] Despite being less severe than IPAH, Sch-PAH affects a young population (between the fourth and fifth decades of life), and its described prognosis justifies the need of specific therapies for this setting. Nevertheless, no information about the hemodynamic and/or clinical response to target PAH therapies in Sch-PAH is available. The objective of this study was to evaluate the clinical, functional, and hemodynamic responses of patients with Sch-PAH followed at a PAH reference center in Brazil who received specific PAH treatment.

Materials and Methods

Patient Population

All patients with Sch-PAH who initiated specific PAH treatment between June 2003 and June 2010 in a single PAH reference center in São Paulo, Brazil, were included in this study. The study was approved by the ethics board of the institution, approval 1359/06. Clinical and hemodynamic data were retrospectively collected.

PAH was defined by a mean pulmonary artery pressure (mPAP) >25 mm Hg with a normal pulmonary artery occlusion pressure <15 mm Hg. Patients were classified as having Sch-PAH when the presence of PAH was associated with liver ultrasonographic findings highly suggestive of mansonic schistosomiasis (left lobe enlargement and/or periportal fibrosis[14]) and at least one of the following features: (1) exposure to endemic region for schistosomiasis, (2) previous treatment of schistosomiasis, and (3) presence of *S mansoni* eggs in stool examination or rectal biopsy.

Functional and Hemodynamic Evaluations

Baseline evaluation included demographics, medical history, physical examination, New York Heart Association (NYHA) functional class assessment, routine laboratory testing, a nonencouraged 6-min walk test (6MWT), as previously described,[15] and right-sided heart catheterization using standard techniques.[16] Both clinical and hemodynamic reevaluation were performed in all patients at different follow-up intervals as dictated by the patient clinical status.

Treatment

In the absence of any contraindication (eg, high risk of gastrointestinal bleeding or presence of esophageal varices), patients received oral anticoagulation; diuretics and oxygen were prescribed as needed during the whole observational period. Patients with Sch-PAH do not receive PAH-specific therapy as a routine in our center due to the absence of controlled clinical data supporting this indication. Also, in Brazil specific PAH treatments are systematically available only for IPAH, connective tissue disease-related PAH, and PAH related to congenital heart disease. Nevertheless, all patients enrolled in this study received specific PAH treatment as rescue therapy due to progressive right ventricular dysfunction, following current recommendations for IPAH[17] as a guideline. Patients in functional class III or IV received first-line therapy with either an ERA or a phosphodiesterase-5 inhibitor. The choice between the agents was based merely on drug availability. One patient presenting in NYHA functional class IV with rapidly progressive disease and worsening symptoms received combination therapy with agents from both classes as first-line therapy.

Statistical Analysis

Analysis was performed using the SPSS 15 statistical package (SPSS, Inc). All continuous variables are expressed as mean $\pm$ SD; categorical data are presented as proportions. For comparison between baseline and posttreatment clinical and hemodynamic characteristics, a paired t test was used. A P value $<.05$ was considered statistically significant.[18,19]

Results

The study population consisted of 12 patients with Sch-PAH. All patients had endemic exposure to schistosomiasis and highly suggestive liver ultrasonographic findings; additionally, four patients examined also had positive stool at the time of diagnostic investigation. Specific treatment was predominantly based on use of phosphodiseterase-5 inhibitors ($n=7$, 58.3%). ERAs were used in four patients (33.3%) and first-line combination therapy in one patient (8.4%).

Baseline and posttreatment clinical, functional, and hemodynamic data are shown in Table 1 and Figure 1. The mean period of treatment between baseline and posttreatment evaluations was 34.9 ± 15.5 months. The majority of patients with Sch-PAH improved functional class with the introduction of specific PAH treatment (nine of 12 patients) (Fig 1A). 6MWT distance (Fig 1B), cardiac index, and indexed pulmonary vascular resistance (Table 1) also improved with the therapy. No difference was found in mean pulmonary arterial pressure (mPAP) as a consequence of treatment.

Discussion

The present study demonstrated that patients with Sch-PAH may have significant clinical, functional, and

Table 1—*Clinical and Hemodynamical Data at Baseline and Post-Specific PAH Treatment for Patients With Sch-PAH (N = 12)*

Parameter	Baseline	Posttreatment	*P* Value
Age, y	46.2 ± 9.8	…	…
NYHA functional class			
I	0	5 (41.6)	.002
II	0	5 (41.6)	…
III	9 (75)	2 (16.8)	…
IV	3 (25)	0	…
6MWT, m	439 ± 85	492 ± 79	.032
Hemodynamics			
RAP, mmHg	11.0 ± 5.9	10.8 ± 3.8	.65
mPAP, mmHg	64.0 ± 19.1	58.7 ± 17.1	.13
CI, L/min/m^2	2.7 ± 0.6	3.1 ± 0.7	.028
PAOP, mmHg	12.1 ± 3	13.7 ± 4.4	.24
PVR, International Units	12 ± 6.5	9.1 ± 4.8	.038
First-line treatment			
PDE-5 inhibitor	0	7 (58.3)	…
ERA	0	4 (33.3)	…
Combined therapy	0	1 (8.4)	…

Data are given as mean ± SD or No. (%). Mean period between evaluations: 34.9 ± 15.5 mo. 6MWT = distance on nonencouraged 6-min walk test; CI = cardiac index; ERA = endothelin receptor antagonist; mPAP = mean pulmonary artery pressure; PAOP = pulmonary artery occlusion pressure; PDE-5 = phosphodiesterase-5 inhibitor; PVR = pulmonary vascular resistance; RAP = right atrial pressure; Sch-PAH = schistosomiasis-associated pulmonary arterial hypertension.

hemodynamic improvements in response to specific PAH treatments. To the best of our knowledge, this is the first time that such an observation has been reported.

Schistosomiasis is a disease directly correlated to poverty and lack of sanitation, with a characteristic geographical distribution.[20,21] Nevertheless, there is an insurgence of new cases in developed countries, following migratory practices and modern tourist habits. According to the US Centers for Disease Control and Prevention, schistosomiasis is one of the 10 leading causes of morbidity among travelers.[22] Pulmonary hypertension represents one of the most severe complications of chronic schistosomiasis, with a prevalence of 5% in patients with mansonic hepatosplenic disease, and it may take years after the initial infestation by the worm to develop.[10] It is probable that, in a few years, other PAH reference centers, beyond the traditional geographic borders of the disease, will have to deal with this etiology of PAH.

Clinical data about presentation of Sch-PAH demonstrate that the disease is similar to IPAH in several aspects, such as mean age and functional class at diagnosis, as well as baseline 6MWT.[13] Furthermore, pathology studies have shown similarities between IPAH and Sch-PAH regarding the histology of small lung arteries and the presence of plexiform lesions in both groups.[23] Therefore, it seems reasonable to empirically use already available classes of medications for PAH to these patients, provided that they also present themselves with dyspnea on exertion and/or symptoms of right ventricular insufficiency. However, there are significant differences between IPAH and Sch-PAH: The hemodynamic profile at diagnosis is markedly better in Sch-PAH, as compared with IPAH and survival in Sch-PAH seems to be better that in other PAH forms. These findings need to be accounted for when designing appropriate controlled studies in this specific subset of patients.

Considering the high prevalence of schistosomiasis worldwide (200 million patients, 8.5 million with hepatoesplenic disease,[24] potentially more than 400,000 patients with Sch-PAH[10]) when compared with the other relatively rare etiologies of PAH, including IPAH (about 170,000 patients worldwide[25]), the 15% 3-year mortality described in Sch-PAH[13] is of absolute relevance. Moreover, although Sch-PAH seems to have a slower progression, eventually patients deteriorate in a similar fashion to IPAH. Thus, one might speculate that specific PAH therapy to Sch-PAH may obey the same general principles of IPAH treatment.[17]

Additionally, the magnitude of response to specific PAH therapy found in patients with Sch-PAH in this study is encouraging. Despite the long time interval between evaluations, an increase of 16% in CI was observed. In the same direction, the 6MWT increased by 12%, and most patients improved the functional class. Even after 35 months, patients with Sch-PAH still demonstrated clear signs of clinical and hemodynamic improvement.

There are several proposed mechanisms of disease for Sch-PAH: (1) embolic disease by egg impact in the pulmonary circulation and mechanical obstruction[26]; (2) passage of the worm or the egg by the lungs, inducing endothelial dysfunction by inflammatory mediator release and abnormal scarring[27,28]; and (3) like portopulmonary hypertension (PoPH), the pulmonary overflow caused by the opening of portocaval shunts in the presence of portal hypertension induces endothelial dysfunction and PAH.[29] Based on the last mechanism, it is tempting to correlate the known benefits of the specific PAH therapy in the setting of PoPH[6] to Sch-PAH. Nevertheless, it is clear today that PoPH and Sch-PAH are not the same disease; while 1% to 2% of portal hypertension patients develop PAH,[30] approximately 5% of schistosomotic hepatosplenic patients present PAH,[10] suggesting that different mechanisms might be involved in PAH genesis. A published cohort of PoPH patients showed that the outcome of these patients is influenced by the degree of liver insufficiency and by cardiac function,[31] but it is important to emphasize that patients with Sch-PAH do not routinely present

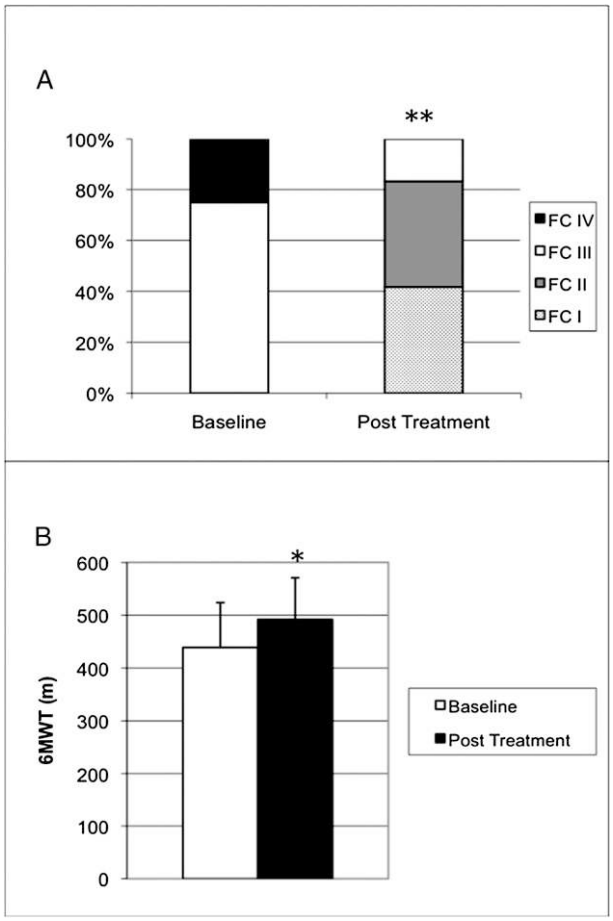

FIGURE 1. Clinical data at baseline and post-specific pulmonary arterial hypertension (PAH) treatment for patients with schistosomiasis-associated pulmonary arterial hypertension. A, Proportion of patients in respective New York Heart Association (NYHA) FC. B, Length in 6MWT. *$P < .05$; **$P < .01$. 6MWT = non-encouraged 6-min walk test; FC = functional class.

liver dysfunction in association with portal hypertension. Nonetheless, data regarding use of specific PAH therapy in patients with PoPH, as in patients with IPAH, should not be directly extrapolated to other groups such as Sch-PAH.

When the data of patients with Sch-PAH is analyzed considering previous information obtained in patients with IPAH, some issues may be noted. Three patients with Sch-PAH had functional class IV at diagnosis while the others had functional class III. However, this does not match with a quite high baseline walking distance (440 m). This kind of discrepancy between functional class and 6MWT has been described in other forms of PAH, such as in PoPH. Considering the comorbidities present in chronic schistosomiasis, it might be expected that other factors may influence dyspnea besides the hemodynamic limitation. However, it is important to emphasize that the high variability of 6MWT may also prevent further speculation in this case series, reinforcing the point with regard to the absence of a consensus on the value of 6MWD in non-IPAH PAH.

Recent data demonstrated no acute response to vasodilator test in Sch-PAH, therefore there would be no indication of a high dose of calcium-channel blockers as primary therapy in this group.[13] The choice between ERA and the phosphodiesterase-5 inhibitor in this study was made mainly by the availability of the drug in our center at the moment of therapy initiation. There was no significant side effect in the seven patients using the phosphodiesterase-5 inhibitor, the four patients using ERAs, or the one using combined therapy. Particular attention was paid to the patients with Sch-PAH using ERAs and the one with combined therapy because patients with hepatosplenic schistosomiasis have hepatic blood flow impaired due to portal hypertension, generating some degree of relative ischemia and possibly amplifying vulnerability to the potential hepatoxicity of this class of drugs. Nevertheless, no significant abnormal levels of liver enzymes were identified during the course of study (data not shown). In fact, some drugs of this class, such as bosentan, have been safely used in PoPH in several reports.[6] Cases of favorable responses with the use of sildenafil in Sch-PAH have been previously reported,[32] but without hemodynamic confirmation of PAH diagnosis and post-treatment control.

Other forms of specific treatment in Sch-PAH also should be considered. Being an infectious disease for which a single dose treatment is widely available, the need for implementing the antiparasitic treatment to this population—even with the purposes of discontinuing the chronic infection, and avoiding both re-infection and infestation of other patients—is quite obvious. Nevertheless, there is a possible role of antiparasitic treatment on pulmonary arteriopathy as well. It is known that, in hepatosplenic disease, this modality of treatment may improve the tissue architectural destruction induced by the disease, sometimes even promoting complete resolution of the granulomatous process.[33] Despite the fact that this effect has never been specifically studied in the pulmonary circulation, at least one case report has been published showing significant improvement in pulmonary hemodynamics after treatment of *Schistosoma hematobium*.[34] Nevertheless, all of our patients with Sch-PAH received adequate treatment of *S mansoni* at the time of diagnosis, therefore, before any specific PAH treatment was initiated.

Our study has several limitations that have to be taken into consideration before any extrapolation of our data. It is a retrospective case series with a limited number of patients followed at a single tertiary center. It should be solely considered as an exploratory hypothesis generating study. Not all patients with

Sch-PAH were treated, and this surely led to selection bias, minimized by the fact that the comparison was done to the patient him or herself and not to a control subject. It would have been extremely valuable if a larger number of patients could have been treated with targeted therapies; however, the limited drug availability imposes a major limitation in this matter. Therefore, it is particularly important to gather data that support the use of specific therapies in Sch-PAH. Nevertheless, this is a first step in establishing the clinical response to specific PAH therapy to patients with Sch-PAH, and also the first report to provide evidence of potential efficacy of target therapies in the setting of Sch-PAH, enabling and reinforcing the need for controlled trials. We conclude that specific PAH therapy may be of benefit to patients with Sch-PAH, considering clinical, functional, and hemodynamical parameters.

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Dr Fernandes: contributed to study conception and design and the drafting and writing of the manuscript.
Dr Dias: contributed to data interpretation and writing of the manuscript.
Dr Jardim: contributed to the revision of the manuscript.
Dr Hovnanian: contributed to data interpretation and writing of the manuscript.
Dr Hoette: contributed to data interpretation and writing of the manuscript.
Dr Morinaga: contributed to the drafting and writing of the manuscript.
Dr S. Souza: contributed to data analysis and writing of the manuscript.
Dr Suesada: contributed to the revision of the manuscript.
Dr Breda: contributed to the revision of the manuscript.
Dr R. Souza: contributed to study conception and design and writing of the manuscript.
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REVIEW

Implementing the ESC/ERS pulmonary hypertension guidelines: real-life cases from a national referral centre

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ABSTRACT: Pulmonary hypertension (PH) comprises a heterogeneous group of disorders characterised by increased pulmonary vascular resistance that results in progressive right ventricular failure. In order to translate current evidence into routine clinical practice, the European Society of Cardiology (ESC) and the European Respiratory Society (ERS) have recently jointly proposed evidence-based guidelines for the optimal management of different PH patient groups. This article describes a series of clinical cases of PH due to various aetiologies that were referred to a large national PH expert referral centre. In each case, the assessment and therapeutic approach undertaken is described in the context of the new ECS/ERS guidelines. The routine diagnostic work-up of suspected idiopathic pulmonary arterial hypertension (PAH) and recommended treatments for patients with functional class II, III and IV disease is emphasised. Familial screening and management of heritable PAH is discussed. Appropriate investigation and therapeutic strategies for patients with chronic thromboembolic disease and PH that is associated with congenital heart disease, pulmonary veno-occlusive disease and systemic sclerosis are also highlighted.

The term pulmonary hypertension (PH) describes a group of devastating and life-limiting diseases, defined by a mean pulmonary artery pressure ($\bar{P}_{pa}$) $\geqslant$25 mmHg at rest [1–8]. PH remains poorly characterised as it is a rare disorder and because there is an incomplete understanding of the diverse underlying pathogenic conditions and mechanisms. Furthermore, effective treatment approaches available to clinicians have traditionally been limited. However, the past decade has witnessed a significant increase in our knowledge base, leading to novel medical, surgical and supportive therapeutic options for patients. In addition, international collaborative efforts have directly led to the development of regularly updated proceedings and guidelines [1, 2, 9]. The recent publication of the joint European Society of Cardiology (ESC) and European Respiratory Society (ERS) guidelines is a major event in our community and it thus appeared timely to comment on these guidelines with real-life cases managed according to this approach [1, 2]. Indeed, it is essential to implement these guidelines in day-to-day care of this fragile patient population [4, 10]. This article describes a number of real-life clinical cases and focuses on the management approaches employed at a large national pulmonary vascular disease referral centre. The level of evidence and the strength of recommendation of particular treatment options are weighed and graded according to pre-defined scales, as presented in tables 1 and 2.

CASE 1: DIAGNOSTIC WORK-UP IN IDIOPATHIC PULMONARY ARTERIAL HYPERTENSION

Case report

A 30-yr-old female presented with progressive dyspnoea associated with intermittent episodes of dizziness. She was a nonsmoker and had no history of venous thromboembolism, Raynaud's phenomenon or exposure to anorexigens. Family history was noncontributory. At initial assessment after referral to a PH expert centre she was deemed to be in World Health Organization (WHO) functional class III. Physical examination was remarkable only for a loud second heart sound over the pulmonic valve. There was no clinical

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TABLE 1 ESC/ERS guidelines: classes of recommendations

	Definition
Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure.
Class IIa	Weight of evidence/opinion is in favour of usefulness/efficacy.
Class IIb	Usefulness/efficacy is less well established by evidence/opinion.
Class III	Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful.

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evidence of connective tissue disease (CTD). Transthoracic echocardiography revealed dilated right heart chambers, moderate impairment of right ventricular contractility and a systolic P_{pa} estimated to be 70 mmHg. Her 6-min walk distance (6MWD) was 310 m. Pulmonary function tests (PFTs) and arterial blood gas analysis were within normal limits. The only abnormality observed on high-resolution computed tomography (HRCT) was mild dilatation of the pulmonary arteries. Ventilation/perfusion lung scintigraphy demonstrated some subsegmental mismatched defects but findings were not consistent with a diagnosis of chronic thromboembolic PH (CTEPH). Testing for infection with hepatitis B, hepatitis C and HIV was negative and liver function tests were normal. Portal hypertension was excluded by abdominal ultrasound. The patient proceeded to diagnostic right heart catheterisation (RHC), which confirmed severe pre-capillary PH ($\bar{P}_{pa}$ 55 mmHg, pulmonary capillary wedge pressure (P_{pcw}) 8 mmHg, cardiac index (CI) 2.88 $L \cdot min^{-1} \cdot m^{-2}$ and pulmonary vascular resistance (PVR) 694 $dyn \cdot s \cdot cm^{-5}$). Acute vasodilator testing with inhaled nitric oxide was negative. As no identifiable underlying cause was revealed by the various investigations performed for the work-up of PH in this patient, a diagnosis of idiopathic pulmonary arterial hypertension (PAH) was established and endothelin receptor antagonist therapy was instituted. Oral anticoagulation for a target international normalised ratio (INR) of 2–3 was initiated, and the patient was advised on effective contraception measures as well as avoidance of excessive physical activity. A clinical and haemodynamic re-evaluation after 4 months was scheduled.

TABLE 2 ESC/ERS guidelines: levels of evidence

Level of evidence A	Data derived from multiple randomised clinical trials[#] or meta-analyses.
Level of evidence B	Data derived from multiple randomised clinical trials[#] or large nonrandomised studies.
Level of evidence C	Consensus of opinion of the experts and/or small studies, retrospective studies, registries.

[#]: or large accuracy or outcome trial(s) in the case of diagnostic tests or strategies. Reproduced from [1] with permission from the publisher.

Commentary: relevance to ESC/ERS guidelines

PH has been defined as an increase in $\bar{P}_{pa} \geqslant 25$ mmHg at rest, as assessed by RHC.

The definition of PH on exercise as a $\bar{P}_{pa} \geqslant 30$ mmHg is not supported by published data and healthy individuals can reach much higher values. Thus no definition for PH on exercise as assessed by RHC can be provided at the present time.

According to various combinations of values of P_{pcw}, PVR and cardiac output (CO), different haemodynamic definitions of PH are shown in table 3.

To avoid possible confusion among the terms PH and PAH, the specific definitions have been included in table 4.

Compared with the previous version of the clinical classification, a number of changes have been made (table 5). 1) In group 1, corresponding to PAH, the term familial PAH has been replaced by heritable PAH that includes clinically sporadic idiopathic PAH with germline mutations and clinical familial cases with or without identified germline mutations. 2) Associated PAH includes conditions that can have a similar clinical presentation to that seen in idiopathic PAH with identical histological findings, and accounts for approximately half of all PAH patients. Schistosomiasis and chronic haemolytic anaemia have been now included among the associated PAH forms. 3) A group 1′ has been created, which includes pulmonary veno-occlusive disease (PVOD) and pulmonary capillary haemangiomatosis (PCH), as these disorders share some characteristics with idiopathic PAH but also demonstrate a number of differences.

