Mesures hémodynamiques dans l'hypertension pulmonaire : précision des méthodes et influences diagnostiques

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Thèse préparée sous la direction du Docteur Frédéric Lador et de la Professeure Anne Bergeron.

" Mesures hémodynamiques dans l'hypertension pulmonaire : précision des méthodes et influences diagnostiques "

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par

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THESE

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Genecand L, Adler D, Beghetti M, Lador F, Cardiac output determination in precapillary pulmonary hypertension: a systematic review. Respiration 2021; 100(12): 1243-1250

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Résumé :

Cette thèse a pour but de décrire l'évaluation hémodynamique dans l'hypertension pulmonaire. Une description détaillée de la précision des différentes mesures hémodynamiques effectuées lors du cathétérisme cardiaque droit est donnée. L'influence de la précision de ces mesures sur l'évaluation diagnostique de l'hypertension pulmonaire est décrite. Certaines méthodes non-invasives d'évaluation hémodynamique dans l'hypertension pulmonaire sont brièvement abordées. Après cette introduction, les 4 articles cités ci-dessus sont résumés.

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Déclaration de conflits d'intérêts

Je déclare ne pas avoir de conflit d'intérêts personnel ou financier en rapport avec la rédaction de cette thèse.

Tables des matières

Table des abréviations

CaO2 : concentration en oxygène artérielle

C$\bar{v}$O2 : concentration en oxygène du sang veineux mêlé

DS : déviation standard

ECG : électrocardiogramme

HTP : Hypertension pulmonaire.

OD : oreillette droite

PAPm : pression artérielle pulmonaire moyenne.

PAPO : pression artérielle pulmonaire occluse.

PVC : pression veineuse centrale

PTDVD pression télédiastolique du ventricule droit

PTDVG : pression télédiastolique du ventricule gauche

$\dot{Q}$: débit cardiaque

RVP : résistance vasculaire pulmonaire.

S$\bar{v}$O2: saturation en oxygène du sang veineux mixé

SaO2 : saturation en oxygène du sang artériel

TD : thermodilution

$\dot{V}$O2 : consommation d'oxygène

Introduction

L'hypertension pulmonaire (HTP) est définie comme une élévation anormale de la pression artérielle pulmonaire moyenne (PAPm) > 20 mmHg mesurée de manière invasive par cathétérisme cardiaque droit (1). L'HTP est fréquente et touche approximativement 1% de la population globale avec une prévalence qui augmente avec l'âge (1). L'HTP a des causes multiples. Les cardiopathies gauches sont la cause la plus fréquente d'HTP suivie par la bronchopneumopathie chronique obstructive (BPCO) (1). Quelle que soit la cause de l'HTP, l'élévation anormale de la pression en regard du ventricule droit peut progressivement entraîner une défaillance cardiaque droite et éventuellement la mort de l'individu (2). Ainsi l'HTP est systématiquement un facteur de mauvais pronostique (3). La symptomatologie de l'HTP est aspécifique souvent sous la forme d'une dyspnée d'effort isolée (3). D'autres symptômes comme une fatigue, une faiblesse, des douleurs thoraciques, des vertiges ou des syncopes peuvent être retrouvés (3). L'examen clinique peut révéler des signes de défaillance cardiaque droite, surtout dans les formes avancées ou rapidement progressive, principalement sous la forme d'œdèmes des membres inférieurs (3). L'échocardiographie transthoracique est l'examen de choix pour dépister l'HTP si elle est suspectée (3). Cet examen est également précieux car il est l'examen de choix pour identifier les cardiopathies gauches (3).

Le traitement de l'HTP dépend de l'étiologie sous-jacente qui doit donc systématiquement être recherchée.

On distingue 5 groupes étiologiques (1) :

- L'HTP du groupe 1 qui est une vasculopathie rare des vaisseaux pulmonaires. On l'appelle également hypertension artérielle pulmonaire (HTAP). Elle peut être induite par différentes causes y compris les connectivites, l'infection avec le virus d'immunodéficience humaine (VIH), l'hypertension portale, les maladies cardiaques congénitales, la

schistosomiase, certains traitements et toxiques, des mutations génétiques ou des affections congénitales (HTP persistante du nouveau-né).

- L'HTP du groupe 2 quand la cause est une défaillance du cœur gauche.
- L'HTP du groupe 3 quand la cause est une maladie pulmonaire et/ou une hypoxie
- L'HTP du groupe 4 quand l'origine est une obstruction des artères pulmonaires dont la cause principale est la maladie thrombo-embolique chronique.
- L'HTP du groupe 5 quand l'origine est mixte ou multifactorielle comme on peut le retrouver dans certaines causes hématologiques (p.e anémie hémolytique chronique), systémiques (p.e sarcoïdose, histiocytose pulmonaire de langerhans, ou la neurofibromatose de type 1), métaboliques (maladie de stockage du glycogène, ou la maladie de Gaucher), dans l'insuffisance rénale chronique, dans la médiastinite fibrosante ou dans les tumeurs pulmonaires thrombotiques microangiopathiques.

Le bilan hémodynamique par cathétérisme cardiaque droit pour confirmer et classifier une suspicion d'HTP n'est pas systématiquement nécessaire. En effet, il doit être effectué uniquement s'il l'on juge qu'il modifiera la prise en charge thérapeutique du patient. Ceci nous amène aux différentes causes d'HTP qui bénéficient de différentes prises en charge thérapeutique.

Le traitement de l'HTP du groupe 2 et 3 est basé essentiellement sur le traitement de la cause sous-jacente, c'est-à-dire la cardiopathie gauche dans le groupe 2 et la maladie pulmonaire et/ou l'hypoxie dans le groupe 3. En effet la large majorité des traitements spécifiques de l'HTP testés jusqu'à ce jour dans ces groupes étiologiques n'ont soit montré aucun effet soit un effet délétère (4, 5). Un cathétérisme cardiaque droit n'est pas donc pas systématiquement nécessaire car le diagnostic précis n'influencera à priori pas la prise en charge. Une exception à cette règle est le récent essai INCREASE incluant des patients du groupe 3 atteints d'une pneumopathie

interstitielle et d'une HTP et démontrant que le treprostinil inhalé pris 4x/j en comparaison au placebo permet une prolongation de la distance de marche, une réduction du NT-proBNP, une baisse de la dégradation clinique (outcome composit), mais sans effet observé sur la mortalité, et une amélioration des fonctions pulmonaires (analyse post-hoc) (6, 7, 8). Ainsi, dans les nouvelles guidelines, ce traitement bénéficie d'une recommandation 2b pour ce groupe de patients (1). A noter que le Treprostinil inhalé n'est à ce jour pas disponible en Suisse et donc qu'un cathétérisme cardiaque droit n'est pour le moment pas utile, même pour ce sous-groupe de patients.

Le cathétérisme cardiaque droit est essentiel pour diagnostiquer et prendre en charge les groupes 1 et 4 qui bénéficient de traitement spécifique (9, 10, 11).

Le groupe 5 bénéficie d'une prise en charge individualisée au vu de l'hétérogénéité importante de ce groupe et un cathétérisme cardiaque droit doit se décider au cas par cas (3, 12).

Le bilan hémodynamique de l'hypertension pulmonaire

Le cathétérisme cardiaque droit permet de mesurer la PAPm, la pression artérielle pulmonaire occluse (PAPO) et le débit cardiaque ($\dot{Q}$). La résistance vasculaire pulmonaire (RVP) peut également être calculée par l'équation suivante :

$$RVP = (PAPm\text{-}PAPO)/\dot{Q}$$

Les facteurs qui peuvent amener à une majoration de la PAPm et donc à une HTP sont : 1) une augmentation de la résistance vasculaire pulmonaire (RVP), 2) une augmentation du débit cardiaque et 3) une augmentation de la pression veineuse pulmonaire secondaire à une augmentation de la pression de l'oreillette gauche, reflétée par la PAPO (HTP postcapillaire).

La PAPO s'obtient par occlusion avec un ballonnet rempli d'air d'une artère pulmonaire. Ceci stoppe le flux sanguin dans l'artère pulmonaire en question et permet d'obtenir un équilibre de pression avec la veine pulmonaire drainant l'artère pulmonaire occluse. Comme la pression dans les veines pulmonaires est très proche de la pression dans l'oreillette gauche, la PAPO est un reflet de la pression de l'oreillette gauche. Elle permet de différencier l'HTP dite postcapillaire de l'HTP précapillaire ou non-spécifiée. Une altération de la fonction du ventricule gauche se traduira par une élévation de pression dans l'oreillette gauche qui se reflétera par une élévation de la PAPO. Une PAPm > 20mmHg, associée à une PAPO > 15 mmHg, est considérée comme anormale et définit une HTP post-capillaire, c'est-à-dire une défaillance de la fonction du cœur gauche, alors qu'une PAPm > 20mmHg, associée à une PAPO ≤ 15 mmmHg est retenue pour définir l'HTP précapillaire et l'HTP non spécifiée qui définissent les HTP sans dysfonction du cœur gauche.

La RVP s'élève lors d'une altération des vaisseaux pulmonaires (remodelage) ou lors de phénomène de vasoconstriction (p.e. lors d'hypoxie). La RVP permet

de différencier les élévations de PAPm qui sont causées par une élévation du $\dot{Q}$ ou une élévation de la PAPO, des élévations de la PAPm qui sont causées par une réelle altération des vaisseaux pulmonaires. Lors d'élévation de la RVP on observe une élévation de la PAPm pour une PAPO et un $\dot{Q}$ donné.

Une RVP > 2 WU est considérée comme anormale (13), mais ne renseigne pas sur la cause de l'altération ni sur la localisation de l'élévation de la RVP (artère pulmonaire, capillaire ou veinule pulmonaire). Une élévation de la RVP est notamment observée lors d'obstruction des artères pulmonaires dans la maladie thrombo-embolique chronique, lors du remodelage des artères, des capillaires ou des veines pulmonaires dans l'HTP du groupe 1, en cas de destruction des vaisseaux pulmonaires comme on peut l'observer dans de nombreuses pneumopathies ou lors d'HTP postcapillaire chronique associée à un remodelage vasculaire. Ainsi une RVP > 2 WU va être retrouvée dans l'hypertension pulmonaire précapillaire pure ou l'hypertension postcapillaire combinée à une composante précapillaire.

L'HTP causée par une élévation du $\dot{Q}$ sans altération de la RVP et sans élévation de la PAPO est nommée HTP non spécifiée (1).

Avec la mesure de tous ces paramètres, 4 groupes sont distingués lors du cathétérisme cardiaque droit (1) :

1) Absence d'hypertension pulmonaire en cas de PAPm ≤ 20mmHg.
2) Hypertension pulmonaire précapillaire en cas de PAPm > 20mmHg, PAPO ≤ 15 mmHg, RVP > 2 WU
3) Hypertension pulmonaire postcapillaire en cas de PAPm > 20mmHg et PAPO > 15mmHg
    a. Isolée si RVP ≤ 2 WU
    b. Combinée à une composante précapillaire si RVP > 2 WU
4) Hypertension pulmonaire non spécifiée en cas de PAPm > 20mmHg, PAPO ≤ 15 mmHg et RVP ≤ 2 WU

La PAPm, la PAPO et le $\dot{Q}$ permettent de définir l'HTP et de la classifier en précapillaire, postcapillaire ou non différenciée. Chacune de ces mesures est soumise à des possibles erreurs qui vont être détaillées ci-dessous. La procédure et la technique du cathétérisme cardiaque droit sont d'abord brièvement décrites.

Cathétérisme cardiaque droit – procédure

Le cathétérisme cardiaque droit est une procédure sure lorsqu'elle est réalisée dans un centre expert avec un taux de complications sérieuses de 1.1% et une mortalité reliée à la procédure de 0.055% (14). La complication la plus crainte est la rupture d'une artère pulmonaire (1). Les contre-indications à la procédure sont la présence d'un thrombus au niveau du ventricule droit, une tumeur dans l'oreillette droite ou le ventricule droit, un pacemaker implanté récemment (<1mois), la présence d'une valve mécanique au niveau de la valve pulmonaire ou de la valve tricuspide, la présence d'un mitraclip ou une infection aigue (1). Le cathétérisme cardiaque droit est indiqué pour l'évaluation d'une HTP si son résultat permet d'influencer la prise en charge du patient, pour les bilans pré-transplantations cardiaques et lors de l'évaluation d'un shunt cardiaque (1).

Le cathéter artériel pulmonaire est introduit de manière stérile par une technique de Seldinger à travers une veine (15). Un port d'insertion du cathéter pulmonaire est ensuite laissé en place pour la procédure. L'abord veineux se fait généralement par la veine céphalique ou la veine angulaire du bras droit. Des abords par des veines plus centrales sont également possibles (veines jugulaires, sous clavières ou fémorales). Dans ces cas, un contrôle échographique lors de l'insertion est souhaité.

Le cathéter pulmonaire standard mesure 110cm de long et est marqué aux 10cm avec au minimum 2 ports reliés à des canaux. 1 port proximal sert à l'injection de soluté froid pour la mesure du débit cardiaque par la méthode de thermodilution intermittente. 1 second port distal est situé au niveau de l'extrémité distale du cathéter et permet la mesure des pressions, les différents prélèvements sanguins et la mesure de la courbe de changement de température lors de la méthode de thermodilution intermittente. Un ballonnet se situe sous la pointe du cathéter et peut être gonflé jusqu'à un volume de 1.5mL d'air pour la mesure de la PAPO.

Avant l'insertion, le cathéter doit être connecté au moniteur et au transducteur (15). Les 2 canaux doivent être flushés et remplis de fluide physiologique. Le cathéter peut ensuite être introduit par le port d'insertion.

La longueur d'insertion nécessaire pour enregistrer les différentes mesures dépend du choix du point de ponction veineux. Comme référence pour une ponction de la veine jugulaire interne droite, l'OD est atteinte après 20cm, le ventricule droit (VD) après 30-35cm, l'artère pulmonaire après 40-45cm et la position d'occlusion après 50cm (15). Pour une insertion au niveau de la jugulaire interne gauche et de la veine céphalique droite, 5cm et 10-15cm doivent être rajoutés respectivement (15). Quand le cathéter est approximativement à hauteur de l'oreillette droite (20cm) le ballonnet peut être gonflé, généralement avec 1.5mL d'air. La pression de l'OD est mesurée, puis le cathéter est avancé jusqu'en position d'occlusion avec mesure de la PAPO. Une fois la PAPO obtenue, le ballonnet est dégonflé et retiré pour mesurer la PAP puis la pression du VD. A noter que le ballonnet doit toujours être gonflé avant d'être avancé (diminue le risque de rupture de l'artère pulmonaire) et dégonflé avant d'être retiré (diminue le risque de lésion valvulaire). La mesure de $\dot{Q}$ par thermodilution se fait lorsque l'extrémité distale du cathéter est au niveau de l'artère pulmonaire. Au minimum 3 mesures sont effectuées et la moyenne de ces mesures est retenue comme le débit cardiaque (1). Si les mesures ont une différence > 15%, d'autres mesures sont généralement effectuées avec élimination des valeurs extrêmes. Au minimum, un échantillon de sang veineux mêlé est prélevé au niveau du tronc pulmonaire pour la mesure de la saturation veineuse mixée en oxygène ($S\bar{v}O_2$). En cas de suspicion clinique de shunt ou si la saturation veineuse mêlée en oxygène est > 75%, des échantillons sanguins sériés dans les différentes cavités sont prélevés. Ceci permet de confirmer la présence d'un shunt gauche – droit et d'évaluer sa localisation (1).

Si la pression du ventricule droit n'apparait pas après 40-45cm ou la position d'occlusion artérielle après 50-55cm, le cathéter doit être retiré jusqu'à 20cm et la procédure doit être recommencée. Une alternative à ceci est un contrôle

de la position du cathéter sous scopie ou par échocardiographie transoesophagienne. En cas de difficulté à passer la valve tricuspide, le patient peut être positionné la tête vers le bas (15). En cas de difficultés à passer la valve pulmonaire, une position avec la tête légèrement surélevée et une rotation vers la droite peut être utile (15). Généralement le cathéter se dirige naturellement vers l'artère pulmonaire droite. Si une cathétérisation de l'artère pulmonaire gauche est souhaitée (par exemple en cas de thrombus proximal de l'artère pulmonaire droite), un guide hydrophile peut être utilisé pour faciliter la procédure.

Cathétérisme cardiaque droit – courbes des pressions mesurées

Les 4 pressions enregistrées lors du cathétérisme cardiaque droit sont illustrés dans la figure 1. Leurs caractéristiques sont les suivantes (15) :

1) La pression veineuse centrale (PVC) équivalente à la pression de l'OD. Elle est composée de 3 ondes : l'onde a pour la contraction atriale, l'onde c (parfois peu visible) pour la contraction ventriculaire isovolumique, l'onde v pour le remplissage de l'OD durant la systole ventriculaire. La reconnaissance des différentes ondes est facilitée par la synchronisation avec l'ECG. L'onde a suit rapidement après l'onde p de l'ECG (dépolarisation atriale et contraction atriale). L'onde c suit le QRS de l'ECG (dépolarisation ventriculaire et début de la contraction ventriculaire) et l'onde v suit l'onde T de l'ECG (fin de repolarisation ventriculaire et fin de la systole ventriculaire). La PVC est généralement mesurée soit au niveau de l'onde a soit juste après le R du QRS (à la base de l'onde c) car cela représente la mesure dans l'OD juste avant le début de la systole ventriculaire (i.e. la pression télédiastolique du VD = PTDVD en l'absence de valvulopathie).
2) Pression du VD : initialement, on note une augmentation importante et rapide de la pression lors de la phase de contraction isovolumique. Ceci est suivi de la systole ventriculaire caractérisée par une ascension, puis une descente lente de la pression ventriculaire. Lorsque la pression dans le tronc pulmonaire devient plus élevée que la pression dans le ventriculaire droit, la valve pulmonaire se ferme. Ceci marque le début de la phase de décontraction isovolumique caractérisée par une descente rapide de la pression jusqu'à l'ouverture de la valve tricuspide. L'ouverture de la valve tricuspide marque le début du remplissage ventriculaire, caractérisé par une pente de pression légèrement ascendante mais quasiment plate due à une compliance importante du VD. La PTDVD est mesurée juste avant l'onde R de l'ECG, soit juste avant le début de l'augmentation importante et marquée représentant

le début de la systole ventriculaire.

3) La PAP : La PAP systolique devrait être quasiment égale à la pression systolique du VD en l'absence de valvulopathie de la valve pulmonaire et en l'absence d'erreur de mesure. A la fin de la systole (fin de l'onde T de l'ECG) on note l'encoche dicrote (dicrotic notch) suivi de la phase de diastole ventriculaire lors de laquelle la PAP continue à baisser doucement jusqu'à la prochaine systole ventriculaire.
4) La PAPO : Elle a la même forme et les mêmes ondes que la POD. En revanche comme c'est une onde réfléchie de l'onde de pouls de l'oreillette gauche, ses ondes sont légèrement retardées. De plus on note un effet d'amortissement de l'onde en raison de la distance parcourue par la réflexion (effet de damping). Dans ce contexte, l'onde a est présente juste après le R du QRS (mais reflète toujours la contraction atriale) et l'onde v après l'onde T du QRS. Généralement, l'onde v est plus importante que l'onde a. Finalement, on ne note généralement pas d'onde c lors de lecture de la PAPO en raison de l'amortissement de l'onde. La PAPO devrait être mesurée à la fin de l'onde a, sur une moyenne de 3 mesures. La plupart des logiciels fournissent des pressions moyennes digitalisées évitant une mesure manuelle.

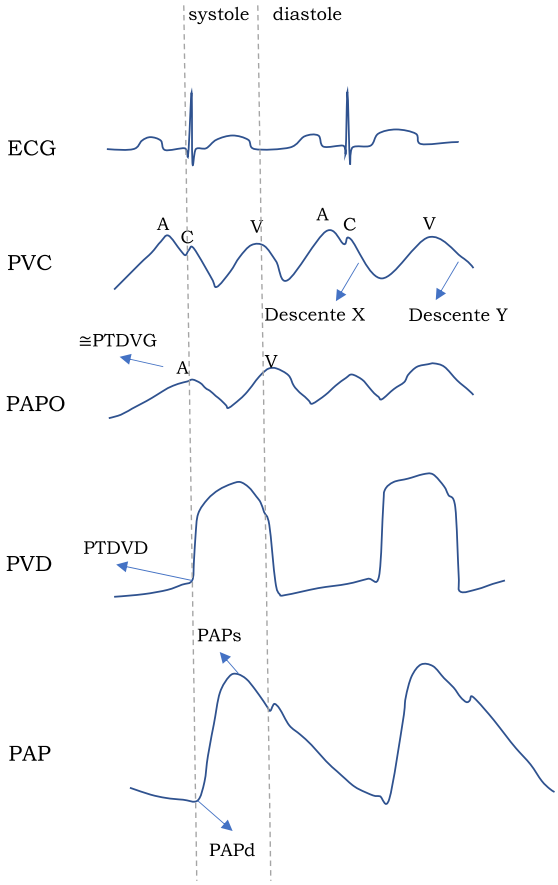


Figure 1 : Différentes formes des pressions obtenues lors du cathétérisme cardiaque droit. L'onde A représente le meilleur reflet théorique de la PTDVG lors de la mesure de la PAPO (≅PTDVG). La descente X représente la relaxation atriale et la descente Y la phase précoce du remplissage ventriculaire. ECG : électrocardiogramme ; PVC : pression veineuse centrale ; PAP : pression artérielle pulmonaire ; PAPd : pression artérielle pulmonaire diastolique ; PAPs : pression artérielle pulmonaire systolique ; PAPO : pression artérielle pulmonaire occluse. PVD : pression dans le ventricule droit ; PTDVD : pression télédiastolique du ventricule droit. PTDVG : pression télédiastolique du ventricule gauche.

Valeurs hémodynamiques normales

Les valeurs normales de PAPm, PAPO, $\dot{Q}$ et RVP ont été déterminées dans une étude systématique et méta-analyse incluant 1187 individus à priori sain sans symptôme respiratoire significatif (16).

Au repos, la PAPm normale moyenne (+/- DS) est 14 +/- 3.3mmHg avec une limite supérieure de la norme (définie comme la moyenne + 2 DS) de 20.6mmHg. La PAPm ne varie pas significativement selon la position, l'origine, l'âge ou le sexe des individus comme montré dans la *figure 2*. Basé sur cette étude, la PAPm > 20 mmHg définit maintenant l'HTP. Cette définition remplace la précédente qui définissait l'HTP par une PAPm de repos ≥ 25 mmHg (17).

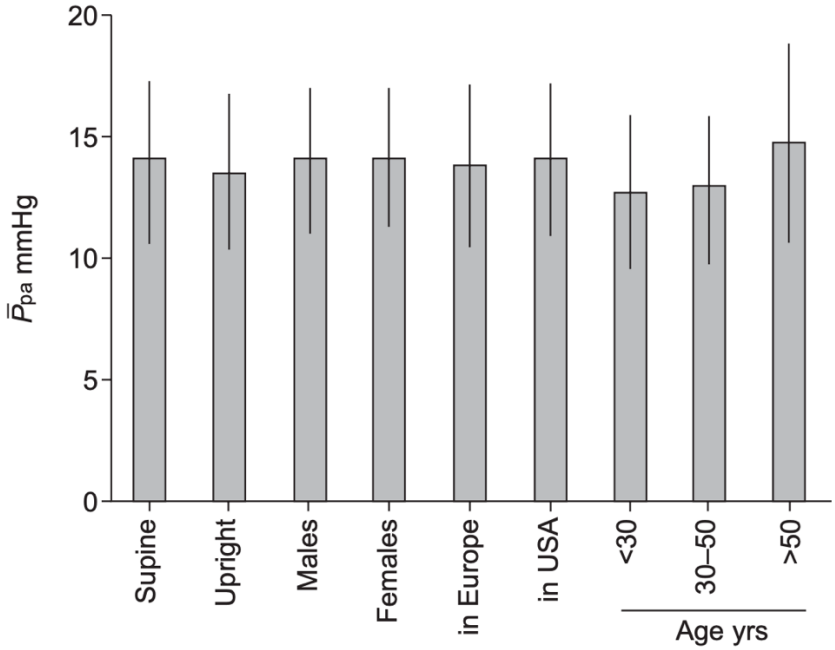


Figure 2 : Pression artérielle pulmonaire moyenne (Ppa) chez des sujets sains au repos selon différents sous-groupes : position couchée (supine), debout (upright), hommes (males), femme (females), en Europe (in Europe), aux USA (in USA) et selon l'âge. Reproduit avec permission de © ERS 2023: European Respiratory Journal 34 (4) 888-894; DOI: 10.1183/09031936.00145608 Published 30 September 2009 (16)

La PAPO moyenne (+/- DS) est de 8 +/- 2.9mmHg et est indépendante de l'âge pour sa mesure au repos. La PAPO normale est considérée comme étant inférieure à 12 mmHg (18). Une valeur > 15 mmHg est toujours anormale et définit une composante postcapillaire à l'HTP (1, 18). La zone entre 12 et 15mmHg constitue donc une zone grise où le contexte clinique doit être pris en considération pour diriger la suite de la prise en charge (18).

Pour la RVP, la valeur moyenne normale (+/- DS) est de 0.93 +/- 0.38 WU. Une RVP > 2WU est considérée comme anormale et définit une composante précapillaire à l'HTP.

Les valeurs hémodynamiques normales de sujets sains asymptomatiques sont résumées dans le tableau 1.

PAPm (mmHg)	14 +/- 3.3
PAPs (mmHg)	20.8 +/- 4.4
PAPd (mmHg)	8.8 +/- 3.0
PAPO (mmHg)	8.0 +/- 2.9
FC (battement/min)	76 +/- 14
$\dot{Q}$ (L/min)	7.3 +/- 2.3
$\dot{Q}$i ($L \cdot min^{-1} \cdot m^{-2}$)	4.1 +/- 1.3
RVP (WU)	0.93 +/- 0.38

Tableau 1 : valeurs hémodynamiques normales. $\dot{Q}$: débit cardiaque. $\dot{Q}$i : débit cardiaque indexé. FC : fréquence cardiaque. PAPd : pression artérielle pulmonaire diastolique. PAPm : pression artérielle pulmonaire moyenne. PAPs : pression artérielle pulmonaire systolique. PAPO : pression artérielle pulmonaire occluse. RVP : résistance vasculaire pulmonaire. Reproduit avec permission de © ERS 2023: European Respiratory Journal 34 (4) 888-894; DOl: 10.1183/09031936.00145608 Published 30 September 2009 (16)

Point clé : Une PAPm > 20 mmHg définit l'HTP. La PAPO normale est considérée comme étant inférieure à 12 mmHg. Une valeur > 15 mmHg est toujours anormale et définit une composante postcapillaire à l'HTP. Une RVP

> 2WU est considérée comme anormale et définit une composante précapillaire à l'HTP.