TABLE 3 ESC/ERS guidelines: haemodynamic definitions of pulmonary hypertension (PH)[#]

Definition	Characteristics	Clinical group(s)[¶]
PH	$\bar{P}_{pa} \geqslant 25$ mmHg	All
Pre-capillary PH	$\bar{P}_{pa} \geqslant 25$ mmHg	1. Pulmonary arterial hypertension
	$P_{pcw} \leqslant 15$ mmHg	3. PH due to lung diseases
	CO normal or reduced[+]	4. Chronic thromboembolic PH
		5. PH with unclear and/or multifactorial mechanisms
Post-capillary PH	$\bar{P}_{pa} \geqslant 25$ mmHg	2. PH due to left heart disease
	$P_{pcw} > 15$ mmHg	
	CO normal or reduced[+]	
Passive	TPG $\leqslant 12$ mmHg	
Reactive (out of proportion)	TPG > 12 mmHg	

$\bar{P}_{pa}$: mean pulmonary arterial pressure; P_{pcw}: pulmonary capillary wedge pressure; CO: cardiac output; TPG: transpulmonary pressure gradient ($\bar{P}_{pa}$-$\bar{P}_{pcw}$). [#]: all values measured at rest; [¶]: according to table 5; [+]: high CO can be present in cases of hyperkinetic conditions such as systemic-to-pulmonary shunts (only in the pulmonary circulation), anaemia, hyperthyroidism, *etc.* Reproduced from [1] with permission from the publisher.

TABLE 4 ESC/ERS guidelines: important definitions

PH is a haemodynamic and pathophysiological condition defined as an increase in $\bar{P}_{pa}$ $\geqslant$25 mmHg at rest as assessed by right heart catheterisation (table 3). PH can be found in multiple clinical conditions (table 5).

The definition of PH on exercise as a $\bar{P}_{pa}$ >30 mmHg as assessed by right heart catheterisation is not supported by published data.

PAH (group 1) is a clinical condition characterised by the presence of pre-capillary PH (table 3) in the absence of other causes of pre-capillary PH such as PH due to lung diseases, chronic thromboembolic PH, or other rare diseases (table 5). PAH includes different forms that share a similar clinical picture and virtually identical pathological changes of the lung microcirculation (table 5).

PH: pulmonary hypertension; $\bar{P}_{pa}$: mean pulmonary arterial pressure; PAH: pulmonary arterial hypertension. Reproduced from [1] with permission from the publisher.

The evaluation process of a patient with suspected PH requires a series of investigations intended to confirm the diagnosis, clarify the clinical group of PH and the specific aetiology within the PAH group, and evaluate the functional and haemodynamic impairment.

Since PAH, and particularly idiopathic PAH, is a diagnosis of exclusion, a diagnostic algorithm may be useful as a starting point in any case of suspected PH (fig. 1), as follows:

1) The symptoms of PAH are nonspecific and include breathlessness, fatigue, weakness, angina, syncope and abdominal distension. In 90% of patients with idiopathic PAH the chest radiograph is abnormal at the time of diagnosis. The ECG may provide suggestive or supportive evidence of PH by demonstrating right ventricular hypertrophy and strain, and right atrial dilatation.

2) Transthoracic echocardiography provides several variables that correlate with right heart haemodynamics, including P_{pa}, and should always be performed in the case of suspected PH. The estimation of P_{pa} during echocardiography is based on the peak velocity of the jet of tricuspid regurgitation. Other echocardiographic variables that might reinforce suspicion of PH include an increased velocity of pulmonic valve regurgitation, short acceleration time of right ventricular ejection into the pulmonary artery, increased dimensions of right heart chambers, abnormal shape and function of the interventricular septum, increased right ventricular wall thickness, and dilatation of the main pulmonary artery.

3) PFTs and arterial blood gases will identify the contribution of underlying airway or parenchymal lung disease. Patients with PAH usually have decreased diffusion capacity for carbon monoxide ($D_{L,CO}$) and mild to moderate reduction of lung volumes.

4) The ventilation/perfusion lung scan should be performed in patients with PH to look for potentially treatable CTEPH. The ventilation/perfusion scan remains the screening method of choice for CTEPH and a normal or low probability effectively excludes CTEPH with a sensitivity >90% and a specificity >94%.

TABLE 5 ESC/ERS guidelines: updated clinical classification of pulmonary hypertension (PH)

1 PAH
- 1.1 Idiopathic
- 1.2 Heritable
  - 1.2.1 BMPR2
  - 1.2.2 ALK-1, endoglin (with or without hereditary haemorrhagic telangiectasia)
  - 1.2.3 Unknown
- 1.3 Drugs and toxins induced
- 1.4 Associated with (APAH)
  - 1.4.1 Connective tissue diseases
  - 1.4.2 HIV infection
  - 1.4.3 Portal hypertension
  - 1.4.4 Congenital heart disease
  - 1.4.5 Schistosomiasis
  - 1.4.6 Chronic haemolytic anaemia
- 1.5 Persistent pulmonary hypertension of the newborn

1′ Pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis

2 PH due to left heart disease
- 2.1 Systolic dysfunction
- 2.2 Diastolic dysfunction
- 2.3 Valvular disease

3 PH due to lung diseases and/or hypoxia
- 3.1 Chronic obstructive pulmonary disease
- 3.2 Interstitial lung disease
- 3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
- 3.4 Sleep-disordered breathing
- 3.5 Alveolar hypoventilation disorders
- 3.6 Chronic exposure to high altitude
- 3.7 Developmental abnormalities

4 Chronic thromboembolic PH

5 PH with unclear and/or multifactorial mechanisms
- 5.1 Haematological disorders: myeloproliferative disorders, splenectomy
- 5.2 Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis, lymphangioleiomyomatosis, neurofibromatosis, vasculitis
- 5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
- 5.4 Others: tumoural obstruction, fibrosing mediastinitis, chronic renal failure on dialysis

PAH: pulmonary arterial hypertension; BMPR2: bone morphogenetic protein receptor, type 2; ALK-1: activin receptor-like kinase 1; APAH: associated pulmonary arterial hypertension. Reproduced from [11] with permission from the publisher.

5) HRCT facilitates the diagnosis of interstitial lung disease and emphysema and may be very helpful where there is a suspicion of PVOD or PCH.

6) Liver cirrhosis and/or portal hypertension can be reliably excluded by the use of abdominal ultrasound.

7) Routine biochemistry, haematology and thyroid function tests are required in all patients, as well as a number of other essential blood tests. Serological testing is important to detect underlying CTD, HIV and hepatitis.

RHC is required to confirm the diagnosis of PAH, to assess the severity of the haemodynamic impairment and to test the

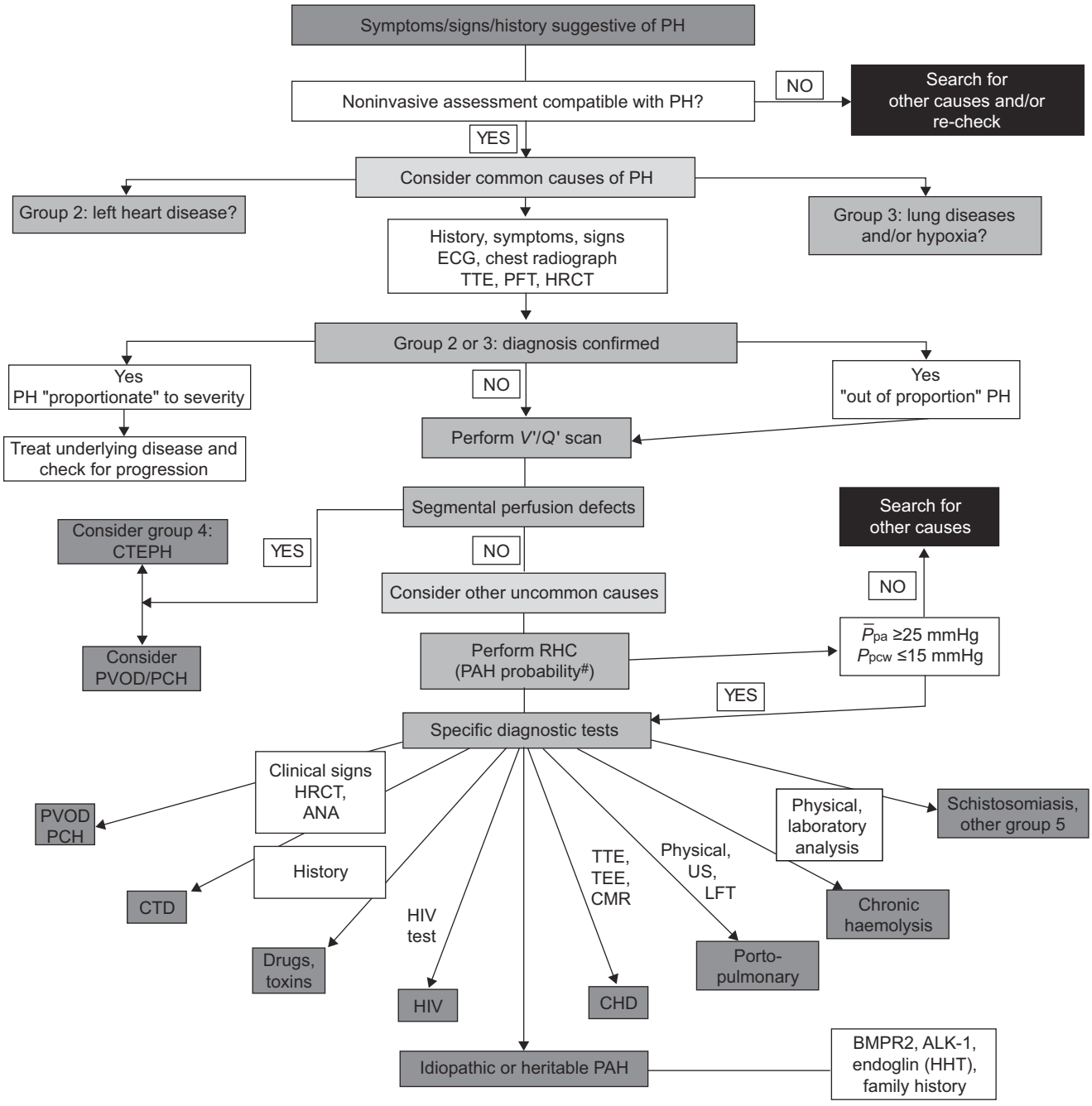

FIGURE 1. Diagnostic algorithm. ALK-1: activin-receptor-like kinase; ANA: antinuclear antibodies; BMPR2: bone morphogenetic protein receptor 2; CHD: congenital heart disease; CMR: cardiac magnetic resonance; CTD: connective tissue disease; CTEPH: chronic thromboembolic pulmonary hypertension; HHT: hereditary haemorrhagic telangiectasia; HRCT: high-resolution computed tomography; LFT: liver function tests; $\bar{P}_{pa}$: mean pulmonary arterial pressure; PAH: pulmonary arterial hypertension; PCH: pulmonary capillary haemangiomatosis; P_{pcw}: pulmonary capillary wedge pressure; PFT: pulmonary function test; PH: pulmonary hypertension; PVOD: pulmonary veno-occlusive disease; RHC: right heart catheterisation; TEE: trans-oesophageal echocardiography; TTE: transthoracic echocardiography; US: ultrasonography; *V'/Q'* scan: ventilation/perfusion lung scan. #: refer also to table 9. Reproduced from [1] with permission from the publisher.

vasoreactivity of the pulmonary circulation. The following variables must be recorded during RHC. 1) P_{pa} (systolic, diastolic and mean), right atrial pressure, P_{pcw} and right ventricular pressure. CO must be measured in triplicate, preferably by thermodilution or by the Fick method. 2) Adequate recording of P_{pcw} is required for the differential diagnosis of PH due to left heart disease.

Special awareness should be directed towards patients with associated conditions and/or risk factors for development of PAH, such as family history, CTD, congenital heart disease (CHD), HIV infection, portal hypertension, haemolytic anaemia or a history of intake of drugs and toxins known to induce PAH. If noninvasive assessment is compatible with PH, clinical history, symptoms, signs, ECG, chest radiograph, transthoracic

TABLE 6 ESC/ERS guidelines: functional classification of pulmonary hypertension modified after the New York Heart Association functional classification according to the World Health Organization

Class I	Patients with pulmonary hypertension but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnoea or fatigue, chest pain, or near syncope.
Class II	Patients with pulmonary hypertension resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnoea or fatigue, chest pain, or near syncope.
Class III	Patients with pulmonary hypertension resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnoea or fatigue, chest pain, or near syncope.
Class IV	Patients with pulmonary hypertension with inability to carry out any physical activity without symptoms. These patients manifest signs of right heart failure. Dyspnoea and/or fatigue may even be present at rest. Discomfort is increased by any physical activity.

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echocardiogram, PFTs and HRCT of the chest are requested to identify the presence of group 2 left heart disease or group 3 lung diseases. If a ventilation/perfusion scan shows multiple segmental perfusion defects, a diagnosis of group 4 CTEPH should be suspected. The final diagnosis of CTEPH (and the assessment of suitability for pulmonary endarterectomy) will require computed tomography (CT) angiography, RHC and selective pulmonary angiography.

TABLE 7 ESC/ERS guidelines: recommendations for pulmonary arterial hypertension (PAH) associated with connective tissue disease (CTD)

Statement	Class#	Level¶
In patients with PAH associated with CTD the same treatment algorithm as in patients with idiopathic PAH is recommended	I	A
Echocardiographic screening for the detection of PH is recommended in symptomatic patients with scleroderma spectrum of diseases	I	B
Echocardiographic screening for the detection of PH is recommended in symptomatic patients with all other CTDs	I	C
RHC is indicated in all cases of suspected PAH associated with CTD, in particular if specific drug therapy is considered	I	C
Oral anticoagulation should be considered on an individual basis	IIa	C
Echocardiographic screening for the detection of PH may be considered in asymptomatic patients with the scleroderma spectrum of disease	IIb	C

PH: pulmonary hypertension; RHC: right heart catheterisation. #: class of recommendation; ¶: level of evidence. Reproduced from [1] with permission from the publishers.

The clinical assessment of the patient has a pivotal role in the choice of the initial treatment, the evaluation of the response to therapy, and the possible escalation of therapy if needed. Despite large interobserver variation in the measurement, WHO functional class (table 6) remains a powerful predictor of survival. In untreated patients with idiopathic or heritable PAH, historical data showed a median survival of 6 months for WHO functional class IV, 2.5 yrs for WHO functional class III, and 6 yrs for WHO functional classes I and II.

CASE 2: SYSTEMIC SCLEROSIS-ASSOCIATED PAH

Case report

A 37-yr-old female with limited systemic sclerosis (LSSc) was referred by her rheumatologist for assessment of increasing exercise intolerance associated with effort-induced chest discomfort and dizziness. Physical examination was remarkable for an accentuated pulmonic component of the second heart sound, a parasternal heave and mucocutaneous features consistent with LSSc. Auscultation of the lungs was unremarkable and there was no clinical evidence of right heart failure. Transthoracic echocardiography revealed a left ventricle compromised by markedly dilated right heart chambers with associated paradoxical motion of the interventricular septum and a 1-cm circumferential noncompressive pericardial effusion. Spirometry and lung volume measurements were normal and there was no evidence of interstitial lung disease on HRCT of the chest. RHC confirmed severe pre-capillary PH ($\bar{P}_{pa}$

TABLE 8 ESC/ERS guidelines: arbitrary criteria for estimating the presence of pulmonary hypertension (PH) based on tricuspid regurgitation peak velocity and Doppler-calculated systolic pulmonary arterial pressure (P_{pa}) at rest (assuming a normal right atrial pressure of 5 mmHg) and on additional echocardiographic variables suggestive of PH

Criteria	Class#	Level¶
Echocardiographic diagnosis: PH unlikely		
Tricuspid regurgitation velocity $\leqslant$2.8 m·s^{-1}, systolic P_{pa} $\leqslant$36 mmHg and no additional echocardiographic variables suggestive of PH	I	B
Echocardiographic diagnosis: PH possible		
Tricuspid regurgitation velocity $\leqslant$2.8 m·s^{-1}, systolic P_{pa} $\leqslant$36 mmHg, but presence of additional echocardiographic variables suggestive of PH	IIa	C
Tricuspid regurgitation velocity 2.9–3.4 m·s^{-1}, systolic P_{pa} 37–50 mmHg with/without additional echocardiographic variables suggestive of PH	IIa	C
Echocardiographic diagnosis: PH likely		
Tricuspid regurgitation velocity >3.4 m·s^{-1}, systolic P_{pa} >50 mmHg, with/without additional echocardiographic variables suggestive of PH	I	B
Exercise Doppler echocardiography is not recommended for screening of PH	III	C

#: class of recommendation; ¶: level of evidence. Reproduced from [1] with permission from the publisher.

TABLE 9 ESC/ERS guidelines: probability of pulmonary arterial hypertension (PAH) diagnosis and suggested management according to the echocardiographic diagnosis of pulmonary hypertension (PH) (table 8), symptoms and additional clinical information

	Class[#]	Level[¶]
Low probability for PAH diagnosis		
Echocardiographic diagnosis of ''PH unlikely'', no symptoms: no additional work-up is recommended	I	C
Echocardiographic diagnosis of ''PH unlikely'', presence of symptoms and of associated conditions or risk factors for group 1–PAH: echocardiographic follow-up is recommended	I	C
Echocardiographic diagnosis of ''PH unlikely'', presence of symptoms and absence of associated conditions or risk factors for group 1–PAH: evaluation of other causes for the symptoms is recommended	I	C
Intermediate probability for PAH		
Echocardiographic diagnosis of ''PH possible'', no symptoms and absence of associated conditions or risk factors for group 1–PAH: echo-cardiographic follow-up is recommended	I	C
Echocardiographic diagnosis of ''PH possible'', presence of symptoms and of associated conditions or risk factors for group 1–PAH: RHC may be considered	IIb	C
Echocardiographic diagnosis of ''PH possible'', presence of symptoms and absence of associated conditions or risk factors for group 1–PAH: alternative diagnosis and echocardiographic follow-up may be considered. If symptoms at least moderate RHC may be considered	IIb	C
High probability for PAH		
Echocardiographic diagnosis of ''PH likely'', with symptoms and presence/absence of associated conditions or risk factors for group 1–PAH: RHC is recommended	I	C
Echocardiographic diagnosis of ''PH likely'', without symptoms and presence/absence of associated conditions or risks factors for group 1–PAH: RHC should be considered	IIa	C

RHC: right heart catheterisation. [#]: class of recommendation; [¶]: level of evidence. Reproduced from [1] with permission from the publisher.

73 mmHg, PVR 1,950 dyn·s·cm^{-5} and P_{pcw} 10 mmHg) with evidence of volume overload (right atrial pressure 20 mmHg) and no acute vasodilator response to inhaled nitric oxide. The patient was deemed to be in WHO functional class III and was commenced on treatment with oral endothelin receptor antagonist. In addition, diuretics and anticoagulation with a target INR of 2.0–3.0 were initiated. Monthly surveillance of liver transaminases was advised and effective contraceptive measures suggested. At re-evaluation after 4 months of therapy, the patient reported a symptomatic improvement and her 6MWD increased to 365 m from a baseline of 250 m. There was also a modest improvement in the pulmonary haemodynamic profile at repeat RHC ($\bar{P}_{pa}$ 65 mmHg, PVR 1,800 dyn·s·cm^{-5} and right atrial pressure 15 mmHg).

TABLE 10 Case 3: invasive pulmonary haemodynamics

	Baseline	After 500 mL fluid challenge
P_{ra} mmHg	7	13
$\bar{P}_{pa}$ mmHg	26	33
P_{pcw} mmHg	8	21
CO L·min^{-1}	4.82	5.43
CI L·min^{-1}·m^{-2}	2.71	3.02
PVR dyn·s·cm^{-5}	299	177

P_{ra}: right atrial pressure; $\bar{P}_{pa}$: mean pulmonary arterial pressure; P_{pcw}: pulmonary capillary wedge pressure; CO: cardiac output; CI: cardiac index; PVR: pulmonary vascular resistance.

Commentary: relevance to ESC/ERS guidelines

PAH is a well-known complication of CTD such as systemic sclerosis, systemic lupus erythematosus, mixed CTD and, to a lesser extent, rheumatoid arthritis, dermatomyositis and Sjögren's syndrome. PAH associated with CTD is the second most prevalent type of PAH after idiopathic PAH.

Systemic sclerosis, particularly in its limited variant, represents the main CTD associated with PAH. The prevalence of haemodynamically proven PAH in large cohorts of patients with systemic sclerosis is between 7% and 12%. Compared with idiopathic PAH, patients with CTD and PAH are mainly females (female to male ratio 4:1), are older (mean age at diagnosis 66 yrs), may present concomitant disorders (pulmonary fibrosis and left heart disease) and have shorter survival.

Echocardiographic screening for the detection of PH has been recommended annually in asymptomatic patients with the scleroderma spectrum of diseases but only in the presence of symptoms in other CTD (table 7).

The reliability of several tricuspid regurgitation velocity cut-off values, using RHC as reference, has been assessed in two large screening studies. A trial evaluating the reliability of prospective screening of patients with scleroderma, based on tricuspid regurgitation velocity >2.5 m·s^{-1} in symptomatic patients or >3.0 m·s^{-1} irrespective of symptoms, found that 45% of cases of echocardiographic diagnoses of PH were falsely positive. Another trial selected a tricuspid regurgitation pressure gradient >40 mmHg (tricuspid regurgitation velocity >3.2 m·s^{-1}) with an assumed right atrial pressure of 10 mmHg as the cut-off value for diagnosis of PH. Those criteria were recently prospectively applied in systemic sclerosis patients.

In tables 8 and 9, the ESC/ERS task force suggests arbitrary criteria for detecting the presence of PH based on tricuspid regurgitation peak velocity and Doppler-calculated systolic P_{pa} at rest (assuming a normal right atrial pressure of 5 mmHg) and additional echocardiographic variables suggestive of PH.