Problèmes influençant la fiabilité de la mesure des pressions

Coefficient de répétabilité des mesures de pression

Pour toute mesure en médecine, il existe une variabilité qui est la conséquence de l'imprécision de la méthode utilisée. La précision intrinsèque de la méthode est souvent estimée avec le coefficient de répétabilité. Celui-ci est calculé en répétant plusieurs fois la même mesure chez un même individu dans des conditions stables. Quand les différences entre les mesures suivent une distribution normale, le coefficient de répétabilité est défini comme la valeur comprenant 95% des différences du test-retest. Autrement dit pour une valeur obtenue lors d'une première mesure, l'observateur peut s'attendre à observer une différence avec la deuxième mesure, qui sera dans 95% des cas inférieure au coefficient de répétabilité.

Lors du cathétérisme cardiaque droit, les coefficients de répétabilité sont de 7.6 mmHg pour la PAPm et 3.6 mmHg pour la PAPO mesurés à une médiane de 12 minutes (test-restest) dans le même état hémodynamique (19). A noter qu'il est impossible de vérifier que cette variabilité est uniquement causée par la variabilité de la mesure et pas également causée par les fluctuations hémodynamiques qui peuvent être observées chez un même sujet laissé au repos dans une position identique lors d'un cathétérisme cardiaque droit. Ces différences sont significatives et peuvent impacter le diagnostic de l'hypertension pulmonaire et sa classification surtout pour les patients ayant des valeurs proches des limites diagnostiques (PAPO 15mmHg, PAPm 20mmHg) engendrant un changement de catégorie (absence d'HTP, précapillaire, post-capillaire, non spécifié).

Point clé : il existe une variabilité intrinsèque de la mesure des pressions lors du cathétérisme cardiaque droit chez un même individu avec un état hémodynamique stable. Si un doute existe quant à la pertinence des pressions mesurées lors du cathétérisme cardiaque, celles-ci devraient être répétées.

Problèmes généraux de mesure des pressions lors du cathétérisme cardiaque droit

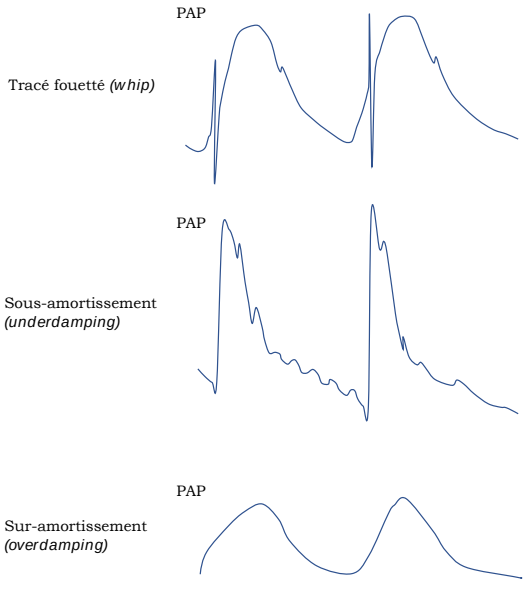
On note certains problèmes communs à toutes les mesures de pression lors du cathétérisme cardiaque droit (15, 20).

Le premier problème est appelé sur ou sous amortissement (*over* ou *underdamping*). Le système de monitoring du cathéter est doté de propriétés physiques (i.e. élasticité, masse et friction) permettant la transmission de la pression intracavitaire jusqu'au moniteur. Une réponse dynamique optimale est nécessaire pour transmettre les pressions de manière fiable. Le système est composé d'un coefficient d'amortissement qui décrit la vitesse à laquelle le système revient à son équilibre après la transmission d'une onde de pression. Quand le système souffre d'un sous-amortissement (*underdamping*), alors les ondes de pressions vont se refléter de multiples fois avant de disparaître. La pression systolique sera surestimée et la pression diastolique sous-estimée. Lorsque le système souffre d'un suramortissement (*overdamping*), la pression systolique sera diminuée alors que la pression diastolique sera surestimée. Un système avec un suramortissement peut être causée par la présence de bulles d'air dans le cathéter lorsque celui-ci est mal flushé. Le cathéter doit alors être soigneusement rincé. Des problèmes sous-amortissement sont parfois causés par des cathéters défectueux. En cas de sur ou sous amortissement, il est possible de bouger le cathéter de 1-2cm pour voir si cela permet une résolution des artéfacts. Si les artéfacts persistent le cathéter doit alors si possible être changé.

Le second problème est appelé tracé fouetté (*whip*). Ce problème est causé par des mouvements excessifs de la pointe du cathéter. Ceci affecte les tracés acquis dans le ventricule droit ou l'artère pulmonaire en créant des pics de pression (soit positif soit négatif) qui sont des artéfacts. Ces artéfacts sont donc essentiellement présents lors de la systole ventriculaire là où les mouvements sont plus importants. Un repositionnement de la pointe du

cathéter de 1-2 cm peut être nécessaire, mais parfois ces artéfacts ne peuvent être supprimés totalement.

Les sur et sous-amortissements et le tracé fouetté sont illustrés dans la figure 3.



Causes	Conséquences	Solutions
Artéfacts de mouvements avec mouvements excessifs du cathéter.	Ondes pointues inappropriées, particulièrement au début de la systole	Replacement du cathéter

Causes	Conséquences	Solutions
Propriétés physiques du cathéter anormales.	Surestimation pression systolique et sous-estimation pression diastolique	Replacement du cathéter. Si persistance, considérer changement de cathéter.

Causes	Conséquences	Solutions
Propriétés physiques du cathéter anormales. Possible bulles d'air dans le cathéter.	Sous-estimation pression systolique et surestimation pression diastolique	Replacement du cathéter. Flush du cathéter Si persistance, considérer changement de cathéter.

Figure 3 : représentation graphique des tracés des différents problèmes de mesure de pression et tableau récapitulatif des causes, des conséquences sur la mesure des pressions et des possibles solutions pour s'aider à résoudre ces problèmes de mesure. PAP : pression artère pulmonaire.

Point clé : Le sur et sous amortissement et le tracé fouetté sont des artéfacts fréquents, qui doivent être reconnus et qui influencent les valeurs de pression mesurées.

Placement du point de référence (niveau 0 et hauteur du transducteur externe)

Lors du cathétérisme cardiaque droit, les pressions sont mesurées avec un cathéter rempli de liquide (21). La pression mesurée correspond à la différence entre la pression hydrostatique (définie par rapport à un point de référence 0

fixé) et la pression présente dans la cavité/ou vaisseau où se trouve la pointe du cathéter de mesure (21).

Avant la mesure des pressions intra-cavitaires, deux étapes sont nécessaires. Tout d'abord le système doit être équilibré avec la pression atmosphérique externe. Ceci permet d'annuler toute variation liée à l'altitude à laquelle le cathétérisme cardiaque est effectué. Ensuite le transducteur externe doit être placé au niveau de référence souhaité qui est généralement le point au milieu du thorax (1). Le transducteur agit comme un point de référence hydrostatique et la colonne d'eau qui réside dans le cathéter annule toute variation de mesure de pression hydrostatique entre la pointe du cathéter et le transducteur. Ainsi, la pression mesurée est indépendante de la position de la pointe du cathéter, dont les variations hydrostatiques par rapport à son emplacement dans la circulation pulmonaire sont ignorées (22). En revanche, les pressions mesurées sont dépendantes de l'emplacement du transducteur externe (22). Si le transducteur externe est surélevé, les pressions mesurées à la pointe du cathéter seront plus basses. A l'inverse, si le transducteur externe est abaissé, les pressions mesurées seront plus hautes. Une différence de 1cm du point de référence engendre une modification de 0.78mmHg lors de la lecture des pressions du cathétérisme cardiaque droit (23). Cette relation simple est obtenue par la gravité spécifique du mercure (1.055) et du sang (13.6) (23). Ainsi une colonne de sang de 1cm équivaut à une colonne de mercure de 0.78mm. Des différences de pression jusqu'à 8mmHg ont été reportées selon le placement du transducteur externe (23). Ces différences ont évidemment un impact majeur sur le diagnostic de l'hypertension pulmonaire compte tenu du seuil diagnostic de PAPm à 20mmHg et de PAPO à 15mmHg.

Il existe un débat sur la localisation de référence à utiliser pour le placement du transducteur externe. Idéalement, ce point devrait se situer au niveau du centre de l'oreillette droite pour la mesure des pressions des cavités droites (oreillette droite, ventricule droit, pression artérielle pulmonaire). La hauteur de l'oreillette droite se situe au 1/3 supérieur du diamètre antéro-postérieur thoracique chez 98.5% des individus (23). En revanche, pour la mesure des

pressions des cavités gauches (PAPO lors du cathétérisme cardiaque droit), ce point devrait se situer idéalement au niveau de l'oreillette gauche. Le point au milieu du thorax (moitié du diamètre antéro-postérieur thoracique) correspond chez 97.5% des individus à la localisation de l'oreillette gauche (23). Ainsi, il est impossible avec un seul emplacement de référence d'obtenir, chez tous les individus, le point idéal pour la mesure de toutes les pressions lors du cathétérisme cardiaque droit.

Le placement du point de référence 0 a été proposé comme devant être placé au milieu du thorax (*mid-thoracic*) défini comme un point entre l'intersection du plan frontal (plan à mi-chemin entre le sternum et le plan du lit), le plan transverse se situant au niveau du 4ème espace intercostal antérieur et le plan médio-sagittal pour tous les cathétérismes cardiaques droits (21, 24). Ce point correspond donc à l'emplacement de l'oreillette gauche chez la plupart des individus (23). Les arguments avancés pour le choix de ce point de référence sont la simplicité de sa localisation et la meilleure estimation de la PAPO. En revanche, il est important de mentionner que l'utilisation systématique du point au niveau du milieu du thorax engendre une surestimation de la PAPm d'en moyenne 3mmHg en comparaison avec l'utilisation du centre de l'oreillette droite et donc probablement un nombre de diagnostic d'HTP plus important que si le centre de l'oreillette gauche était utilisé comme centre de référence (23).

Les points de référence utilisant une valeur fixe en lien avec un point de référence extérieur (par exemple + 10cm par rapport au niveau de la table ou -5cm par rapport au niveau du sternum) ne sont plus considérés comme fiables car la localisation obtenu par rapport à la localisation des oreillettes droite ou gauche dépend du diamètre thoracique et est donc hautement variable entre les individus (23).

L'étude épidémiologique historique de référence ayant fournie les valeurs normales du cathétérisme cardiaque droit a été décrite précédemment (16). On note dans cette étude que le niveau de la table de + 10cm était utilisé

comme référence dans 90% des cas et que le niveau de 5 cm au-dessous du sternum ou la ligne médio-axillaire dans <10% des cas (16). Les valeurs retrouvées dans cette étude sont en moyenne de 2 mmHg plus élevée que celles qui auraient été trouvées en utilisant le niveau de référence du milieu du thorax. Cette moyenne de 2 mmHg est hautement influencée par la taille du thorax dont le facteur déterminant principal est l'obésité (23). L'impact diagnostique de ceci ne pourra probablement jamais être déterminé précisément car le facteur correctif (taille du thorax et distance entre les différents points de référence chez les individus inclus) n'est pas connu et que des cathétérismes cardiaques droits ne sont plus pratiqués chez des sujets sains. En revanche, nous pouvons en déduire que le cutoff modifié de la définition de l'HTP à > 20 mmHg au lieu de ≥ 25 mmHg est conservateur. En effet, si le niveau de référence au milieu du thorax avait été utilisé pour déterminer les valeurs hémodynamiques des sujets sains, la limite supérieure de la norme serait probablement discrètement plus basse. Ceci est également vrai pour la mesure de la PAPO.

Les différences induites sur les pressions intravasculaires relativement au choix du point de référence sont rapportés dans le tableau 2.

	Distance jusqu'au milieu de l'OD (cm)	Différence de pression comparé au milieu de l'OD (mmHg)	Patients avec niveau de référence au niveau de l'OD
5 cm en dessous de la surface antérieure du sternum	-3.9 (-10.3 – -0.5)	-3.0 (-8.0 – -0.4)	57/196 (29.1%)
1/3 diamètre thoracique	-0.4 (-3.8 – 1.7)	-0.3 (-3.0 – 1.3)	193/196 (98.5%)
1/2 diamètre thoracique	3.8 (1.7 – 6.3)	3.0 (1.3 – 4.9)	49/196 (25%)
10 cm au-dessus du niveau de la table	6.5 (1.0 – 12.1)	5.0 (0.7 – 9.4)	7/196 (3.6%)

Tableau 2 : Distance et différence de pression calculée du niveau de référence par rapport au centre de l'oreillette droite et fréquence du centre de référence étant au niveau de l'oreillette droite. Les données sont en médiane (range). OD : oreillette droite. Reproduit avec permission de @ERS 2023 : European

Respiratory Journal 42 (6) 1586-1594 DOI: 10.1183/09031936.00050713 Published 30 November 2013 (23).

Point clé : Le point de référence 0 proposé est situé au niveau du milieu du thorax correspondant à la localisation de l'oreillette gauche chez la plupart des individus. Ce point engendre une lecture optimale de la PAPO et une surestimation systématique des pressions des cavités droites avec une médiane à 3mmHg.

Variations des pressions liées à la respiration

La respiration influence la mesure de toutes les pressions vasculaires. Chez un sujet sans pathologie, le point d'équilibre du système respiratoire se trouve à la fin de l'expiration où la pression atmosphérique est équivalente à la pression alvéolaire avec une pression pleurale restant généralement très discrètement négative à -1 ou -2 mmHg (21). Les différentes pressions aux alentours du poumon sont représentées dans la figure 4.

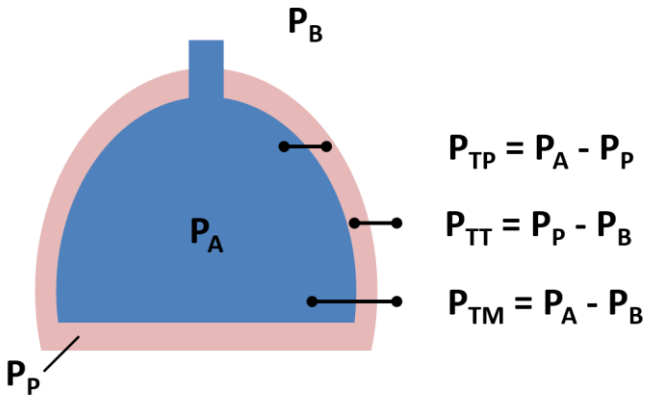


Figure 4. Représentation des différentes pressions aux alentours du poumon. D'après Frédéric Lador, cours de mécanique ventilatoire, faculté de médecine, Université de Genève. P_B : pression atmosphérique (barométrique) ; P_A : pression alvéolaire ; P_P : pression pleurale ; P_{TM} : pression transmurale ; P_{TP} : pression transpleurale ; P_{TT} : pression transthoracique

Lors de l'inspiration, la pression pleurale diminue (i.e. devient plus négative), ceci abaisse la pression alvéolaire engendrant une différence de pression entre l'alvéole et la bouche (pression atmosphérique) créant le flux d'air inspiratoire. L'abaissement de la pression pleurale lors de l'inspiration se répercute également sur les pressions intravasculaires les abaissant. Il a été démontré chez des patients référés pour cathétérisme cardiaque droit pour une suspicion d'HTP que la mesure de la PAPO en fin d'expirium représentait plus exactement la PTDVG que la PAPO moyennée sur l'ensemble du cycle respiratoire (25). La PAPO moyennée engendre une sous-estimation de la PTDVG d'environ -3 à -4 mmHg alors qu'une différence de seulement -0.8mmHg est retrouvée en comparant la PAPO en fin d'expirium avec la PTDVG. Le meilleur moment pour la mesure des pressions vasculaires se situent donc théoriquement à la fin de l'expirium lorsque le point d'équilibre du système respiratoire est atteint et est l'approche recommandée par les guidelines internationales (1). Ceci s'applique pour toutes les pressions mesurées (PVC, PAP, PAPO).

Dans une étude rétrospective de 329 cathétérismes cardiaques droits, BL Levarge et collaborateurs retrouvent que la mesure de la PAPO en fin d'expirium va mal classifier 29% patients des patients avec un phénotype clinique et échographique d'HTP précapillaire en prenant la PAPO moyennée sur l'ensemble du cycle respiratoire ≤ 15mmHg comme critère d'inclusion dans l'étude (26). Les auteurs stipulent que cette observation de « fausses » élévations de la PAPO pourrait être causée par des variation intra-thoraciques importantes avec des pressions intra-thoraciques positives en fin d'expirium engendrant une surestimation de la PAPO. En revanche, on pourrait argumenter que ceci pourrait être expliqué par la sous-estimation systématique de la PAPO moyennée par rapport à la PAPO en fin d'expirium qui va par définition « sécuriser » le diagnostic d'HTP précapillaire qu'il soit vrai ou non. En effet, une sous-estimation systématique de la PAPO va obligatoirement diminuer le nombre de faux positifs de diagnostic d'HTP précapillaire (PAPO > 15mmHg quand le sujet a en réalité une PTDVG ≤ 15mmHg sans insuffisance cardiaque gauche) au prix d'une augmentation de

faux négatifs de diagnostic d'HTP postcapillaire (PAPO ≤ 15mmHg quand le sujet a en réalité une PTDVG > 15mmHg causée par une insuffisance cardiaque gauche).

Dans certaines conditions comme l'obésité (particulièrement en position couchée) (27, 28, 29), ou la bronchopneumopathie chronique obstructive (BPCO) (30), on peut observer une pression intra-thoracique positive en fin d'expirium. Les pressions positives en fin d'expirium moyenne (+/- DS) pour des sujets obèses en respiration spontanée et au repos sont de l'ordre de 1.4 +/- 1mmHg en position debout et de 4 +/- 3 mmHg en position couchée en moyenne (29). Pour les BPCO des valeurs moyennes (+/- DS) au repos de 3 +/- 2 mmHg ont été rapportées (30).

Pour la BPCO, la pression positive en fin d'expirium est expliquée par la limitation importante du flux expiratoire avec certaines zones pulmonaires n'ayant pas le temps de se vider entièrement lors d'une expiration normale (30). Dans ce contexte, le patient n'atteint pas le point d'équilibre du système respiratoire où les pressions alvéolaires sont égales à 0mmHg et une pression positive persiste à la fin de l'expirium (*intrsinsic positive end expiratory pressure iPEEP*) (30).

Chez les patients obèses, c'est la baisse des volumes mobilisables, y compris la capacité résiduelle fonctionnelle, qui causent un effet de limitation expiratoire (31). En effet, à bas volume pulmonaire, le débit expiratoire maximal chute (31). Si la restriction est suffisamment sévère on observe même une limitation expiratoire aux débits expiratoires non forcés. Ceci explique également pourquoi le phénomène de pression intrinsèque est plus important lors de la position couchée où la restriction est majorée (29). Contrairement à la BPCO, l'effet de limitation expiratoire va diminuer lors de l'exercice (31). En effet pour le sujet obèse, l'exercice va avoir pour effet de réaugmenter les volumes opérationnels et donc de diminuer la limitation du flux expiratoire (31). Par contre, les variations de pression intra-thoracique restent importantes au vu de la compliance du système pulmonaire-cage thoracique

diminuée avec une répercussion importante sur les pressions mesurées lors du cathétérisme cardiaque droit. L'évolution du volume en fin d'expirium et de la limitation expiratoire à l'effort chez le sujet obèse est illustrée dans la figure 5.

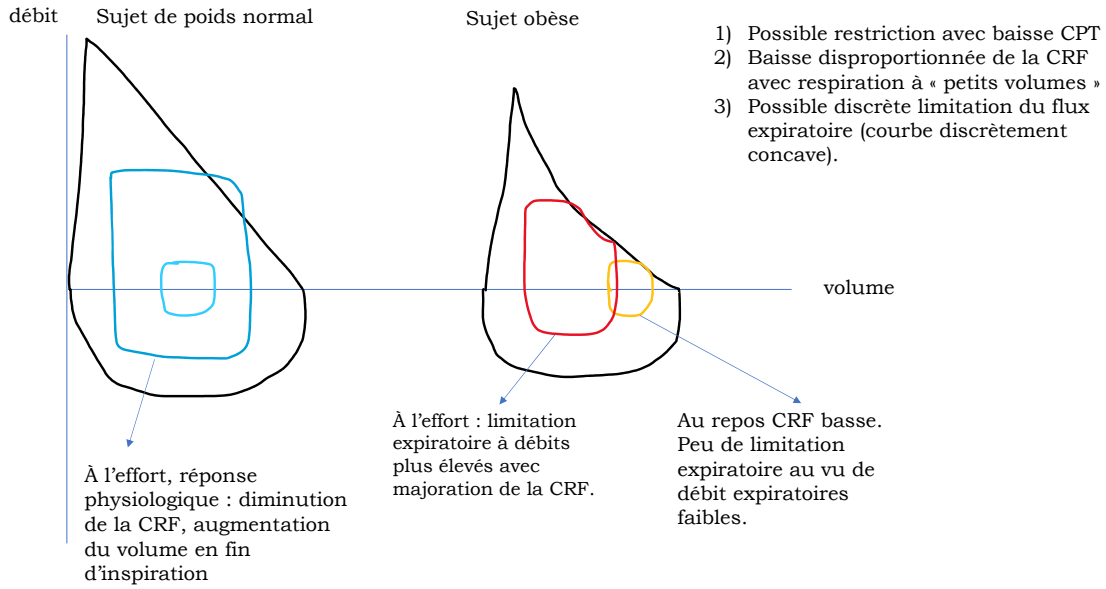


Figure 5 Courbe débit-volume au repos, au seuil ventilatoire et au pic de l'exercice illustré dans la courbe débit-volume maximal au repos chez un individu obèse et de poids normal. CPT : capacité pulmonaire total, CRF : capacité résiduelle fonctionnelle représentant le volume restant dans les poumons à la fin de l'expiration.

Dans les situations avec variations intra-thoraciques importantes au repos (particulièrement obésité et BPCO), la mesure des pressions moyennes sur plusieurs cycles respiratoires est préférée à la mesure en fin d'expirium pour équilibrer les pressions positives et négatives lors du cycle resiratoire (1). Cette approche a montré une meilleure capacité à prendre en compte les pressions intra-thoraciques que la mesure en fin d'expirium, notamment chez le sujet BPCO (30). Un exemple de variation de pression intra-vasculaire importante causée par des variations de pressions intra-thoraciques majeures lors du cycle respiratoire est illustré dans la figure 6.

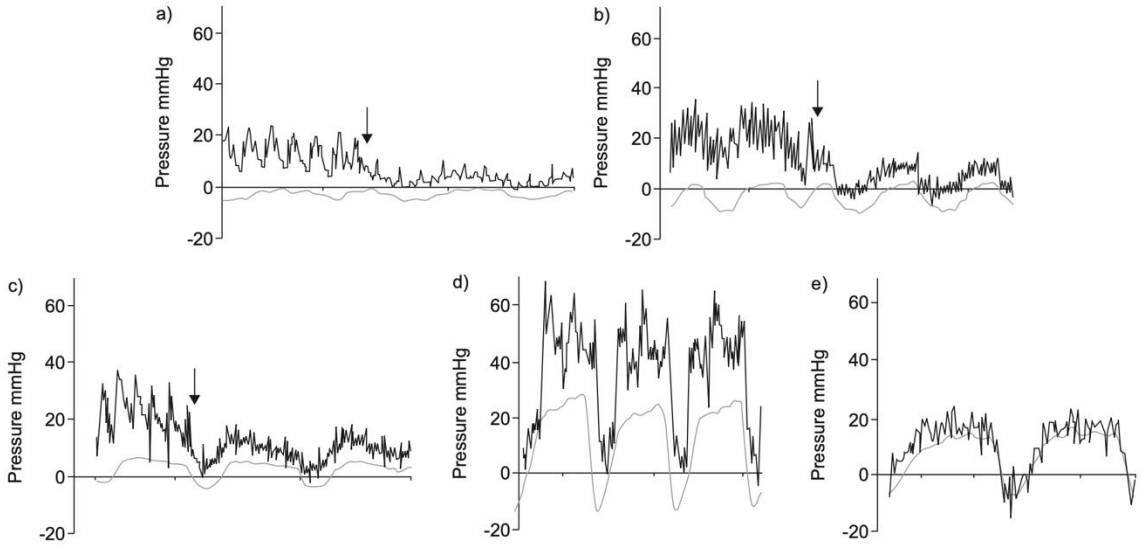


Figure 6 : enregistrement simultané de la PAP et de la PAPO (ligne noire) avec la pression œsophagienne (ligne grise) chez a) un sujet sain au repos et b) durant l'exercice ; et chez un patient avec BPCO (VEMS à 30% du prédit) c) au repos, d) durant l'exercice (PAP) e) durant l'exercice (PAPO). Reproduit avec permission de © ERS 2023: European Respiratory Journal 41 (5) 1002- 1004; DOl: 10.1183/09031936.00173512 Published 30 April 2013 (32).

Point clé : la mesure des pressions vasculaires devrait être faite en fin d'expirium excepté pour les situations avec des variations de pressions intra-thoraciques importantes comme la BPCO et l'obésité où la mesure de pression moyenne sur plusieurs cycles respiratoires est préférée.