CASE 3: SYSTEMIC SCLEROSIS-ASSOCIATED POST-CAPILLARY PH

Case report

A 67-yr-old female in whom LSSc was diagnosed 11 yrs previously was referred for assessment of PH. She reported worsening dyspnoea on exertion over the preceding several

TABLE 11 ESC/ERS guidelines: factors favouring diagnosis of left ventricular diastolic dysfunction in the presence of pulmonary hypertension as assessed by Doppler echocardiography

Clinical features
Age >65 yrs
Elevated systolic blood pressure
Elevated pulse pressure
Obesity, metabolic syndrome
Hypertension
Coronary artery disease
Diabetes mellitus
Atrial fibrillation
Echocardiography
Left atrial enlargement
Concentric remodelling of the LV (relative wall thickness >0.45)
LV hypertrophy
Presence of echocardiographic indicators of elevated LV filling pressure [13, 14]
Interim evaluation (after echocardiography)
Symptomatic response to diuretics
Exaggerated increase in systolic blood pressure with exercise
Re-evaluation of chest radiograph consistent with heart failure [14]

LV: left ventricle. Modified from [15] with permission from the publisher.

months associated with intermittent episodes of chest discomfort and mild leg swelling, in addition to severe Raynaud's phenomenon and gastro-oesophageal reflux symptoms. Physical examination was remarkable for severe calcinosis involving both hands and extensive telangiectasia. She was normotensive and there was no clinical evidence of cardiac failure. PFTs revealed normal spirometry and lung volume measurements and a $D_{L,CO}$ of 60% predicted. She was referred to an expert centre for evaluation of suspected PAH as transthoracic echocardiography demonstrated enlarged right heart chambers and an estimated systolic P_{pa} of 50 mmHg with normal left ventricular function, mild left atrial enlargement, normal valvular structure and a normal pericardium. At review, she was in WHO functional class III with a 6MWD of 320 m. HRCT showed mild bibasal interstitial infiltrates. Liver function tests, blood gas analysis, lung scintigraphy, abdominal ultrasound and polysomnography were normal and HIV test was negative. RHC was performed and confirmed mild PH ($\bar{P}_{pa}$ 26 mmHg) with normal P_{pcw} (table 10). Because of the strong suspicion of underlying left heart disease, a fluid challenge (500 mL saline over 10 min) was administered and repeat measurements of pulmonary haemodynamics were made, revealing a profile consistent with post-capillary PH in the context of diastolic left heart disease associated with scleroderma (table 10).

TABLE 12 ESC/ERS guidelines: recommendations for pulmonary hypertension (PH) due to left heart disease

Statement	Class#	Level¶
The optimal treatment of the underlying left heart disease is recommended in patients with PH due to left heart disease	I	C
Patients with "out of proportion" PH due to left heart disease (table 3) should be enrolled in RCTs targeting PH specific drugs	IIa	C
Increased left-sided filling pressures may be estimated by Doppler echocardiography	IIb	C
Invasive measurements of P_{pcw} or LV end-diastolic pressure may be required to confirm the diagnosis of PH due to left heart disease	IIb	C
RHC may be considered in patients with echocardiographic signs suggesting severe PH in patients with left heart disease	IIb	C
The use of PAH specific drug therapy is not recommended in patients with PH due to left heart disease	III	C

RCT: randomised controlled trial; P_{pcw}: pulmonary capillary wedge pressure; LV: left ventricular; RHC: right heart catheterisation; PAH: pulmonary arterial hypertension. #: class of recommendation; ¶: level of evidence. Reproduced from [1] with permission from the publisher.

Commentary: relevance to ESC/ERS guidelines

The diagnostic approach to PH due to left heart disease is similar to that for PAH, doppler echocardiography being the best tool for screening purposes.

Left ventricle diastolic dysfunction should be suspected in the presence of a dilated left atrium, atrial fibrillation, characteristic changes in mitral flow profile, pulmonary venous flow profile, and mitral annulus tissue Doppler signals and left ventricle hypertrophy. Characteristic clinical and echocardiographic features of PH associated with left ventricle diastolic dysfunction are listed in table 11.

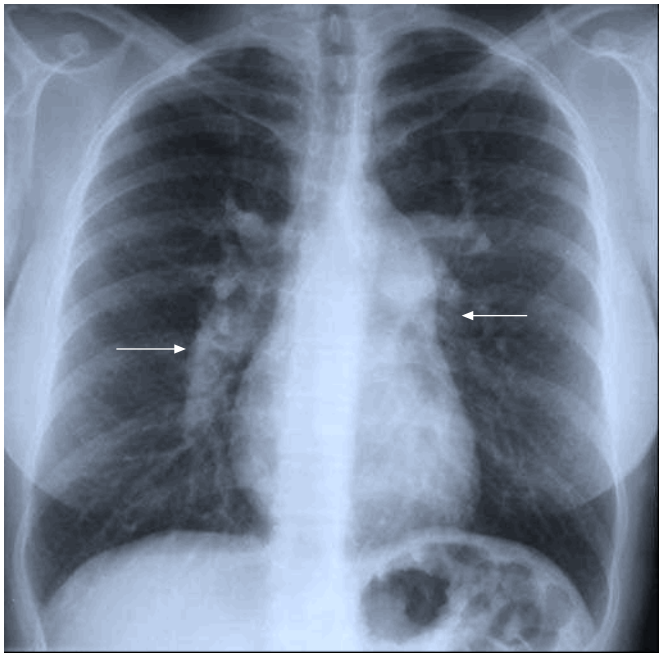

FIGURE 2. Chest radiograph showing markedly dilated pulmonary arteries (arrows).

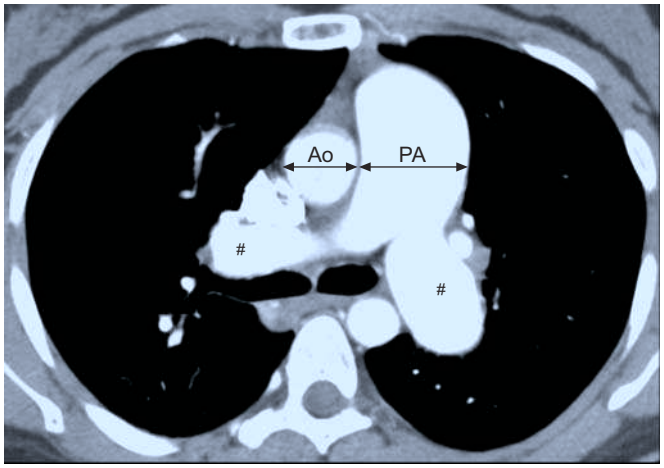

FIGURE 3. Contrast-enhanced computed tomography of the chest of a patient with pulmonary arterial hypertension associated with congenital heart disease (large atrial septal defect). Massive dilatation of the pulmonary arterial trunk and branches (#). The ratio of the diameter of aorta (Ao) to the diameter of main pulmonary artery (PA) is >1.5.

Adequate recording of P_{pcw} is required for the differential diagnosis of PH due to left heart disease. In rare cases, left heart catheterisation may be required for direct assessment of left ventricular end-diastolic pressure.

A P_{pcw} >15 mmHg excludes the diagnosis of pre-capillary PAH.

One of the most challenging differential diagnoses of PAH is heart failure with normal left ventricular ejection fraction and diastolic dysfunction. In this population, P_{pcw} may be mildly elevated or at the higher end of the normal range at rest. P_{pcw} and left ventricular end-diastolic pressure can be ''pseudo-normal'', especially when patients have been treated with diuretics. In this setting, exercise haemodynamic volume challenge has been proposed to identify left ventricular dysfunction, but these diagnostic tools require further standardisation.

An elevated transpulmonary gradient ($\bar{P}_{pa}$-$\bar{P}_{pcw}$) >12 mmHg is suggestive of intrinsic changes in the pulmonary circulation overriding the passive increase in P_{pcw}.

Recommendations for PH due to left heart disease are summarised in table 12.

CASE 4: PAH AND CONGENITAL HEART DISEASE

Case report

A 24-yr-old female was referred for assessment of suspected PH. Except for mild asthma treated with a short-acting β_2-adrenergic agonist, she had no significant personal or familial medical history and denied illicit drug or appetite suppressant intake. 2 months before admission, a chest radiograph was performed for tuberculosis contact screening and revealed markedly dilated pulmonary arteries (fig. 2). She reported mild dyspnoea on exertion (WHO functional class II) over the preceding several months. Physical examination revealed an accentuated second heart sound over the pulmonic valve but was otherwise normal. ECG showed right ventricular hypertrophy and an incomplete right bundle branch block pattern. 6MWD was 505 m, during which a decrease in arterial oxygen saturation to 87% was recorded. Echocardiography demonstrated a large atrial septal defect of the posterior ostium secundum (15×15 mm) associated with a bi-directional shunt that was predominantly right to left. Significant tricuspid regurgitation was also noted and systolic P_{pa} was estimated at 55 mmHg. Systemic and pulmonary venous returns were normal. Contrast-enhanced chest CT was remarkable for massive dilatation of the pulmonary arteries associated with marked right ventricular hypertrophy and dilatation (fig. 3). RHC confirmed PAH with a pre-capillary pattern: $\bar{P}_{pa}$ 57 mmHg, P_{pcw} 3 mmHg, and PVR 880 dyn·s·cm^{-5}. The pressures in right and left atria were equivalent at 3 mmHg. The pulmonary CI measured by the Fick method was 3.2 L·min^{-1}·m^{-2} and the systemic CI was 2.6 L·min^{-1}·m^{-2}, resulting in a pulmonary to systemic CI ratio of 1.22. Because of the high level of PVR and the presence of right-to-left shunt, repair surgery was not performed. Instead, oral specific PAH therapy with an endothelin receptor antagonist was initiated. After 6 months, the patient remained in WHO functional class II with a moderate clinical and haemodynamic improvement (70 m increase in 6MWD and 25% reduction in PVR). Repeat echocardiography confirmed persistence of the right-to-left shunt. Specific PAH therapy was therefore maintained and repair surgery was definitively contraindicated.

TABLE 13 ESC/ERS guidelines: clinical classification of congenital, systemic-to-pulmonary shunts associated with pulmonary arterial hypertension (PAH)

A. Eisenmenger's syndrome

Eisenmenger's syndrome includes all systemic-to-pulmonary shunts due to large defects leading to a severe increase in PVR and resulting in a reversed (pulmonary-to-systemic) or bidirectional shunt. Cyanosis, erythrocytosis and multiple organ involvement are present.

B. PAH associated with systemic-to-pulmonary shunts

In these patients with moderate-to-large defects, the increase in PVR is mild to moderate, systemic-to-pulmonary shunt is still largely present, and no cyanosis is present at rest.

C. PAH with small# defects

In cases with small defects (usually ventricular septal defects, 1 cm and atrial septal defects, 2 cm of effective diameter assessed by echocardiography) the clinical picture is very similar to idiopathic PAH.

D. PAH after corrective cardiac surgery

In these cases, congenital heart disease has been corrected but PAH is either still present immediately after surgery or has recurred several months or years after surgery in the absence of significant post-operative residual congenital lesions or defects that originate as a sequela to previous surgery.

PVR: pulmonary vascular resistance. #: the size applies to adult patients. Reproduced from [1] with permission from the publisher.

Commentary: relevance to ESC/ERS guidelines

PAH associated with CHD is included in group 1 of the PH clinical classification. A specific clinical classification (table 13) and an anatomical–pathophysiological classification (table 14) are useful to better define each individual patient with PAH associated with CHD.

TABLE 14 ESC/ERS guidelines: anatomical–pathophysiological classification of congenital systemic-to-pulmonary shunts associated with pulmonary arterial hypertension

1 Type
- 1.1 Simple pre-tricuspid shunts
  - 1.1.1 ASD
    - 1.1.1.1 Ostium secundum
    - 1.1.1.2 Sinus venosus
    - 1.1.1.3 Ostium primum
  - 1.1.2 Total or partial unobstructed anomalous pulmonary venous return
- 1.2 Simple post-tricuspid shunts
  - 1.2.1 VSD
  - 1.2.2 Patent ductus arteriosus
- 1.3 Combined shunts
  - Describe combination and define predominant defect
- 1.4 Complex congenital heart disease
  - 1.4.1 Complete atrioventricular septal defect
  - 1.4.2 Truncus arteriosus
  - 1.4.3 Single ventricle physiology with unobstructed pulmonary blood flow
  - 1.4.4 Transposition of the great arteries with VSD (without pulmonary stenosis) and/or patent ductus arteriosus
  - 1.4.5 Other

2 Dimension (specify for each defect if more than one congenital heart defect exists)
- 2.1 Haemodynamic (specify Q_P/Q_S)#
  - 2.1.1 Restrictive (pressure gradient across the defect)
  - 2.1.2 Nonrestrictive
- 2.2 Anatomical¶
  - 2.2.1 Small to moderate (ASD $\leqslant$2.0 cm and VSD $\leqslant$1.0 cm)
  - 2.2.2 Large (ASD $>$2.0 cm and VSD $>$1.0 cm)

3 Direction of shunt
- 3.1 Predominantly systemic-to-pulmonary
- 3.2 Predominantly pulmonary-to-systemic
- 3.3 Bidirectional

4 Associated cardiac and extracardiac abnormalities

5 Repair status
- 5.1 Unoperated
- 5.2 Palliated (specify type of operation(s), age at surgery)
- 5.3 Repaired (specify type of operation(s), age at surgery)

ASD: atrial septal defect; VSD: ventricular septal defect. #: ratio of pulmonary (Q_P) to systemic (Q_S) blood flow; ¶: the size applies to adult patients. Modified from [16] with permission from the publisher.

The persistent exposure of the pulmonary vasculature to increased blood flow due to systemic-to-pulmonary shunts as well as increased pressure may result in a typical pulmonary obstructive arteriopathy that leads to the increase of PVR. If PVR approaches or exceeds systemic vascular resistance, the shunt is reversed (Eisenmenger's syndrome).

In patients listed for lung or heart–lung transplantation when no medical treatment was available, Eisenmenger's syndrome had better survival compared with idiopathic PAH, with a 3-yr survival rate of 77% compared with 35% for untreated idiopathic PAH.

Recommendations for PAH associated with congenital cardiac shunts are summarised in table 15.

TABLE 15 ESC/ERS guidelines: recommendations for pulmonary arterial hypertension associated with congenital cardiac shunts

Statement	Class#	Level¶
The ERA bosentan is indicated in WHO FC III patients with Eisenmenger's syndrome	I	B
Other ERAs, phosphodiesterase type-5 inhibitors, and prostanoids should be considered in patients with Eisenmenger's syndrome	IIa	C
In the absence of significant haemoptysis, oral anticoagulant treatment should be considered in patients with PA thrombosis or signs of heart failure	IIa	C
The use of supplemental O_2 therapy should be considered in cases in which it produces a consistent increase in arterial oxygen saturation and reduces symptoms	IIa	C
If symptoms of hyperviscosity are present, phlebotomy with isovolumic replacement should be considered usually when the haematocrit is $>$65%	IIa	C
Combination therapy may be considered in patients with Eisenmenger's syndrome	IIb	C
The use of CCBs is not recommended in patients with Eisenmenger's syndrome	III	C

ERA: endothelin receptor antagonist; WHO FC: World Health Organization functional class; PA: pulmonary arterial; CCB: calcium channel blockers. #: class of recommendation; ¶: level of evidence. Reproduced from [1] with permission from the publisher.

CASE 5: HERITABLE PAH

Case report

A 10-yr-old male presented with a 2-month history of progressive dyspnoea on exertion. Clinical examination revealed an accentuated second heart sound over the pulmonic valve. Although the child had no medical history, a strong familial history of PAH had previously been established (fig. 4). 10 yrs earlier, the patient's father had been diagnosed with severe PAH at age 30 yrs that was initially deemed idiopathic given the absence of familial history at time of diagnosis. However, 2 yrs thereafter, the patient's paternal grandmother was also diagnosed with severe PAH. She had developed symptoms at age 52 yrs, presenting in WHO functional class III with marked haemodynamic impairment. A screening of point mutations and large rearrangements of bone morphogenetic protein receptor type 2 (*BMPR2*) gene found a c.418+3A$>$T mutation (a defect that affects a putative spicing regulatory element in intron 3), thereby confirming the diagnosis of heritable PAH. Genetic counselling sessions were conducted with family members in order to provide information on the risks of developing PAH and to inform them of disease symptoms and signs. These interventions helped facilitate the early referral of the child to a PAH referral centre in order to expedite a diagnostic work-up. RHC confirmed severe PAH ($\bar{P}_{pa}$ 73 mmHg, CI 2.71 $L \cdot min^{-1} \cdot m^{-2}$ and PVR 1,510 $dyn \cdot s \cdot cm^{-5}$) and endothelin receptor antagonist therapy was initiated. However, after 6 months of treatment there was only a modest

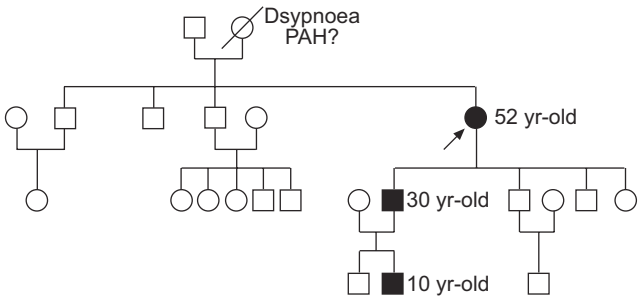

FIGURE 4. Genealogical tree of heritable pulmonary arterial hypertension (PAH) with *BMPR2* mutation, demonstrating the phenomenon of genetic anticipation. PAH in the first generation was diagnosed at age 52 yrs, then at age 30 yrs in the second generation and at age 10 yrs for the last generation.

clinical and haemodynamic improvement, justifying the addition of a phosphodiesterase-5 (PDE-5) inhibitor.

Commentary: relevance to ESC/ERS guidelines

When PAH occurs in a familial context, germline mutations in the *BMPR2* gene are detected in $\geqslant$70% of cases.

Mutations of this gene can also be detected in 11–40% of apparently sporadic cases, thus representing the major genetic predisposing factor for PAH.

The *BMPR2* gene encodes a type 2 receptor for bone morphogenetic proteins, which belong to the transforming growth factor-β superfamily, involved in the control of vascular cell proliferation.

Mutations of other receptors for these substances, such as *activin receptor-like kinase 1* (*ALK-1* or *ACVRL-1*) and endoglin, have been identified mostly in PAH patients with a personal or family history of hereditary haemorrhagic telangiectasia (Osler–Weber–Rendu syndrome).

CASE 6: CHRONIC THROMBOEMBOLIC PULMONARY HYPERTENSION

Case report

A 21-yr-old male professional soccer player presented with a 1-yr history of exercise intolerance and intermittent pleuritic chest pain. He was a cigarette smoker (2 pack-yrs) but otherwise had no significant past medical history, denied previous illicit or performance-enhancing drug intake and had no personal or family history of venous thromboembolism. Initial chest radiograph, PFTs and echocardiography were negative and no further exams were performed. The patient represented 18 months later with worsening of breathlessness. Repeat echocardiography showed moderately dilated right heart chambers with an estimated systolic P_{pa} of 55 mmHg. A working diagnosis of pulmonary embolism was made; however, both CT pulmonary angiography and lower limb compression ultrasonography were normal. 1 month later, he represented with severe pleuritic chest pain. On this occasion, ventilation/perfusion lung scintigraphy confirmed bilateral pulmonary emboli and compression ultrasonography identified a left leg deep vein thrombosis. Anticoagulation therapy was therefore initiated. 4 months thereafter, the patient had persistent WHO functional class II symptoms. Repeat echocardiography demonstrated persistent PH (systolic P_{pa} 60 mmHg). 6MWD was 540 m. Thrombophilia screening was negative. RHC confirmed mild PH at rest with a significant increase in $\bar{P}_{pa}$ with exercise at 100 W (table 16). Repeat CTPA and formal pulmonary angiography confirmed the presence of chronic thromboembolic disease in a proximal distribution (fig. 5a and b) and treatment by pulmonary thromboendarterectomy (PEA) was proposed. However, the patient declined surgery, though agreed to continue oral anticoagulation. 18 months later, he was readmitted with increasing breathlessness. The patient was in WHO functional class III and 6MWD was 477 m (decrease of 63 m from baseline). Haemodynamic reassessment confirmed worsening PH (table 16) while progressive occlusive vasculopathy was noted

TABLE 16 Case 6: clinical data

	First evaluation		After 18 months of evolution without PEA	6 months after PEA
	At rest	Exercise (100 W)		
WHO functional class	II		III	I
6MWD m	540		477	748
P_{ra} mmHg	2	NA	6	4
$\bar{P}_{pa}$ mmHg	31	69	43	18
P_{pcw} mmHg	2	NA	4	6
CO L·min^{-1}	4.6	12.3	4.7	5.8
TPR dyn·s·cm^{-5}	539	449	732	248
S_{V,O_2} %	68	27	63	73
Decision for therapy	VKA		VKA	VKA
	Patient declined PEA		Patient accepted PEA	

PEA: pulmonary thromboendarterectomy; WHO: World Health Organization; 6MWD: 6-min walk distance; P_{ra}: right atrial pressure; $\bar{P}_{pa}$: mean pulmonary arterial pressure; P_{pcw}: pulmonary capillary wedge pressure; CO: cardiac output; TPR: total pulmonary resistance; S_{V,O_2}: mixed venous oxygen saturation; VKA: oral vitamin K antagonist anticoagulation.

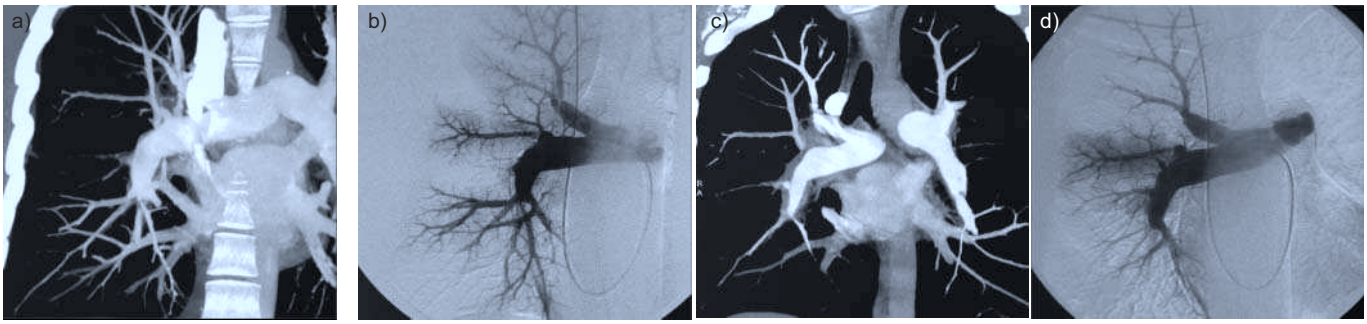

FIGURE 5. Case 6. a) Computed tomography pulmonary angiography and b) formal pulmonary angiography confirmed the presence of chronic thromboembolic disease. c) and d) Progressive occlusive vasculopathy was noted on repeat imaging studies.

on repeat imaging studies (fig. 5c and d). On this occasion, the patient proceeded to PEA during which obstructing material was successfully removed from all major pulmonary artery branches. His post-operative course was unremarkable and oral anticoagulation was recommenced. At follow-up 6 months later, he was asymptomatic and repeat RHC confirmed normal pulmonary haemodynamics (table 16).