Variations de mesure spécifiquement liées à la mesure de la PAPO

Lors de la mesure de la PAPO, le ballonnet est gonflé d'un certain volume d'air puis progressivement avancé jusqu'à la position d'occlusion. Généralement cette position se trouve au niveau d'une branche de l'artère pulmonaire droite

Critères de qualité du tracé

Plusieurs critères de qualité sont nécessaires pour s'assurer de la bonne qualité d'un tracé de PAPO. Premièrement, une courbe physiologique de PAPO

doit être obtenue avec une onde a et une onde v (24). Si la courbe est aplatie sans les ondes a et v caractéristique, un effet d'amortissement (*damping*) doit être recherchée et traduit un défaut de transmission rétrograde de la courbe de pression de l'oreillette gauche (24). On doit également s'assurer que la PAPO moyenne est plus faible que la PAP diastolique (33). Finalement, en cas de doute, un prélèvement sanguin en position de wedge est probablement la méthode la plus fiable pour s'assurer d'une position wedge optimale (1). En effet, un prélèvement montrant une saturation proche de la SaO2 confirme une occlusion idéale (34). Une étude s'est intéressée à la mesure prospective et systématique de la saturation en position occluse chez 110 patients avec une PAPO > 15 (34). Malgré une courbe de PAPO semblant de qualité, une confirmation de la position d'occlusion optimale par prélèvement sanguin était obtenue que dans 50% des cas (34). Après 2 essais supplémentaires, une PAPO en position d'occlusion était confirmée par saturation veineuse chez 91% des patients. En comparaison avec la PAPO obtenue sans mesure de la saturation veineuse mêlée, la confirmation par la saturation veineuse mêlée engendrait une PAPO en moyenne (+/- DS) plus basse (20+/-6 vs 25+/- 7) avec 31% des sujets ayant une différence de PAPO > 3mmHg (34).

Un prélèvement sanguin en position occluse permet de s'assurer de l'absence de sous-occlusion (*under-wedging*). Par contre, cette méthode n'est parfois techniquement pas possible avec impossibilité à retirer du sang en position de wedge, particulièrement lorsque le ballonnet n'est pas gonflé à son volume maximal (33). De plus, il ne permet pas d'exclure les autres problèmes qui peuvent être rencontrés (notamment surocclusion, courbes aplaties (damping)).

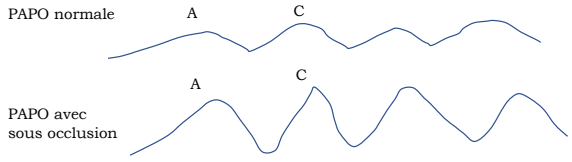
Finalement, en cas de doute persistant une fluoroscopie en position d'occlusion peut être obtenue pouvant confirmer le placement du ballonnet et l'occlusion sans reflux et avec l'absence de flux antérograde (20).

Sous-occlusion et surocclusion du ballonnet lors de la mesure de la PAPO

Le ballonnet gonflé d'air peut ne pas parfaitement occlure l'artère pulmonaire (33). Ceci engendre un mélange de mesure entre la PAP et la PAPO et cause donc une surestimation de la PAPO (33). On peut également observer la présence d'anastomose en distalité de l'occlusion du ballonnet avec mélange entre la PAP et la PAPO engendrant également une surestimation de la PAPO (33). La sous-occlusion est probablement plus fréquemment rencontrée dans l'HTP en lien avec des artères pulmonaires parfois tortueuses et doit impérativement être suspectée en cas d'HTP sévère et de PAPO mesurée > 15mmHg chez un patient avec un phénotype clinique d'une HTP précapillaire (20).

La surocclusion est également un problème fréquent qui engendre généralement une surestimation de la PAPO et plus rarement une sous-estimation de celle-ci. C'est un problème qui est causé par la pointe du cathéter se trouvant contre la paroi de l'artère pulmonaire occluse (15). La surocclusion peut être suspectée en cas de PAPO supérieure à la PAP diastolique, si la PAPO augmente progressivement jusqu'à ce que le ballonnet soit dégonflé ou retiré ou si la courbe de PAPO ne présente pas d'ondes a et v. Ce problème a plus tendance à arriver lorsque le ballonnet est plus faiblement gonflé en raison d'un diamètre d'artère occluse plus petit (15).

Dans les deux cas (sur ou sous occlusion), le problème peut être réglé en adaptant le volume du ballonnet. Pour la sous-occlusion, le ballonnet peut être légèrement dégonflé et avancé plus distalement jusqu'à trouver une meilleure position d'occlusion (20). Pour la sur-occlusion, le ballonnet peut être retiré puis regonflé puis avancé pour trouver une position d'occlusion plus proximale (15). Si cela ne suffit pas une autre branche de l'artère pulmonaire peut être cathétérisé. Il faut cependant s'assurer de ne pas gonfler et dégonfler le ballonnet en position d'occlusion en raison d'un risque de rupture de l'artère pulmonaire (20). Les problèmes de sur et sous-occlusion sont représentés dans les figures 7 et 8.



Causes	Conséquences	Solutions
Occlusion incomplète de l'artère pulmonaire	Majoration de la PAPO absolue et de ses ondes.	Replacer le ballonnet. Si sous-occlusion persiste : dégonfler le ballonnet et l'avancer plus distalement

Sous occlusion
(underwedge)

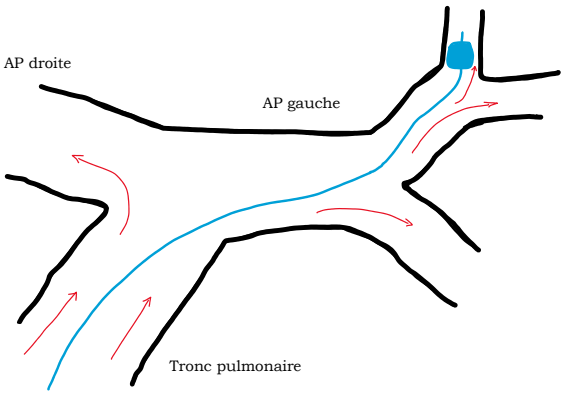
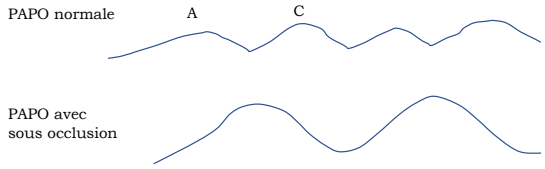


Figure 7 : causes, conséquences et solutions du problème de sous occlusion. AP : artère pulmonaire. PAPO : pression artérielle pulmonaire occluse.



Causes	Conséquences	Solutions
Occlusion complète de l'artère pulmonaire avec pointe du cathéter contre la paroi.	Majoration ou sous estimation de la PAPO absolue et de ses ondes (possible disparition des ondes a et v)	Replacer le ballonnet. Si surocclusion et ballonnet pas gonflé au volume recommandé : retirer le ballonnet, regonfler le ballonnet et l'avancer à nouveau

Sur occlusion
(overwedge)

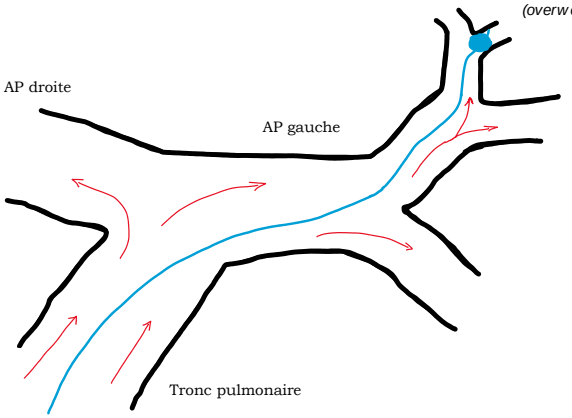


Figure 8 : causes, conséquences et solutions du problème de surocclusion. AP : artère pulmonaire. PAPO : pression artérielle pulmonaire occluse.

Message clé : les problèmes de sous occlusion et de surocclusion sont fréquents. Ils doivent être détectés et peuvent être résolus en modifiant le volume d'inflation du ballonnet et la position d'occlusion.

Volumes du ballonnet

Généralement, les ballonnets de cathétérisme classique ont un volume de remplissage de 1.5mL d'air (15). En comparant chez 37 sujets des mesures de PAPO avec un ballonnet gonflé à 1.5mL (standard) ou à moitié (0.75mL), il a été démontré que la PAPO variait significativement (33). Lorsque le ballonnet est gonflé entièrement (1.5mL) la PAPO moyenne (+/- DS) mesurée était de 23.1 +/- 2mmHg, alors qu'elle était de 19.1 +/- 2 quand le ballonnet était gonflé à moitié. L'accord et le biais de la mesure en comparaison avec la mesure gold standard étaient meilleurs quand la mesure se faisait avec un ballonnet à moitié gonflé (33). Cette surestimation de la mesure de la PAPO avec un ballonnet gonflé au volume recommandé (1.5mL) est probablement causée par une sous-occlusion (*under-wedging*) plus fréquente lorsque le ballonnet est gonflé à 1.5mL. Un effet de sur-occlusion chez certains patients lorsque le ballonnet était gonflé à moitié ne peut cependant pas être exclu et était observé (33). Les auteurs proposent dans ce contexte d'essayer d'obtenir une PAPO correcte avec le ballonnet gonflé à son volume recommandé (1.5mL) et en cas de doute d'obtenir une nouvelle PAPO avec le ballonnet gonflé à moitié (permettant l'occlusion d'une branche plus distale et selon l'anatomie possiblement plus favorable) et de répéter ceci d'abord dans l'artère pulmonaire gauche puis à droite si nécessaire et en l'absence d'obtention d'une mesure fiable à gauche (33). Avec cette approche, 100% des courbes de PAPO remplissaient finalement les critères de qualité nécessaires à leur interprétation (33).

Message clé : Le ballonnet doit être gonflé à son volume physiologique (1.5mL) et peut être dégonflé pour être avancé plus distalement en cas de PAPO > 15mmHg avec doute sur un phénomène de sous-occlusion.

Placement du cathéter dans les zones de West

Le poumon est composé de 3 zones théoriques de West qui correspondent à une physiologie différente (15). Les pressions vasculaires sont soumises à la gravité et on note une dissipation de pression ou une majoration de pressions selon la hauteur qui est parcourue par la colonne de sang. Dans la zone de West 1, la pression alvéolaire est supérieure à la pression artérielle pulmonaire et à la pression veineuse pulmonaire. Dans la zone de West 2, la pression dans les artères pulmonaires est plus importante que la pression alvéolaire qui est plus importante que la pression dans les veines pulmonaires. Dans la Zone 3, la pression dans les artères pulmonaires est plus grande que la pression dans les veines pulmonaires qui est plus grande que la pression alvéolaire. Théoriquement seule une PAPO mesurée dans la zone de West 3 reflètera la pression de l'OD. Une PAPO mesurée dans les zones de West 1 ou 2 représentera théoriquement la pression alvéolaire.

Chez le patient couché (position utilisée lors du cathétérisme droit de repos et d'effort), les zones de West sont moins importantes en raison de la forme du poumon avec une distance antéro-postérieure plus faible que la distance apico-basale. Il y a donc moins d'influence de la gravité sur le poumon dans la position couchée que dans la position debout. En pratique, chez un sujet au repos, en respiration spontanée, et en position couchée, la majorité du poumon est en zone de West 3 et l'influence des zones de West sur la mesure de la PAPO semble négligeable dans la majorité des situations. Néanmoins, l'influence des zones de West sur la mesure de la PAPO peut être plus importante chez des patients sous ventilation mécanique notamment lors de pressions positives en fin d'expirium élevées (PEEP > 10cmH_2O) et surtout lorsque la pression dans l'oreillette gauche est basse (notamment dans des situations d'hypovolémie importante) (35). Dans ce contexte, l'évaluation des variations de PAPm (ΔPAPm) et de PAPO (ΔPAPO) à différents niveaux de PEEP peut être utile pour vérifier que la PAPO reflète bien la pression de l'oreillette gauche (35). En effet, dans la zone de West 3, les variations de pression de PAPO devraient se refléter par une variation d'amplitude égale à la PAPm avec

un ratio ΔPAPO/ΔPAPm de 1. Dans les zones de West 2 et 3, les variations de PAPO reflètent théoriquement exactement les variations de PEEP et le ratio ΔPAPO/ΔPAPm sera > 1. Ceci devrait motiver la recherche d'un nouvel emplacement pour la mesure de la PAPO. Cet emplacement devrait être si possible plus basal, dans le réseau artériel pulmonaire déclive avec une proportion plus importante de zone de West 3. A noter que la ventilation mécanique aura systématiquement une influence importante sur la mesure des pressions intravasculaires et leur interprétation. En effet, l'augmentation de la pression intrathoracique se traduira systématiquement par une élévation de toutes pressions intravasculaires intrathoraciques. Différentes stratégies dépassant les objectifs de cette thèse ont été proposées pour corriger l'effet de la PEEP sur la mesure des pressions vasculaires lors du cathétérisme (36, 37).

Message clé : la mesure de la PAPO doit se faire dans la zone de West 3. En pratique, chez un sujet au repos, en respiration spontanée et en position couchée, les zones de West ont peu d'influence sur la mesure de la PAPO. Les zones de West peuvent influencer les mesures de la PAPO chez des sujets en état critique (surtout lors d'hypovolémie sévère) et sous ventilation mécanique, particulièrement avec des PEEP élevées >10cmH_2O.

Différences de mesure entre pression artérielle pulmonaire occluse et pression télédiastolique du ventricule gauche.

La PAPO est le reflet de la pression en fin de diastole du ventricule gauche (PTDVG). La PTDVG peut soit être mesurée directement par cathétérisme cardiaque gauche, soit être estimée avec la PAPO. La mesure de la PAPO est plus facile car directement accessible lors du cathétérisme cardiaque droit. En revanche la fiabilité de la PAPO doit être connue avant de pouvoir l'utiliser librement comme un reflet de la PTDVG.

L'analyse de Bland et Altman est la méthode statistique de choix pour comparer deux méthodes mesurant la même variable (ici la pression en fin de diastole du ventricule gauche) (38). Dans cette méthode, l'axe des y montre la

différence de la mesure obtenue par les deux méthodes (dans cette situation PAPO – PTDVG), alors que l'axe des x représente la moyenne des deux mesures [dans cet exemple (PAPO + PTDVG)/2].

Par exemple, si la PAPO mesurée est de 17mmHg et la PTDVG est de 13mmHg, la différence sera de – 4mmHg et la moyenne de 15mmHg donnant 1 point sur le graphique de Bland et Altman pour une mesure. Lorsque de multiples paires de mesures sont obtenues, l'analyse de Bland et Altman permet d'obtenir la différence moyenne entre les deux mesures (aussi appelée le biais systématique) et la dispersion de la différence des mesures représentée par les limites d'accord à 95%. Les limites d'accord à 95% contiennent 95% des différences, si la distribution des différences suit une loi normale. Ainsi c'est un excellent reflet de la précision de la méthode testée par rapport à la méthode gold-standard. Les limites d'accord à 95% sont grandes, plus la précision de la méthode testée est faible.

De larges données épidémiologiques chez 3926 patients avec HTP comparant la PTDVG et la PAPO mesurées en fin d'expirium montrent que le biais est de -2.9 mmHg et des intervalles d'accord à 95% de – 15.2 à 9.5 mmHg comme représenté sur la figure 7 (28). Cela démontre une erreur de mesure importante entre ces deux méthodes. Ceci a bien évidemment un impact diagnostique majeur. En effet les mêmes auteurs ont montré que sur les 580 patients ayant une PAPO ≤ 15 mmHg, 310 (53.5%) avaient une PTDVG > 15 mmHg avec pour conséquence une erreur diagnostique majeure, ainsi que l'utilisation possiblement inappropriée et dangereuse de traitement d'HTP.

Les imprécisions liées à la mesure de la PAPO sont d'origines multiples. Il existe une imprécision liée à la méthode elle-même (précision intrinsèque de la mesure) comme démontré précédemment avec le coefficient de répétabilité de la PAPO. Il existe également de multiples facteurs extrinsèques à la méthode influençant sa précision. Ceux-ci ont déjà été détaillés précédemment (variation liée à la respiration, types de pathologies respiratoires sous-

jacentes, placement du niveau de référence 0, variations liées à l'inflation du ballonnet, artéfact de lecture des courbes de pression).

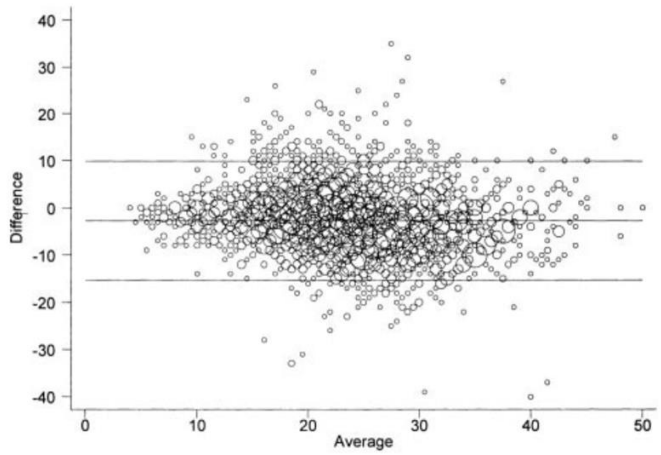


Figure 9 Graphique de Bland-Altman comparant la mesure de la PAPO et de la PTDVG chez 3926 patients avec HTP. Difference = PAPO – PTDVG. Average = (PAPO+PTDVG)/2. Les cercles élargis représentent des représentations identiques chez différents patients. Biais moyen = -2.9mmHg. Limites d'accord à 95% = -15.2 à 9.5mmHg. Reproduit de Misclassification of pulmonary hypertension due to reliance on pulmonary capillary wedge pressure rather than left ventricular end-diastolic pressure, Halpern SD, Taichman DB, 136(1): 37-43 Copyright 2023, avec permission d'Elsevier (28).

Message clé : La PAPO n'est qu'un reflet imprécis de la PTDVG. On note un biais systématique avec une sous-estimation de la PAPO par rapport à la PTDVG (biais de – 3mmHg) et une imprécision importante avec de larges intervalles d'accord entre les deux méthodes. Ainsi si la PAPO ne correspond pas à la valeur attendue, soit une PAPO > 15 ou une PAPO ≤ 15 mmHg respectivement en présence et en l'absence de facteur de risque d'insuffisance cardiaque gauche, une mesure complémentaire de la PTDVG par cathétérisme cardiaque gauche doit être obtenue.

Le débit cardiaque

Dans l'HTP, le $\dot{Q}$ joue un rôle diagnostique par le calcul de la RVP et un rôle pronostique important (1).

Le gold standard pour estimer le $\dot{Q}$ est la méthode de Fick (39). Selon la méthode de Fick la consommation d'oxygène ($\dot{V}O_2$) est égale au débit cardiaque multiplié par l'extraction périphérique d'oxygène (différence entre la concentration artérielle (CaO_2) et du sang veineux en oxygène ($C\bar{v}O_2$). Ainsi le débit cardiaque peut être calculé par l'équation suivante :

$$\dot{Q} = \dot{V}O_2/(CaO_2 - C\bar{v}O_2).$$

La $\dot{V}O_2$ est mesurée par un analyseur de gaz directement à la bouche. La concentration artérielle et veineuse mêlée en oxygène sont analysées simultanément par un prélèvement sanguin artériel et de sang veineux central (au niveau du tronc pulmonaire lors du cathétérisme cardiaque droit). La CaO_2 et la $C\bar{v}O_2$ peuvent donc être calculées considérant que la partie dissoute libre d'oxygène est négligeable par les équations suivantes :

$$CaO_2 = SaO_2 \cdot Hb \cdot 1.34$$
$$C\bar{v}O_2 = S\bar{v}O_2 \cdot Hb \cdot 1.34$$

Où la SaO_2 et la $S\bar{v}O_2$ sont respectivement la saturation artérielle en oxygène et la saturation du sang veineux mêlé en oxygène, l'Hb est la concentration d'hémoglobine et 1.34 est le coefficient de liaison de l'oxygène à l'hémoglobine (mL d'O_2 par g d'Hb).

La méthode de Fick directe, où chacun des composant de l'équation est mesuré, représente le gold standard pour déterminer le débit cardiaque (39). Malheureusement, sa mesure est compliquée en pratique clinique due à la nécessité d'échantillons multiples ainsi que de matériel, notamment un analyseur de gaz pour mesurer la $\dot{V}O_2$.

Les méthodes de Thermodilution et la méthode de Fick indirecte ont largement remplacé la méthode de Fick directe en pratique clinique à cause de leur simplicité d'utilisation (17). La méthode de Fick indirecte utilise des valeurs estimées pour calculer le $\dot{Q}$. Généralement, c'est la $\dot{V}O_2$ qui est estimée à l'aide de tables prenant en compte le poids, le sexe et l'âge du patient (40). Différentes formules existent (Dehmer, Lafarge, Bergstra) qui proviennent de différentes populations de validation. Bien que fréquemment utilisée en pratique, la méthode de Fick indirecte est largement imprécise et peu corrélée avec les outcomes cliniques, y compris la mortalité dans une large cohorte (41). Au vu de ses résultats, les récentes recommandations internationales de l'hypertension pulmonaire ne recommandent plus son utilisation contrastant avec les précédentes recommandations (1, 17).

La méthode de thermodilution est la plus utilisée en pratique clinique. Cette méthode est basée sur l'injection d'un soluté froid au niveau de l'atrium droit (port proximal du cathéter) et par mesure du changement de température au niveau de l'extrémité du cathéter qui doit être située dans l'artère pulmonaire. La courbe température-temps est reliée au débit cardiaque. La thermodilution permet donc une mesure du débit sortant des cavités droites qui est égal au débit sortant des cavités gauches en l'absence de shunt. Une conséquence de ceci est que la méthode de thermodilution est imprécise en cas de shunt important (42). La thermodilution peut souffrir de plusieurs imprécisions : perte de l'indicateur avant l'injection (faux volume d'injection ou température d'injection), perte de l'indicateur pendant l'injection (espace mort durant l'injection et le flush), perte de l'indicateur après l'injection (réchauffement dû au bas débit, à une insuffisance tricuspidienne ou à un shunt), recirculation lors de mesures multiples, fluctuations de la température de base et lors de l'extrapolation de la courbe de thermodilution par l'analyseur (42). Généralement, la mesure de thermodilution doit être moyennée sur au minimum 3 mesures pour augmenter sa précision (1).

Différentes mesures de débit cardiaque non-invasive existent. Dans l'HTP, la bioimpédance, la bioréactance, la respiration de gaz inerte, l'analyse de pouls artérielle, l'échographie cardiaque et l'imagerie par résonnance magnétique ont été testées. La méthodologie de la plupart de ces différentes méthodes a déjà été discutée lors de mon travail de master (Léon Genecand, Determination of cardiac output by invasive and noninvasive methods in pulmonary hypertension, mai 2018, Université de Genève, sous la direction du Dr Frédéric Lador) et ne sera donc pas détaillée ici. La précision des méthodes non-invasives et de l'IRM cardiaque est détaillée dans les articles 1 et 2 présentés ci-dessous.

Résumé et introduction aux articles publiés

La mesure hémodynamique lors du cathétérisme cardiaque droit de la PAPm, de la PAPO et du $\dot{Q}$ est la pierre angulaire du diagnostic de l'HTP. En revanche, ces mesures sont soumises à de nombreuses erreurs potentielles. Certaines erreurs de mesure peuvent et doivent être corrigées. Dans ce contexte il semble important :

1) D'optimiser notre connaissance de l'imprécision des mesures hémodynamiques.
2) De développer de nouvelles méthodes fiables et si possible non-invasives de mesure hémodynamique.
3) De développer des modèles qui nous permettent de prédire chez quel patient il existe une probabilité d'erreur diagnostique liée à la méthode utilisée de mesure hémodynamique.

C'est dans ce contexte que nous avons publié les 4 articles ci-dessous qui traitent de ces 3 différents points. Les articles sont disponibles via pubmed.

Cardiac output determination in precapillary pulmonary hypertension: a systematic review.

Genecand L, Adler D, Beghetti M, Lador F, Cardiac output determination in precapillary pulmonary hypertension: a systematic review. Respiration 2021; 100(12): 1243-1250

Abstract:

Background: Cardiac output determination is essential in precapillary pulmonary hypertension. While direct Fick is the gold standard, thermodilution is commonly used as the reference method. Moving to noninvasive methods would be highly beneficial for patients, avoiding repetitive invasive assessments. This systematic review followed 3 objectives: (1) assessing the validity of indirect Fick and thermodilution in precapillary pulmonary hypertension, (2) assessing the interchangeability of noninvasive cardiac output measurement methods against reference methods in precapillary pulmonary hypertension, and (3) detecting methodological heterogeneity in the included studies.

Methods: We systematically reviewed the literature using medical databases and following PRISMA guidelines. We included articles comparing an invasive or noninvasive cardiac output measurement method with thermodilution or direct Fick in precapillary pulmonary hypertension patients. Cutoffs of limits of agreement and percentage error derived from the Bland and Altman graph were used to accept interchangeability. To study methodological heterogeneity, we extracted 9 quality criteria from all studies.

Results: Eleven studies were included. None reached the suggested interchangeability criteria. The median number of the 9 assessed quality criteria was 2 with interquartile range (0–4).

Conclusions: Further studies evaluating the reliability of thermodilution and the consequences of its use in precapillary pulmonary hypertension patients

are necessary. No evidence supports the use of indirect Fick in precapillary pulmonary hypertension. The studied noninvasive methods could not be considered interchangeable with invasive methods. A robust methodology should be used to draw sensible conclusions.

Non-invasive cardiac output determination using magnetic resonance imaging and thermodilution in pulmonary hypertension

Crowe L-A*, **Genecand L*,** Hachulla A-L, Noble S, Beghetti M, Vallée J-P, Lador F Non-invasive cardiac output determination using magnetic resonance imaging and thermodilution in pulmonary hypertension J Clin Med 2022 May 11;11(10):2717. ***These authors contributed equally to this work as first co-author.**

Abstract:

Background: Magnetic resonance imaging (MRI) can be used to measure cardiac output (CO) non- invasively, which is a paramount parameter in pulmonary hypertension (PH) patients.

Methods: We retrospectively compared stroke volume (SV) obtained with MRI (SV_{MRI}) in six localisations against SV measured with thermodilution (TD) (SV_{TD}) and against each other in 24 patients evaluated in our PH centre using Bland and Altman (BA) agreement analyses, linear correlation, and intraclass correlation (ICC).

Results: None of the six tested localisations for SV_{MRI} reached the predetermined criteria for interchangeability with SV_{TD}, with two standard deviations (2SD) of bias between 24.1 mL/beat and 31.1 mL/beat. The SV_{MRI} methods yielded better agreement when compared against each other than the comparison between SV_{MRI} and SV_{TD}, with the best 2SD of bias being 13.8 mL/beat. The inter-observer and intra-observer ICCs for CO_{MRI} were excellent (inter-observer ICC between 0.889 and 0.983 and intra-observer ICC between 0.991 and 0.999).

Conclusions: We could not confirm the interchangeability of SV_{MRI} with SV_{TD} based on the predetermined interchangeability criteria. The lack of agreement between MRI and TD might be explained because TD is less precise than

previously thought. We evaluated a new method to estimate CO through the pulmonary circulation (COp) in PH patients that may be more precise than the previously tested methods.

Correlation between Pulmonary artery pressure and Vortex duration determined by 4D Flow MRI in Main Pulmonary Artery in patients with suspicion of chronic thromboembolic pulmonary hypertension

Deux JF, Crowe LA, **Genecand L**, Hachulla AL, Glessgen CG, Noble Stéphane, Beghetti M, Ning J, Giese D, Lador Frédéric, Vallée JP Correlation between Pulmonary artery pressure and Vortex duration determined by 4D Flow MRI in Main Pulmonary Artery in patients with suspicion of chronic thromboembolic pulmonary hypertension J Clin Med 2022 Sep 5 ;11(17):5237

Background: Chronic thromboembolic pulmonary hypertension (CTEPH) is one of the causes of pulmonary hypertension (PH) and requires invasive measurement of the mean pulmonary artery pressure (mPAP) during right heart catheterisation (RHC) for the diagnosis. 4D flow MRI could provide non-invasive parameters to estimate the mPAP.

Methods: Twenty-five patients with suspected CTEPH underwent cardiac MRI. Mean vortex duration (%), pulmonary distensibility, right ventricular volumes and function were measured using 4D flow MRI and cine sequences, and compared with the mPAP measured by RHC.

Results: The mPAP measured during RHC was 33 ± 16 mmHg (10–66 mmHg). PH (defined as mPAP > 20 mmHg) was present in 19 of 25 patients (76%). A vortical flow was observed in all but two patients (92%) on 4D flow images, and vortex duration showed good correlation with the mPAP ($r = 0.805$; $p < 0.0001$). Youden index analysis showed that a vortex duration of 8.6% of the cardiac cycle provided a 95% sensitivity and an 83% specificity to detect PH. Reliability for the measurement of vortex duration was excellent for both intra-observer ICC = 0.823 and inter-observer ICC = 0.788.

Conclusions: Vortex duration could be a useful parameter to non-invasively estimate mPAP in patients with suspected CTEPH.

The influence of methods for cardiac output determination on the diagnosis of precapillary pulmonary hypertension: a mathematical model.

Genecand L, Simian G, Desponds R, Wacker J, Ulrich S, Lechartier B, Fellrath JM, Sitbon O, Beghetti M, Lador F. The influence of methods for cardiac output determination on the diagnosis of precapillary pulmonary hypertension: a mathematical model. J Clin med 2023 Jan 1; 12(2):410.

Background: Precapillary pulmonary hypertension (PH, PcPH) is now defined as a mean pulmonary artery pressure (mPAP) > 20 mmHg, a pulmonary artery wedge pressure (PAWP) ≤ 15 mmHg and a pulmonary vascular resistance (PVR) > 2 WU. For PVR calculation, the measurement of cardiac output (CO) is necessary. It is generally measured using thermodilution. However, recent data showed that the agreement with direct Fick method, historically the gold standard, is less than previously reported. We aimed to create a mathematical model that calculated the probability of being classified differently (PcPH or unclassified PH) if CO measured by direct Fick was used instead of thermodilution for any individual patients with a mPAP > 20 mmHg and a PAWP ≤ 15 mmHg.

Methods: The model is based on Bland and Altman analysis with a normally distributed difference of cardiac output, fixed 1.96 standard deviation of bias, bias and physiological cardiac output limits.

Results: Following a literature review of the studies comparing CO measured with direct Fick and thermodilution, we fixed the 1.96 standard deviation of bias at 2 L/min, bias at 0 L/min and physio- logical resting CO limits between 1.3 L/min and 10.2 L/min.

Conclusions: This model can help the clinician to evaluate the potential benefit of measuring CO using direct Fick during the diagnostic work-up and its

utility in confirming or ruling out a diagnosis of PcPH in any given patient with a mPAP > 20 mmHg and a PAWP ≤ 15 mmHg.

Discussion

Le diagnostic d'HTP est basé sur l'évaluation hémodynamique lors du cathétérisme cardiaque droit. Les différents composants nécessaires à la définition de l'HTP (PAPm, PAPO, $\dot{Q}$) sont tous sujets à des imprécisions qui doivent être connues pour permettre un diagnostic correct de l'HTP.

Dans le premier article publié nous montrons par une revue systématique de la littérature que les méthodes non-invasives de débit cardiaque étudiées (bioimpédance, bioréactance, respiration des gaz inerte et analyse de l'onde de pouls) sont insuffisamment précises en comparaison aux méthodes de référence invasive pour être utilisées dans le diagnostic de l'HTP. Nous montrons également que la méthode de Fick indirecte est insuffisamment précise et qu'il existe très peu de données concernant la précision de la méthode de Thermodilution chez les patients souffrant d'HTP précapillaire en comparaison au gold standard soit la méthode de Fick directe.

Dans le second article, nous montrons que l'IRM cardiaque est une méthode non-invasive prometteuse de mesure du débit cardiaque et que cette méthode pourrait s'avérer plus précise que la méthode de Thermodilution. En effet, alors que la comparaison entre les différentes méthodes de mesure par IRM du débit cardiaque (avec des mesures de flux ou des mesures de volume) n'atteint pas les critères d'interchangeabilité avec la méthode de thermodilution, l'accord entre les différentes méthodes de mesure du débit cardiaque à l'IRM (flux et volumétrie) est souvent excellent. Dans ce contexte, l'imprécision et le désaccord entre les méthodes de mesure du débit cardiaque par IRM et par thermodilution est possiblement le fruit de l'imprécision de la méthode de thermodilution dans l'HTP plus que de l'imprécision des méthodes de mesure par IRM cardiaque. Ceci doit toutefois être prouvé avec une étude dédiée comparant les méthodes de mesure par IRM avec le gold standard Direct Fick en plus de la thermodilution.

Dans le troisième article nous démontrons la capacité non-invasive de l'IRM cardiaque pour le diagnostic de l'HTP à travers l'évaluation de la durée de vortex dans l'artère pulmonaire permettant d'estimer la PAPm. L'IRM cardiaque semble au moins autant performante que l'échographie pour le diagnostic de l'HTP et pourrait se révéler utile particulièrement pour les patients chez lesquels l'échographie transthoracique est incapable d'estimer la probabilité d'hypertension pulmonaire.

Dans le dernier article, nous illustrons l'imprécision de la méthode de thermodilution en comparaison avec la méthode gold standard de Fick directe. En se basant sur les données existantes dans l'HTP précapillaire, nous avons créé un modèle mathématique qui permet d'estimer, pour un patient donné, la probabilité de classification incorrecte en utilisant la méthode de thermodilution plutôt que la méthode de Fick directe. Ceci devrait permettre au clinicien une approche personnalisée avec l'utilisation de la méthode de Fick directe pour le diagnostic d'HTP lorsque le risque de mauvaise classification en utilisant la méthode de thermodilution est élevé.

Conclusions

Parmi les enjeux à venir, les progrès doivent nous amener à mieux détailler la précision des différentes mesures hémodynamiques dans l'HTP, à trouver de nouveaux outils non invasifs fiables évitant aux patients des examens invasifs et à comprendre l'influence de l'imprécision des méthodes hémodynamiques sur la prise en charge des patients souffrants d'une hypertension pulmonaire.

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Cardiac Output Determination in Precapillary Pulmonary Hypertension: A Systematic Review

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Keywords
Cardiac output · Pulmonary hypertension · Direct Fick · Thermodilution · Indirect Fick

Abstract
Background: Cardiac output determination is essential in precapillary pulmonary hypertension. While direct Fick is the gold standard, thermodilution is commonly used as the reference method. Moving to noninvasive methods would be highly beneficial for patients, avoiding repetitive invasive assessments. This systematic review followed 3 objectives: (1) assessing the validity of indirect Fick and thermodilution in precapillary pulmonary hypertension, (2) assessing the interchangeability of noninvasive cardiac output measurement methods against reference methods in precapillary pulmonary hypertension, and (3) detecting methodological heterogeneity in the included studies. ***Methods:*** We systematically reviewed the literature using medical databases and following PRISMA guidelines. We included articles comparing an invasive or noninvasive cardiac output measurement method with thermodilution or direct Fick in precapillary pulmonary hypertension patients. Cutoffs of limits of agreement and percentage error derived from the Bland and Altman graph were used to accept interchangeability. To study methodological heterogeneity, we extracted 9 quality criteria from all studies. ***Results:*** Eleven studies were included. None reached the suggested interchangeability criteria. The median number of the 9 assessed quality criteria was 2 with interquartile range (0–4). ***Conclusions:*** Further studies evaluating the reliability of thermodilution and the consequences of its use in precapillary pulmonary hypertension patients are necessary. No evidence supports the use of indirect Fick in precapillary pulmonary hypertension. The studied noninvasive methods could not be considered interchangeable with invasive methods. A robust methodology should be used to draw sensible conclusions.

Introduction

Pulmonary hypertension (PH) is classified into 5 etiological groups according to current guidelines [1]. It was recently suggested that the mean pulmonary arterial pressure cutoff to define PH should be >20 mm Hg instead of ≥25 mm Hg [2]. Additionally, the definition of precapillary

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pulmonary hypertension (PcPH) should be the combination of PH (mean pulmonary arterial pressure >20 mm Hg) with a pulmonary artery wedge pressure (PAWP) ≤15 mm Hg and a pulmonary vascular resistance (PVR) ≥3WU, adding PVR to the definition [2]. Cardiac output (CO) determination is an important prognostic factor for PH patients and would become mandatory to diagnose PcPH if the PVR becomes an obligatory criterion. While direct Fick (DF) remains the gold standard for CO measurement, thermodilution (TD) is usually used due to easier feasibility [3]. However, only 2 studies directly compared TD to DF in PcPH [4, 5]. Indirect Fick (IF) is also used although it apparently lacks reliability in PH [1]. Complications of right heart catheterization are rare but can be severe, even leading to death [6]. In this context, noninvasive, safe, cheap, reproducible, and reliable methods to evaluate CO would be of great value for PH patients. Studies evaluating noninvasive methods of CO measurement in PcPH have been published but not systematically reviewed to assess their interchangeability with invasive CO measurement methods. The ideal CO monitoring method should be accurate (i.e., small bias), precise (i.e., small dispersion of the variables), noninvasive, rapid to perform, operator independent with no inter/intraobserver variability, cost-effective, continuous, and with short learning curve. In addition, it should have the ability to detect relative CO change. This systematic review follows 3 objectives: (1) assessing the validity of IF and TD in PcPH, (2) assessing the interchangeability of noninvasive CO measurement methods against reference methods (DF or TD) in PcPH, and (3) assessing methodological heterogeneity in the included studies.

Methods

Our methodology is based on the PRISMA guidelines [7]. We reviewed the literature using PubMed, Embase, Web of Science, and Google Scholar. We included all articles with PcPH patients (PH groups 1, 3, and 4) that were comparing, during rest, invasive or noninvasive methods of CO determination to a reference method using a Bland and Altman analysis. The search on Web of Science was made of 2 sets. Set 1: TI=(Pulmonary Hypertension); set 2: TI=([Cardiac output] OR [Right heart catheterization] OR [thermodilution] OR [direct Fick] OR [Indirect Fick] OR [inert gas rebreathing] OR [acetylene rebreathing] OR [Innocor] OR [bioimpedance] OR [PhysioFlow] OR[bioreactance] OR [Nicom]). We then associated "set 1 AND set 2." The bibliography of the included studies was screened in order to find other studies that would have been missed by the initial search.

Study Selection

Inclusion criteria were (1) inclusion of PcPH patients, (2) use of Bland and Altman analysis, and (3) comparing TD, IF, or noninvasive CO measurement methods to a reference method (TD or DF). Exclusion criteria were (1) studies comparing only transthoracic echocardiography (TTE) to a reference method, (2) studies comparing only cardiac magnetic resonance (CMR) to a reference method, (3) studies not showing their results in CO (L/min) (e.g., stroke volume or indexed CO), and (4) only exercise CO measurement. Two authors (L.G. and F.L.) systematically screened the articles. All relevant studies were reviewed in full text. The search was performed until January 2021. Studies fulfilling all inclusion criteria with no exclusion criterion were included. We had no limitation concerning year of publication, type of patients (i.e., hospitalized or ambulatory), or predefined outcomes. Only studies published in English were screened for inclusion.

Data Extraction

One author (L.G.) independently extracted data from the included articles. A second author (F.L.) read the included articles and checked the data. To assess the interchangeability of TD, IF, and noninvasive methods in PcPH, we collected the following data: brand of the device used concerning noninvasive methods, number of patients, repartition of patients in each group of PH, mean CO, Bland and Altman [8] analysis with bias (i.e., mean difference of CO), 95% limits of agreement (LoA), and percentage error (PE)). If possible, LoA and PE were calculated from published data when the authors did not give them ("#" is noted next to calculated values). LoA were calculated as bias ± 2SD of bias. PE was calculated as (2SD of bias/mean CO of both methods) × 100 [9]. If necessary, when data were unavailable in the article text, we estimated them from the published figures ("*" is noted next to estimated values).

Bland and Altman [8] analysis is the commonly accepted statistical technique to evaluate the agreement when 2 methods assessing the same variable are compared. Coefficient of correlation and linear regression are not suitable in this situation [8]. PE was suggested because it helps the interpretation of agreement when high or low mean CO is studied [9]. Its use was initially suggested when CO differs from 5 L/min [9]. PE is now commonly used even in CO around 5 L/min [10]. Trend analysis informs about the ability of the method to detect relative CO changes. Relative changes are often considered more important than absolute CO measurement in intensive care medicine and anesthesiology where it gives rapid data about the patient's condition.

Based on the interchangeability criteria widely used in the fields of anesthesiology and critical care medicine, we accepted the interchangeability of 2 CO measurement methods when one of the following criteria was reached: (1) 2SD of bias ≤ ±1L/min when comparing the tested method to the gold standard DF, (2) PE ≤ ±20% when comparing the tested method to the gold standard DF, and (3) PE ≤±30% when comparing the tested method to the reference method TD [9, 11].

To evaluate methodological pitfalls in studies comparing CO measurement methods, we used an extrapolation chart systematically looking for 9 methodological criteria. Seven criteria were directly derived from the original article from Bland and Altman [8]: (1) correct definition of LoA as "bias ± 2SD of the differences," (2) evaluation of a relation between difference and mean, (3) confidence interval of the bias and of the LoA, (4) use of an objective cutoff to conclude to interchangeability, (5) assessment of repeatability (i.e., using coefficient of variation), (6) assessment of the effect of multiple measurements, and (7) presence of one or more suggested criteria to reach interchangeability [8]. The 2 remaining

criteria are specifically used in the field of CO measurement methods: (8) PE calculation and (9) trend analysis according to one of the methods described elsewhere [12].

Results

The search in Web of Science yielded 61 studies. Sixteen were retained for full readings. Nine corresponded to the inclusion criteria with no exclusion criteria. Their bibliography was screened adding 2 other articles that could be included. On the 11 articles included, 1 compared DF and TD [4], 3 compared IF and TD [13–15], 1 evaluated pulse wave analysis (PWA) with Modelflow® [16], 4 evaluated bioimpedance (BI) using Physioflow® [17–19] or whole body impedance cardiography [20], 1 evaluated bioreactance with Nicom® (NI) [15], and 3 evaluated inert gas rebreathing (IGR) with acetylene rebreathing [4, 21] or Innocor® [22]. Figure 1 shows the flowchart.

About the Validity of IF and TD in PcPH

Studies comparing TD and DF: Hoeper et al. [4] compared CO_{TD} and CO_{IGR} with CO_{DF} in 35 PcPH patients. When comparing TD with DF, they found a bias ($CO_{TD} - CO_{DF}$) (±LoA) of +0.01 L/min (−1.09 and +1.11) and a PE of ±29.7% (#) [4].

Studies comparing IF and TD: Fares et al. [13] retrospectively compared CO_{IF} with CO_{TD} in 198 PH patients and found a bias ($CO_{IF} - CO_{TD}$) (±LoA) of +0.39 L/min (−3.67 to +4.45) and a PE of ±71.9% (#). Alkhodair et al. [14] retrospectively compared CO_{IF} with CO_{TD} in 168 PH patients and found a bias ($CO_{IF} - CO_{TD}$) (±LoA) of −0.62L/min (−3.3 to +2.1) and a PE of ±58.7% (#). Rich et al. [15] prospectively compared CO_{NI} and CO_{IF} with CO_{TD} in 50 PH patients and showed a bias ($CO_{IF} - CO_{TD}$) (±LoA) of −0.83 L/min (−2.63 and +0.98) and a PE of ±34.2% (#). Table 1 summarizes data for the 4 studies comparing invasive CO methods (TD against DF and IF against TD).

About Interchangeability of Noninvasive CO Measurement Methods against Reference Methods (DF or TD)

Study evaluating Modelflow®: Lador et al. [16] compared CO_{PWA} with CO_{TD} in 50 PcPH patients. They found a bias ($CO_{TD} - CO_{PWA}$) (±LoA) of +0.72 L/min (−1.32 and +2.76) and a PE of ±35.7% when comparing noncalibrated Modelflow® with TD [16]. After calibration with a correction factor derived from the reference method, they found a bias ($CO_{PWA} - CO_{TD}$) (±LoA) of −0.03 L/min (−1.23 and +1.17) and a PE of ±19.8% [16].

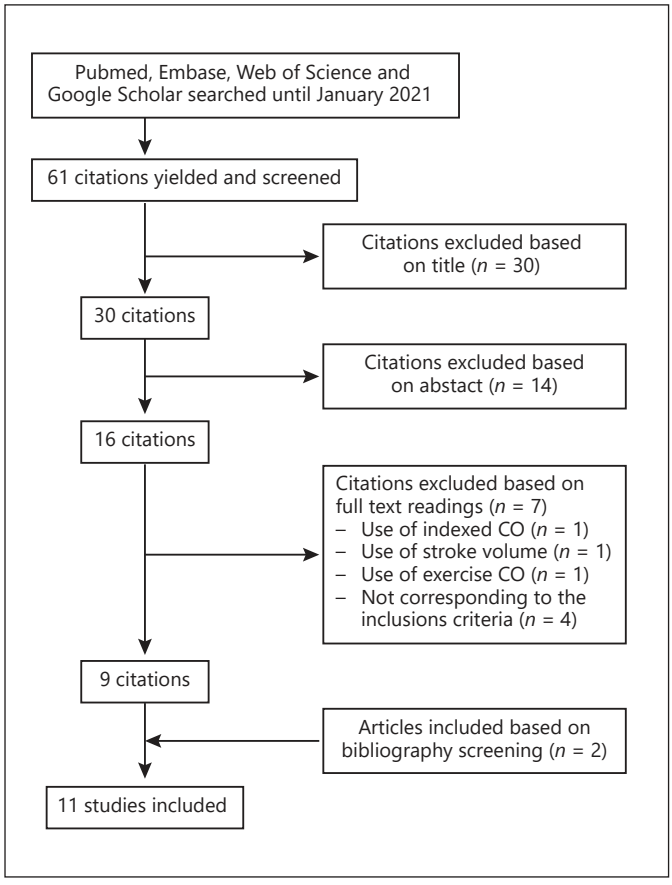

Fig. 1. Flowchart of the study.

Studies evaluating impedance cardiography: the studies found all used the PhysioFlow® method, except for Taniguchi et al. [20] who used whole body impedance cardiography. Dupuis et al. [17] compared CO_{BI} with CO_{DF} and CO_{TD} in 75 PcPH patients. When comparing CO_{BI} with CO_{DF}, they found a bias ($CO_{BI} - CO_{DF}$) (±LoA) of −0.149 L/min (−3.56 and +3.27). Dupuis et al. [17] acknowledged a mistake in the calculation of their PE, which was the subject of a letter to the editor [23]. The recalculated PE with the authors' data was ±60.7% (#). Panagiotou et al. [18] compared CO_{BI} with CO_{TD} in 22 patients with suspected PH. They found a bias ($CO_{BI} - CO_{TD}$) (±LoA) of +1.21 L/min (−2.33 and +4.75) and a PE of ±64.5% (#) [18]. Tonelli et al. [19] compared CO_{BI} and CO_{TD} in 30 patients with PH. They found a bias ($CO_{BI} - CO_{TD}$) (±LoA) of −0.3 L/min (−2.8 and +2.2) and a PE of ±43.5% (#) [19]. Taniguchi et al. [20] compared CO_{TD} with CO_{BI} in 61 PcPH patients. They found a bias ($CO_{BI} - CO_{TD}$) (±LoA) of −0.50 L/min (−2.61 and +1.61) and a PE of ±45.2% (#) [20].

Table 1. Data concerning invasive CO measurement methods

Studies	Compared CO	Mean CO, L/min	Bias, L/min	LoA, L/min	PE, %	Pop, *N*	PH groups				
							1	2	3	4	5
Hoeper et al. [4]	TD versus DF	CO_{DF}: 3.7 CO_{TD}: 3.7	0.0	−1.1 to 1.1	±29.7#	35	31	0	0	4	0
Fares et al. [13]	TD versus IF	CO_{IF}: 5.9# CO_{TD}: 5.5#	0.4	−3.7 to 4.5	±71.9#	198	79	119 (unspecified)			
Alkhodair et al. [14]	TD versus IF	CO_{IF}: 4.2 CO_{TD}: 4.8	−0.6	−3.3 to 2.1	±58.7#	168	71	62	101	29	0
Rich et al. [15]	TD versus IF	CO_{IF}: 4.8 CO_{TD}: 5.7	−0.8	−2.6 to 1.0	±34.2#	50	27	7	10	3	3

Data are shown with 1 decimal number. Hoeper et al. [4] and Rich et al. [15] are prospective studies. Fares et al. [13] and Alkhodair et al. [14] are retrospective studies. Alkhodair et al. [14] classified 38% of their patients as having multifactorial PH (therefore, the addition of the separate groups is more than the total population). Bias, mean CO difference ($CO_{TD} - CO_{DF}$) [4] or ($CO_{IF} - CO_{TD}$) [13–15]. CO, cardiac output; PH, pulmonary hypertension; DF, direct Fick; IF, indirect Fick; LoA, limits of agreement = bias±2SD of the difference; PE, percentage error = (2SD of bias)/(mean CO of the tested method) × 100; TD, thermodilution. #Is noted next to calculated values derived from the authors' data.

Study evaluating bioreactance: 1 study published by Rich et al. [15] compared bioreactance using Nicom® with TD in 50 PH patients. They found a bias ($CO_{NI} - CO_{TD}$) (±LoA) of +0.81L/min (−1.92 and +3.54) and a PE of ±51.9% (#) [15].

Studies evaluating IGR: 2 studies evaluated CO determined by IGR using acetylene rebreathing in PcPH. Hoeper et al. [4] compared IGR with DF in 35 PcPH patients. They showed a bias ($CO_{IGR} - CO_{DF}$) (±LoA) of −0.23 L/min (−1.37 to +0.91) and a PE of ±31.7% (#) [4]. Schwaiblmair et al. [21] found a bias ($CO_{IGR} - CO_{TD}$) (±LoA) of +0.16 L/min (−2.32 to +2.64) and a PE of ±62.0% (#) when comparing IGR with TD in 72 PAH patients. Results were worse when comparing IGR with TD in 32 CTEPH patients showing a bias ($CO_{IGR} - CO_{TD}$) (±LoA) of +0.56L L/min (−3.84 and +4.96) and a PE of ±129.4% (#) [21]. Farina et al. [22] compared Innocor® (N_2O), another technique of IGR, with DF in 37 PcPH patients. They showed a bias ($CO_{IGR} - CO_{DF}$) (LoA) of +0.8 L/min (*) (−2.6 and +4.2 [*]) and a PE of ±66.7% (*#) [22].

Table 2 summarizes data from the 9 studies evaluating noninvasive methods in PcPH. All are prospective studies.

About Methodological Heterogeneity in the Included Studies

All included studies used a B&A graph. Six studies correctly defined the LoA [4, 13, 15–17, 19]. Four studies evaluated the presence of a proportional bias in the B&A graph [13, 16, 17, 19]. One study gave the 95% CI of LoA and 5 gave the 95% CI of the bias [4, 14, 17, 19, 22]. Repeatability was assessed in 3 studies [15, 16, 19]. No study assessed the effect of averaging multiple measurements. Terms "precision" or "accuracy" were used in all studies. "Precision" was defined in 3 studies (defined as "SD of mean difference" [16], "2SD of mean difference" [13], and the "coefficient of variation" [15]). "Accuracy" was defined in 2 studies as "the mean CO difference" [16, 17]. Three studies gave a fixed cutoff to accept interchangeability defined as a PE of ≤±30% [16, 17, 19]. PE was calculated in 3 studies [4, 16, 17]. One study reached one of our suggested criteria for interchangeability [16]. However, this was achieved after using a correction factor derived from the reference method [16]. Three studies evaluated trend analysis using analysis of change methods [4, 15, 16].

Table 3 shows the results for the 9 quality criteria. In the 11 studies included, median number of assessed quality criteria was 2 with interquartile range (0–4).