Commentary: relevance to ESC/ERS guidelines

CTEPH is one of the most prevalent forms of PH. Nevertheless, it is almost impossible to determine the overall prevalence of CTEPH since not all of these patients have a history of acute pulmonary embolism.

Any patient with unexplained PH should be evaluated for the presence of CTEPH. 1) A normal ventilation/perfusion scan rules out CTEPH. 2) Multi-row CT angiography is indicated when the ventilation/perfusion lung scan is indeterminate or reveals perfusion defects. Even in the era of modern multi-row CT scanners, there is not yet enough evidence to suggest that a normal CT angiography excludes the presence of operable CTEPH.

Once ventilation/perfusion scanning and/or CT angiogram show signs compatible with CTEPH, the patient should be referred to a centre with expertise in the medical and surgical management of these patients.

To determine the appropriate therapeutic strategy, invasive tools, including RHC and traditional pulmonary angiography, are usually required. The final diagnosis of CTEPH is based on the presence of pre-capillary PH in patients with multiple chronic/organised occlusive thrombi/emboli in the elastic pulmonary arteries (main, lobar, segmental and subsegmental).

The decision on how to treat patients with CTEPH should be made at an experienced centre based upon interdisciplinary discussion among internists, radiologists, and expert surgeons: 1) PEA is the treatment of choice for patients with CTEPH, as it is a potentially curative option; 2) patients with CTEPH should receive life-long anticoagulation, usually with vitamin K antagonists adjusted to a target INR of 2.0–3.0.

Recommendations for PH due to CTEPH are summarised in table 17.

CASE 7: ACUTE VASOREACTIVITY TEST RESPONDER

Case report

A 69-yr-old female presented with a 3-month history of dyspnoea and exercise intolerance. Her past medical history was significant for breast cancer diagnosed 2 yrs previously treated by surgery and adjuvant combination cytotoxic therapy with cyclophosphamide, 5-fluoro-uracil and farmorubicin. At the time of initial referral, she was in WHO functional class III.

TABLE 17 ESC/ERS guidelines: recommendations for chronic thromboembolic pulmonary hypertension (CTEPH)

Statement	Class[#]	Level[¶]
The diagnosis of CTEPH is based on the presence of pre-capillary PH ($\bar{P}_{pa}$ ⩾25 mmHg, P_{pcw} ⩽15 mmHg, PVR>2 Wood units) in patients with multiple chronic/organised occlusive thrombi/emboli in the elastic pulmonary arteries (main, lobar, segmental, subsegmental)	I	C
In patients with CTEPH lifelong anticoagulation is indicated	I	C
Surgical pulmonary endarterectomy is the recommended treatment for patients with CTEPH	I	C
Once perfusion scanning and/or CT angiography show signs compatible with CTEPH, the patient should be referred to a centre with expertise in surgical pulmonary endarterectomy	IIa	C
The selection of patients for surgery should be based on the extent and location of the organised thrombi, on the degree of PH, and on the presence of comorbidities	IIa	C
PAH-specific drug therapy may be indicated in selected CTEPH patients such as patients not candidates for surgery or patients with residual PH after pulmonary endarterectomy	IIb	C

PH: pulmonary hypertension; $\bar{P}_{pa}$: mean pulmonary arterial pressure; P_{pcw}: pulmonary capillary wedge pressure; PVR: pulmonary vascular resistance; CT: computed tomography; PAH: pulmonary arterial hypertension. [#]: class of recommendation; [¶]: level of evidence. Reproduced from [1] with permission from the publisher.

TABLE 18 Case 7: clinical characteristics

	First evaluation		After 12 months of high-dose CCB	
	At rest	Acute vasodilator testing	At rest	Acute vasodilator testing
WHO functional class	III		II	
6MWD m	210		310	
P_{ra} mmHg	6	5	6	6
$\bar{P}_{pa}$ mmHg	52	25	31	23
P_{pcw} mmHg	10	6	11	9
CO L·min^{-1}	6.6	7.3	7.0	6.8
PVR dyn·s·cm^{-5}	509	208	286	200

CCB: calcium channel blockers; WHO: World Health Organization; 6MWD: 6-min walk distance; P_{ra}: right atrial pressure; $\bar{P}_{pa}$: mean pulmonary arterial pressure; P_{pcw}: pulmonary capillary wedge pressure; CO: cardiac output; PVR: pulmonary vascular resistance.

Clinical examination revealed an accentuated second heart sound over the pulmonic valve without evidence of cardiac failure. Transthoracic echocardiography estimated systolic P_{pa} 62 mmHg. Additional routine diagnostic testing for an underlying cause of PH was negative. The patient proceeded to RHC in order to confirm the diagnosis and assess severity of haemodynamic impairment. This revealed severe pre-capillary PH ($\bar{P}_{pa}$ 52 mmHg and PVR 509 dyn·s·cm^{-5}) with a preserved CO and no evidence of hypervolaemia (table 18). An acute vasodilator challenge testing using inhaled nitric oxide at a dose of 10 ppm was then performed to assess for vasoreactivity. This showed a significant acute vasodilator response with near normalisation of $\bar{P}_{pa}$, reduction in PVR and an associated increase in CI (table 18). A treatment with high-dose oral calcium channel antagonist (CCB) therapy was therefore initiated and titrated up to the maximum tolerated dose, in conjunction with oral anticoagulation. At haemodynamic reassessment 12 months later, the patient had improved to WHO functional class II and had increased her 6MWD from 210 m to 310 m. Subsequent RHC confirmed a sustained favourable pulmonary haemodynamic response and the dose of oral CCB was increased because of persistence of an acute vasoreactivity to inhaled nitric oxide.

Commentary: relevance to ESC/ERS guidelines

In PAH, vasoreactivity testing should be performed at the time of diagnostic RHC to identify patients who may benefit from long-term therapy with CCBs.

Acute vasodilator challenge should only be performed with short-acting, safe and easy to administer drugs with no or limited systemic effects. Currently the agent most used in acute testing is nitric oxide based on previous experience; *i.v.* epoprostenol or *i.v.* adenosine may also be used as an alternative (but with a risk of systemic vasodilator effects) (table 19). Due to the risk of potentially life-threatening complications, the use of CCBs given orally or *i.v.* as an acute test is discouraged.

A positive acute response (positive acute responder) is defined as a reduction of $\bar{P}_{pa} \geqslant 10$ mmHg to reach an absolute value of $\bar{P}_{pa} \leqslant 40$ mmHg with an increased or unchanged CO. Only 10% of patients with idiopathic PAH will meet these criteria (table 20).

Positive acute responders are most likely to show a sustained response to long-term treatment with high doses of CCBs and they are the only patients that can safely be treated with this type of therapy. About half of idiopathic PAH-positive acute responders are also positive long-term responders to CCBs and only in these cases is the continuation of a CCB as a single treatment warranted.

The usefulness of acute vasoreactivity tests and long-term treatment with CCBs in patients with other PAH types, such as heritable PAH, CTD, and HIV patients is less clear than in idiopathic PAH. Nevertheless, experts recommend performing acute vasoreactivity studies in these patients and to look for a long-term response to CCBs in those in whom the test is positive.

TABLE 19 ESC/ERS guidelines: route of administration, half-life, dose ranges, increments and duration of administration of the most commonly used agents for pulmonary vasoreactivity tests

Drug	Route	Half-life	Dose range[#]	Increments[¶]	Duration[+]
Epoprostenol	Intravenous	3 min	2–12 ng·kg^{-1}·min^{-1}	2 ng·kg^{-1}·min^{-1}	10 min
Adenosine	Intravenous	5–10 s	50–350 μg·kg^{-1}·min^{-1}	50 μg·kg^{-1}·min^{-1}	2 min
Nitric oxide	Inhaled	15–30 s	10–20 ppm		5 min[§]

[#]: initial dose and maximal tolerated dose suggested (maximal dose limited by side-effects such as hypotension, headache, flushing, *etc.*); [¶]: increments of dose by each step; [+]: duration of administration on each step; [§]: for nitric oxide, a single step within the dose range is suggested. Reproduced from [1] with permission from the publisher.

TABLE 20 ESC/ERS guidelines: recommendations for right heart catheterisation (RHC) (A) and vasoreactivity testing (B)

	Class#	Level¶
A. RHC		
RHC is indicated in all patients with PAH to confirm the diagnosis, to evaluate the severity and when PAH specific drug therapy is considered	I	C
RHC should be performed for confirmation of efficacy of PAH-specific drug therapy	IIa	C
RHC should be performed for confirmation of clinical deterioration and as baseline for the evaluation of the effect of treatment escalation and/or combination therapy	IIa	C
B. Vasoreactivity testing		
Vasoreactivity testing is indicated in patients with IPAH, heritable PAH and PAH associated with anorexigen use to detect patients who can be treated with high doses of a CCB	I	C
A positive response to vasoreactivity testing is defined as a reduction of $\bar{P}_{pa} \geqslant 10$ mmHg to reach an absolute value of $\bar{P}_{pa} \leqslant 40$ mmHg with an increased or unchanged CO	I	C
Vasoreactivity testing should be performed only in referral centres	IIa	C
Vasoreactivity testing should be performed using nitric oxide as vasodilator	IIa	C
Vasoreactivity testing may be performed in other types of PAH	IIb	C
Vasoreactivity testing may be performed using *i.v.* epoprostenol or *i.v.* adenosine	IIb	C
The use of an oral or *i.v.* CCB in acute vasoreactivity testing is not recommended	III	C
Vasoreactivity testing to detect patients who can be safely treated with high doses of a CCB is not recommended in patients with other PH groups (groups 2, 3, 4 and 5)	III	C

PAH: pulmonary arterial hypertension; IPAH: idiopathic pulmonary arterial hypertension; CCB: calcium channel blocker; $\bar{P}_{pa}$: mean pulmonary arterial pressure; CO: cardiac output; PH: pulmonary hypertension. #: class of recommendation; ¶: level of evidence. Reproduced from [1] with permission from the publisher.

TABLE 21 ESC/ERS guidelines: recommendations for general measures

Statement	Class#	Level¶
It is recommended to avoid pregnancy in patients with PAH	I	C
Immunisation of PAH patients against influenza and pneumococcal infection is recommended	I	C
Physically deconditioned PAH patients should be considered for supervised exercise rehabilitation	IIa	B
Psychosocial support should be considered in patients with PAH	IIa	C
In-flight O_2 administration should be considered for patients in WHO FC III and IV and those with arterial blood O_2 pressure consistently <8 kPa (60 mmHg)	IIa	C
Epidural anaesthesia instead of general anaesthesia should be utilised, if possible, for elective surgery	IIa	C
Excessive physical activity that leads to distressing symptoms is not recommended in patients with PAH	III	C

PAH: pulmonary arterial hypertension; WHO FC: World Health Organization functional class. #: class of recommendation; ¶: level of evidence. Reproduced from [1] with permission from the publisher.

The CCBs that have been predominantly used in reported studies are nifedipine, diltiazem, and amlodipine, with particular emphasis on the first two. The choice of CCB is based upon the patient's heart rate at baseline, with a relative bradycardia favouring nifedipine and amlodipine and a relative tachycardia favouring diltiazem. The daily doses of these drugs that have shown efficacy in idiopathic PAH are relatively high, 120–240 mg for nifedipine, 240–720 mg for diltiazem, and up to 20 mg for amlodipine.

Patients with idiopathic PAH who meet the criteria for a positive vasodilator response and are treated with a CCB should be followed closely for both safety and efficacy with an initial reassessment after 3–4 months of therapy including RHC. If the patient does not show an adequate response, defined as being in WHO functional class I or II and with a marked haemodynamic improvement, additional PAH therapy should be instituted.

Patients who have not undergone a vasoreactivity study or those with a negative study should not be started on a CCB because of potential severe side-effects.

CASE 8: IDIOPATHIC PAH WITH WHO FUNCTIONAL CLASS II SYMPTOMS

Case report

A 48-yr-old male was referred for evaluation of breathlessness associated with effort-associated palpitations and chest discomfort. He reported that his symptoms occurred with moderate exertion and was therefore deemed to be in WHO functional class II. He denied dizziness, syncope or ankle swelling. The only positive sign elicited on physical examination was an accentuated pulmonary component to the second heart sound. Baseline 6MWD was 450 m. RHC confirmed precapillary PH of moderate severity without associated acute vasodilator response (right atrial pressure 2 mmHg, $\bar{P}_{pa}$ 35 mmHg, P_{pcw} 5 mmHg, PVR 260 dyn·s·cm^{-5} and CI 5.6 L·min^{-1}·m^{-2}). Routine testing to assess for underlying causes of PH was negative and a diagnosis of idiopathic PAH was made. He was commenced on PAH-specific therapy with an endothelin antagonist in addition to oral anticoagulation. At reassessment after 6 months of treatment, he remained in WHO functional class II, had a 6MWD of 466 m and showed a stable pulmonary haemodynamic profile (right atrial pressure 7 mmHg; $\bar{P}_{pa}$ 39 mmHg; P_{pcw} 8 mmHg; PVR 238 dyn·s·cm^{-5} and CI 5.8 L·min^{-1}·m^{-2}). He was reassessed thereafter on a 6-monthly basis. On each occasion, he was

TABLE 22 ESC/ERS guidelines: recommendations for supportive therapy

Statement	Class[#]	Level[¶]
Diuretic treatment is indicated in PAH patients with signs of RV failure and fluid retention	I	C
Continuous long-term O_2 therapy is indicated in PAH patients when arterial blood O_2 pressure is consistently <8 kPa (60 mmHg)[+]	I	C
Oral anticoagulant treatment should be considered in patients with IPAH, heritable PAH and PAH due to use of anorexigens	IIa	C
Oral anticoagulant treatment may be considered in patients with APAH	IIb	C
Digoxin may be considered in patients with PAH who develop atrial tachyarrhythmias to slow ventricular rate	IIb	C

PAH: pulmonary arterial hypertension; RV: right ventricular; IPAH: idiopathic PAH; APAH: associated PAH. [#]: class of recommendation; [¶]: level of evidence; [+]: see also recommendations for PAH associated with congenital cardiac shunts (table 15). Reproduced from [1] with permission from the publisher.

noted to be in WHO functional class II and had stable exercise capacity, as evidenced by 6MWD consistently in the 475–500 m range. Treatment was therefore continued without modification. Since diagnosis of PAH 5 yrs ago, the patient has shown no evidence of clinical or haemodynamic deterioration.

Commentary: relevance to ESC/ERS guidelines

The management of PAH patients includes general and supportive measures, as follows. 1) Patients should avoid excessive physical activity that leads to distressing symptoms, but when physically deconditioned may undertake supervised exercise rehabilitation. 2) Pregnancy is associated with 30–50% mortality in patients with PAH and, as a consequence, pregnancy is contraindicated in PAH. There is less consensus relating to the most appropriate methods of birth control. Barrier contraceptive methods are safe and progesterone-only preparations are effective approaches to contraception and avoid potential issues of oestrogens. 3) Patients should avoid going to altitudes above 1,500–2,000 m without supplemental oxygen. 4) It is recommended to vaccinate against influenza and pneumococcal pneumonia.

Recommendations for general measures are summarised in table 21.

Advice regarding the target INR in patients with idiopathic PAH varies from 1.5–2.5 in most centres of North America to 2.0–3.0 in European centres.

Diuretic treatment is indicated in PAH patients with signs of right ventricular failure and fluid retention.

When arterial blood oxygen pressure is consistently <8 kPa (60 mmHg) patients are advised to take oxygen to achieve a arterial blood oxygen pressure of.8 kPa for $\geqslant$15 h·day^{-1}.

Recommendations for general measures are summarised in table 22.

TABLE 23 ESC/ERS guidelines: recommendations for efficacy of specific drug therapy, balloon atrial septostomy and lung transplantation for pulmonary arterial hypertension (group 1) according to World Health Organization functional class (WHO FC)

Measure/treatment		Classes of recommendation–level of evidence		
		WHO FC II	WHO FC III	WHO FC IV
Calcium channel blockers		I–C[#]	I–C[#]	–
Endothelin receptor antagonists	Ambrisentan	I–A	I–A	IIa–C
	Bosentan	I–A	I–A	IIa–C
	Sitaxentan	IIa–C	I–A	IIa–C
Phosphodiesterase type-5 inhibitors	Sildenafil	I–A	I–A	IIa–C
	Tadalafil[¶]	I–B	I–B	IIa–C
Prostanoids	Beraprost	–	IIb–B	–
	Epoprostenol (intravenous)	–	I–A	I–A
	Iloprost (inhaled)	–	I–A	IIa–C
	Iloprost (intravenous)	–	IIa–C	IIa–C
	Treprostinil (subcutaneous)	–	I–B	IIa–C
	Treprostinil (intravenous)	–	IIa–C	IIa–C
	Treprostinil (inhaled)[¶]	–	I–B	IIa–C
Initial drugs combination therapy		–	–	IIa–C
Sequential drugs combination therapy		IIa–C	IIa–B	Iia–B
Balloon atrial septostomy		–	I–C	I–C
Lung transplantation		–	I–C	I–C

[#]: only in responders to acute vasoreactivity tests, I for idiopathic pulmonary arterial hypertension (PAH), heritable PAH and PAH due to anorexigens; IIa for associated PAH conditions; [¶]: under regulatory review in the European Union. Reproduced from [1] with permission from the publisher.

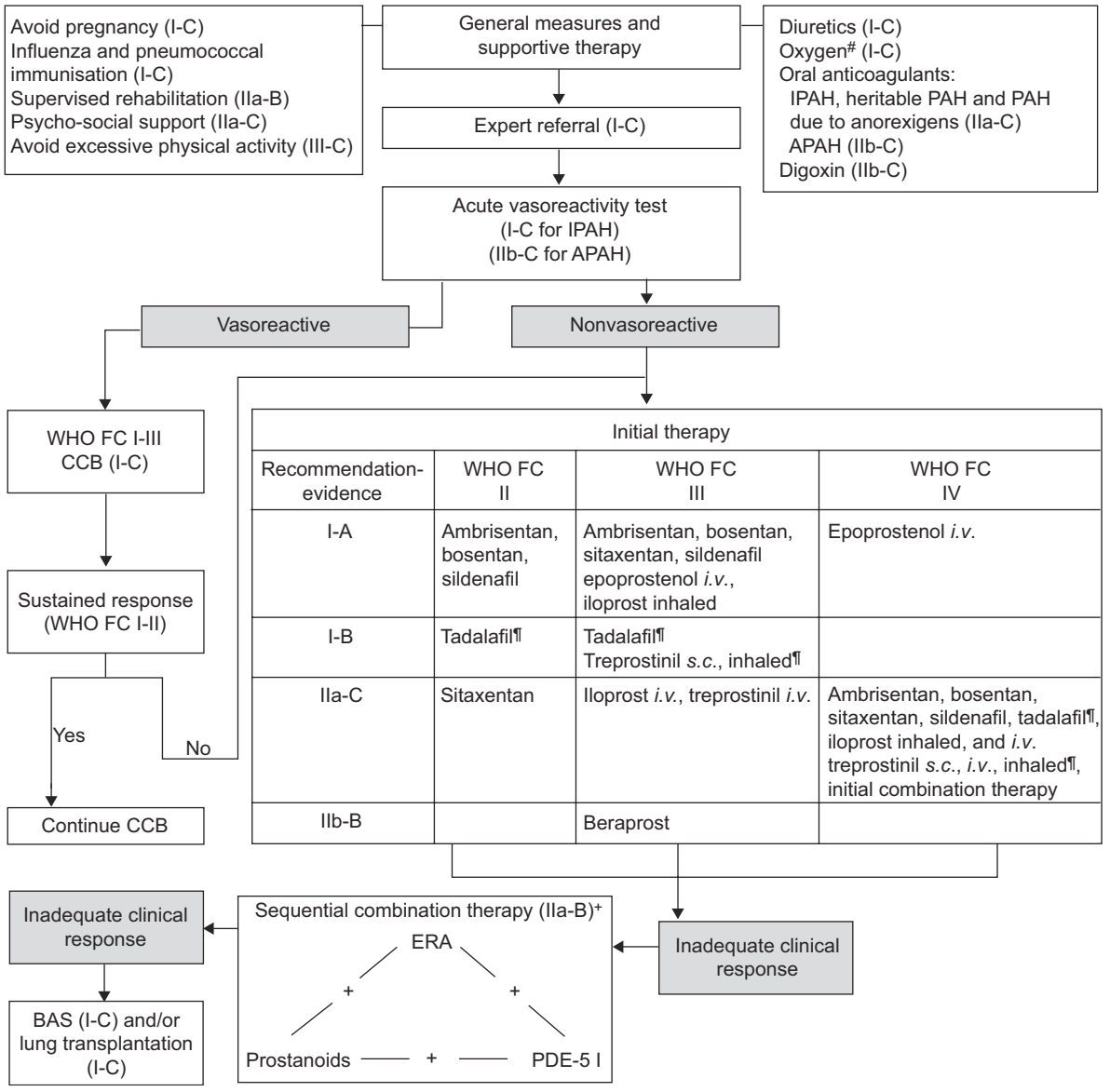

FIGURE 6. Evidence-based treatment algorithm for pulmonary arterial hypertension patients (PAH; for group 1 patients only). APAH: associated PAH; BAS: balloon atrial septostomy; CCB: calcium channel blocker; ERA: endothelin receptor antagonist; IPAH: idiopathic PAH; PDE-5I: phosphodiesterase type-5 inhibitor; WHO FC: World Health Organization functional class. #: to maintain arterial blood O_2 pressure >8 kPa (60 mmHg); ¶: under regulatory review in the European Union; +: IIa-C for WHO FC II. Reproduced from [1] with permission from the publisher.

As head-to-head comparisons among different compounds are not available, no evidence-based first-line treatment can be proposed. In this case the choice of the drug is dependent on a variety of factors, including the approval status, the route of administration, the side-effect profile, patients' preferences and physicians' experience.

Classes of recommendations and level of evidence for first-line therapy in PAH patients (group 1) depends on the WHO functional class (table 23). Nonresponders to acute vasoreactivity testing who are in WHO functional class II should be treated with an endothelin receptor agonist or a PDE-5 inhibitor.

CASE 9: IDIOPATHIC PAH WITH WHO FUNCTIONAL CLASS IV SYMPTOMS TREATED BY FIRST-LINE COMBINATION THERAPY

Case report

A 27-yr-old female with previously well-controlled asthma since childhood was referred for evaluation of a 1-month history of progressive dyspnoea unresponsive to augmentation of inhaled corticosteroids. There was no family history of pulmonary vascular disease. At presentation she was in WHO functional class IV, being breathless on minimal exertion and having experienced several pre-syncopal episodes. Physical examination revealed a loud pulmonic component to the second heart sound and a soft pansystolic murmur over the tricuspid valve without

TABLE 24 Case 10: clinical characteristics

Treatment at evaluation	None	ERA (for 4 months)	ERA and PDE-5I (for 5 months)	ERA, PDE-5I and *i.v.* prostacyclin (for 4 months)
WHO functional class	III	III	III	II
6MWD m	519	525	441	601
P_{ra} mmHg	7	8	8	3
$\bar{P}_{pa}$ mmHg	55	60	65	47
CI L·min^{-1}·m^{-2}	2.01	2.5	2.09	3.35
PVR dyn·s·cm^{-5}	1248	1066	1368	649
BNP pg·mL^{-1}		217	360	62
Modification of specific PAH therapy	Initiation of ERA	Addition of PDE5-I	Addition of *i.v.* prostacyclin	No change

ERA: endothelin receptor agonist; PDE5-I: phosphodiesterase type-5 inhibitor; WHO: World Health Organization; 6MWD: 6-min walk distance; P_{ra}: right atrial pressure; $\bar{P}$pa: mean pulmonary arterial pressure; CI: cardiac index; PVR: pulmonary vascular resistance; BNP: brain natriuretic peptide; PAH: pulmonary arterial hypertension.

jugular venous distension or peripheral oedema. Chest radiograph demonstrated an enlarged heart and clear lung fields. Transthoracic echocardiography revealed a systolic P_{pa} >100 mmHg and associated dilated right heart chambers without evidence of intracardiac shunt. Arterial blood gas analysis showed a respiratory alkalosis pattern and hypoxaemia. Antinuclear antibody, anti-double-stranded DNA, rheumatoid factor and HIV test were negative. Abdominal ultrasound showed no evidence of portal hypertension. PFTs demonstrated normal airway function and lung volumes, but a $D_{L,CO}$ of 60% pred. Lung scintigraphy was unremarkable. The patient's 6MWD was 150 m, during which an oxygen desaturation to 81% was recorded, despite the use of supplementary oxygen. RHC confirmed severe pre-capillary PH with $\bar{P}_{pa}$ 74 mmHg, PVR 1,450 dyn·s·cm^{-5}, CI 1.9 L·min^{-1}·m^{-2} and a mixed venous oxygen saturation of 57%. Acute vasodilator testing with nitric oxide was negative. Because of the severity of the patient's symptoms, advanced functional class, marked limitation of exercise capacity and significant haemodynamic impairment, a decision was made to initiate a dual targeted therapy regimen with combination continuous *i.v.* prostacyclin and oral endothelin antagonist.

Commentary: relevance to ESC/ERS guidelines

The treatment algorithm (fig. 6) does not apply to patients in other clinical groups, and in particular not to patients with PH associated with group 2 (left heart disease) or with group 3 (lung diseases). In addition, the different treatments have been evaluated by randomised controlled trials mainly in idiopathic PAH, heritable PAH, PAH due to anorexigen drugs, and in PAH associated with CTD or with CHD (surgically corrected or not). The grades of recommendation and levels of evidence for the other PAH subgroups are lower.

The suggested initial approach after the diagnosis of PAH is the adoption of the general measures, the initiation of the supportive therapy and referral to an expert centre. Acute vasoreactivity testing should be performed in all patients with group 1 PAH. Vasoreactive patients should be treated with optimally tolerated doses of CCBs.

Nonresponders to acute vasoreactivity testing, or responders who remain in (or progress to) WHO functional class III should be considered candidates for treatment with an endothelin receptor agonist, a PDE-5 inhibitor, or a prostanoid.

TABLE 25 ESC/ERS guidelines: parameters with established importance for assessing disease severity, stability and prognosis in pulmonary arterial hypertension

Better prognosis	Determinants of prognosis	Worse prognosis
No	Clinical evidence of RV failure	Yes
Slow	Rate of progression of symptoms	Rapid
No	Syncope	Yes
I, II	WHO FC	IV
Longer (>500 m)[#]	6MWT	Shorter (<300 m)
Peak O_2 consumption >15 mL·min^{-1}·kg^{-1}	Cardiopulmonary exercise testing	Peak O_2 consumption <12 mL·min^{-1}·kg^{-1}
Normal or near-normal	BNP/NT-proBNP plasma levels	Very elevated and rising
No pericardial effusion TAPSE[¶] >2.0 cm	Echocardiographic findings[¶]	Pericardial effusion TAPSE[¶] <1.5 cm
P_{ra} <8 mmHg and CI ⩾2.5 L·min^{-1}·m^{-2}	Haemodynamics	P_{ra} >15 mmHg or CI ⩽2.0 L·min^{-1}·m^{-2}

RV: right ventricular; WHO FC: World Health Organization functional class; 6MWT: 6-min walk test; BNP: brain natriuretic peptide; NT-proBNP: N-terminal proBNP; TAPSE: tricuspid annular plane systolic excursion; P_{ra}: right atrial pressure; CI: cardiac index. [#]: depending on age; [¶]: TAPSE and pericardial effusion have been selected because they can be measured in the majority of the patients. Reproduced from [17] with permission from the publisher.

TABLE 26 ESC/ERS guidelines: definition of inadequate response to pulmonary arterial hypertension treatments

Inadequate clinical response for patients who were initially in WHO FC II or III:
1) Resulting clinical status defined as stable and not satisfactory
2) Resulting clinical status defined as unstable and deteriorating
Inadequate clinical response for patients who were initially in WHO FC IV:
1) No rapid improvement to WHO FC III or better
2) Resulting clinical status defined as stable and not satisfactory

WHO FC: World Health Organization functional class. Reproduced from [1] with permission from the publisher.

Continuous *i.v.* epoprostenol is recommended as first-line therapy for WHO functional class IV PAH patients, because of the survival benefit in this subset. In WHO functional class IV patients, initial combination therapy should also be considered.

CASE 10: INADEQUATE RESPONSE TO PAH THERAPY

Case report

A previously healthy 39-yr-old female presented to her local hospital with a 1-month history of progressive dyspnoea associated with exercise-induced palpitations. She reported that her symptoms had begun approximately 1 month after the birth of her third child. Initial transthoracic echocardiography demonstrated enlarged right heart chambers with estimated systolic P_{pa} 100 mmHg without evidence of intracardiac shunt. She was referred to an expert centre for further evaluation. Initial RHC confirmed severe pre-capillary PH ($\bar{P}_{pa}$ 55 mmHg, PVR 1,250 dyn·s·cm^{-5}, CI 2.0 L·min^{-1}·m^{-2}; table 24) without acute vasodilator response. A diagnosis of idiopathic PAH was made after additional investigations for associated causes of PH were negative. As she was deemed to be in functional class III, with a baseline 6MWD of 519 m, oral endothelin antagonist therapy was initiated.

When the patient was reassessed after 4 months of treatment, she was still in functional class III with a similar 6MWD and haemodynamic profile that showed only a modest improvement (table 24). Because of a lack of improvement in either subjective or objective parameters, a decision was made to add oral PDE-5 inhibitor therapy. At subsequent re-evaluation 6 months after this therapeutic modification, there was both a clinical worsening (80 m reduction in 6MWD) and haemodynamic deterioration (increased $\bar{P}_{pa}$ and PVR, with associated significant reduction in CI; table 24). In view of this objectively defined deterioration in spite of dual oral targeted therapy, continuous *i.v.* prostacyclin was added to her treatment regimen. At the next assessment after 6 months of this three-drug combination approach, a marked clinical and haemodynamic improvement was observed (table 24). 3 yrs after initiation of triple therapy the patient is alive and well.

Commentary: relevance to ESC/ERS guidelines

Regular evaluation of patients with PAH should focus on variables with established prognostic importance, as outlined above. Treatment decisions should be based on parameters that reflect symptoms and exercise capacity and that are relevant in terms of predicting outcome. Table 25 lists several parameters of known prognostic importance that are widely used as follow-up tools. Patients with better or worse prognosis are separated by an intermediate group for which prognostication is more difficult.

Based on the clinical, noninvasive and invasive findings the clinical condition of a patient can be defined as stable and satisfactory, stable but not satisfactory, unstable and deteriorating, as follows. 1) Stable and satisfactory. Patients in this condition should fulfil the majority of the findings listed in the ''better prognosis'' column. 2) Stable and not satisfactory. This is a patient who, although stable, has not achieved the status that the patient and treating physician would consider desirable. Some of the limits described above for a stable and satisfactory condition and included in the ''better prognosis'' column are not fulfilled. These patients require re-evaluation and consideration for additional or different treatment following full assessment. 3) Unstable and deteriorating. Patients in this condition fulfil the majority of the findings listed in the ''worse prognosis'' column.

A goal-oriented treatment strategy is recommended in patients with PAH. Treatment goals for PAH patients that may be

TABLE 27 ESC/ERS guidelines: suggested assessments and timing for the follow-up of patients with pulmonary arterial hypertension

	At baseline (prior to therapy)	Every 3–6 months[#]	3–6 months after initiation or changes in therapy	In case of clinical worsening
Clinical assessment WHO FC/ECG	X	X	X	X
6MWT[¶]	X	X	X	X
Cardiopulmonary exercise testing[¶]	X		X	X
BNP/NT-proBNP	X	X	X	X
Echocardiography	X		X	X
RHC	X[+]		X[§]	X[§]

WHO-FC: World Health Organization functional class; X: assessment is suggested; 6MWT: 6-min walk test; BNP: brain natriuretic peptide; NT-proBNP: N-terminal proBNP; RHC: right heart catheterisation. [#]: intervals should to be adjusted to individual patients needs; [¶]: usually one of the two exercise tests is performed; [+]: is recommended (table 20); [§]: should be performed (table 20). Reproduced from [1] with permission from the publisher.

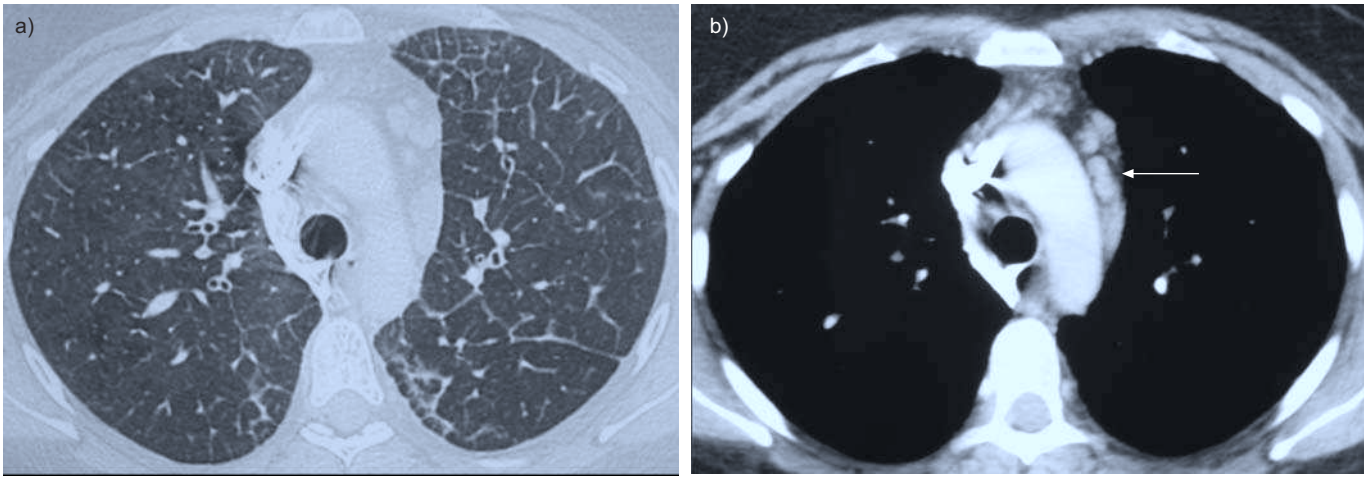

FIGURE 7. High-resolution computed tomography in a pulmonary veno-occlusive disease patient showing septal lines and ground-glass opacities (a) associated with mediastinal lymph node enlargement (arrow, b).

considered are those listed in the ''stable and satisfactory definition'' and in the ''better prognosis'' column.

In the case of inadequate clinical response (table 26), sequential combination therapy should be considered. Combination therapy can include either an endothelin receptor agonist plus a PDE-5 inhibitor, or a prostanoid plus an endothelin receptor agonist, or a prostanoid plus a PDE-5 inhibitor. Appropriate protocols for timing and dosing to limit possible side-effects of the combination have still to be defined. In expert centres triple combination therapy is also considered.

Balloon atrial septostomy and/or lung transplantation are indicated for PAH with inadequate clinical response despite optimal medical therapy or where medical treatments are unavailable. These procedures should be performed only in experienced centres.

Suggested follow-up strategies for patients with PAH are reported in table 27.

CASE 11: PULMONARY VENO-OCCLUSIVE DISEASE

Case report

A previously healthy 37-yr-old female cigarette smoker (8 pack-yrs) was referred with a 2-month history of intermittent chest pain on a background of a 2-yr history of progressive dyspnoea. On admission, the patient was in WHO functional class IV; physical examination revealed a loud pulmonic component to the second heart sound and normal pulmonary auscultation. ECG demonstrated complete right bundle branch block. Arterial blood gases showed severe hypoxaemia at rest (arterial oxygen tension (P_{a,O_2}) 5.8 kPa) while PFTs found normal values for forced expiratory volume in 1 s, forced vital capacity and total lung capacity, associated with a moderate impairment of $D_{L,CO}$ (52%). Echocardiography estimated systolic P_{pa} at 72 mmHg. RHC confirmed severe pre-capillary PH with normal left heart filling pressures ($\bar{P}_{pa}$ 68 mmHg, right atrial pressure 9 mmHg, P_{pcw} 11 mmHg, CI 2.27 $L \cdot min^{-1} \cdot m^{-2}$ and PVR 1,010 $dyn \cdot s \cdot cm^{-5}$). Acute vasodilatator testing with nitric oxide showed a degree of vasoreactivity that was insufficient to fulfil criteria for an acute vasodilator response (decrease in $\bar{P}_{pa}$ to 56 mmHg without change in CI). 6MWD was not feasible. Ventilation/perfusion lung scintigraphy found multiple mismatched subsegmentary perfusion defects. HRCT showed patchy areas of centrilobular ground-glass opacification, septal lines and mediastinal lymph node enlargement (fig. 7). This combination of radiological abnormalities associated with low P_{a,O_2} at rest and low $D_{L,CO}$ was highly suggestive of a diagnosis of PVOD. Neither surgical nor transbronchial lung biopsy, being contraindicated in suspected PVOD, was performed. The patient was hospitalised in the intensive care unit and treated with oxygen, diuretics and dobutamine. Because of the poor prognosis associated with PVOD, the risk of life-threatening pulmonary oedema with specific PAH therapy and the requirement for inotropic support in this case, the patient was listed for urgent double-lung transplantation and was transplanted 1 week later. The diagnosis of PVOD was confirmed by pathological assessment of the explanted lungs.

Commentary: relevance to ESC/ERS guidelines

Both PVOD and PCH are uncommon conditions, but are increasingly recognised as causes of PAH. They have been classified in a specific subgroup (group 1′) of the clinical classification for the pathological, clinical and therapeutic differences with the other forms of PAH included in group 1.

The diagnosis of PVOD can be established with a high probability by the combination of clinical suspicion, physical examination, bronchoscopy and radiological findings. Most patients complain of dyspnoea on exertion and fatigue, a clinical presentation that is indistinguishable from idiopathic PAH. Physical examination may reveal digital clubbing and bibasal crackles on lung auscultation, these being unusual in other forms of PAH. Case series suggest that patients with PVOD are more severely hypoxaemic and have a much lower $D_{L,CO}$ than in other forms of PAH. HRCT scanning is the investigation of choice. Typical findings suggestive of PVOD are the presence of subpleural thickened septal lines, centrilobular ground-glass opacities and mediastinal lymphadenopathy. Because PVOD may be associated with occult alveolar haemorrhage, bronchoscopy with bronchoalveolar lavage may be a useful tool in the diagnostic strategy. This noninvasive approach may avoid lung biopsy in most of the cases.

TABLE 28 ESC/ERS guidelines: recommendations for pulmonary veno-occlusive disease (PVOD)

Statement	Class#	Level¶
Referral of patients with PVOD to a transplant centre for evaluation is indicated as soon as the diagnosis is established	I	C
Patients with PVOD should be managed only in centres with extensive experience in PAH due to the risk of lung oedema after the initiation of PAH-specific drug therapy	IIa	C

PAH: pulmonary arterial hypertension. #: class of recommendation; ¶: level of evidence. Reproduced from [1] with permission from the publisher.

Haemodynamic presentation of PVOD is similar to idiopathic PAH. Importantly, P_{pcw} is almost invariably normal because the pathological changes occur in small venulae and do not affect the larger pulmonary veins.

There is no established medical therapy for PVOD. Most importantly, vasodilators and especially prostanoids must be used with great caution because of the high risk of pulmonary oedema (table 28).

There are reports of sustained clinical improvement in individual patients treated with these medications. Therefore, therapy for PVOD should be undertaken only at centres with extensive experience in the management of PH, and patients should be fully informed about the risks.

Atrial septostomy may be considered but is usually limited by hypoxaemia. The only curative therapy for PVOD and PCH is lung transplantation, and similarly to idiopathic PAH there are no reports of recurrence of disease following transplantation. Patients with PVOD should be referred to a transplant centre for evaluation as soon as the diagnosis is established.

CONCLUSION

We hope that these real-life cases and their accompanying commentaries have emphasised the high clinical relevance of the ESC and ERS guidelines, which should be largely disseminated and implemented. On this occasion, the authors wish to thank N. Galiè, University of Bologna, Bologna, Italy, who chaired the PH guidelines group, and all task force members, as well as members of the guideline committees from the ESC and the ERS.

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STATEMENT OF INTEREST

D. Montani, X. Jaïs, F. Parent, O. Sitbon and G. Simonneau have relationships with drug companies including Actelion, BayerSchering, GlaxoSmithKline, Pfizer and United Therapeutics. In addition to being an investigator in trials involving these companies, relationships include consultancy services and membership of scientific advisory boards. M. Humbert has relationships with drug companies including AB Science, Actelion, Altair, Amgen, Astrazeneca, Chiesi, GlaxoSmithKline, MSD, Novartis and Pfizer. In addition to being an investigator in trials involving these companies, relationships include consultancy services and membership of scientific advisory boards.

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EUROPEAN RESPIRATORY UPDATE

Contemporary issues in pulmonary hypertension

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In recent years, important contributions to the understanding of pulmonary hypertension (PH) have been published in core clinical journals [1]. Relevant and thought-provoking studies evidencing the high quality of research in the PH field have been carried out by specialists worldwide. We have decided to focus on special issues we believe to be, on the one hand, pertinent to the understanding of what has happened hitherto and, on the other hand, useful to lay the new foundations on which future research will be based.

Amongst the articles published in the last couple of years, we believe that the following groups of interest deserve special attention: the summary of the fourth World Symposium on PH; the guidelines on PH (both the American and the European); and the studies that shed new light on the discussion of survival in PH.

FOURTH WORLD SYMPOSIUM ON PH

In June 2009, the results of the discussion of working groups on specific issues of PH were published in 11 articles and one editorial in the *Journal of the American College of Cardiology* [2–13]. The articles covered a vast array of topics on PH, from basic research (comprising development, pathology, inflammation, genetics, and cellular and molecular basis of PH) to clinical issues, such as classification, diagnosis, the role of surgery and medical treatment in pulmonary arterial hypertension (PAH). Interestingly, there were also papers on end-points and clinical trials, and on future perspectives for the treatment of PAH.

The article entitled ''Updated clinical classification of pulmonary hypertension'' [3] aimed at grouping together different PH manifestations with similar pathophysiological mechanisms, clinical presentation and therapeutic options. In spite of the maintenance of the general architecture of the classification compared to the previous classifications (Second and Third World Symposium on Pulmonary Hypertension in 1998 (Evian, France) and 2003 (Venice, Italy), respectively) [14], some changes have been made to incorporate new knowledge on the disease.

The current classification of PH comprises the following groups, namely: 1) PAH, 1′) pulmonary veno-occlusive disease (PVOD) and/or pulmonary capillary hemangiomatosis (PCH), 2) PH owing to left heart disease, 3) PH owing to lung diseases and/or hypoxia, 4) chronic thromboembolic hypertension, and 5) PH with unclear and/or multifactorial mechanisms [3].

Most changes were incorporated in group 1, in which we find different subgroups. The first aspect to be highlighted is that the term idiopathic PAH (IPAH) was maintained, once again avoiding the use of primary and secondary PH; as stated since the Third World Symposium in PH (Venice, 2003) [14].

PAH may occur in a familial context and in this setting up to 70% of the patients may present with bone morphogenetic protein receptor (BMPR)-2 mutations [15, 16]. In addition, a mutation may be found in cases with no family history of PAH (up to 40% of such cases) [17]. Thus, it was reasonable to replace the term ''familial PAH'' by the term ''heritable PAH''. In this subgroup, identifiable mutations are acknowledged, such as BMPR2 and activin receptor-like kinase-1 or endoglin. Recently, the prognostic importance of identifying the presence of mutations has been highlighted [18, 19]. Mutation carriers not only present the genetic anticipation phenomena, in which symptoms start at earlier age as compared to the parents, but are also prone to present worse clinical course or a less favourable prognosis.