Discussion

About the Validity of IF and TD in PcPH

The actual PH international guidelines state "CO should be measured using TD or the DF method. TD measured in triplicate is the preferred method because it can provide reliable measurements even in patients with low CO and/or severe tricuspid regurgitation" [1]. For

Table 2. Data concerning noninvasive CO measurement methods

Studies	Compared CO	Mean CO, L/min	Bias, L/min	LoA, L/min	PE, %	Pop, *N*	PH groups					
							1	2	3	4	5	No
Lador et al. [16]	PWA versus TD BC	CO_{PWA}: 6.2 CO_{TD}: 5.5	0.7	−1.3 to 2.8	±35.7	50	30	0	0	20	0	0
	PWA versus TD AC		0.0	−1.2 to 1.2	±19.8							
Dupuis et al. [17]	BI versus DF	CO_{BI}: 5.5 CO_{DF}: 5.7	−0.1	−3.6 to 3.3	±60.7#	75	60	0	0	15	0	0
Panagiotou et al. [18]	BI versus TD	CO_{BI}: 5.9 CO_{TD}: 4.7	1.2	−2.3 to 4.8	±64.5#	22	14	3	4	1	0	3
Tonelli et al. [19]	BI versus TD	CO_{BI}: 5.6 CO_{TD}: 5.9	−0.3	−2.8 to 2.2	±43.5#	30	16	10	1	2	1	9
Taniguchi et al. [20]	BI versus TD	CO_{BI}: 4.4 CO_{TD}: 4.9	−0.5	−2.6 to 1.6	±45.2#	61	38	0	3	20	0	0
Rich et al. [15]	BR versus TD	CO_{BR}: 4.7 CO_{TD}: 5.7	0.8	−1.9 to 3.5	±51.9#	50	27	7	10	3	3	0
Hoeper et al. [4]	IGR versus DF	CO_{IGR}: 3.5 CO_{DF}: 3.7	−0.2	−1.4 to 0.9	±31.7#	35	31	0	0	4	0	0
Schwaiblmair et al. [21]	IGR versus TD	CO_{IGR}: 3.9 CO_{TD}: 4.1	0.2	−2.3 to 2.6	±62.0#	72	72	0	0	0	0	0
	IGR versus TD	CO_{IGR}: 3.1 CO_{TD}: 3.7	0.6	−3.8 to 5.0	±129.4#	32	0	0	0	32	0	0
Farina et al. [22]	IGR versus DF	CO_{IGR}: 5.4 CO_{DF}: 4.8	0.8*	−2.6 to 4.2*	±66.7*, #	37	Precapillary PH (unspecified)					

Data are shown with 1 decimal number. Panagiotou et al. [18] and Tonelli et al. [19] recruited patients with suspected PH and had in their final analysis some patients with no PH (in column "no"). Dupuis et al. [17] acknowledged a mistake in the calculation of their PE, which was the subject of a letter to the editor. The PE exposed here is recalculated from the original data. Farina et al. [22] recruited precapillary PH without specifying the groups. Schwaiblmair et al. [21] analyzed separately group 1 PH and group 4 PH patients. These 2 groups are shown separately in the tables. AC, after calibration; BC, before calibration; BI, bioimpedance; Bias, $CO_{\text{tested method}} - CO_{\text{reference method}}$; BR, bioreactance CO, cardiac output; PH, pulmonary hypertension; DF, direct Fick; PWA, pulse wave analysis; IGR, inert gas rebreathing; LoA, limits of agreement = bias±2SD of the difference; PE, percentage error = (2 SD of bias)/(mean CO) × 100; TD, thermodilution. #Is noted next to calculated values derived from the authors' data. *Is noted next to estimated values derived from the authors' graphs.

this recommendation, 1 study comparing CO determined by TD and DF in 35 PcPH patients is cited [4]. In this study, they found a small bias, but admitted a considerable dispersion of the variables. However, they concluded that TD should be reliable enough in most cases of PH patients. An objective cutoff to accept interchangeability was unfortunately not clearly defined. Their results did not reach our suggested interchangeability criteria when comparing a reference method to the gold standard DF (i.e., LoA ±1L/min or PE ≤20). Another study compared DF and TD in 75 PAH patients at rest [5]. This study was excluded from the main analysis because they used the cardiac index (CO normalized with body surface area), which prevents the direct comparison of absolute LoA. However, PE is still comparable in this context. The authors found a PE of ±43%, which is over the accepted criteria for interchangeability. Hsu et al. [24] investigated exercise PH in patients with no resting PH and showed that TD underestimated CO compared to DF. In this context, the use of TD led to an overestimation of PVR inducing an erroneous diagnosis of exercise PH. Recently, a new definition of PcPH including a PVR ≥3 was suggested [2]. PVR is the quotient between the transpulmonary gradient (PAPm – PAWP) and the CO. Overestimation

Table 3. Extraction chart of statistical data used to compare 2 methods

	[4]	[13]	[14]	[16]	[17]	[18]	[19]	[20]	[15]	[21]	[22]
B&A analysis	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Correct definition of 95% LoA	Y	Y	N	Y	Y	N	Y	N	Y	N	N
Evaluation of a proportional bias	N	Y	N	Y	Y	N	Y	N	N	N	N
CI of bias/CI of LoA	Y	N	Y/N	N	Y/N	N	Y/N	N	N	N	Y/N
Assessment of repeatability	N	N	N	Y	N	N	Y	N	Y	N	N
Consequence of multiple measurements	N	N	N	N	N	N	N	N	N	N	N
Terms: "precision" or "accuracy"	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Definition of an acceptable PE or LoA	N	N	N	Y	Y	N	Y	N	N	N	N
PE calculated	Y	N	N	Y	Y	N	N	N	N	N	N
Meeting criteria for interchangeability	N	N	N	Y	N	N	N	N	N	N	N
Trend analysis	Y	N	N	Y	N	N	N	N	Y	N	N

Hoeper et al. [4], Fares et al. [13], Alkhodair et al. [14], Rich et al. [15], Lador et al. [16], Dupuis et al. [17], Panagiotou et al. [18], Tonelli et al. [19], Taniguchi et al. [20], Schwaiblmair et al. [21], and Farina et al. [22]. B&A, Bland and Altman; LoA, limits of agreements; CO, cardiac output; CI, confidence interval; PE, percentage error.

of CO would lead to underestimation of PVR, and a patient having PcPH could be missed. Underestimation of CO would lead to overestimation of PVR and therefore PcPH diagnosis, as recently debated [25]. Obviously, the ability of TD to offer a correct CO determination should be assessed more deeply. In this context, we could discuss the mandatory use of DF when borderline PVR is found in the context of PH >20 mm Hg, especially without a postcapillary component (PAWP ≤15).

Other studies have measured CO_{TD} and CO_{DF} simultaneously in PcPH patients [17, 22, 26]. Unfortunately, they did not evaluate the agreement between TD and DF.

Two retrospective studies and 1 prospective study compared IF against TD and demonstrated LoA and PE far from the suggested interchangeability criteria [13–15]. One study directly compared IF with DF [5]. However, the authors used the cardiac index and therefore was not included in the main analysis. Interestingly, they found PE far above the ±20% limit when comparing a method to the gold standard for all the tested equations to determine CO by IF (Bergstra, Lafarge, and Miettinen). The current PH guidelines acknowledge this lack of reliability but state that IF is acceptable [1]. We would recommend a more prudent statement when considering IF performance in the published data.

About Interchangeability of Noninvasive CO Measurement Methods against Reference Methods (DF or TD)

No studies using bioimpedance, bioreactance, or IGR reached the suggested interchangeability criteria. One study comparing PWA system Modelflow® to TD after calibration reached 1 interchangeability criterion [16]. However, the interchangeability cannot be concluded since Modelflow® needs an individual correction factor, which is found with the reference method TD. For now, Modelflow® can only be used in parallel with a reference method or to determine CO variations.

TTE and CMR are other noninvasive methods for CO determination. CMR is constantly developing, and new methods to estimate CO are being developed. These range from the measurement of the difference between the diastolic and systolic cardiac chamber's volumes to velocity curves analysis. It could be the most promising method to reliably evaluate CO noninvasively in PcPH, but it is very expensive and not easily accessible. Due to the different methods to assess CO using CMR, we estimated that it deserves a focused review. TTE has been used for years. It incontestably provides mandatory data for PH diagnostic workup and follow-up. However, limitations for CO determination with TTE are acknowledged [27]. Importantly, TTE demonstrated poor reliability and reproducibility when compared with TD in a recent meta-analysis [10].

About Methodological Heterogeneity in the Included Studies

Methodological heterogeneity is frequent in the field of CO measurement. One review comparing different studies in the fields of anesthesia showed that defining a priori LoA, assessing repeatability, and evaluating a proportional bias were evaluated in, respectively, 7.1, 21.4, and 7.1% of the included studies [28]. This review was

published in 2000, and a call for rigorous methodology was made at this time [28]. However, inconsistencies in the methodology persisted in this field. For example, a recent meta-analysis comparing CO measurement methods showed discordance between objective measurement of agreement and authors' conclusions [29]. In addition, even though some methods have been shown to have a poor agreement when compared to gold standards, they are used in the clinical practice in anesthesia or critical care medicine. This is, for example, the case for bioimpedance [30].

Repeatability (assessed in 3/11 studies) helps to understand the contribution of each of the compared methods to the lack of agreement [11]. The relation between difference and the mean (assessed in 4/11 studies) can reveal a proportional bias [24]. Confidence interval of the bias and LoA (assessed in 4/11 for CI of bias and 1/11 for CI of LoA) is important for generalization of results. Multiple measurements influence the intrinsic precision of the method. This criterion was unfortunately not determined in any of the reviewed studies. Hence, our results show the seldom assessment of criteria stated above, making interpretation of agreement difficult. The majority of studies did not assess trend analysis (assessed in 3/11 studies), and consequently we have scarce information on the ability of the studied methods to detect a relative change in CO.

The most important step when interpreting a Bland and Altman [8] graph is defining a clinically acceptable cutoff (defined in 3/11 studies). Many authors encouraged the use of their CO measurement methods without mentioning objective cutoffs [15, 18–22]. None of these studies reached our suggested interchangeability criteria. To accept interchangeability, we used cutoffs derived from anesthesiology and critical care medicine. However, a clinically acceptable cutoff has never been officially decided in the field of PH. Whether these values are acceptable for studies in the field of PH remain unsure. The questions "Who should decide?" and "How should these be decided?" must be addressed. To answer these questions, limitations concerning LoA and PE must be acknowledged. First, the Bland and Altman [8] graph is a subjective approach to interchangeability, and the chosen cutoffs are specific to a clinical condition, which differs between anesthesiology or intensive care medicine and PH patients. Second, the PE does not take into account the distribution of values over a range. The first limitation confirms the need of clearly determined cutoffs in order to ease the interpretation of studies and to allow implementation of new CO measurement methods. The second limitation could be addressed by using more complex methodology described elsewhere [31]. The precision and accuracy needs depend on the clinical question asked and vary whether this question is (1) the correct definition of PH (through PVR measurement) or (2) CO measurement or changes for prognostic information and risk stratification. To precisely solve the question of the correct cutoff, it would be valuable to evaluate the influence of the cutoff used on the diagnostic accuracy and the risk stratification. This could be achieved through studies specifically addressing these questions.

Conclusion

If the new definition for PcPH is accepted, incorrect determination of CO could lead to misdiagnosis of PcPH. Data concerning the reliability of TD in PcPH are scarce. The interchangeability of IF with TD could not be demonstrated. No noninvasive methods could be considered interchangeable with invasive methods. A robust methodology using criteria suggested in the original study of Bland and Altman [8] and other criteria specific in the field of CO measurement methods should be used for further studies to draw sensible conclusions.

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Only the authors in the article participated in this systematic review.

Statement of Ethics

This article summarizes studies that were conducted ethically.

Conflict of Interest Statement

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Author Contributions

L.G. performed the literature research, extracted data from the included articles analysis, and wrote the manuscript. D.A. participated in elaboration of the methodological approach of the data and participated substantially in writing and reviewing of the manuscript. M.B. participated in supervision of the work and reviewing of the manuscript. F.L. initiated and supervised the project, controlled data from the included articles, and substantially participated in manuscript writing and reviewing.

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Non-Invasive Cardiac Output Determination Using Magnetic Resonance Imaging and Thermodilution in Pulmonary Hypertension

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Abstract: Magnetic resonance imaging (MRI) can be used to measure cardiac output (CO) non-invasively, which is a paramount parameter in pulmonary hypertension (PH) patients. We retrospectively compared stroke volume (SV) obtained with MRI (SV_{MRI}) in six localisations against SV measured with thermodilution (TD) (SV_{TD}) and against each other in 24 patients evaluated in our PH centre using Bland and Altman (BA) agreement analyses, linear correlation, and intraclass correlation (ICC). None of the six tested localisations for SV_{MRI} reached the predetermined criteria for interchangeability with SV_{TD}, with two standard deviations (2SD) of bias between 24.1 mL/beat and 31.1 mL/beat. The SV_{MRI} methods yielded better agreement when compared against each other than the comparison between SV_{MRI} and SV_{TD}, with the best 2SD of bias being 13.8 mL/beat. The inter-observer and intra-observer ICCs for CO_{MRI} were excellent (inter-observer ICC between 0.889 and 0.983 and intra-observer ICC between 0.991 and 0.999). We could not confirm the interchangeability of SV_{MRI} with SV_{TD} based on the predetermined interchangeability criteria. The lack of agreement between MRI and TD might be explained because TD is less precise than previously thought. We evaluated a new method to estimate CO through the pulmonary circulation (COp) in PH patients that may be more precise than the previously tested methods.

Keywords: pulmonary hypertension; cardiac output; magnetic resonance imaging; thermodilution

1. Introduction

Pulmonary hypertension (PH) is defined as a resting mean pulmonary artery pressure (mPAP) $\geq$ 25 mmHg measured by right heart catheterisation (RHC) [1]. Five groups with different aetiologies can be differentiated. Pulmonary arterial hypertension (PAH) is a rare pulmonary vasculopathy diagnosed after exclusion of other class of PH (groups 2, 3, 4, and 5) and confirmed with RHC showing a precapillary PH (PcPH) that is characterised by an mPAP $\geq$ 25 mmHg and a pulmonary artery wedge pressure (PAWP) $\leq$ 15 mmHg [1]. Group 4 is defined as an obstruction of the pulmonary arteries leading to PH. The main entity of this group is called chronic thrombo-embolic pulmonary hypertension (CTEPH).

Cardiac output (CO) measurement is important for the prognosis of patients with PAH via risk class stratification. It is also essential for diagnoses using the calculation of pulmonary vascular resistance (PVR). A proposal suggested redefining PH with a lower mPAP threshold of >20 mmHg and the inclusion of PVR > 3 WU as an obligatory criterion for PcPH [2]. In this context, a reliable non-invasive method to measure CO could be valuable for the patients and the clinician in order to avoid some invasive procedures.

Invasive methods are acknowledged to be the methods of choice to measure CO [1]. Direct Fick (DF) is the historical gold standard [1]. However, CO measurement using DF is cumbersome due to the measurement of oxygen consumption. Thermodilution (TD) has been accepted as the reference method in the current international guidelines [1]. This proposal was based on one study showing a good agreement between TD and DF [3]. TD is nowadays the most used method for the determination of CO for PH patients. Indirect Fick (IF) lacks reliability, and poor agreement with DF or TD was shown both retrospectively and prospectively in large mixed PH population [4–6].

Many different non-invasive methods to measure CO have been studied in precapillary PH patients including bioimpedance, bioreactance, inert gas rebreathing, and pulse wave analysis [3,6–12]. None of the studied non-invasive method reached predetermined criteria for interchangeability with an invasive method (DF or TD) in a recent systematic review [13]. CO determined with transthoracic echocardiography (TTE) also showed poor performance in comparison to TD in a meta-analysis [14].

MRI is acknowledged as an important emerging tool in PH management. It allows anatomical evaluation of the right ventricle (RV) and the pulmonary artery (PA), offers some new prognostic variables, and can be helpful for the diagnosis and classification of PH in specific cases [15–18]. Its role in the determination of CO remains under investigation. SV determination using flow measurement in the ascending aorta (AAO) (SV_{AAO}) and volumetric assessment of the left ventricle (LV) (SV_{LV}) agreed closely with the SV derived from the DF (SV_{DF}) in 32 PAH patients with a 2SD of bias of +/−7.5 mL/beat and +/−9.6 mL/beat, respectively, with no significant bias [19]. However SV derived with flow measurement in the pulmonary artery (SV_{PA}) and volume assessment of the right ventricle (SV_{RV}) showed poor agreement with SV_{DF} [19]. To the best of our knowledge, no methods have shown the ability to precisely calculate CO through the pulmonary circulation (COp) in precapillary PH.

Our aims were to determine (1) the agreement between SV_{MRI} and SV_{TD} in a population evaluated in our PH centre; (2) the inter- and intra-observer reproducibility, and the agreement between the different SV_{MRI} methods in the same population. We hypothesised that a new strategy for COp estimation based on the sum of the right pulmonary artery (RPA) and the left pulmonary artery (LPA) SV ($SV_{(RPA+LPA)}$) would be more precise than the localisations tested thus far in PH patients (SV_{PA} and SV_{RV}).

2. Materials and Methods

2.1. Study Population and Setting

We retrospectively included patients in our PH centre evaluated with both RHC and MRI imaging. We included all patients from variable settings, including (1) diagnosis evaluation of suspected PH, (2) follow-up of PH, and (3) follow-up of PH patients after treatment. Patients were excluded if (1) the delay between RHC and MRI was more than 3 weeks, (2) their age was <18 years, (3) a clinical deterioration occurred between RHC and MRI, and (4) in the case of concomitant pregnancy. The local ethical committee approved our study (2017-00716).

2.2. Right Heart Catheterisation

The RHC exam was performed in a supine position with continuous monitoring of the electrocardiogram and arterial oxygen saturation using pulse oximetry (SpO_2). The mean systemic arterial pressure was measured at the brachial artery with an automatic inflating cuff. The modified Seldinger technique was used for venous catheterisation of the

femoral, basilic, or cephalic vein with a 7F Terumo Glidesheath Slender radial introducer sheath (Terumo, Tokio, Japan), which has an outer diameter of a 6F sheath. The Swan Ganz catheter (7F) allowed the resting haemodynamic evaluation and included mPAP, PAWP, and CO_{TD}. The mid-thoracic line was used for the zero-level reference.

PVR, cardiac index (CI), and stroke volume (SV) were calculated with the respective formulae: PVR = (mPAP − PAWP)/CO_{TD}; CI = CO/(body surface area); and SV = CO/(heart rate).

CO Determined by TD

TD was performed with 10 mL of iced, cold, sterile isotonic glucosaline solution injected in the proximal catheter's lumen. The temperature change was recorded at the distal end of the probe with a thermistor. Measurements were performed in triplicate, and the mean value was recorded if the difference between the highest and lowest value was ≤10%. Otherwise, two more measurements were performed with the deletion of the highest and lowest values. The mean of three remaining values was then calculated.

2.3. CO Determined by MRI

The MRI was acquired on a clinical Siemens 1.5 T AERA and 3 T PRISMA FIT (Siemens, Erlangen, Germany) and analysed using SyngoVia software from Siemens (Siemens, Erlangen, Germany). The CO_{MRI} measurements were made with flow velocity analysis in (1) AAO, (2) PA, (3) RPA + LPA, and (4) descending aorta (DAO) + superior vena cava (SVC), and the volumetric measurements were performed during the systole and diastole of (5) RV and (6) LV. The SV was then derived from the CO measurement (SV = CO/heart rate). The averaged heart rate was measured from the electrocardiogram (Siemens, Erlangen, Germany) used for the synchronisation of the MRI acquisitions. In the absence of a shunt or valvular leak, all of the 6 SV_{MRI} estimations should reflect the same value. The images were acquired for the flow analysis using phase-contrast 2D FLASH with the image plane perpendicular to the flow direction, a slice thickness of 6 mm, and a 1.5–2 mm in-plane resolution according to the patient size, with a typical velocity encoding 250 cm/s for the aorta, 150 cm/s for the pulmonary arteries, and 120 cm/s for the superior vena cava (which was increased in the case of aliasing). The TR/TE was 28–37/2.5 ms; the flip angle was 20; the bandwidth was 450 Hz; and there were 2–3 signal averages according to the breathing pattern. For the volumetric analysis, a 2D true-FISP cine sequence was used with the following typical parameters: retrospective ECG gating, a resolution of 1.5 mm × 1.5 mm, a slice thickness of 8 mm, GRAPPA acceleration factor 3, TE of 1.3 ms, TR of 24 ms, flip angle of 30, with the left and right 2-chamber, 4-chamber, and contiguous short axes covering the whole heart.

Two different experienced investigators estimated CO_{MRI}. They were unaware of the CO_{TD} measurements when analysing the MRI data.

2.4. Statistics

The statistical analysis was conducted with SPSS (version 21, IBM, Armonk, New York). The data are given in mean +/− standard deviation (SD) unless otherwise stated. Statistical significance was defined as $p < 0.05$. Linear correlations were determined using linear regression with slope and intercept (y = ax + b), and the coefficient of correlation (r) was calculated. Bland and Altman (BA) analysis was used to determine bias (mean difference of SV), limits of agreement (LoA), and percentage error (PE) when comparing SV_{MRI} against SV_{TD} and the 6 SV_{MRI} against each other. The LoA were calculated as bias +/−2SD of bias. PE for SV was calculated as (2SD of bias/mean SV) × 100. We used the predetermined 2SD of bias of 17.9 mL/beat and a PE of 30% to accept interchangeability between the two methods of SV determination [20]. The cut-off of 17.9 mL/beat was calculated from the proposed predetermined CO 2SD of bias of 1.25 L/min (1250 mL/min) and a mean heart rate in the cohort of 70 beats/min [20].

The 6 estimations of SV_{MRI} were compared to SV_{TD} and against each other. The SV_{MRI} agreement between the methods comprised 15 pairs of measurements (the 6 methods

compared against one another). SV was used for the comparison between different methods because SV is more stable than CO when two methods are not performed exactly at the same time due to possible variation of the HR [19]. Indeed, while HR variations will influence CO, SV is more stable in PAH even with exercise [21].

The results of the heart rate of the different tests (RHC and MRI) were compared using Student's *t* test.

Inter- and intra-observer reproducibility was assessed using intraclass correlation (ICC) for the MRI CO measurements using flow assessment (AAO, DAO + SVC, RPA + LPA, and PA) in 10 randomly selected patients. For inter-observer ICC, the measurements were made independently by two different investigators (L.C. and A-L.H.). For intra-observer ICC, the same investigator (L.C.) made the measurements separated by a period of two months.

3. Results

3.1. Patients

A total of 41 patients met the inclusion criteria. A total of 17 patients were excluded, mainly due to excessive delays between RHC and MRI (n = 12). The flow chart is given in Figure 1. A total of 24 patients were included for the analysis, including 9 males and 15 females aged 60 ± 14 years at time of MRI (range 20–79 years). A total of 12 patients had PH during RHC (group 1, n = 4; group 4 (CTEPH), n = 7; group 2, n = 1). A total of 12 patients had no PH during RHC (no PH, n = 3; treated CTEPH, n = 5, including four patients after pulmonary endarterectomy and one patient after balloon pulmonary angioplasty; chronic thrombo-embolic pulmonary disease (CTEPD), n = 2; and treated group 1 PAH, n = 2). The time between RHC and MRI was 6 ± 6 days (range 0–21). The patients' details are given in Table 1.

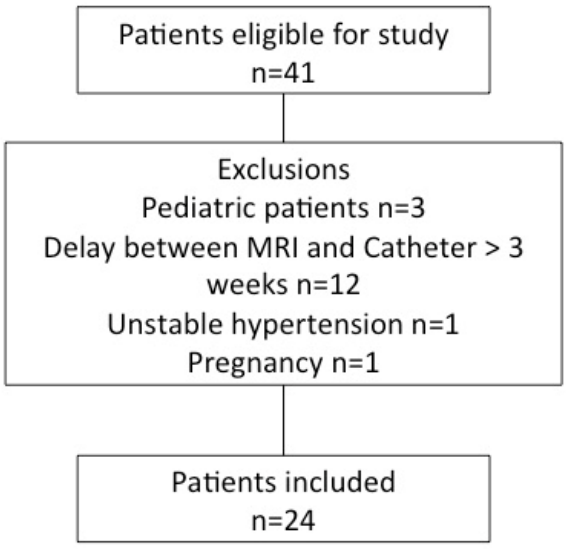

Figure 1. Flow chart.

Flow chart of the patients. Patients who were followed up in our PH centre who benefited from both right heart catheterisation and cardiac magnetic resonance were screened for inclusion. After exclusion of patients not fulfilling the predetermined criteria, we included 24 patients in the final analysis. MRI = magnetic resonance imaging.

Table 1. Patient characteristics.

Parameter	Value
Total patients	$n = 24$
Male:Female	9:15
Age at MRI	60 ± 14
Interval between MRI and RHC	5.8 ± 5.6
mPAP (mmHg)	29 ± 15
mPAP < 25 mmHg (no PH)	$n = 12$
mPAP $\geq$ 25 mmHg (with PH)	$n = 12$
CI (TD) (L min^{-1} m^{-2})	2.5 ± 0.7
PVR (WU)	5.3 ± 4.1
TAPSE (mm)	19 ± 4
HR (MRI) (beats/min)	73 ± 13
HR (RHC) (beats/min)	70 ± 9
PH group 1	$n = 4$
PH group 4	$n = 7$
Other	$n = 1$

Data are in mean $\pm$ SD unless otherwise stated. CI: cardiac index; HR: heart rate; mPAP: mean pulmonary arterial pressure; PH: pulmonary hypertension; PVR: pulmonary vascular resistance; TAPSE: tricuspid annular plan systolic excursion.

3.2. CO Measurement Using MRI

Figure 2 shows the placement of images for the major vessels and the resulting phase-contrast flow image, followed by the calculated flow curve.

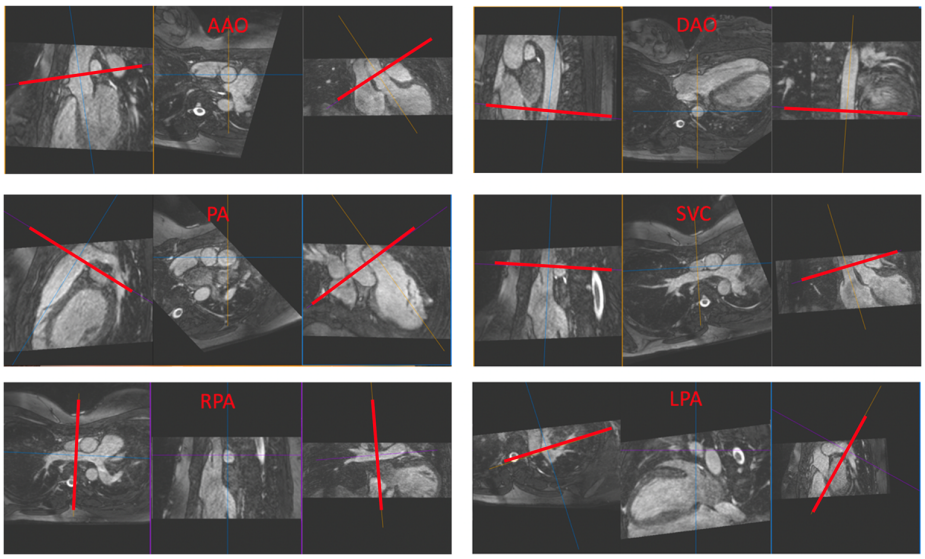

Figure 2. *Cont.*

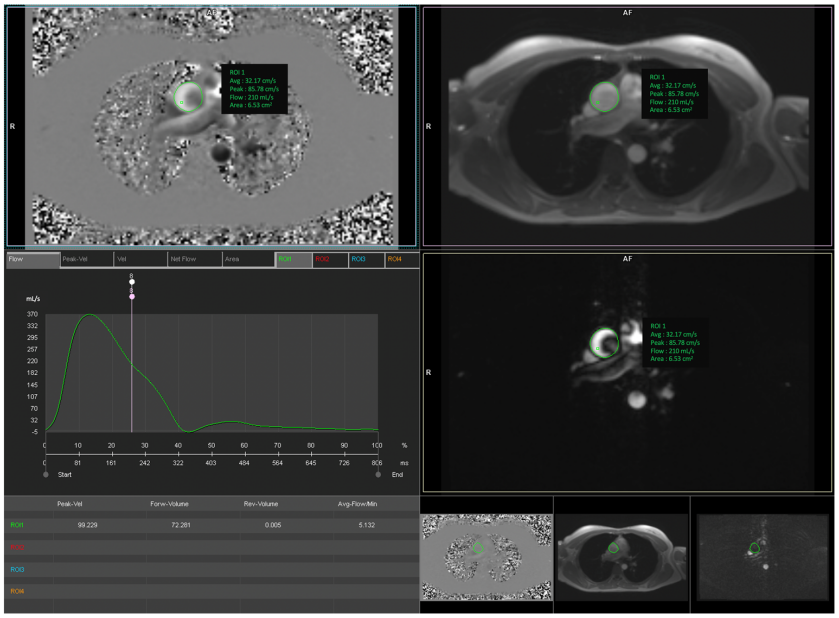

Figure 2. Placement of images for the major vessels, the resulting phase-contrast flow image, and the calculated flow curve. The green circle is placed in the AAO in this figure. Flow quantification using Syngovia was semi-automated. AAO: ascending aorta, DAO: descending aorta, LPA: left pulmonary artery, PA: pulmonary artery, RPA: right pulmonary artery, SVC: superior vena cava.

Inter- and intra-observer reproducibility (single-measure ICC) for all MRI flow quantification ranged from 0.826 to 0.983 and 0.866 to 0.999, respectively, as shown in Table 2.

Table 2. Inter- and intra-observer ICC.

ICC	AAO	DAO	SVC	PA	LPA	RPA
Inter	0.981	0.983	0.826	0.926	0.889	0.901
Intra	0.995	0.991	0.995	0.998	0.996	0.999

AAO: ascending aorta, DAO: descending aorta, ICC: intraclass correlation; inter: inter-observer; intra: intra-observer LPA: left pulmonary artery, PA: pulmonary artery, RPA: right pulmonary artery, SVC: superior vena cava.

3.3. Comparison between MRI and TD

The mean heart rate did not differ between the RHC and MRI as confirmed by the paired *t*-test with $p = 0.4$.

Table 3 summarizes the mean and SD values for all the parameters. Overall, the mean SV was 70 mL (SD = 20).

Table 3. Mean and standard deviation values for CO and SV.

	CO L/min	SV mL/Beat
TD	4.7 ± 1.0	67 ± 16
LV	5.1 ± 1.1	71 ± 19
RV	5.1 ± 1.2	73 ± 21
AAO	4.9 ± 1.2	70 ± 20
PA	5.5 ± 1.4	76 ± 23
RPA + LPA	5.1 ± 1.1	71 ± 20
DAO + SVC	4.8 ± 1.2	69 ± 21

Data are in mean ± SD. AAO: ascending aorta, CO: cardiac output, DAO: descending aorta, LV: left ventricle, LPA: left pulmonary artery, PA: pulmonary artery, RV: right ventricle, TD: thermodilution; RPA: right pulmonary artery, SV: stroke volume, SVC: superior vena cava.

Figure 3 shows the BA analyses of the six SV_{MRI} methods against SV_{TD}. Table 4 summarises the BA analyses of the six SV_{MRI} against SV_{TD} as well as the coefficient of correlation and linear regression. The 2SD of bias ranged from 24.1 to 31.1 mL/beat, and the bias ranged from −2.9 to −11.3 mL/beat. PE ranged from 34.9% to 42.8%.

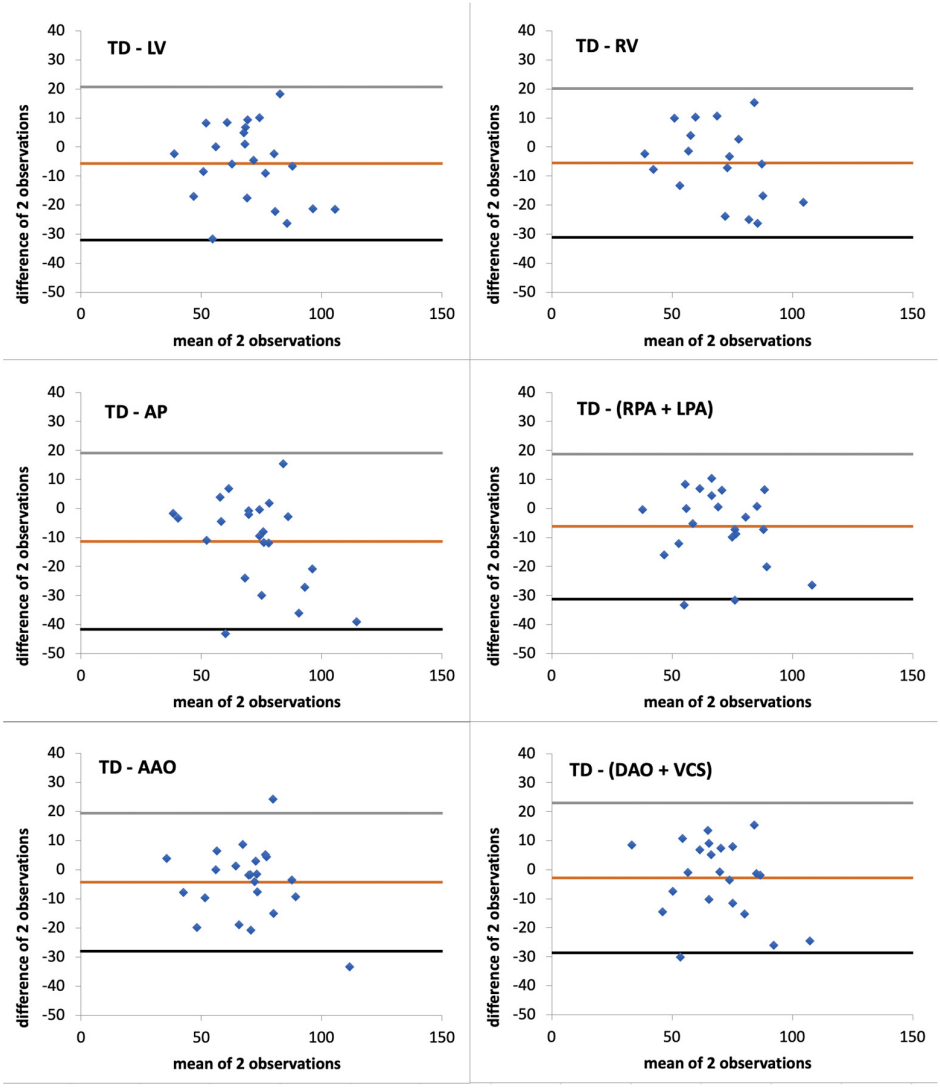

Figure 3. Bland and Altman analyses of SV_{MRI} against SV_{TD}. LoA are in grey and black. Bias is in orange. Results are in stroke volume (mL/beat). AAO: ascending aorta, DAO: descending aorta, LV: left ventricle, LPA: left pulmonary artery, PA: pulmonary artery, RV: right ventricle, RPA: right pulmonary artery, TD: thermodilution, SVC: superior vena cava.

Table 4. Comparison between the six different SV_{MRI} methods against SV_{TD}.

	Bland and Altman Analysis			Linear Regression with Coefficient of Correlation (r), Slope (a), and Intercept (b) with SV_{MRI} on the y-Axis and Axis SV_{TD} on the x-Axis		
Compared SV_{MRI} Method	**Bias, mL/Beat**	**2SD of Bias, mL/Beat**	**PE (%)**	**r**	**a**	**b mL/Beat**
LV	−5.6	±26.9	38.5	0.80	0.93	11.8
RV	−5.5	±26.2	37.5	0.87	0.91	9.7

Table 4. *Cont.*

	Bland and Altman Analysis			Linear Regression with Coefficient of Correlation (r), Slope (a), and Intercept (b) with SV_{MRI} on the y-Axis and Axis SV_{TD} on the x-Axis		
Compared SV_{MRI} Method	**Bias, mL/Beat**	**2SD of Bias, mL/Beat**	**PE (%)**	**r**	**a**	**b mL/Beat**
AAO	−4.3	±24.1	34.9	0.65	0.91	17.3
PA	−11.3	±31.1	42.8	0.65	0.82	16.9
RPA + LPA	−6.2	±25.4	36.3	0.66	0.33	18.3
DAO + SVC	−2.9	±26.3	38.2	0.61	0.85	14.3

AAO: ascending aorta, CO: cardiac output, DAO: descending aorta, LV: left ventricle, LPA: left pulmonary artery, MRI: magnetic resonance imaging, PA: pulmonary artery, PE: percentage error, RV: right ventricle, RPA: right pulmonary artery, SD: standard deviation, SV: stroke volume, SVC: superior vena cava, thermodilution: TD.

3.4. Comparison between Different MRI Methods

Figure 4 shows the Bland and Altman analysis of $SV_{(RPA+LPA)}$ compared with (1) SV_{AAO} and (2) $SV_{(DAO+SVC)}$ showing narrow LoA and a small bias. $SV_{(RPA+LPA)}$ compared with $SV_{(DAO+SVC)}$ yielded the best agreement, with a bias of 4.1 mL/beat, a 2SD of bias of 13.8 mL/beat, and a PE of 19.7%. The agreement between $SV_{(RPA+LPA)}$ compared with SV_{AAO} was also very good, with a bias of −2.1 mL/beat, a 2SD of bias of 17.9 mL/beat, and a PE of 25.5%. Table 5 summarises the Bland and Altman analysis of the comparisons between the six different MRI methods, as well as the coefficient of correlation and linear regression. The bias ranged from −6.8 to +8.6 mL/beat; the 2SD of bias ranged from 13.8 to 29.1 mL/beat; and the PE ranged from 19.7% to 39.4%.

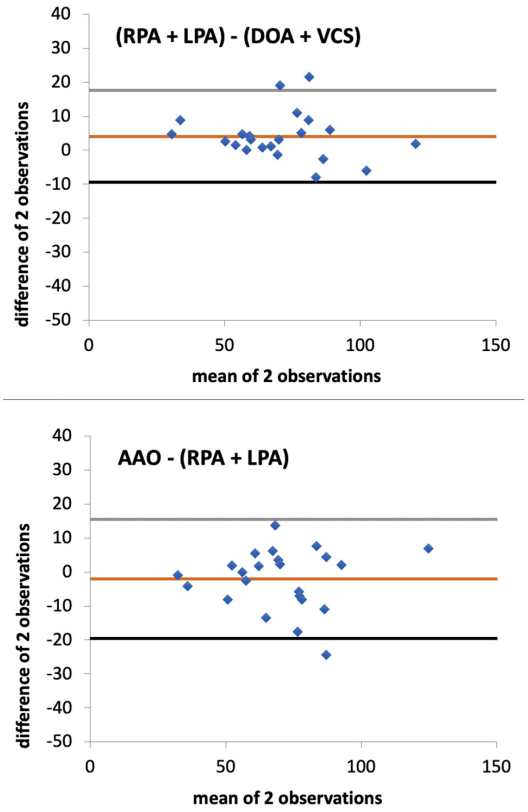

Figure 4. Bland and Altman analyses of $SV_{(RPA+LPA)}$ against $SV_{(DOA+VCS)}$ and SV_{AAO}. LoA are in grey and black. Bias is in orange. Results are in stroke volume (mL/beat). AAO: ascending aorta, DAO: descending aorta, LPA: left pulmonary artery, RPA: right pulmonary artery, SVC: superior vena cava.

Table 5. Fifteen paired comparisons of the six different MRI methods.

	Bland and Altman Analysis			Linear Regression with Coefficient of Correlation (r), Slope (a), and Intercept (b) with the First Method on the y-Axis and the Second Method on the x-Axis		
Compared SV_{MRI} (First Method/ Second Method)	**Bias, mL/Beat**	**2SD of Bias, mL/Beat**	**PE (%)**	**r**	**a**	**b, mL/Beat**
RV/PA	−6.4	±23.7	31.3	0.89	0.83	7.8
RV/(RPA + LPA)	−3.1	±18.3	**25.2**	0.91	0.91	4.9
RV/AAO	0.5	±21.6	**29.9**	0.88	0.91	7.7
LV/PA	−5.1	±29.1	39.4	0.85	0.78	12.8
LV/(RPA + LPA)	−0.9	±24.8	34.9	0.88	0.86	10.1
LV/AAO	1.7	±21.8	31.0	0.90	0.88	10.9
AAO/(DAO + SVC)	1.7	±19.4	**27.9**	0.94	0.86	10.3
PA/(DAO + VCS)	8.6	±18.3	**25.1**	0.93	0.91	13.6
(RPA + LPA)/(DAO + VCS)	4.1	±**13.8**	**19.7**	0.97	0.89	11.0
PA/(RPA + LPA)	5.0	± 19.8	**26.8**	0.93	0.99	4.8
PA/AAO	−6.8	±18.7	**25.6**	0.93	0.99	6.9
(RPA + LPA) /AAO	−2.1	±**17.9**	**25.5**	0.94	0.94	6.3
LV/RV	−0.5	±**17.1**	**23.7**	0.91	0.99	1.5
LV/(DAO + VCS)	3.5	±23.8	33.9	0.83	0.89	4.3
RV/(DAO + VCS)	2.0	±18.4	**25.1**	0.90	0.92	3.6

Bold values meet the predetermined interchangeability criteria either for PE or for 2 SD of bias. Methods in bold are meeting both interchangeability criteria. AAO: ascending aorta, DAO: descending aorta, LV: left ventricle, LPA: left pulmonary artery, MRI: magnetic resonance imaging, PA: pulmonary artery, PE: percentage error, RV: right ventricle, RPA: right pulmonary artery, SD: standard deviation, stroke volume: SV, SVC: superior vena cava.

4. Discussion

In this study, we showed that (1) SV_{MRI} was not interchangeable with SV_{TD} using predetermined criteria; (2) $SV_{(RPA+LPA)}$ yielded the best agreement with the other SV_{MRI} methods including the already validated SV_{AAO} method; and (3) the agreement between the different SV_{MRI} methods was globally better than when SV_{MRI} was compared against SV_{TD}.

4.1. Regarding the Statistical Analysis

BA graphs are the analysis of choice when two methods measuring the same variable are compared. They provide information on the degree of agreement between the compared methods [22]. For proper BA analysis, a specific cut-off for the acceptance of the interchangeability of two methods is mandatory, otherwise this choice is left to the subjectivity of the authors [22]. In the field of anaesthesiology and intensive care medicine, a 2SD of bias of 1 L/min or a PE of 20% when comparing a new CO estimation method to the gold standard (DF), or an LoA of 1.25 L/min or PE of 30% when comparing a new method to a reference method (TD) that is not the gold standard, have been suggested [20,23]. The use of a wider LoA and PE when comparing a new method to a reference method (TD) are suggested because the LoA and PE are the results of the intrinsic imprecision of both methods with a reference method that is supposed to be less precise than the gold standard [20]. By precision, we refer to how close the values of repeated measurements are [20]. The predetermined cut-off should be determined based on the clinical purpose of

CO measurement, which will influence the degree of precision needed. In the field of PH, a cut-off has never been proposed [13]. In this context, we admitted it was reasonable to rely on an existing cut-off (1.25 L/min, with a derived cut-off for SV of 17.9 mL/beat) even though it might not be the ideal cut-off for the clinical context studied.

4.2. Regarding Interchangeability between MRI and TD

None of the six SV_{MRI} reached the predetermined interchangeability criteria when compared against SV_{TD}. Therefore, in our population, SV_{MRI} cannot be considered interchangeable with the reference SV_{TD} method. This is concordant with previous results in the field showing a wide range of the 2SD of bias (ranging from 1.9 L/min to 2.4 L/min) and PE when comparing MRI with TD [24–27]. As aforementioned, the LoA and PE are the results of the imprecision of the two studied methods. The LoA and PE were globally smaller when compared between different MRI measurement methods than when we compared MRI with TD. This raises the question of whether the actual reference method (TD) could be the cause of the observed lack of agreement. TD is a reference method based on an analysis of 35 PcPH patients in 1999, which showed good agreement between TD and DF with a 2SD of bias of 1.1 L/min [3]. However, recent published data have shown that the agreement between DF and TD is probably lower than previously thought, with a wide range of PE (42% and 44.6%) and LoA (2SD of bias of 2.48 L/min), leading to misclassification in the prognosis assessment of patients with PAH and misclassification of exercise PH [28–30]. In this context, it is likely that TD might be the cause of the lack of agreement when we compared TD with MRI. This would also explain the constant lack of agreement between CO_{MRI} and CO_{TD} in other studies in this field, while a good agreement between SV_{AAO} and SV_{RV} was demonstrated against the gold standard SV_{DF} [19,24–27]. In our study, the delay between MRI and TD could also contribute to lower the observed agreement between MRI and TD due to change in the haemodynamic condition of the patients. The exclusion of patients with conditions that could lead to rapid change in haemodynamic (e.g., pregnancy and clinical deterioration between RHC and MRI) probably lowered this potential effect. Since we obtained similar results to those of previous studies in the field, we do not think that the delay made a significant change in the observed agreement.

4.3. Regarding the Comparison between Different MRI Methods

We provided an assessment of six different types of SV_{MRI} data, including measurements of flow in localisations such as (LPA + RPA) and (SVC + DOA) that have never been tested in this population thus far. COs and COp were both measured in three localisations i.e., (AAO, DAO + SVC, and LV) and (RV, PA, and RPA + LPA). All of these CO estimates and SV derivates should be equal in the absence of a significant shunt.

One issue related to MRI in the evaluation of PH is the lack of a method to evaluate the COp. Indeed, SV_{RV} and SV_{PA} lacked agreement with the gold standard DF [19]. SV_{RV} could be less precise in PH patients due to (1) tricuspid insufficiency, (2) large trabeculations in the RV, and (3) the complicated anatomy of the RV with difficult delimitation of the inner border of the cavity. SV_{PA} imprecision could be due to (1) the presence of a vortex and non-laminar flow in dilated PA with an irregular border and (2) pulmonary regurgitation.

COp could be a valuable measurement, especially for PH populations, because it could allow the measurement of shunts between the pulmonary and systemic circulation. Congenital heart disease, including shunts, are one of the most common causes of PAH in the adult population [1]. The measurement of COp in patients with shunts could also allow the calculation of the correct PVR, which is necessary for diagnosis and treatment decisions in some of these patients, including discussion about the shunt's closure. For PVR calculation, mPAP and PAWP measurements are necessary. MRI can provide an estimation of mPAP and PAWP, even though the methods used require further validation [31]. Furthermore, a new method to determine COp is greatly needed because the TD and Fick methods are known to lack precision, especially in the case of shunts and extreme CO [32].

In our study, we found that SV_{PA} yielded poor results, which is consistent with previous publications and is probably caused by the reasons explained above [19]. SV_{RV} yielded results similar to those of other methods of SV determination and was not worse than SV_{AAO} or SV_{LV} for SV estimation, as had been previously shown [19]. This could be explained by the mildly elevated mPAP in our cohort that is associated with a low degree of tricuspid regurgitation. Anatomical determination of the RV's contour is also becoming easier with the improvements in MRI techniques and analysis software. Tricuspid regurgitation might be the main mechanism leading the lack of agreement of the method. Indeed, the volume moving forward through the pulmonary valve or returning back through the tricuspid valve cannot be differentiated. This is of interest as SV_{RV} could be a method used to calculate the severity of tricuspid regurgitation by comparing the SV calculated with SV_{RV} and the true SV (i.e., through the pulmonary artery) estimated with another method such as $SV_{(RPA+LPA)}$.

As shown in Table 5 and Figure 4, $SV_{(RPA+LPA)}$ was the only surrogate of COp that reached the two prespecified interchangeability criteria with two SV surrogates of COs (SV_{AAO} and $SV_{(DOA+SVC)}$). The agreement between $SV_{(RPA+LPA)}$ and $SV_{(DOA+SVC)}$ even reached the more restrictive agreement necessary for the acceptance of a new method with a gold standard method (2SD of bias for SV $\leq$ 14.3 and PE $\leq$ 20%). In this context, $SV_{(RPA+LPA)}$ may be the most promising method for SV determination in patients with PH. In comparison to SV_{PA}, it might be less influenced by (1) vortexes, which mainly appear in the main PA; (2) main PA dilatation with possible issues in contour determination; and (3) pulmonary regurgitation. Indeed, the main PA acts as a blood reservoir during the diastolic time, and the pulmonary regurgitation would probably be of lesser impact if the measurement is made distally to the main PA. Even though this seems the most promising method for SV measurement, this needs to be prospectively validated against the gold standard DF and in patients with significant haemodynamic PH severity.

The main limitations of our study include the small number of subjects, the mildly elevated mean mPAP, the retrospective analysis, the delay between MRI and RHC, and the absence of a direct comparison to a gold standard DF. However, TD is widely used, and thus our data may be considered a comparison with a real-life setting. The strengths of our study are related to the rigorous methodology with a predetermined cut-off for the 2SD of bias, which is unfortunately rarely used in this field, and the use of new localisations for flow determination in PH, with the measurement in RPA + LPA for the pulmonary circulation and DAO + SVC for the systemic circulation.

5. Conclusions

We could not demonstrate the interchangeability of SV_{MRI} and SV_{TD}, but this is probably due to an overestimation of TD precision in PH. Estimation of COp with $SV_{(RPA+LPA)}$ was shown to agree more closely to methods of COs estimation than the previously described methods for COp determination in this population (SV_{RV} and SV_{PA}). $SV_{(RPA+LPA)}$ may be the best non-invasive MRI method to determine COp in precapillary PH.

Author Contributions: L.A.C. extracted the data, participated in the CO_{MRI} measurements, performed the statistical analysis, and participated in the writing of the manuscript. L.G. analysed the data and drafted the manuscript. A.-L.H. participated in the CO_{MRI} measurements. S.N. participated in the CO_{TD} measurements. M.B. participated in the analysis of the data and reviewed the manuscript. J.-P.V. and F.L. supervised the plan of the study and the analysis of the data, and participated in the writing of the manuscript. All the authors read and brought significant intellectual contributions to the final manuscript and fulfilled the ICMJE criteria for authorship. All authors have read and agreed to the published version of the manuscript.

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Correlation between Pulmonary Artery Pressure and Vortex Duration Determined by 4D Flow MRI in Main Pulmonary Artery in Patients with Suspicion of Chronic Thromboembolic Pulmonary Hypertension (CTEPH)

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Abstract: Chronic thromboembolic pulmonary hypertension (CTEPH) is one of the causes of pulmonary hypertension (PH) and requires invasive measurement of the mean pulmonary artery pressure (mPAP) during right heart catheterisation (RHC) for the diagnosis. 4D flow MRI could provide non-invasive parameters to estimate the mPAP. Twenty-five patients with suspected CTEPH underwent cardiac MRI. Mean vortex duration (%), pulmonary distensibility, right ventricular volumes and function were measured using 4D flow MRI and cine sequences, and compared with the mPAP measured by RHC. The mPAP measured during RHC was 33 ± 16 mmHg (10–66 mmHg). PH (defined as mPAP > 20 mmHg) was present in 19 of 25 patients (76%). A vortical flow was observed in all but two patients (92%) on 4D flow images, and vortex duration showed good correlation with the mPAP (r = 0.805; $p < 0.0001$). Youden index analysis showed that a vortex duration of 8.6% of the cardiac cycle provided a 95% sensitivity and an 83% specificity to detect PH. Reliability for the measurement of vortex duration was excellent for both intra-observer ICC = 0.823 and inter-observer ICC = 0.788. Vortex duration could be a useful parameter to non-invasively estimate mPAP in patients with suspected CTEPH.

Keywords: cardiac MRI; 4D flow MRI; pulmonary hypertension; vortical flow; vortex duration; chronic thromboembolic disease; right heart catheterisation

1. Introduction

Pulmonary hypertension (PH) is a haemodynamic condition defined as a resting mean pulmonary artery pressure (mPAP) above 20 mmHg, as measured by right heart catheterisation (RHC) which is the gold standard for pressure measurement [1]. PH can arise from multiple conditions, including pulmonary and left heart diseases. More rarely, it may be due to a proliferative disease involving pulmonary vessels (pulmonary arterial

hypertension, PAH) or to chronic thromboembolic pulmonary hypertension (CTEPH) [2]. CTEPH can lead to right ventricular failure and is associated with a poor prognosis if not treated [3]. Therefore, the early detection of this pathology is a major challenge in order to set up an early treatment and improve patient survival, in particular before right ventricular dysfunction occurs [4]. Non-invasive imaging may play an important role to meet this challenge [5]. Transthoracic echocardiography is currently the most commonly used screening technique to determine PH probability [6]. RHC remains the gold standard for measuring the mean pulmonary artery pressure (mPAP). Other non-invasive techniques as alternatives to echocardiography could be useful for the diagnostic work up of PH. Several authors have already assessed the ability of cardiac MRI to detect PH and to quantify it, based on the right ventricular function and mass, the curvature of the interventricular septum [7], the flow rate across the pulmonary artery [8], the wall shear stress [9,10] and the presence of vortices in the pulmonary artery using 4D flow MRI [11–13]. In addition, it has been reported that the duration of the vortices in the pulmonary artery was related to the mPAP and could be used to detect and quantify PH [14–18], in patients with different causes of PH.