The role of drugs and toxins has been stressed and the categorisation of risk factors and the likelihood of developing PAH have been modified. In the previous classification, drugs and toxins were regarded as an associated condition, *i.e.* just as connective tissue disease [14]. However, recently published data suggest that the drugs act more like a trigger not necessarily influencing the clinical course of the disease [20]. We have also learnt that BMPR2 mutations can be found in anorexigen-induced PH [20, 21]. Based on these data, a subtle but significant change was made and instead of an associated condition, the classification now states ''drug and toxin-induced PAH''. In terms of epidemiology, this assumption allows the inclusion of this subgroup of patients together with patients with IPAH in clinical studies.

In the associated conditions, we have seen the incorporation of schistosomiasis as an associated condition for the development of PAH, and the limitation of the subgroup formerly generically called haemoglobinopathies [13] to the more specific subgroup of chronic haemolytic anaemia.

Schistosomiasis has been studied for decades and its association with PH has been described in the first half of the 20th Century [22, 23]. Formerly in group 4, schistosomiasis-associated PAH (Sch-PAH) has been reclassified into group 1. A recent study [24] confirmed earlier studies [25], demonstrating that in schistosomiasis most of the vascular injuries are not solely explained by egg embolism. In addition, the occurrence of

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plexiform lesions in Sch-PAH might be indistinguishable from those seen in IPAH. Furthermore, there is growing evidence based on experimental models emphasising the role of inflammatory mechanisms on the pathogenesis of Sch-PAH [26]. Invasive haemodynamic assessment showed a PAH prevalence of 4.6% in patients with the hepatosplenic form of schistosomiasis. The development of PAH in this subgroup of patients may be related to inflammation, co-existence of porto-pulmonary hypertension and occasional increased cardiac output to the pulmonary circulation [27]. These multiple possible pathways may somehow explain the better clinical course of Sch-PAH. When compared to IPAH, Sch-PAH patients present with a better haemodynamic profile at diagnosis and better prognosis; nonetheless, they still have a 3-yr mortality rate of ~15% [28]. Since schistosomiasis is a highly prevalent disease worldwide and given the non-negligible mortality rate, the reclassification of Sch-PAH in group 1 based on pathological and haemodynamic studies may warrant trials with specific treatments for this highly prevalent condition.

PAH associated with chronic haemolytic anaemias, such as sickle-cell disease or thalassemia, remained in group 1, replacing the generic term haemoglobinopathies, which was present on the previous classification. The possible mechanisms for the development of PH in this group include a high cardiac output with consequential pulmonary vascular hyperflow and impaired nitric oxide action in the pulmonary vessels due to chronic haemolysis. Because one or more of these mechanisms may contribute to the elevation of pulmonary pressure in this setting, patients may present with either predominant pre- or post-capillary PH [29]. However, since a significant proportion of patients with PH and haemolytic anaemias have PAH, they were kept in group 1.

It is important to highlight that other conditions, such as connective tissue diseases [30] or schistosomiasis [31], may present pre- or post-capillary PH. Based on this, the classification cannot be done solely according to the baseline disease; it is absolutely indispensible to combine the clinical information and the results of the invasive haemodynamic evaluation in order to appropriately classify an individual with PH.

Finally, in group 1′ we find PVOD and PCH. Although presenting with different phenotypes, they have been placed together for occasionally having similar risk factors, genetic mutations and pathological findings, most of which they share with IPAH. However, when it comes to response to treatment, data is somewhat disappointing. In fact, some treatments to IPAH may actually be deleterious for these conditions if not used cautiously [32–35].

Group 2 comprises what is believed to be the most frequent cause of PH. In the previous classification, left ventricular heart disease was divided into atrial/ventricular or valvular disease [14]. In the current classification, PH owing to left heart disease was divided into systolic or diastolic dysfunction, maintaining valvular disease as a separate cause. There has been an increased interest of left ventricular dysfunction with normal ejection fraction. Specific algorithms have been proposed to better diagnose this clinical condition avoiding the possible deleterious effects that inadequate treatments strategies might cause when this condition is not recognised [4].

In group 3, a new category was added: mixed obstructive/restrictive disease. It has been recently recognised that patients presenting with upper lobe emphysema combined with lower lobes interstitial infiltrate have higher incidence of PH, with direct implication on prognosis [36, 37].

In group 4 we find chronic thromboembolic pulmonary hypertension (CTEPH). Formerly, all causes of thromboembolic disease were subclassified in proximal and distal obstruction [38]. Since CTEPH may be an operable form of PH with potential cure (or significant improvement in right ventricle function), the new classification avoids the distinction between proximal end distal obstruction, to underline the need of specific multidisciplinary assessment of such cases in experienced reference centres in order to evaluate operability.

Finally, in group 5 we find PH with unclear multifactorial mechanisms. Haematological, systemic and metabolic disorders are described in this group, recognising the relationship between these conditions and PH; however, expressing the uncertainties about pathophysiology, treatment and outcome. The classification working team has fortunately found an adequate name for this set of conditions within group 5 instead of simply calling it ''PH caused by disorders directly affecting the pulmonary vasculature'' or ''miscellaneous'', as in previous classifications [14].

The definition of resting PH has not changed, being defined as the presence of mean pulmonary artery pressure ($\bar{P}_{pa}$) $\geqslant$25 mmHg. A resting $\bar{P}_{pa}$ between 8 and 20 mmHg should be considered normal. The authors consider that further studies are needed to determine the natural history of individuals with a resting $\bar{P}_{pa}$ between 21 and 24 mmHg. The definition of exercise PH is still awaiting better evidence to support it, therefore, being excluded from the current classification [39].

A thorough search of the literature and a strict classification of the levels of evidence of each intervention were performed to put together an algorithm to treat patients in group 1, in each functional class [12]. General interventions, such as anticoagulants, oxygen and diuretics, were incorporated into the algorithm as expert opinion level of evidence. When it comes to specific treatment, the following data are presented for the same level of recommendation, in alphabetical order, not in order of importance (all oral therapy, unless otherwise stated).

PAH class II: Level of recommendation A: ambrisentan, bosentan, sildenafil; level of recommendation B: sitaxsentan, tadalafil.

PAH class III: Level of recommendation A: ambrisentan, bosentan, epoprostenol (intravenous), iloprost (inhaled), sildenafil; level of recommendation B: sitaxsentan, tadalafil, treprostinil (subcutaneous); level of recommendation C: beraprost; expert opinion B: iloprost (intravenous), treprostinil (intravenous).

PAH class IV: Level of recommendation A: epoprostenol (intravenous); level of recommendation B: iloprost (inhaled); level of recommendation C: treprostinil (subcutaneous); expert opinion B: iloprost (intravenous), treprostinil (intravenous), initial combination therapy; expert opinion C: ambrisentan, bosentan, sildenfil, sitaxsentan, tadalafil.

It is also interesting to note that in the event of lack of clinical response, a sequential combination therapy is considered with either three classes of drugs available (phosphodiesterase-5 inhibitors, endothelin receptor antagonists and prostanoids). This treatment approach has been reported in different settings and with different combinations of drugs [40–42]; no specific combination is formally recommended.

The relevance of this article is to organise the available data on treatment in an evidence-based algorithm, considering the incorporated practice of combination therapy, either upfront (for the most severe cases) or add-on (in the event of lack of clinical response).

THE EUROPEAN SOCIETY OF CARDIOLOGY/EUROPEAN RESPIRATORY SOCIETY AND THE AMERICAN COLLEGE OF CHEST PHYSICIANS/AMERICAN HEART ASSOCIATION GUIDELINES

Following the publication of the summary of the Fourth World Symposium on PH, joint guidelines from the European Society of Cardiology/European Respiratory Society [43] for the diagnosis and treatment of pulmonary hypertension were published, as was the American College of Chest Physicians (ACCP)/American Heart Association (AHA) expert consensus on pulmonary hypertension [44]. These guidelines offered another unique opportunity to propose useful approaches to issues in clinical practice. Some aspects of both documents deserve closer attention.

In the European guidelines, an interesting approach to the likelihood of the presence of PH based on echocardiogram findings was presented. Since echocardiogram is usually the first assessment to detect the possibility of PH [45], it may be reasonable to consider combined parameters to establish the likelihood of PH. By combining the tricuspid regurgitation velocity to other echocardiographic variables suggestive of PH an arbitrary criteria suggest the stratification in PH unlikely, possible and likely. The interesting aspect of this stratification is its combination to the presence of symptoms or associated baseline conditions in order to obtain a rational use of right heart catheterisation or to propose the follow-up approach for a given patient. Although arbitrary, these recommendations are from an expert consensus and may represent innovative ways for daily practice or at least suggest new approaches to be addressed in future studies [46].

Conversely, the ACCP/AHA consensus suggests a practical approach on diagnosing PH with a table of pivotal and contingent tests. For instance, ventilation/perfusion scans are considered to be pivotal test, whereas computed tomography angiograms are considered to be contingent in the investigation process. By such a diagnostic approach, a more reasonable use of the diagnostic tools is possible, based on the probability of diagnosis, timesaving and resources.

These provocative suggestions might be considered when adapting the diagnostic algorithms to a specific socio-geographical condition, putting together the regional characteristics and the availability of the different diagnostic tools.

SURVIVAL

In 2009, we emphasised the role of contemporary registries in PAH not only to better characterise the disease itself but also to recognise that regional characteristics have to be identified in order to appropriately extrapolate and/or adapt international guidelines for diagnosis and treatment [1]. Interestingly, over the past year, the survival data of some of these registries have become available. One of the problems of dealing with an orphan disease is its low prevalence. Consequently, an important part of the gathered knowledge results from a small observation series, precluding the generalisation of the findings [47]. One alternative to bypass this obvious limitation is to set up multicenter registries. However, significant caveats may take place in such an approach and should be taken into consideration when analysing data coming from registries of rare diseases. Retrospective cohorts have the limitation imposed by missing data and reliable diagnosis, while prospective cohorts may limit the inclusion criteria too much in order to homogenise the study population [48]. Both characteristics may limit the extrapolation of data and should be carefully considered. Nevertheless, three different registries had their survival data published during the last year and from all of them new prediction equations have emerged. This is particularly interesting since it reinforced a common feeling that the National Institute of Health equation, published in the early 1990s [49], was no longer accurate to evaluate contemporary data, considering the significant development in knowledge and available therapies that has taken place in the past decades.

THENAPPAN *et al.* [50] published a large monocentric registry of PAH patients. One of the findings that was also confirmed by the other registries is that current PAH patients present at an older age compared to earlier studies. While in the late 1980s the mean age at diagnosis was 37 yrs [51], in this study the authors found a mean age of 48 yrs (patients were even older in the other published registries). Moreover, older age at diagnosis was independently associated with long-term survival. Of note, the majority of patients presented in functional class III or IV at diagnosis, although the predominant retrospective nature of the study may have biased this finding. The authors also described that connective tissue disease, functional capacity, right atrial pressure, cardiac index and pulmonary vascular resistance were predictors of survival. Surprisingly, the authors decided to build a prediction equation based not on the prognostic variables found in their study but only on the same hemodynamic variables used in the National Institute of Health equation alleging their intention to make a direct comparison to the previously described equation. The proposed model was certainly a step further in the analysis of survival data in PAH; however, by excluding significant parameters the authors may have limited the extrapolation of their prediction model.

In 2006, baseline data from the French National Registry on PAH were published evidencing a PAH incidence of 2.4 cases per 1 million adult inhabitants per year and a prevalence of 15 cases per 1 million inhabitants for PAH (5.9 cases per 1 million inhabitants for IPAH) [52]. The study included 674 cases from 17 different reference centres. By that time, the authors had already described older age at diagnosis and a less preserved functional class (III or IV) for the vast majority of the patients, reinforcing the concept that even with the development obtained in recent years the diagnosis was still late on the disease progression.

The 3-yr survival data for idiopathic, heritable and anorexigen-associated PAH have been addressed in two publications this year [12, 48]. The first study demonstrated 1-, 2- and 3-yr survival rates of 82.9%, 67.1% and 58.2%, respectively [53]. These results, when compared to the results of the National Institute for Health registry, suggest that survival has been significantly but still too modestly improved, reinforcing the concept that PAH is still a devastating clinical condition. Of note, the authors identified three independent prognostic factors: cardiac output and 6-min walk test (6MWT) distance at diagnosis, and sex. Male patients notably presented with worse prognosis compared to the predominant female subgroup. The possible mechanisms that justify this association of male sex and prognosis in IPAH are not clear but this now constitutes a new issue to be addressed in future studies. Some methodological aspects of this study deserve better attention. The authors decided to limit their observations to a more homogeneous population; for this, not only did they limit the population to patients with idiopathic, heritable and anorexigen-induced PAH but also decided to consider only the data obtained at diagnosis, in an attempt to deal with a more robust data set. Another important aspect was the distinction between newly diagnosed patients (incident) and prevalent patients (diagnosed before study enrolment). It is well known that the inclusion of prevalent cases in observational studies may impose a significant bias if the mortality rate is not constant during time, which is the case for PAH.

By distinguishing both populations, the authors tried to minimise this bias. However, the arbitrary cut-off for combining the prevalent and incident groups in order to perform the survival analysis (the authors joined prevalent patients diagnosed <3 yrs of study enrolment and performed a left truncation analysis) still imposed a bias to the analysis. It is important to notice that no specific treatment algorithm, besides the international guidelines available at the time [54], was imposed; thus the study tried to reflect ''real life'' in PAH management.

In another study, the authors analysed the significant difference on survival between incident and prevalent cases [55]. In addition, the trend in survival was associated with the time from diagnosis in the prevalent population; the shorter the time from diagnosis the more the prevalent subgroup resembled the incident group, with worse prognosis. This study also reinforced the concept that different diagnoses within group 1 have different survival rates. We also have to consider that there are different survival rates in different groups of PAH, *e.g.* a worse prognosis in connective tissue disease-PAH and a better prognosis in HIV-PAH, congenital heart disease-PAH and Sch-PAH [56–58].

Moreover, a new prognostic equation for idiopathic, heritable and anorexigen-induced PAH was proposed based on the three prognostic markers found on the multivariate analysis (sex, 6MWT and cardiac output), thus incorporating markers other than the common haemodynamic ones, possibly increasing the representativeness of the equation. This assumption, however, has to be properly validated in a different population prior to being accepted.

Another important registry whose data have been published this year is the REVEAL registry (Registry to Evaluate Early and Long-Term PAH Disease Management). The registry comprises the efforts of 54 different centres in the USA and has been evaluated in three articles addressing different characteristics of this comprehensive study on PAH [59–61].

The first article described the baseline demographic characteristics of the 2,967 patients included in the registry [59]. This study confirmed the shift toward older age at diagnosis in PAH. 46% of included patients presented with IPAH; considering patients with associated causes for PAH, connective tissue disease associated-PAH accounted for almost half of the cases. It is interesting to note the low prevalence of HIV associated-PAH in the REVEAL study (~2.2%) as compared to the prevalence found in the French Registry (6.2%). How much of this can be attributed to lower awareness about the association in the US as compared to France where a quite recent multicenter prevalence study was performed [62] is still a matter of debate.

An interesting comparison between the REVEAL registry and other historic or non-US contemporary registries recently became available, reported by FROST *et al.* [61]. In this study the authors selected the subgroups within the REVEAL registry that could be directly compared to other studies. In addition, different aspects of the registry not previously addressed were analysed. One peculiar aspect is the behaviour of the female/male ratio increasing with survival post-diagnosis. One might link this finding to a worse prognosis for the male sex found in the French Registry [53], strengthening the need to address the role of sex in PAH survival in a specific study with an appropriate design.

The incidence for idiopathic and familial PAH found in the registry was 1.1 cases per million while the prevalence of PAH was 12.4 cases per million which is comparable to the previously described rates [52] providing consistent data for contemporary use.

Finally, a third study analysing survival of PAH patients included in the REVEAL registry has been published [60]. The authors decided not to limit their study population, including all forms of PAH now within group 1 of the classification and available at the time of the study initiation [14]. By doing so, the authors tried to make the analyses reproducible in all subgroups; as if a proposition of this approach is of indubitable value, it may impose limitations to the analysis itself. Another methodological issue that has to be accounted for is the fact that the data used in the analyses was collected within a certain period of time and not necessarily at the diagnosis. In addition, prevalent and incident cases were considered together which could have resulted in somehow optimistic survival rates. The authors, however, carefully included time from diagnosis in the analysis in order to categorise the patients; nevertheless, no statistical significance was found regarding this dichotomisation of the study population. Of note is the fact that the comparison was made between patients diagnosed within 90 days prior to study enrolment and patients diagnosed >90 days before enrolment, a rather small time-frame to properly distinguish the two study populations if the results of the prevalent population from the French study is considered [55]. This is particularly important since the vast majority of the REVEAL population comprises prevalent patients.

This large cohort allowed the identification of multiple prognostic factors, such as the origin of PAH (different diagnoses within group 1), age, functional class, 6MWT distance, cardiac function, B-type natriuretic peptide, echocardiographic finding of pericardial effusion and diffusing capacity of the lung for carbon monoxide. Based on these variables, the authors were able not only to develop a prognostic equation but to create a ''stratification of risk'' considering 1-yr survival. This stratification confirmed a concept suggested in 2006 in an article by MCLAUGHLIN and MCGOON [63] in which the authors described several conditions that could be reflecting a higher risk of death. The REVEAL study allowed the proper validation of the concept and also identified the group of variables that should be considered in this matter.

Taken together, these registries brought important information to the field by identifying subgroups with worse prognosis that should be better addressed in terms of treatment strategies. There are certainly numerous possibilities to explore in the future, such as upfront combination therapy and earlier indication for epoprostenol. These studies provided us with goals to be reached in order to possible interfere in the prognosis of PAH patients.

In summary, the last couple of years have been quite prolific in terms of baseline concepts that will allow the delineation of better studies in the near future. Besides the development of new therapies, the advances to be reached will depend on strong foundations regarding concepts and understanding of the natural course of the disease; doubtlessly these recent studies represent a significant step forward in this sense.

STATEMENT OF INTEREST

None declared.

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The role of imaging techniques in the assessment of pulmonary circulation*

O papel dos exames de imagem na avaliação da circulação pulmonar

André Hovnanian, Eduardo Menezes, Susana Hoette, Carlos Jardim, Dany Jasinowodolinski, Rogério Souza

Abstract

Knowledge of the structure and function of pulmonary circulation has evolved considerably in the last few decades. The use of non-invasive imaging techniques to assess the anatomy and function of the pulmonary vessels and heart has taken on added importance with the recent advent of novel therapies. Imaging findings not only constitute a diagnostic tool but have also proven to be essential for prognosis and treatment follow-up. This article reviews the myriad of imaging methods currently available for the assessment of pulmonary circulation, from the simple chest X-ray to techniques that are more complex and promising, such as electrical impedance tomography.

Keywords: Pulmonary circulation; Diagnostic imaging; Hypertension, pulmonary.

Resumo

O conhecimento sobre a estrutura e a função da circulação pulmonar evoluiu sensivelmente nas últimas décadas. A utilização de exames de imagem não invasivos para a avaliação da anatomia e da função dos vasos pulmonares e do coração ganhou ainda mais importância com o advento de tratamentos até então indisponíveis. Além do auxílio para o diagnóstico, as informações obtidas têm se mostrado fundamentais para o estabelecimento de prognósticos e como parâmetro de sucesso dos tratamentos. A presente revisão discute os diversos métodos que podem ser utilizados para a avaliação da circulação pulmonar por imagens existentes nos dias de hoje, desde técnicas amplamente disponíveis e de relativa baixa complexidade técnica, como a radiografia de tórax, até métodos complexos e promissores, como a tomografia de impedância elétrica.

Descritores: Circulação pulmonar; Diagnóstico por imagem; Hipertensão pulmonar.

Introduction

The physiology of the pulmonary circulation has only recently come to be understood. That is because the techniques available at the beginning of the 20th century did not allow direct assessment of the pulmonary vasculature. Until the late 1930s, there were no methods capable of providing information about cardiopulmonary interaction or the ventilation/perfusion ratio. The milestone breakthrough came in 1940, when the integration of the physiological studies by Cournard et al.[1] and Forssmann's self-experimentation in 1929,[2] which consisted of radiographic documentation of the presence of a catheter in his own heart, culminated in catheterization of the right ventricle (RV) and pulmonary arteries, thereby revolutionizing knowledge in the area of cardiopulmonary medicine. Access to hemodynamic pressure and flow measurements, as well as to blood gas measurements, provided a unique opportunity for advances in the assessment of pulmonary circulation, which became recognized as an exclusively arterial system, characterized by high compliance and low resistance, capable of accommodating large blood volumes and high blood flows at low pressures.[3]

Invasive hemodynamic assessment has become a valuable imaging tool, because it has

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clarified not only the physiological aspect of the pulmonary circulation but also the anatomical distribution of the pulmonary vessels and features of the right heart.

After the anatomical and functional status of the pulmonary circulation had been addressed, right heart catheterization came to be widely used for the assessment of the pulmonary vasculature, especially in the presence of disease, such as pulmonary hypertension (PH). However, despite being considered the gold standard, the method has major limitations by current standards, because it is invasive in nature, costly, and involves the use of radiation. However, the push to develop noninvasive techniques for monitoring pulmonary circulation was soon to begin.

Great efforts have been made to identify noninvasive imaging methods that reflect the anatomical and functional status of the pulmonary circulation in an accurate and reproducible way. However, noninvasive assessment of the pulmonary circulation is quite difficult. First, because no method has sufficient sensitivity to assess the most important aspect of the pulmonary circulation and the seat of most diseases: the microcirculation. Second, because much of the information about the pulmonary vasculature is indirect. When diseased, the small blood vessels lose the mutual exclusivity between high compliance and low resistance.[3] The loss of elasticity and increased vascular impedance directly affect the RV. Therefore, imaging of the RV might indirectly characterize the status of the pulmonary circulation. However, it is also difficult to study the RV, because of its anatomical position in relation to the left ventricle (LV), its complex crescent-shaped geometry, and its thin walls. All of this makes the assessment of systolic function, as well as the assessment of myocardial volumes and mass, a challenge for noninvasive imaging methods. The available methods employ different imaging technologies to generate information about pulmonary circulation. Chest X-ray is the simplest example. Despite its limitations, chest X-ray can reveal abnormalities that are not identified clinically. Echocardiography and CT of the pulmonary arteries (CT angiography), both of which are well-known and widely used, provide valuable information about the right heart and pulmonary arteries. Novel CT and magnetic resonance imaging (MRI) techniques have been found to play an important role in the dynamic, real-time assessment of the microcirculation. The innovative technique known as electrical impedance tomography (EIT) is a promising tool.