In this study, we hypothesised that abnormalities of duration of vortical flow in the main pulmonary artery should be encountered on 4D flow MRI in a specific population of patients with suspected CTEPH, and could be a marker of PH. We therefore evaluated the changes in pulmonary flow on MRI in a population of patients with suspected CTEPH, and compared our results with other MRI parameters as well as with the values measured by RHC.

2. Materials and Methods

2.1. Study Population

All consecutive patients with suspected CTEPH and evaluated by both cardiac MRI and RHC at our institution over a period of 3 years were considered for inclusion in this retrospective study. The suspicion of CTEPH was based on the presence of suggestive symptoms and pulmonary perfusion anomalies as assessed by at least ventilation/perfusion scintigraphy and CT angiography as recommended [19]. Criteria of exclusion were: no patient agreement for the use of the data (n = 5), incomplete MR investigation (n = 8) and a delay > 6 months between cardiac MRI and RHC (n = 2). In total, 25 patients were included (Figure 1).

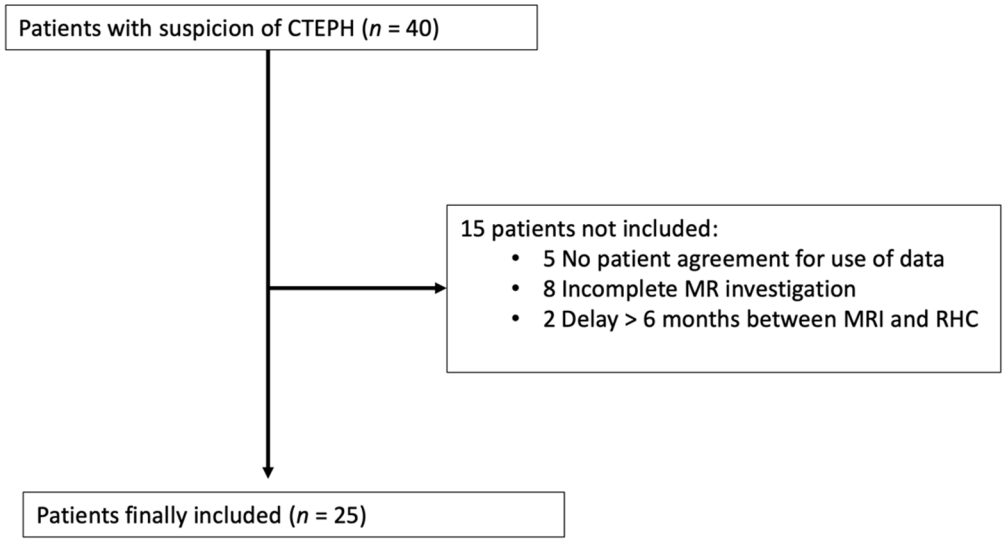


Figure 1. Flow chart of the study.

2.2. Cardiac MRI

All studies took place using a 3T system (PrismaFit; Siemens Healthcare; Germany). The imaging protocol included cine MR balanced Steady State Free Precession (bSSFP) sequences acquired in the long axis planes of the right ventricle (1 horizontal long axis (HLA) and 1 vertical long axis (VLA)) and contiguous sections acquired in the short axis plane for evaluation of right ventricular function. Following parameters were used for the acquisition: temporal resolution = 20 or 40 ms according to the cardiac rhythm of the patient; TE = 1.5 ms; pixel size = 2 mm × 2 mm × 8 mm, 25 reconstructed cardiac phases, flip angle = 30°. A 2D phase contrast flow sequence was acquired on the pulmonary artery (single slice) with the following parameters: temporal resolution = 28 ms; TE = 2.5 ms; pixel size = 2 × 2 × 6 mm; flip angle = 20°; velocity encoding (venc) = 150 cm/s. Lastly, a prototype 4D phase contrast flow sequence (Work In Progress number: 785) was acquired in the oblique sagittal orientation after contrast medium injection (0.2 mmol/kg of Dotarem; Guerbet; France) with the following parameters: prospective cardiac gating; 60 slices, temporal resolution of 20–40 ms (depending on patient physiology), 24 ± 5 cardiac phases, pixel size = 2 × 2 × 2 mm, 3 directions of flow quantification, venc = 150 cm/s. Flow images were acquired during free breathing using a liver dome respiratory navigator; mean duration of the sequence was 16 ± 7 min.

2.3. Right Heart Catheterisation (RHC)

The RHC exam was performed in a supine position with continuous monitoring of the electrocardiogram and arterial oxygen saturation using pulse oximetry (SpO2). The modified Seldinger technique was used for venous catheterisation of the femoral (7F Terumo introducer, Tokyo, Japan), basilic or cephalic vein (7F Terumo Glidesheath Slender radial introducer sheath, which has an outer diameter of a 6F sheath.) The Swan Ganz catheter (7F) allowed the resting haemodynamic evaluation with measurements of mPAP, pulmonary capillary wedge pressure (PCWP) and cardiac output (CO) as determined by thermodilution (TD). Left heart catheterisation with measurement of left ventricular end diastolic pressure (LVEDP), systemic arterial pressure was also routinely performed. The coronary arteries were injected only if clinically indicated. The mid-thoracic line was used for the zero-level reference. Pulmonary vascular resistance (PVR) and cardiac index (CI) were calculated with the respective formulae: PVR = (mPAP − PCWP)/CO or (mPAP − LVEDP)/CO if LVEDP was measured; CI = cardiac output/body surface area. TD was performed with 10 mL of iced, cold, sterile isotonic glucosaline solution injected in the proximal catheter's lumen. The temperature change was recorded at the distal end of the probe with a thermistor. Measurements were performed in triplicate, and the mean value was recorded if the difference between the highest and lowest value was ≤10%. Otherwise, 2 more measurements were performed after exclusion of the highest and lowest values. The mean of those three remaining values was then calculated.

2.4. Image Analysis

Cine sequences were analysed with a dedicated software (CVI; circle) and following MRI parameters were recorded: right ventricular end diastolic volume (RV EDV; mL/m^2), right ventricular end systolic volume (RV ESV; mL/m^2), right ventricular ejection fraction (RVEF; %) and right ventricular cardiac index (RV cardiac index; L/min/m^2).

The mean diameter of the pulmonary artery (mm) as calculated from maximal and minimum diameters on diastolic phase was recorded. Diastolic and systolic pulmonary artery cross-section area (mm^2) was measured on the 2D flow sequence, the pulmonary artery distensibility, defined as the variation of surface between diastolic and systolic phase (%) was calculated, and the peak velocity in the pulmonary artery.

For 4D flow image analysis, streamlines in the pulmonary artery were automatically reconstructed using a dedicated prototype software (4D flow, Siemens Healthcare; Germany). A background phase correction was used to reconstruct the images. One operator (LC), blinded to clinical information, performed a visual analysis of all images. They considered that the vortex was present in the pulmonary artery with the appearance of a

circular formation, whose axis of rotation is perpendicular to the axis of the vessel. The end of the vortex was defined as the last image showing this structure in the artery. The presence of a vortical blood flow was noted and its relative duration with respect to the whole cardiac cycle (%) was calculated. A vortical blood flow was defined as a closed concentric ring-shaped flow with the vortical blood flow's axis of rotation being perpendicular to the pulmonary artery (PA) on visual analysis, as previously reported [16]. A second visual analysis of 4D flow images was performed 3 months later in a blinded fashion by the same operator in order to assess the intra-observer reproducibility. A second operator (ALH) performed a visual analysis of 4D flow images of all patients in a blinded fashion in order to calculate inter-observer reproducibility.

2.5. Statistical Analysis

Data are presented as mean ± SD, or median (interquartile range) depending on data distribution, or percentage. Differences between continuous data were tested with the Mann–Whitney rank-sum test for two-group comparisons. Pearson correlation coefficients (r) were calculated to assess the correlation between continuous variables. Simple regression analysis test was performed between mPAP measurements by RHC and MRI-derived vortex duration for patients with a mPAP > 20 mm Hg. Comparison between mPAP values measured by RHC and those calculated from the vortex duration by the regression equation was performed by Bland–Altman analysis. A multiple regression analysis was performed between mPAP values, vortex duration and MRI parameters that were non-significantly correlated with vortex duration. Receiver operating characteristic (ROC) analysis was applied to MR calculated parameters to assess the performance of each parameter to detect patient with PH. In order to facilitate comparison with studies that used a 25 mmHg cut-off to define PH, two different cut-offs were tested to define PH (>20 mmHg and ≥ 25 mmHg). The DeLong test was carried out to compare the ROC curves. A Youden index was used to evaluate the sensibility and specificity of different thresholds of vortex duration for the diagnosis of PH. Inter- and intra-observer intraclass correlation coefficient (ICC) were calculated for all subjects to evaluate the reproducibility of measurement of vortex duration [20]. A p value < 0.05 was considered as significant. Analyses were performed with the SPSS software (version 20.0, IBM SPSS Statistics; Chicago, IL, USA).

3. Results

3.1. Population Characteristics

Twenty-five patients with suspected CTEPH were included. The mean age was 63 ± 16 years and 10 patients were male (42%). Patient characteristics, including the results of RHC, are reported in Table 1. Mean mPAP was 33 ± 16 mmHg (10–66 mmHg) on RHC. PH was present in 19 of 25 patients (76%) for a threshold of 20 mmHg, as recently recommended [1], and in 16 patients (64%) if using a threshold of pulmonary pressure ≥ 25 mmHg [19]. A final diagnosis of CTEPH was retained in 19 patients. Among the remaining patients, 2 had a chronic thromboembolic disease without pulmonary hypertension, 2 had primary arterial hypertension (group 1), 1 had a PH related to left heart disease (group 2) and 1 patient had no PH and no definite diagnosis.

Table 1. Population characteristics.

A. Clinical Parameters	
Age, years	63 ± 16
Men, *n* (%)	10 (40)
Overweight, *n* (%)	5 (20)
HBP, *n* (%)	7 (28)
Diabetes, *n* (%)	4 (16)
WHO functional class, *n* (IQR)	2 (2–3)
B. Right Heart Catheterization	
Heart rythm, bpm	83 ± 13
Mean PAP, mm Hg	33 ± 15
PCWP, mm Hg	7.4 ± 3.9
LVEDP, mm Hg	10.2 ± 4.7
PVR, Wood unit	5.8 ± 3.9
Cardiac output, L/min	4.4 ± 1.2
Cardiac index, L/min/m^2	2.4 ± 0.8

HBP = high blood pressure, LVEDP = left ventricle end diastolic pressure, PCWP = pulmonary capillary wedge pressure, PVR = pulmonary vascular resistance.

3.2. Cardiac MRI Parameters

Mean delay between cardiac MRI and RHC was 39 ± 82 days. A vortex was observed in all but 2 patients (92%) on 4D flow images (Figure 2). Patients with PH (defined as a mPAP > 20 mmHg on RHC) exhibited significantly higher right ventricular end systolic volumes, mean PA diameters and vortex durations than patients without PH. If mPAP ≥ 25 mmHg was used as a threshold to define PH, as recommended before 2019 [19], the same significant differences with the addition of right ventricular end diastolic volume and distensibility were noticed between patients with and without PH. All data are reported in Tables 2 and 3.

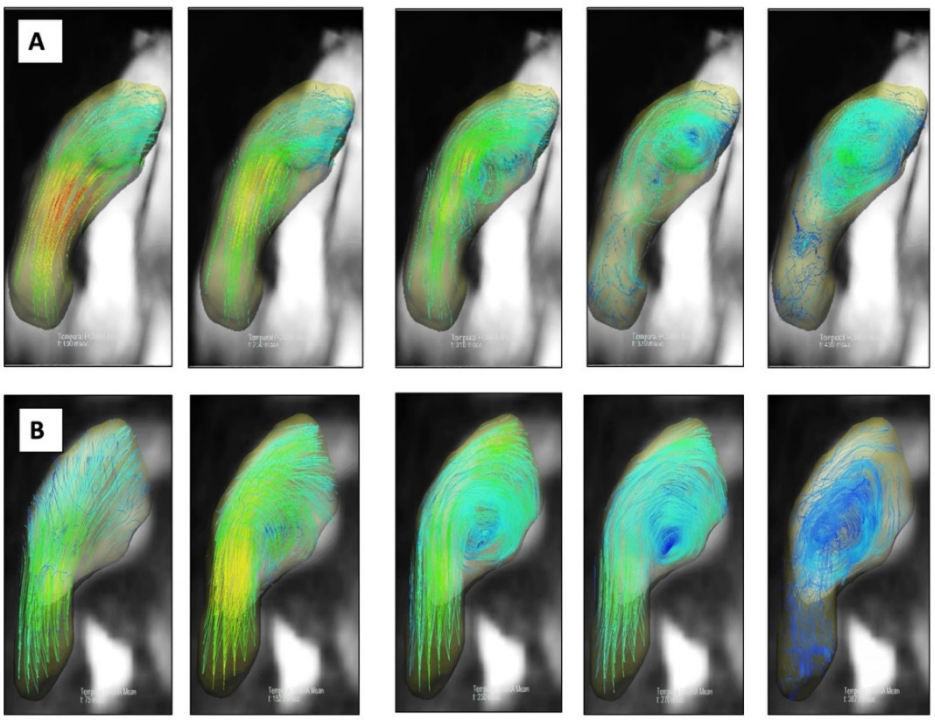


Figure 2. Examples of two patients with CTEPH, PH and vortical flow on 4D flow MR images. Patient 1 ((**A**) first image row) exhibited a vortical flow within pulmonary artery, detected during 60%

of the cardiac cycle. Mean PAP was 46 mmHg by RHC. Patient 2 ((**B**) second image row) exhibited a vortical flow within pulmonary artery, detected during 32% of the cardiac cycle. Mean PAP was 26 mmHg by RHC.

Table 2. Cardiac MRI parameters in the overall population and between patients with and without pulmonary hypertension on RHC (defined as a mean pulmonary pressure > 20 mmHg).

	All (*n* = 25)	PH (*n* = 19)	No PH (*n* = 6)	*p*
Mean heart rate, bpm	79 ± 17	82 ± 18	72 ± 8	0.08
RV EDV, ml/m²	95 ± 43	101 ± 48	75 ± 14	0.1
RV EDS, ml/m²	52 ± 35	58 ± 38	34 ± 10	0.02
RV EF, %	48 ± 12	46 ± 13	55 ± 6	0.2
RV cardiac index, L/min/m²	2.9 ± 0.2	3.0 ± 0.9	2.5 ± 0.6	0.2
Mean PA diameter, mm	32 ± 6	33 ± 7	29 ± 2	0.01
PA distensibility, %	8.6 ± 6.6	7.3 ± 5.3	12.9 ± 9.1	0.07
Mean peak velocity in PA, cm/s	63 ± 20	61 ± 23	70 ± 7	0.1
Vortex duration, %	23 ± 16	27 ± 14	8.3 ± 13	0.007

EDV = end diastolic volume; EF = ejection fraction; ESV = end systolic volume; PA = pulmonary artery; PH = pulmonary hypertension; RV = right ventricle.

Table 3. Cardiac MRI parameters in the overall population and between patients with and without pulmonary hypertension on RHC (defined as a mean pulmonary pressure ≥ 25 mmHg.)

	All (*n* = 25)	PH (*n* = 16)	No PH (*n* = 9)	*p*
Mean heart rate, bpm	79 ± 17	84 ± 19	73 ± 6	0.07
RV EDV, ml/m²	95 ± 43	107 ± 50	73 ± 16	0.03
RV EDS, ml/m²	52 ± 35	63 ± 40	33 ± 11	0.004
RV EF, %	48 ± 12	44 ± 13	56 ± 7	0.03
RV cardiac index, L/min/m²	2.9 ± 0.2	3.0 ± 0.9	2.7 ± 0.6	0.6
Mean PA diameter, mm	32 ± 6	35 ± 4	28 ± 7	0.008
PA distensibility, %	8.6 ± 6.6	6.6 ± 5.3	12.2 ± 7.5	0.02
Mean peak velocity in PA, cm/s	63 ± 20	61 ± 24	63 ± 20	0.2
Vortex duration, %	23 ± 16	30 ± 13	9 ± 11	0.001

EDV = end diastolic volume; EF = ejection fraction; ESV = end systolic volume; PA = pulmonary artery; PH = pulmonary hypertension; RV = right ventricle.

3.3. Receiver Operating Characteristic Curve Analysis

To evaluate the performance of cardiac MRI in detecting PH, patients were subdivided in a positive group (with PH) and a negative group (without PH). The highest areas under the curve (AUC) for participants with PH as opposed to participants without PH were obtained for vortex duration measured with MRI with AUCs of 0.860 [95% CI: 0.637, 1] and 0.896 [95% CI: 0.597, 1] for a PH definition threshold of >20 mmHg and ≥25 mmHg, respectively. Right ventricular volumes; RVEF, RV cardiac index, mean diameter of PA and pulmonary distensibility showed lower AUCs but no significant differences ($p > 0.1$) were noted between AUCs (Tables 4 and 5, and Figure 3). Youden index showed that a vortex duration of 8.6% of cardiac cycle provided a 95% sensitivity and an 83% specificity to detect PH (defined as a pulmonary pressure >20 mmHg). If a cut-off of ≥25 mmHg was used to define PH, the vortex duration increased to 10.0% of cardiac cycle, providing a 100% sensitivity and a 78% specificity to detect PH.

Table 4. Receiver operating characteristic curve analysis of MR parameters to detect pulmonary hypertension (mean pulmonary pressure > 20 mmHg on RHC).

	AUC	95% CI	95% CI
RV EDV (mL/m²)	0.715	0.509	0.921
RV ESV (mL/m²)	0.803	0.619	0.988
RV EF (%)	0.697	0.495	0.900
RV cardiac index (L/min/m²)	0.680	0.455	0.905
Mean diameter of PA (mm)	0.842	0.687	0.998
PA distensibility (%)	0.754	0.563	0.946
Vortex duration	0.860	0.637	1

AUC = area under curve; RV = right ventricle; EF = ejection fraction; EDS = end diastolic volume; ESV = end systolic volume; PA = pulmonary artery.

Table 5. Receiver operating characteristic curve analysis of MR parameters to detect pulmonary hypertension (defined a mean PAP ≥ 25 mmHg).

	AUC	95% CI	95% CI
RV EDV (mL/m²)	0.767	0.582	0.952
RV ESV (mL/m²)	0.844	0.690	0.998
RV EF (%)	0.760	0.571	0.995
RV cardiac index (L/min/m²)	0.563	0.331	0.794
Mean diameter of PA (mm)	0.819	0.643	0.996
PA distensibility (%)	0.785	0.403	0.972
Vortex duration	0.896	0.597	1

AUC = area under curve; RV = right ventricle; EF = ejection fraction; EDS = end diastolic volume; ESV = end systolic volume; PA = pulmonary artery.

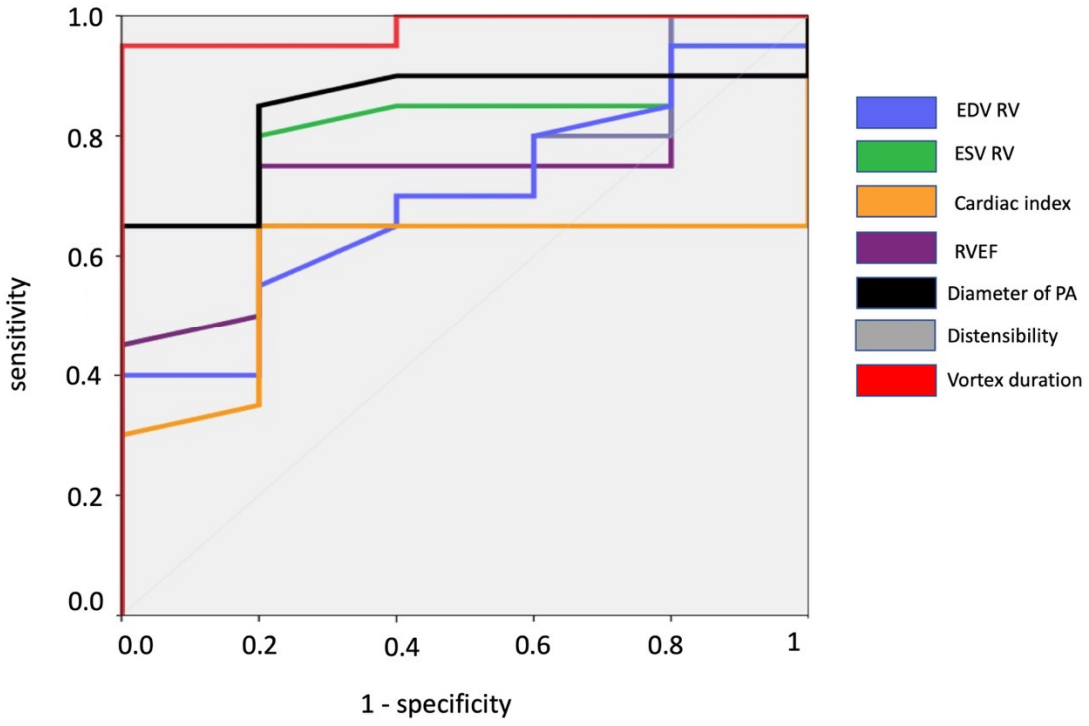
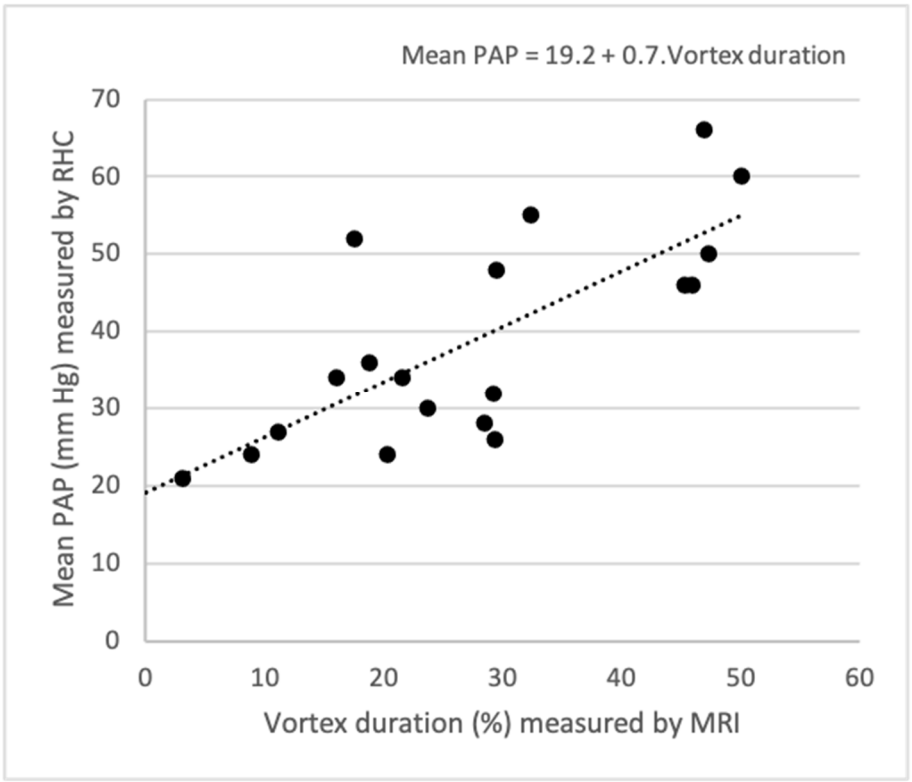


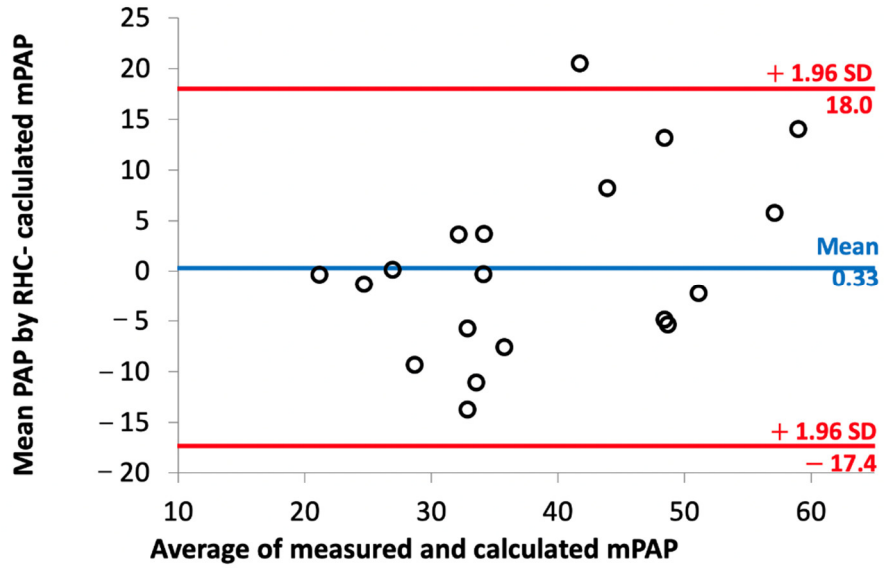
Figure 3. ROC curves analysis to detect PH in patients. The cut-off for definition of PH was 20 mmHg.

3.4. Relationships between Vortex Duration, mPAP and Other RHC and MRI Parameters

In patients with pulmonary hypertension defined as mPAP > 20 mmHg (n = 19), vortex duration showed good correlation with the mPAP (r = 0.745; p < 0.0001) (Figure 4A). Linear regression analysis between vortex duration and mPAP revealed that the corresponding linear regression equation was mPAP (mmHg) = 19.2 + 0.7 × vortex duration (%). The comparison of the mPAP as measured by RHC and as calculated resulted in a nonsignificant bias of 0.18 mmHg. The SD of differences was 9.4 mmHg, and 95% limits of agreement were 18.0 and −17.4 mmHg (Figure 4B).



(A)



(B)

Figure 4. (**A**) Correlation and linear regression line between vortex duration (%) measured by MRI and mPAP (mmHg) measured by RHC. (**B**) Bland–Altman plot of mPAP measured by RHC and

calculated by the regression equation mPAP (mmHg) =19.2 + 0.7 × vortex duration (%), with 95% limits of agreement.

A weaker correlation between mean vortex duration and other RHC and MR parameters was also observed: PVR (r = 0.518; $p = 0.002$), PCWP (r = 0.556; $p = 0.007$), RV EDV (r = 0.467; $p = 0.02$), RV ESV (r = 0.551; $p = 0.004$), RVEF (r = −0.610; $p = 0.001$), mean diameter of PA (r = 0.470; $p = 0.02$) and PA distensibility (r = −0.360; $p = 0.04$).