This article reviews the characteristics, limitations, and roles of the various imaging technologies currently available for the assessment of the pulmonary circulation, as well as for the diagnosis and management of PH and pulmonary thromboembolism (PTE).

Chest X-ray

Chest X-ray should be among the initial tests in the assessment of PH because it is readily available, is inexpensive, and facilitates the diagnosis.

Chest X-ray changes are seen in more than 85% of patients with a confirmed diagnosis of PH.[4] The major changes found include increased pulmonary artery diameter at the hilar level, in 78% of cases (Figure 1); peripheral tapering of vessels, in 62%; and hyperlucent lung periphery, in 9% (Figure 2). The pulmonary artery diameter at the hilar level can be determined by measuring the interlobar artery diameter. The maximum transverse diameter of the right interlobar artery, as measured from its lateral aspect to the air column of the intermediate bronchus, is 16 mm in men and 15 mm in women.[5] Because of the difficulty in assessing the left pulmonary artery by posteroanterior chest X-ray, the vessel should be assessed by lateral X-ray, beginning at the circular transparency created by the left upper lobe bronchus (which is visualized as being telescoped) and extending to the posterior margin of the vessel saddling the bronchus (Figure 1). The maximum limit of normality is 18 mm. A hilar-thoracic index (sum of the diameters of the pulmonary hila divided by that of the chest) above 38% is classically described, being present in approximately 75% of patients with PH (Figure 1).[6] Vascular calcification, usually located in the pulmonary artery trunk (PAT) or in its hilar branches, is rarely detected. This change is most commonly associated with congenital heart diseases and chronic central embolism.

Chest X-ray can facilitate the differential diagnosis with pulmonary parenchymal disease, heart failure, COPD, and kyphoscoliosis, as well as raising the suspicion of pulmonary

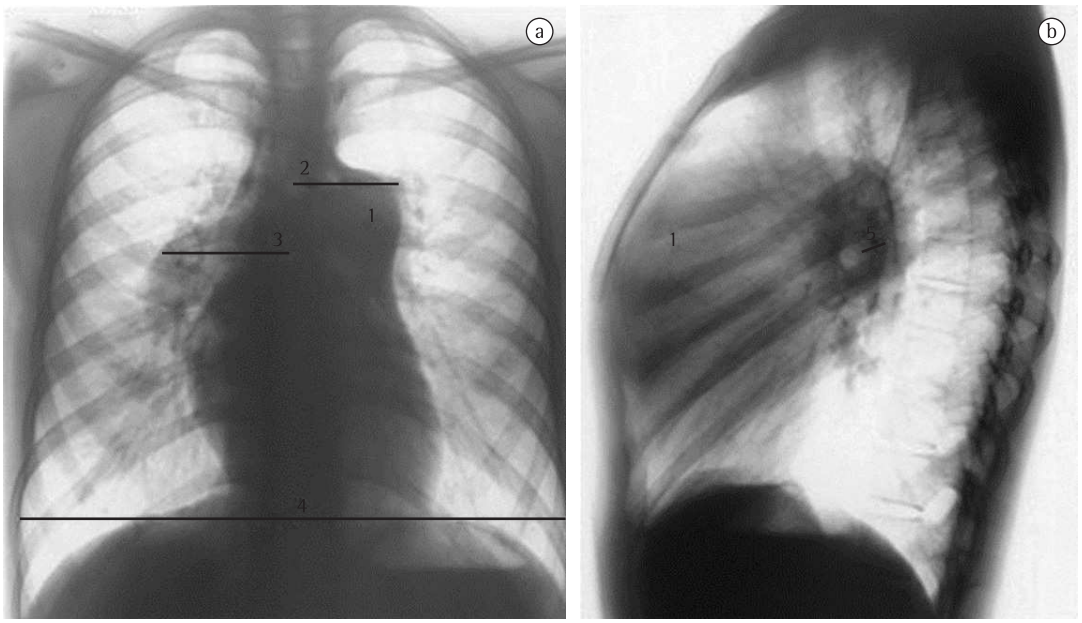

Figure 1 - Posteroanterior chest X-ray (in a) and lateral chest X-ray (in b) of a 28-year-old female patient with idiopathic pulmonary arterial hypertension. Note the dilated pulmonary artery trunk (1), the hilar-thoracic index (2) + (3) > 38% (4), and the left pulmonary artery > 18 mm (5) in profile.

thromboembolic disease when there are findings of oligemia, multiple areas of consolidation suggestive of pulmonary infarction, or asymmetry among the major pulmonary arteries (Figure 2).[7]

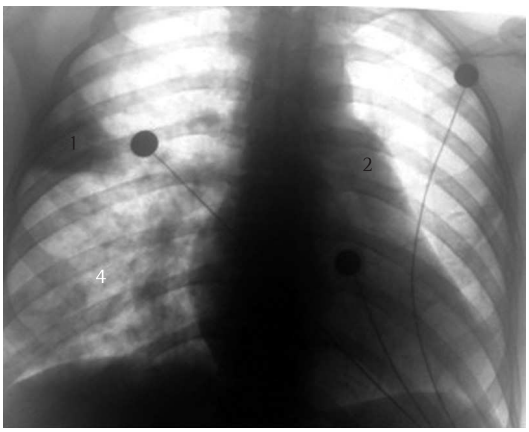

Figure 2 - Anteroposterior chest X-ray of a 41-year-old female patient. Note the following: subsegmental wedge-shaped opacity in the right upper lobe (1), suggestive of pulmonary infarction; prominence of the 2nd arch (2), suggestive of pulmonary hypertension; left lung oligemia (3); and nodular opacities with ill-defined borders (4). The patient had metastatic choriocarcinoma with tumor embolism.

Although the presence of PH can be suggested by conventional X-ray, the specificity of this method and its degree of accuracy in estimating the severity of PH are controversial.[7] Several factors, such as the size of the patient, the distance between the X-ray tube and the film, and the distance between the pulmonary artery and the film, affect the interlobar artery measurements. Many of the parameters used are subjective, and the measurements correlate poorly with the degree of PH.[7] Nevertheless, routine chest X-ray plays a central role in the initial investigation of dyspnea, as well as in the initial evaluation of patients with suspected PH.

Echocardiography

Transthoracic Doppler echocardiography is the most sensitive noninvasive method for estimating pulmonary artery pressure (PAP) when there is suspicion of PH.[8]

However, RV ejection fraction and volumes cannot be calculated with the use of the mathematical equations usually employed to study the LV. Therefore, several echocardiographic parameters have been developed to assess RV function and the hemodynamics of the pulmonary artery. The most widely used of those methods is based on the identification of

tricuspid regurgitation (TR). Measurement of TR provides an estimate of the pressure gradient in the right heart. The first studies involving continuous wave Doppler echocardiography were published in the mid-1980s.[9,10] The technique consists of measuring peak velocity of tricuspid regurgitation (V_{TR}), which provides an estimate of the regurgitant flow from the RV to the right atrium (RA), as shown in Figure 3. With the use of the simplified Bernoulli equation ($\Delta P = 4 \times V_{TR}^2$), it is possible to convert the flow measurement into an estimate of pressure. By adding this pressure gradient and an estimate of RA pressure, we obtain RV peak systolic pressure (RVSP), an approximation of the pulmonary artery systolic pressure (PASP), provided that there is no obstruction of the RV outflow tract. An RVSP > 35-40 mmHg is suggestive of PH.[10] In the presence of low regurgitant flow, the estimation of RVSP becomes less sensitive, because of the low signal intensity, which might lead to the underestimation of pressure values. However, the presence of extremely severe TR might also lead to the underestimation of pressure measurements, because equalizes the RA and RV pressures, resulting in a weak Doppler signal. Conversely, the method might also overestimate RVSP values.

Another way to estimate PASP by echocardiography is by calculating the inferior vena cava compressibility index, as described by Pepi et al.[11] The authors found a strong correlation between RA pressure and the aforementioned index. With the use of a more reliable RA measurement, the percentage error in estimating PASP by the Bernoulli equation

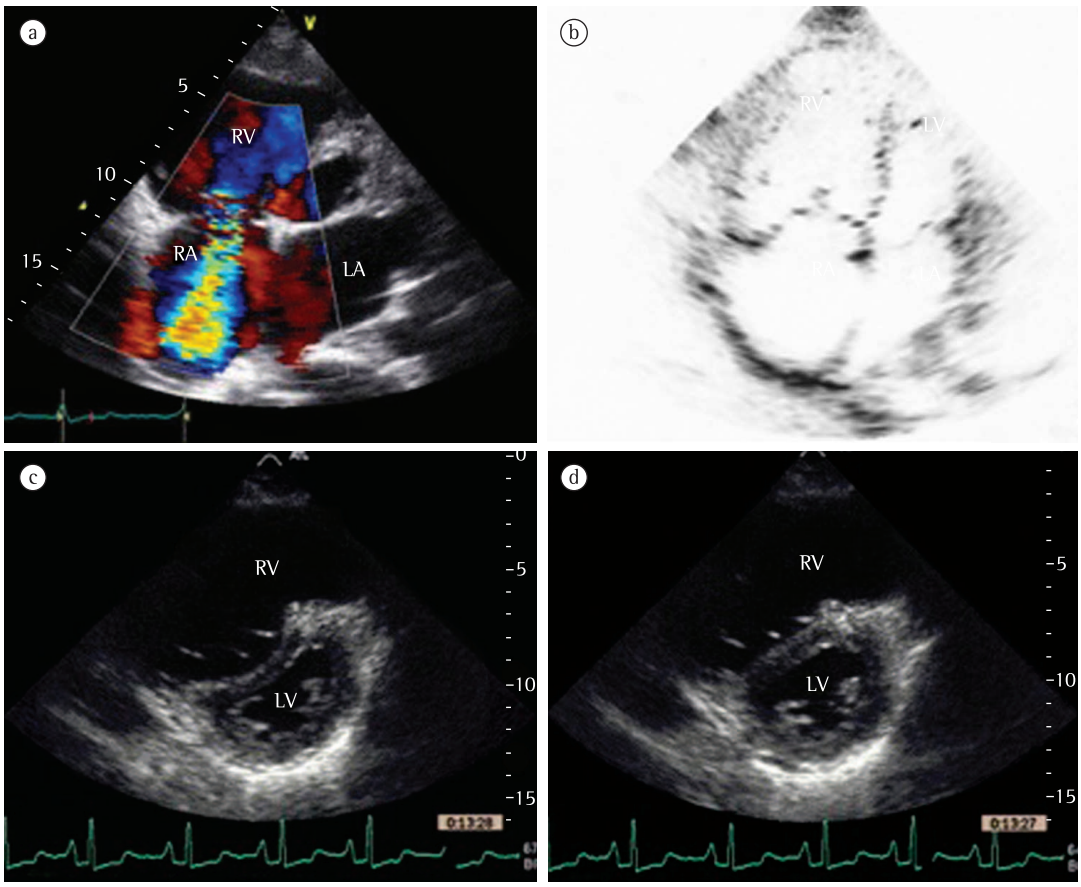

Figure 3 - Echocardiography images. Note the intensity of the continuous wave Doppler signal of the tricuspid regurgitant jet during ventricular systole (in a) and the dilated right heart (in b). Note the pressure overload in the right ventricle (RV), leading to paradoxical interventricular (IV) septal motion to the left, and the reduction in the size of the left ventricle (LV) during diastole (in c). During ventricular systole, the IV septum remains flattened (in d). Imaging provided by Dr. Fabio Lario, attending physician in the Department of Echocardiography of the Heart Institute of the University of São Paulo School of Medicine *Hospital das Clínicas*.

decreases, thus increasing the accuracy of the method.

In the 1990s, in order to improve the accuracy of the echo signal, the addition of intravenous contrast material to continuous wave Doppler echocardiography provided the opportunity to improve the sensitivity of the method. Materials such as 5% glucose microbubbles, sonicated human albumin, and indocyanine green increase echo intensity without affecting V_{TR}. One group of authors[12] observed that, in a small patient sample (comprising 39 patients, most of whom had left heart disease), the estimation of PASP with the use of contrast resulted lower than the estimation of PASP with the use of right heart catheterization, the standard error for the latter being ± 5 mmHg in 51% of the patients and ± 10 mmHg in 82%.

At the beginning of the 21st century, two other indexes gained popularity in the echocardiographic evaluation of patients with PH. In a population of 26 patients with PH (known as primary PH at the time), Tei et al.[13] described an index of combined systolic and diastolic function, known as the Tei index, which is obtained by dividing the sum of systolic and diastolic isovolumetric intervals by the ejection time. The Tei index was found to be a good predictor of survival in this population. Described in 1984 for the LV, the tricuspid annular plane systolic excursion (TAPSE) index reflects the longitudinal tricuspid annular motion during ventricular systole and correlates strongly with RV ejection fraction. Because TAPSE is a direct method that does not depend on ventricular geometry, it is quite reproducible and easy to obtain. In 2006, one group of authors[14] showed that a TAPSE index < 1.8 cm is indicative of more advanced RV dysfunction and correlates with a lower 19-month survival rate, especially in patients with pulmonary arterial hypertension (PAH).

Other echocardiographic parameters can also be used in the evaluation of PH. Measurement of TR at the opening of the pulmonary valve is used for estimating pulmonary artery diastolic pressure (PADP).[15] It is also possible to estimate pulmonary vascular resistance, which correlates with invasive hemodynamic measurement.[16] Atrial contraction and the subsequent increase in intracavitary pressure result in the formation of a characteristic wave, known as the A-wave. A less pronounced or absent A-wave on the PAP curve, probably attributable to increased PADP, is highly suggestive of PH. However, in patients with RV dysfunction, a normal A-wave does not rule out PH. Measurement the acceleration time of the pulmonary artery flow also has good accuracy in detecting increased PAP, representing an estimate of the mean pulmonary artery pressure (mPAP).[17] In addition, the finding of an increased RV systolic time interval is a highly specific echocardiographic sign of PH, albeit one with low sensitivity.[16] Other echocardiographic signs, such as right heart enlargement, pericardial effusion, RV dysfunction, paradoxical interventricular septal motion, and reduced LV filling volumes, also corroborate the presence of PH (Figure 3).[18] Provided that their limitations are taken into account and that they are evaluated and interpreted in the light of the clinical context, all these parameters can be useful in the diagnosis and follow-up of patients with PH.

Variations in PASP values can depending on the conditions and the characteristics of the population evaluated (age, level of exercise, level of fitness, and stress level). It has been reported that RVSP values are above 40 mmHg in 6% of subjects over 50 years of age and in 5% of those with a body mass index of 30 kg/m^2.[18] Therefore, slightly increased values should be interpreted with caution.

In the context of acute PTE, echocardiography is highly valuable. Despite having no diagnostic power, except in cases of saddle PTE that can be visualized by Doppler, the method can predict mortality from thromboembolic events and possibly assist in the decision-making process regarding treatment. By providing morphological and functional information about the RV, echocardiography directly assesses the magnitude of the effect that pulmonary circulation obstruction has on the RV. Analyzing a cohort of a large population-based study,[19] one group of authors[20] observed that the finding of RV dysfunction on baseline echocardiography has a high positive predictive value for lower 30-day survival. The risk of death, reported in that study, was nearly twice as high in the patients with such dysfunction. In one systematic review,[21] the combined results of five studies evaluating the prognostic role of RV dysfunction as assessed by echocardiography

revealed that the relative risk of death in patients with such dysfunction was 2.5 (95% CI: 1.2-5.5). This finding is of great importance because it identifies a subgroup of patients who are at high risk for complications and who, at admission, are stable from a hemodynamic standpoint.

In summary, echocardiography is widely available, inexpensive, and quite safe. Despite its limitations, echocardiography represents an important diagnostic and monitoring tool in PH and in PTE when used in combination with other markers.

Ventilation/perfusion scintigraphy

The major role of ventilation/perfusion scintigraphy in patients with PH is to distinguish chronic thromboembolic PH from other causes of PH.

The role of scintigraphy in the assessment of patients with PH, as well as in the assessment of patients with acute pulmonary embolism,[22] is well-established. A study conducted in 1994 involved 75 patients with documented causes of PH.[23] Of the 25 patients with chronic thromboembolic PH, 24 (96%) had high-probability scans and 1 (4%) had an intermediate-probability scan. Conversely, of the 35 patients with primary PH, 33 (94%) had low-probability scans, 1 (3%) had an intermediate-probability scan, and 1 (3%) had a high-probability scan. Of the 15 patients with non-thromboembolic secondary PH, the result was less accurate: 10 (67%) had low-probability scans, 3 (20%) had intermediate-probability scans, and 2 (13%) had high-probability scans. In view of the poorer yield in this third group of patients, the great importance of scintigraphy, in the context of PH, lies in the fact that it can rule out thromboembolic disease: a low-probability scan definitely excludes this disease. Another study showed that, in comparison with multidetector CT (MDCT), scintigraphy has far greater sensitivity for detecting chronic pulmonary embolism (96% vs. 51%).[24]

The typical pattern of scintigraphy findings in primary PH is that of poor perfusion (mottled pattern) in the periphery of the lung.[25] There is some correlation between the degree of perfusion heterogeneity in primary PH and patient prognosis.[25] Occasionally, multiple, small perfusion defects can be found in pulmonary veno-occlusive disease, pulmonary capillary hemangiomatosis, fibrosing mediastinitis, pulmonary vasculitis, and pulmonary artery sarcoma.

The most recent PH guidelines[26] recommend scintigraphy as the diagnostic method of choice for ruling out chronic PTE. In a patient with PH, a negative or low-probability scan virtually excludes chronic PTE, whereas a high-probability scan has a specificity of 96% for the diagnosis of chronic PTE in the presence of one or more segmental perfusion defects (Figure 4).[26]

CT

Obtaining images with the CT technique essentially consists of rotating a system comprising an X-ray tube and detectors around the body, and this introduces an innovation compared with routine X-ray: cross-sectional visualization of the various anatomical structures without overlap. However, because it is a system with weighty components, image acquisition speed has always been a major limitation of the method, presenting a particular hindrance in the assessment of the thoracic structures, which are constantly in motion.

The development of MDCT scanners, also known as multislice CT scanners, has revolutionized the history of CT, overcoming the temporal limitations of image acquisition. When compared with the conventional technology, MDCT allows a larger volume of tissues or structures to be represented in thinner slices (0.60-1.25 mm vs. 2-5 mm) at shorter intervals (2-8 s vs. 18-30 s), improving spatial resolution and reducing the occurrence of motion artifacts, all of this in a single breath hold.

In the assessment of the pulmonary circulation, the combination of the MDCT technology and automated injection of intravenous contrast material allows anatomical distinction of vascular structures and high-quality pulmonary vessel opacification. In addition, the nearly isotropic characteristic of voxels substantially improves image reformatting, optimizing multiplanar image acquisition.

In PH, CT angiography has diagnostic importance and is of great value in the etiological investigation.[27] The method allows the imaging assessment of the RV, PAT, and peripheral pulmonary circulation.

In CT angiography, the RV can be visualized with high spatial resolution. Interventricular

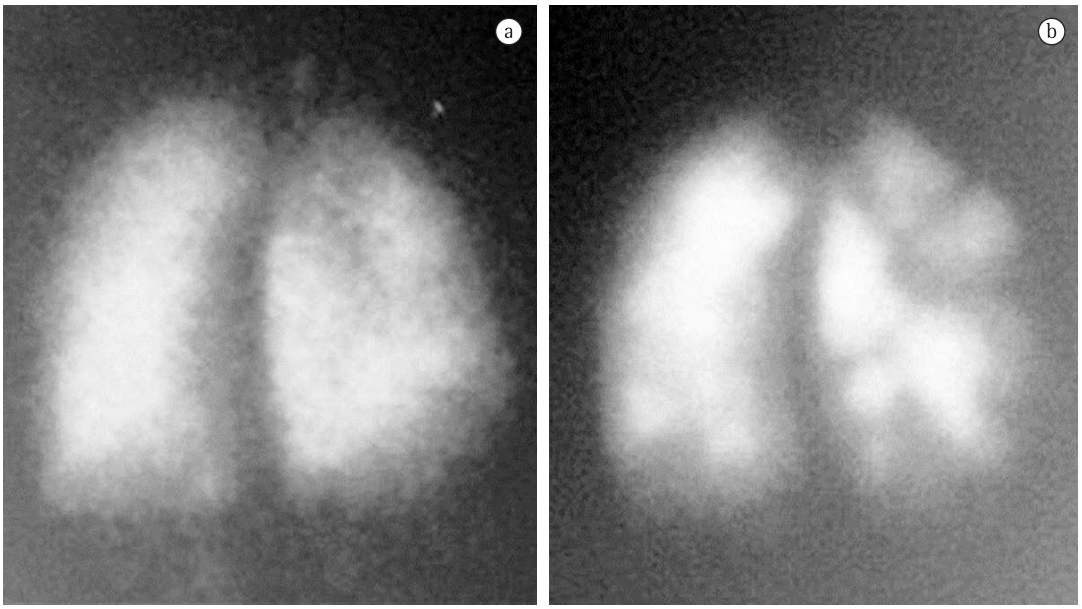

Figure 4 - Ventilation/perfusion lung scintigraphy images of a 59-year-old male patient undergoing etiological investigation of pulmonary hypertension and with normal findings on CT angiography of the pulmonary arteries. Right posterior oblique images: ventilation (in a) and perfusion (in b). Note the normal distribution of ventilation and the multiple, bilateral segmental perfusion defects, predominantly in the right lung. The patient was diagnosed with distal, chronic pulmonary thromboembolism.

septal dilatation, hypertrophy, flattening, and bowing are findings that strongly correlate with the presence of PH (Figure 5). Traditionally, however, the tomographic image of the RV is only static, causing a major limitation in its functional assessment. The use of electrocardiographic gating, that is, coupling of image acquisition with cardiac electrical phenomena, provides a partial solution to this limitation, allowing image reconstruction in any phase of the cardiac cycle as well as access to measurements of ventricular function and volumes.[28]

When technically well performed, CT angiography provides anatomically precise images of the PAT and allows its morphological assessment. Measurement of the PAT, with the use of axial slices, is performed at its bifurcation orthogonally to its longest axis and laterally to the ascending aorta. In a study of 32 cases of PH,[29] the 28.6 mm PAT diameter was strongly associated with the presence of PH as determined by invasive hemodynamic assessment. In a small population of 5 cases of HIV-related PH,[30] a PAT diameter > 29 mm showed a sensitivity and specificity, for the diagnosis of PH, of 87% and 89%, respectively; this aspect, combined with the presence of an artery-to-bronchus ratio > 1 in more than three lung lobes, was found to have a specificity of 100%.[31] Very similar findings were observed in a retrospective study of PH in patients with parenchymal lung disease.[31]

In the assessment of peripheral pulmonary circulation, CT angiography can uniformly access vessels of up to 2-3 mm with nearly constant opacification, high resolution, and no image overlap. This characteristic greatly contributes to the anatomical assessment of the pulmonary circulation. However, when it comes to visualization and quantification of the pulmonary microcirculatory flow, the method once again has functional limitations. The limited microcirculatory blood flow during vasoconstriction and vascular remodeling, characteristic of PH, can be visualized on HRCT scans (parenchymal window) as a mosaic perfusion pattern, which is present in patients with PH of various causes (Figure 5).[32] In some cases, there are also areas of increased lung parenchymal attenuation that are attributable to microcirculatory flow redistribution when the number and diameter of the vessels are increased in these regions. Both phenomena, mosaic perfusion and flow redistribution, are findings that are particularly more prevalent in

chronic PTE. Dual-source CT, a new imaging technique in which images are obtained with two X-ray tubes, each with a different voltage, can access regional lung perfusion with greater accuracy, providing functional information.[33] This technology makes it possible to perform a CT angiography study and a perfusion study in a single test.

Having been widely studied, CT angiography has gained significant ground in the evaluation of acute PTE, becoming as accurate as pulmonary angiography but without its invasive nature. Some authors consider CT angiography to be the diagnostic imaging method of choice in the assessment of acute PTE.[34-36] This is explained by the various advantages of CT angiography: its high resolution allows the visualization of arteries and filling defects up to the distal portion of the pulmonary vasculature, reaching subsegmental vessels of 2-3 mm (Figure 6); it has excellent interobserver agreement, far superior to that of scintigraphy; its sensitivity is so high that a negative test result allows the safe discontinuation of anticoagulation therapy.[37] One must be alert, however, to the dangers inherent in the method. Technical or pathophysiological factors might lead to the interpretation of pseudo-filling defects, providing false-positive results. The possibility of motion artifacts in patients with tachypnea should be taken into consideration, as should the time interval between contrast injection and image acquisition, as well as the occurrence of hypoxic pulmonary vasoconstriction in poorly aerated regions. The advent of 64-channel scanners created another danger: the possibility of an excessive number of false-positive results. However, that possibility was ruled out in a recent study.[38]

Because CT angiography analyzes the RV with high image resolution, it can serve as a marker of risk in patients with acute PTE, who have traditionally been stratified by echocardiography findings.[39] It is well established that the finding of RV dysfunction by echocardiography identifies a subgroup of patients at high risk for complications, worse prognosis, and higher mortality. A multiplanar reconstruction of a four-chamber view of the heart[40] or an axial view of the ventricles[41] allows the calculation of a simple ratio—RV diastolic diameter ÷ LV diastolic diameter = the RV/LV ratio. An RV/LV ratio > 0.90 correlates strongly with RV dysfunction as determined by echocardiography,[42] as well as showing potential cost-effectiveness and being a potential prognostic marker for CT angiography. In a recent systematic review,[21] the analysis of the combined results of two studies evaluating the prognostic role of RV dysfunction as assessed by tomography revealed that the relative risk of this dysfunction for predicting death was 2.3 (95% CI: 0.90-5.98). In cases of distal chronic PTE, however, CT angiography has limitations, and ventilation/perfusion scintigraphy has become the test of choice.[43]

MRI

The MRI technique holds great prospects for the assessment of the pulmonary circulation.

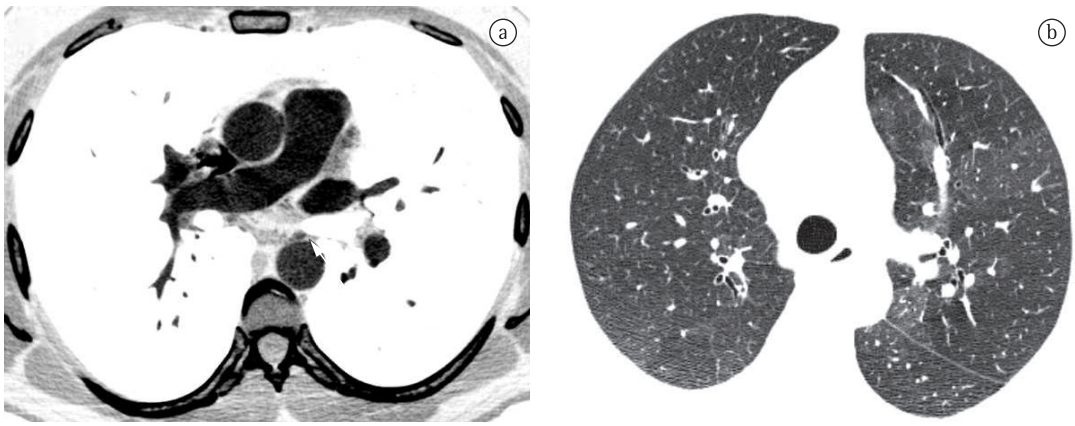

Figure 5 - CT angiography image (in a) and HRCT image (in b) of a male patient with thrombotic pulmonary hypertension. In a, note the increased pulmonary artery trunk and the increased bronchial artery diameter (arrow). In b, note the mosaic perfusion pattern.

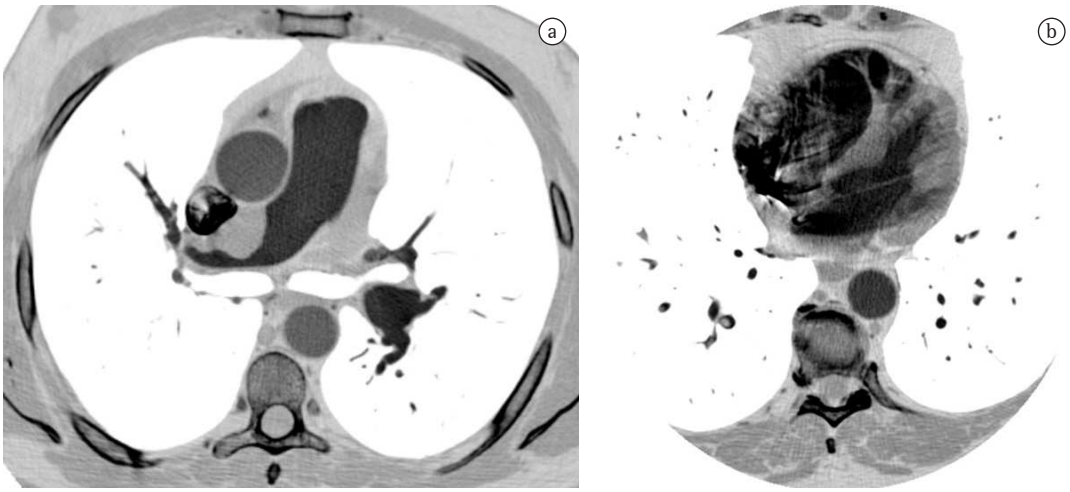

Figure 6 - CT angiography images of patients with chronic thromboembolism (in a) and acute thromboembolism (in b). In a, note the increased pulmonary artery trunk and the eccentric thrombus in the right pulmonary artery. In b, the arrow indicates a central filling defect in a subsegmental arterial branch.

The method comprises excellent characteristics, such as low operator dependence, high accuracy, and good reproducibility.[44]

The MRI technique can be used for the assessment of the lung parenchyma and pulmonary circulation, as well as for the dynamic analysis of the heart. In the assessment of the lung parenchyma, MRI faces some challenges: low proton density of the lung parenchyma, resulting in a low signal/noise ratio; signal loss during physiological motion of the intrathoracic organs; and the combination of air and soft tissues, which increases its susceptibility to artifacts. Despite these problems, some adjustments in the form of image acquisition make MRI an interesting tool in the assessment of the lung parenchyma. Some authors have suggested that, for specific applications, MRI findings are equivalent to CT findings, although MRI should not yet be used for the aforementioned purpose in routine clinical practice.[45] There is as yet no systematic evaluation of MRI as a means of assessing the lung parenchyma of patients with PH.

Since 1993, when the technique known as enhanced three-dimensional magnetic resonance arteriography (MRA) was published,[46] there have been many advances in the assessment of the intrathoracic vessels. This technique consists of the injection of paramagnetic contrast material and ultra-fast T1-weighted image acquisition, resulting in high spatial resolution during periods of apnea lasting less than 30 s.

Chief among the useful functions of pulmonary MRA is its great importance in detecting acute or chronic pulmonary embolism. In this context, a study published in 2002[47] evaluated 141 patients with suspected PTE and with abnormal perfusion scintigraphy findings. The sensitivity of MRA for segmental and central embolism (84% and 100%, respectively) was found to be comparable to that of pulmonary arteriography. However, for subsegmental embolism, the sensitivity of MRA was low (40%). Other studies[48,49] have confirmed these findings, and MRA plays a very interesting role in patients with suspected PTE who have contraindications to the use of iodinated contrast material or who want to avoid ionizing radiation. Another promising use of MRA is in the noninvasive evaluation of patients with PAH. One group of authors[50] investigated the use of MRI in the evaluation of responders to vasodilator testing with inhaled NO. When analyzing the mean pulmonary artery distensibility, those authors found a sensitivity of 100% in the identification of responders, with a specificity of 56% when compared with hemodynamic evaluation with a pulmonary artery catheter.

The functional assessment of microcirculation is also possible with the use of MRI. One group of authors[51] compared perfusion changes detected on MRI with those detected on

pulmonary perfusion scintigraphy in patients with pulmonary embolism, pneumonia, and COPD. The tests were evaluated by two observers, and there was moderate concordance (kappa coefficient range: 0.52-0.57) between the two techniques.

The most common use of MRI in PH remains the assessment of the RV. This technique allows the acquisition of high-resolution dynamic images of myocardial contraction and does not depend on anatomical conditions (pulmonary emphysema, obesity, etc.) as does echocardiography.

In patients with PH, cardiac MRI is especially important for the assessment of the following parameters (Figure 7):

- Ventricular morphology—CT images that make it possible to determine the size and volume of the heart chambers, as well as wall thickness, and muscle mass. End-diastolic RV volume is significantly increased in PH. One group of authors[52] studied the role of cardiac MRI in the prognostic evaluation of patients with PH and observed that patients with increased diastolic RV volume and reduced systolic RV volume or reduced diastolic LV volume have a worse prognosis at 12-month follow-up. The study suggests that MIR can also be used as a tool for monitoring and evaluating treatment response.[52] In addition, MRI can analyze RV mass, which, during increased afterload, is significantly increased. Evidence suggests that RV mass index correlates well with mPAP.[53]
- Ventricular function—dynamic images that reproduce the entire cardiac cycle can be obtained with electrocardiographic gating and have high accuracy and reproducibility in the analysis of ventricular function.[54] Another interesting tool is the evaluation of diastolic RV dysfunction and the behavior of the RV following treatment.
- Interventricular septal configuration—distortions in the normal morphology of the interventricular septum can be observed in patients with PH. These quantifiable changes correlate with mPAP and prognosis.[55]
- Flow analysis—volumetric flow measurements can be obtained with the use of contrast material and sequential image acquisition, which provides data for the determination of cardiac output, the evaluation of valvular regurgitation, the assessment of diastolic ventricular filling, and the quantification of cardiac shunts. Cardiac MRI has advantages over thermodilution in the acquisition of cardiac output measurements because it is noninvasive, it is less dependent on changes from one cardiac cycle to another, and it is not as strongly affected by TR.[56]
- Myocardial viability assessment—the assessment of myocardial contrast after gadolinium infusion can directly show nonviable areas of the myocardium. One group of authors[57] described a pattern of myocardial contrast enhancement in patients with PH. Delayed contrast enhancement was present within the RV insertion points and interventricular septum of 23 of the 25 patients studied. The extent of delayed contrast enhancement correlated with worse RV function.

In addition, the method shows potential for the molecular assessment of the pulmonary circulation and the heart. It is possible, for instance, to evaluate and quantify areas of apoptosis and the degree of apoptosis in vivo.[58]

In Brazil, MRI is quite costly and is not widely available. Although preliminary in nature, the findings related to the use of MRI as a diagnostic and prognostic tool in the assessment of PH seem promising.

EIT

The concept of electrical impedance can be defined in various ways: the relationship between the voltage gradient generated in an electrical circuit and the resulting electrical current; the combination of resistance and reactance; and the total opposition that a circuit offers to the flow of alternating current at a particular frequency. Essentially, higher resistance (or lower conductance) in a circuit, structure, or tissue translates to higher electrical impedance values.

A system developed in the 1980s in the United Kingdom makes it possible to measure the impedance of a structure or tissue by placing pairs of electrodes in rows on its surface. Sending electrical currents of low amperage and low frequency through these electrodes generates a voltage gradient, which, in turn, results in

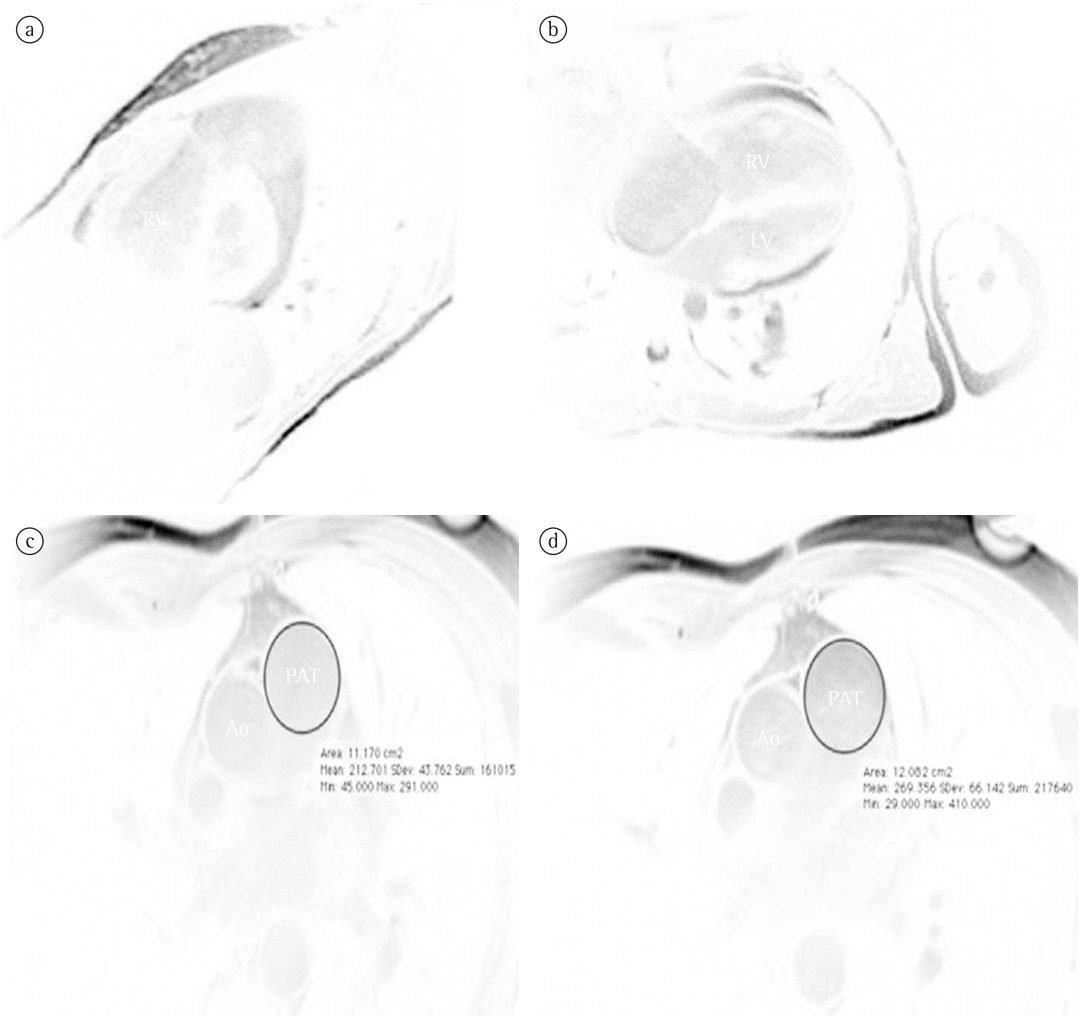

Figure 7 - Magnetic resonance images of a 35-year-old male patient with idiopathic pulmonary arterial hypertension. In a and b, note the dilated right ventricle (RV), interventricular septal flattening; and increased RV mass. Axial images acquired at end-diastole (in c) and at end-systole (in d). Note the following: the diameter of the pulmonary artery trunk (PAT) is greater than that of the aorta (Ao); the PAT diameter during diastole differs from its diameter during systole, allowing the estimation of the PAT pulsatility index; and contrast enhancement of the PAT is greater during ventricular systole.

an electron flow that can be estimated or measured. A mathematical algorithm for image reconstruction can transform the measured value of electrical impedance into pixels, the basic unit of the composition of an image. With the cross-sectional distribution of the electrodes in rows, it is possible to obtain a cross-sectional image of the distribution of electrical impedance within the geometric plane defined by the electrodes. This system is known as EIT.

The biological properties of the chest provide a valuable opportunity for assessment with the use of EIT, because air and blood, two materials with opposite resistances, share the same compartment and vary their volumes rhythmically during the cardiorespiratory cycle. The periodic change in intrathoracic blood volume during cardiac work and the distension of pulmonary microcirculation resulting from the blood flow through the pulmonary vessels are associated with the cyclic change in the electrical properties of the lung parenchyma over time. The increased blood volume in the lung parenchyma results in a 1% decrease in lung electrical impedance (blood being five time less resistant than is air).

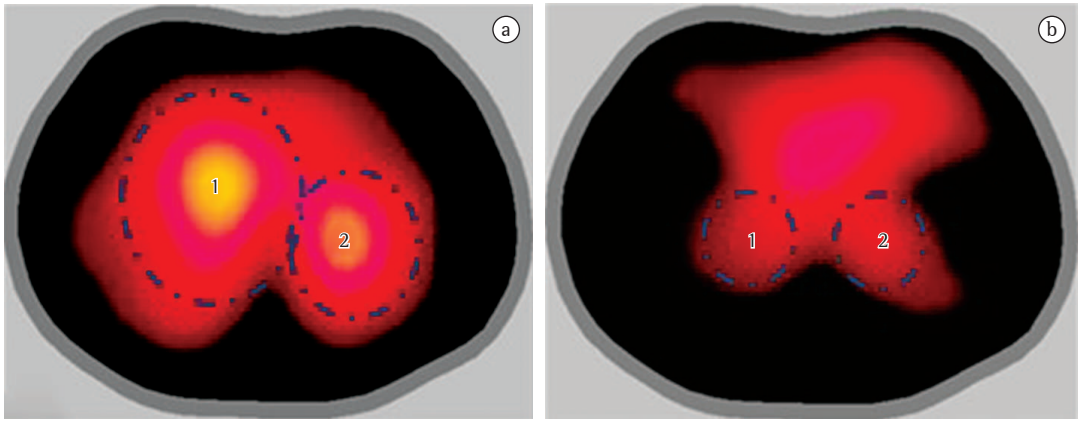

Figure 8 - Electrical impedance tomography images obtained at the level of the 4th intercostal space. In a, normal findings in a 27-year-old female patient. In b, abnormal findings in a 31-year-old female patient with a 20-year history of idiopathic pulmonary arterial hypertension. Note the difference in the range of the electrical impedance signal (intensity and extent) in areas 1 and 2, probably associated with normal vascular compliance (in a) and reduced vascular compliance (in b).

Regional changes in blood flow can be visualized by EIT in two ways. The first, which is based on the indicator dilution technique, involves the use of an electrically conducting fluid as contrast material, similarly to CT and MRI studies. The second approach analyzes the changes in the lung parenchyma impedance resulting from the change in systolic volume during the cardiac cycle, cycle by cycle. Coupling of image acquisition with the R-wave on electrocardiogram (the ECG-gated technique) filters ventilation-related fluctuations, obtaining only those that are due to circulation. The resulting image is likely to reflect pulmonary circulation pulsatility or distensibility.

An excellent model of disease in the pulmonary microcirculation is PAH, in which vascular remodeling directly affects the distensibility properties of microcirculation. When vascular compliance is reduced, with consequent accommodation of lower volumes, the electrical impedance change in PH is likely to be decreased as well. In one study,[59] EIT was used in patients with PH for determining vascular response to vasodilator testing with epoprostenol during invasive hemodynamic assessment. Of the 8 patients evaluated, 7 did not meet the vasodilator response criteria, EIT showing no impedance change in those 7. In the lone responder, the increase in impedance change was found to correlate strongly with decreases in mPAP and pulmonary vascular resistance, regardless of the increase in systolic volume. In another study,[60] the differences in the impedance of the pulmonary circulation were analyzed in 21 patients with idiopathic PAH (IPAH) and 30 healthy subjects. The authors observed a reduction in impedance change in the IPAH group, which provides support for the use of EIT in the assessment of the pulmonary circulation and of PH.

In Brazil, a 32-electrode EIT scanner is being developed for the assessment of lung perfusion. In the context of IPAH, the images obtained with this new scanner (Figure 8) are encouraging, demonstrating not only a reduction in electrical impedance, as in the two aforementioned studies, but also a change in the impedance wave morphology, which might correlate with the pulse wave of the pulmonary circulation.

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