Several MR parameters also displayed a correlation with the mPAP but in a lesser manner than vortex duration: RV ESV (r = 0.492; $p = 0.01$), RVEF (r = −0.695; $p < 0.001$), mean diameter of pulmonary artery (r = 0.485; $p = 0.01$) and pulmonary distensibility (r = −0.365; $p = 0.07$).

Multiple regression analysis showed that other MR parameters registered did not correlate independently with vortex duration and could not be associated with a multiparametric model to improve diagnosis performances.

3.5. Reproducibility

Reliability for the measurements of the vortex duration was found to be excellent with intra-observer ICC = 0.823 (95% confidence interval:0.754–0.952) and inter-observer ICC = 0.788 (95% confidence interval:0.733–0.942).

4. Discussion

In this study, we report that patients with PH showed a vortical flow within PA on 4D MRI and that the vortex duration correlated with the mPAP as measured during RHC, suggesting that the mPAP could be non-invasively estimated by cardiac MRI. Our results confirm the potential of measuring vortex durations in patients with suspected PH in comparison to invasive measurements through RHC.

The vortex duration method was first introduced by Reiter et al. who went from using a single slice with 3D velocity encoding initially [16], in order to harvest signal-to-noise-ratio by using the in-flow effect. A 4D-flow approach was used more recently by this author [17,18] and several other groups [10,15], but this technique is not currently used in clinical practice. This present work is therefore important to further validate and promote such an approach. Having an automatic measurement of the vortex duration, as recently proposed [21,22], could also facilitate the development of this technique in clinical routine.

Recently, other approaches have been tested to assess PH from 4D-MRI. These schemes are looking for a relationship between PH and abnormalities on 4D flow images, but used more complex quantitative parameters (like vorticity or helicity) instead of visual analysis of vortex duration [8,23,24], making their use in clinical routine more difficult. These more complex approaches remain to be compared with the visual assessment of vortex duration in terms of accuracy and clinical feasibility. Interestingly, despite a visual analysis to measure vortex duration, which may reduce reproducibility, we reported a good inter-observer and intra-observer ICC.

The correlation between vortex duration and mPAP which we report was not as high as reported in two different series of patients with PH (defined as pulmonary pressure ≥ 25 mmHg), with correlation coefficients of 0.94 (AUC = 1) and 0.95 (AUC = 0.994) [16,17]. The potential explanations mainly include the different patient population and the timing between RHC and MRI. Indeed, most of our patients had a PH attributable to CTEPH unlike several studies in which this pathology was not the primary cause of PH [10,17,25]. Kamada et al. published a study including only patients with CTEPH and reported the interest of 4D flow MRI in such patients before and after treatment [8] but visual analysis of vortex duration was not performed, precluding direct comparison with our results.

The study of the ROC curves shows a higher AUC for the duration of the vortex. The lack of statistical difference with the other parameters is probably due to the relatively small number of patients. Interestingly our cut-off value for vortex duration to detect a PH with mPAP ≥ 25 mmHg was 10% of the cardiac cycle (sensitivity 100%, specificity

78%), in the same range (14.3%) as previously reported [17]. This value dropped to 8.6% using the newly suggested threshold of mPAP > 20 mmHg to diagnose PH [1], with values of sensitivity and specificity remaining high (95% and 83%, respectively). These values seemed to be at least equivalent or even superior to transthoracic echocardiography. A meta-analysis of the performance of transthoracic echocardiography showed a sensitivity of 88% and a specificity of 56% for the diagnosis of PH using the estimation of the velocity of tricuspid flow regurgitation [26]. However, the evaluation of the velocity of tricuspid flow regurgitation was not possible in 54 to 90% of the patients depending on the aetiology of PH and the morphology of the patients (e.g., especially obese patients) [26]. MRI could therefore be a valuable non-invasive tool for the screening of PH, especially in situations where transthoracic echocardiography is not able to estimate systolic PAP. Transthoracic echocardiography currently remains the best screening and follow-up tool for PH patients [27].

Several explanations have been advanced to explain the formation of vortices in PH, including reduction of arterial compliance and wall shear stress, increased PVR and endothelial cell dysfunction [28,29]. These abnormalities affect the laminar flow pattern of the PA causing turbulence and the eventual vortex. We report here a significant correlation between vortex duration, pulmonary distensibility and PVR that are consistent with these hypotheses. Similarly, Kheyfets et al. reported a significant correlation between vorticity in the main PA and PVR and proposed a multivariate linear regression model based on MRI parameters to estimate PVR [23]. Computational fluid dynamics has also suggested that a change from narrow to wider vessels (i.e., PA dilatation) could cause a vortex [30]. This could also explain the moderate correlation of mPAP and vortex duration with PA diameter which we observed. In addition, it has been reported that vortices can also be encountered in a low percentage (3%) of subjects without history of PH [31]. The relationship between right ventricular dysfunction and vortex duration in our study was also found by Odagiri et al. [10], and probably reflects the consequences of PH on the right ventricle. We did not notice significant differences between patients with and without PH regarding cardiac index, possibly because pulmonary dilatation in patients with PH could act as an adaptive phenomenon in order to maintain pulmonary flow, as reported in animals [10,28].

Our study has some limitations. First, the scan time for the 4D Flow sequence was relatively long. However, acceleration techniques, such as compressed sensing are emerging and will allow such sequences to fit more easily into the clinical routine [32,33]. Second, the encoding velocity used for the 4D flow (150 cm/s) was significantly higher than the average speed of the patients (63 cm/s), which may have led to poorer visualisation of vortices. As vortices have a large range of velocities, multi-venc acquisition techniques in combination with acceleration techniques may be of interest for the proposed application [34]. Lastly, RHC and cardiac MRI were not performed on the same day in most of the patients, and it is possible that variations of mPAP could have occurred between the two examinations.

In conclusion, our results show a relationship between vortex duration in the pulmonary artery and pulmonary arterial pressure, suggesting that this non-invasive parameter could be used to estimate pulmonary arterial pressure.

Author Contributions: L.A.C. and A.-L.H. extracted the data and participated in the MRI measurements. J.-F.D. performed the statistical analysis, and participated in the writing of the manuscript. L.G. analysed the data and drafted the manuscript. J.-F.D., J.N. and D.G. implemented the acquisition and reconstruction methods. S.N. participated in the COTD measurements. M.B., S.N. and C.G.G. participated in the analysis of the data and reviewed the manuscript. J.-P.V. and F.L. supervised the plan of the study and the analysis of the data, and participated in the writing of the manuscript. All the authors read and brought significant intellectual contributions to the final manuscript and fulfilled the ICMJE criteria for authorship. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: The study complies with the guidelines for human studies and was conducted ethically in accordance with the World Medical Association's Declaration of Helsinki. The local ethical committee (Swiss ethics) approved our study (2017-00716).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The datasets used during the current study are available from the corresponding author on reasonable request.

Conflicts of Interest: The authors declare that they have no conflict of interest. Jin Ning and Daniel Griese, employed by the Siemens Healthcare company, declare that they have no conflict of interest regarding the publication of the article entitled Correlation between pulmonary artery pressure and vortex duration determined by 4D flow MRI in main pulmonary artery in patients with suspicion of Chronic Thromboembolic Pulmonary Hypertension (CTEPH).

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The Influence of Methods for Cardiac Output Determination on the Diagnosis of Precapillary Pulmonary Hypertension: A Mathematical Model

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Abstract: Background: precapillary pulmonary hypertension (PH, PcPH) is now defined as a mean pulmonary artery pressure (mPAP) > 20 mmHg, a pulmonary artery wedge pressure (PAWP) ≤ 15 mmHg and a pulmonary vascular resistance (PVR) > 2 WU. For PVR calculation, the measurement of cardiac output (CO) is necessary. It is generally measured using thermodilution. However, recent data showed that the agreement with direct Fick method, historically the gold standard, is less than previously reported. We aimed to create a mathematical model that calculated the probability of being classified differently (PcPH or unclassified PH) if CO measured by direct Fick was used instead of thermodilution for any individual patients with a mPAP > 20 mmHg and a PAWP ≤ 15 mmHg. Methods: The model is based on Bland and Altman analysis with a normally distributed difference of cardiac output, fixed 1.96 standard deviation of bias, bias and physiological cardiac output limits. Results: Following a literature review of the studies comparing CO measured with direct Fick and thermodilution, we fixed the 1.96 standard deviation of bias at 2 L/min, bias at 0 L/min and physiological resting CO limits between 1.3 L/min and 10.2 L/min. Conclusions: This model can help the clinician to evaluate the potential benefit of measuring CO using direct Fick during the diagnostic work-up and its utility in confirming or ruling out a diagnosis of PcPH in any given patient with a mPAP > 20 mmHg and a PAWP ≤ 15 mmHg.

Keywords: pulmonary hypertension; cardiac output; thermodilution; direct Fick; mathematical model

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1. Introduction

Pulmonary hypertension (PH) is now defined as a rise of mean pulmonary artery pressure (mPAP) > 20 mmHg measured during right heart catheterisation (RHC) [1]. The addition of a pulmonary vascular resistance (PVR) > 2 WU and a pulmonary artery wedge pressure (PAWP) ≤ 15 mmHg defines all types of precapillary pulmonary hypertension (PcPH) [1]. The PVR is useful to differentiate between an increase in mPAP caused by a high cardiac output (CO) or a high PAWP and pulmonary vascular disease with increased PVR leading to an increase in mPAP for a given PAWP and CO. PVR is calculated by dividing

the difference between the mPAP and the PAWP by the CO (PVR = (mPAP − PAWP)/CO). Precise measurements of mPAP, PAWP and CO are thus essential for PVR calculation.

The gold standard for estimating CO is the direct Fick (DF) method. CO measured using DF (CO_{DF}) is calculated by dividing the oxygen consumption ($V'O_2$) by the difference between the arterial oxygen content (CaO_2) and mixed venous oxygen content ($Cv'O_2$) ($CO_{DF} = V'O_2/(CaO_2 - Cv'O_2)$). While CO_{DF} is acknowledged to be the most accurate and precise method to determine CO, its measurement is cumbersome due to the measurement of $V'O_2$ during RHC and the necessity of arterial and mixed venous blood drawl and analysis, which challenges repetitive assessment in transient haemodynamic situations such as during exercise.

CO measurement using thermodilution (TD, CO_{TD}) widely replaced CO_{DF} in the field of PH based on the results of one study comparing CO_{TD} against CO_{DF} and demonstrating acceptable agreement between the two methods in 35 PcPH patients [2]. Recent studies, however, did not confirm the previous results and demonstrated a poorer agreement between CO_{TD} and CO_{DF} using Bland and Altman (BA) analysis for patients with PcPH [3,4], or with a suspicion of PH [5].

As PVR calculation is dependent on the estimation of CO, a difference in estimated CO values using the different methods could result in a different diagnosis and classification of PH. Indeed, according to the currently proposed haemodynamic definition of PH, a patient with a mPAP > 20 mmHg, a PAWP $\leq$ 15 mmHg and PVR of >2 WU is classified as having PcPH, while a patient with a mPAP > 20 mmHg, a PAWP $\leq$ 15 mmHg but a PVR of $\leq$2 WU is classified as having unclassified PH [1].

The influence of using CO_{TD} value instead of CO_{DF} on the diagnosis of PcPH is unknown. Thus, we aimed to create a mathematical model which estimates the probability of a patient with a mPAP > 20 mmHg and a PAWP $\leq$ 15 mmHg being classified differently (PcPH or unclassified PH) if CO_{DF} was used instead of CO_{TD}.

2. Materials and Methods

2.1. Study Population

This study is based on a mathematical model and a literature review of previous published studies comparing the agreement between CO_{DF} and CO_{TD} in PcPH patients.

2.2. Mathematical Model

In order to create this mathematical model, it was necessary to estimate the agreement between CO_{TD} and CO_{DF} using BA statistics. A BA graph is one statistical method used for evaluating two methods comparing the same variable [6]. The BA graph plots the differences of the variable measured using the two different methods against their mean. This graph mainly shows the mean difference between the two methods (i.e., bias) and the 1.96 standard deviation (SD) of the bias also called the "limits of agreement" (LoA), which contains 95% of the differences when the distribution of the differences follows a normal distribution. The 1.96 SD of bias estimates the agreement between the two methods: the bigger the 1.96 SD of bias, the poorer the agreement between the two methods. When two methods comparing the same variable are evaluated, the differences between their measurements often follow a normal distribution [6]. This occurs as, by comparing a variable obtained in a same person, the individual variation is eliminated and the comparison of the two methods depends mainly on measurement errors [6].

This mathematical model is based on the following elements: a normal distribution of the CO differences as well as fixed bias, 1.96SD of bias and physiological CO limits at rest.

The creation of this model followed a three-step approach. Firstly, a literature review of studies comparing CO_{TD} and CO_{DF} in PcPH was performed to evaluate the most appropriate bias, 1.96 SD of bias, physiological CO limits at rest and to confirm that the CO differences between CO_{TD} and CO_{DF} probably follows a normal distribution in this population. Second, we created two sets of fictive CO values, with their differences following a normal distribution based on the most probable bias, 1.96 SD of bias and

physiological CO limits at rest in PcPH. Lastly, we created the model allowing an assessment of the probability for any individual to have a different diagnosis using CO_{TD} or CO_{DF}.

2.2.1. Comparison between CO_{TD} and CO_{DF} at Rest in PcPH Patients

We updated our recent literature review concerning the methods of cardiac output measurement in PcPH patients but with a focus only on CO_{TD} and CO_{DF} [7]. We included articles published until May 2022. The following filters were applied to PubMed: ("thermodilution" OR "Direct Fick") AND "pulmonary hypertension" and the following filter on web of science: Set 1: TI = (Pulmonary Hypertension), set 2: TI = ((thermodilution) OR (direct Fick)). We then associated "Set 1 AND Set 2". The PubMed search yielded 146 articles. 132 articles were excluded after reading the abstract or based on their titles. 14 were selected for full text reading. Of those 14, 8 studies did not compare TD and DF and 3 studies used TD and DF but did not assess the agreement between these methods [8–10]. These articles were subsequently excluded. Three articles comparing CO_{TD} and CO_{DF} in PcPH using BA analysis were finally included and are summarised in Table 1 [2–4].

2.2.2. Creation of a Set of Data with a Normal Distribution of CO Differences within a Plausible CO Range

We assumed that the difference between CO_{DF} and CO_{TD} followed the normal distribution of:

$$CO_{TD} - CO_{DF} = X \sim N(\mu, \sigma) \quad (1)$$

On the BA graph, μ corresponds to the bias and σ corresponds to the SD of the CO differences. For a random variable X following a normal distribution $N(\mu,\sigma)$, X will lie in the interval $[\mu - 1.96\ \sigma, \mu + 1.96\ \sigma]$ with a probability of 95% [6]. By fixing the 1.96 SD of the bias, the SD could be calculated.

A large amount of random data was then generated following a normal distribution of CO differences on a BA graph using Python (version 3.10.4) with fixed bias, 1.96 SD of CO differences and limits of physiological CO at rest. The normal distribution of the generated data was then verified using a histogram.

2.2.3. Diagnostic Disagreement Calculation with Limits of Plausible CO Values

A model was then created to calculate the individual probability of being classified differently (PcPH or unclassified PH) if CO_{DF} was used instead of CO_{TD} based on the patient's haemodynamic characteristics (mPAP, PAWP and CO_{TD}).

We defined diagnostic disagreement (DgDis) as the probability for a given patient to be misdiagnosed using the method CO_{TD} compared to the method CO_{DF}. There are two possible scenarios. Either a diagnosis of PcPH would be made using CO_{TD} but not using CO_{DF}, or a diagnosis of PcPH would be made using CO_{DF} but not using CO_{TD}. The first scenario was defined as DgDis+, meaning a false positive diagnosis and the second scenario as DgDis−, which corresponded to a false negative diagnosis.

We required both CO_{TD} and CO_{DF} to be in a defined interval [a, b] and the difference between CO_{TD} and CO_{DF} to follow a normal distribution. In this context, the mean value of CO_{TD} and CO_{DF} (i.e., $(CO_{TD} + CO_{DF})/2$) obligatory lies in the same interval [a, b] as both individual CO measurements (CO_{TD} and CO_{DF}).

To implement computation with these conditions, we used conditional probabilities. For two events A and B, the probability of A conditioned to B is the probability that the event A happens, knowing that the event B has already occurred. This is defined through the formula:

$$P(A \mid B) = P(A \cap B)/P(B) \quad (2)$$

In our case, we knew that CO_{DF} lies within the defined interval of physiological CO [a, b], (event "B"). Event "A" is the probability that a DgDis exists, meaning that the use of CO_{DF} leads to another diagnosis than the use of CO_{TD}.

Thus, we needed to compute $P(A \cap B)$ and $P(B)$, which are given by the following steps.

If the difference between CO_{TD} and CO_{DF} follows a normal distribution:

$$CO_{TD} - CO_{DF} = X \sim N(\mu,\sigma), \quad (3)$$

$$\text{then } CO_{DF} = CO_{TD} - X \quad (4)$$

The event B corresponds to CO_{DF} lying in [a, b], this means that $CO_{TD} - X \geq a$ and $CO_{TD} - X \leq b$, which is equivalent to $X \leq CO_{TD} - a$ and $X \geq CO_{TD} - b$.

Thus, the following event B corresponds to the inequalities ($CO_{TD} - b \leq X \leq CO_{TD} - a$).

For a patient having PcPH defined by CO_{TD} measurement, the event DgDis+ corresponds to the transpulmonary gradient (TPG), which is the difference between mPAP and PAWP, divided by CO_{DF}, equal to or less than 2: $TPG/CO_{DF} \leq 2$. This corresponds to the absence of PcPH using CO_{DF}.

This is equivalent to $TPG/(CO_{TD} - X) \leq 2$. So DgDis+ corresponds to $CO_{TD} - TPG/2 \geq X$.

Analogous reasoning shows that DgDis− corresponds to $CO_{TD} - TPG/2 \leq X$.

In summary, the probability needed to compute the above conditional probabilities are given by:

$$P(\text{DgDis+} \cap B) = P(CO_{TD} - b \leq X \leq \min(CO_{TD} - TPG/2, CO_{TD} - a)) \quad (5)$$

$$P(\text{DgDis−} \cap B) = P(\max(CO_{TD} - TPG/2, CO_{TD} - b) \leq X \leq CO_{TD} - a) \quad (6)$$

$$P(B) = P(CO_{TD} - b \leq X \leq CO_{TD} - a), \quad (7)$$

where the TPG is equal to mPAP − PAWP.

3. Results

Table 1 summarises the studies comparing CO_{TD} and CO_{DF} in PcPH [2–4]. In total, 113 patients had pulmonary arterial hypertension (PAH) (group 1) patients and 21 patients had chronic thromboembolic PH (CTEPH). The bias varied between 0.01 and 0.45 L/min. The 1.96 SD of bias varied between 1.1 L/min and 2.48 L/min. The limits of mean resting CO extracted visually from the BA graph were between 1.6 L/min (lowest mean CO observed from Hoeper et al.) and 8.5 L/min (highest CO observed by Duknic et al.). None of the authors demonstrated a proportional bias (i.e., increasing or decreasing CO difference with CO mean). This supports the hypothesis of a normal distribution of the CO differences. Based on these results, we arbitrarily chose to construct our model with a bias of 0 L/min, 1.96 SD of 2 L/min and limits of physiological resting CO between 1.3 L/min and 10.2 L/min (observed mean CO limits with a subjective 20% safety margins).

Table 1. Studies comparing CO_{TD} and CO_{DF} in PcPH.

	Patients	mPAP	Mean CO_{DF}	Mean CO_{TD}	Bias	1.96 SD of Bias
Hoeper et al. [2]	35 (31 PAH, 4 CTEPH)	56 ± 12	3.7 ± 1.2	3.7 ± 1.3	0.01	1.10
Khirfan et al. * [4]	75 PAH patients	48 ± 14	4.6 ± 1.5	4.6 ± 1.6	0.02	2.02
Duknic et al. [3]	24 (7 PAH 17 CTEPH)	37 ± 11	5.9 ± 1.5	5.5 ± 1.2	0.45	2.48

* Data are given in cardiac index in the original article. CO data are given based on oral communication of the corresponding author Dr. Tonelli. CO_{TD}: Cardiac output measured using TD. CO_{DF}: Cardiac output measured using direct Fick; CTEPH: chronic thrombo-embolic pulmonary hypertension; mPAP: mean pulmonary artery pressure; PAH: pulmonary arterial hypertension; SD: standard deviation.

Figure 1 shows a BA graph of two randomly created CO sets with the differences of CO following a normal distribution. The data were randomly created using Python based on a bias of 0 L/min, 1.96 SD of 2 L/min and resting CO limits between 1.3 L/min and 10.2 L/min. The histogram showing the distribution of the CO differences exposed in Figure 1, confirms the normal distribution of the data as shown in Figure 2.

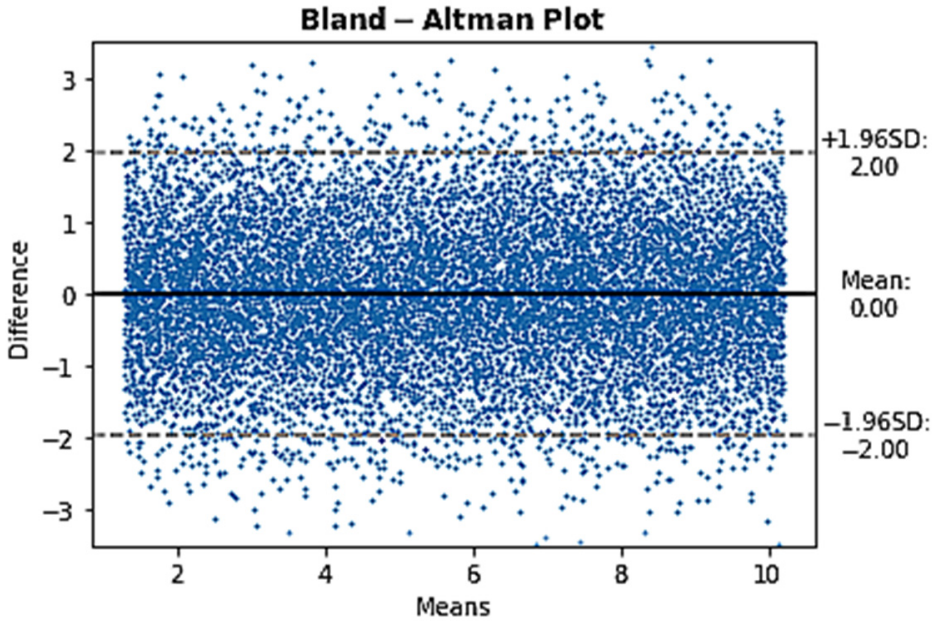

Figure 1. Bland and Altman graph showing a normal distribution of CO differences based on the model's characteristics with fictive data. Randomly generated data using Python following the model's characteristics (1.96 SD of 2 L/min, bias of 0 L/min and limits of CO of 1.3 and 10.2 L/min) and a normal distribution of CO differences. SD: standard deviation.

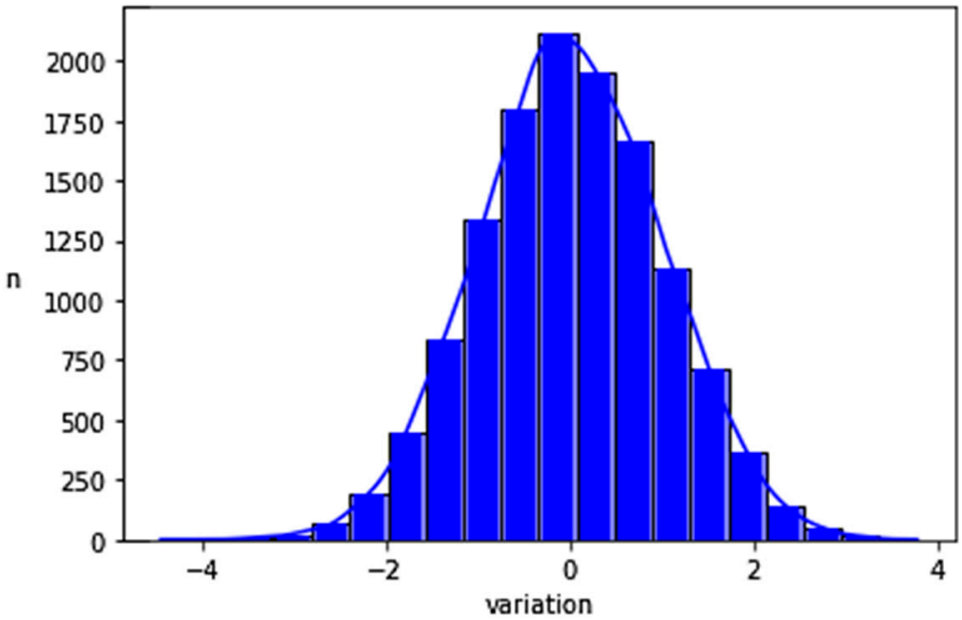

Figure 2. Histogram of the CO differences following a normal distribution.

Tables 2 and 3 give examples of fictitious patients with corresponding probabilities of DgDis− and DgDis+, respectively using the mathematical model. Figure 3 plots the TPG and the CO. The diagnosis cut-off isoPVR line (2 WU) and DgDis lines corresponding to a probability of 10% and 20% are pictured. The isoPVR lines of 1 WU and 3 WU are shown in Figure 4.

Table 2. Patients diagnosed with «unclassified PH» using TD and corresponding DgDis− probability.

TPG	CO_{TD}	PVR_{TD}	DgDis−
6	3.5	1.7	30.0%
7	4	1.75	29.4%
7	5	1.4	6.9%
8	5	1.6	16.2%
8	6	1.3	2.5%
9	5	1.8	31.1%
9	6	1.5	7.1%
10	6	1.7	15.4%
10	7	1.4	2.5%
11	6	1.8	31.2%
11	7	1.6	7.07%

DgDis− (diagnosis disagreement−) refers to the probability of being categorised as having PcPH using DF for a patient diagnosed with unclassified PH using TD (false negative). The TPG is equal to the difference between the mPAP and the PAWP. For example, a TPG of 11 corresponds to a mPAP of 21 and a PAWP of 10 or a mPAP of 22 and PAWP of 11. The percentage of DgDis− is higher when PVR is close to 2. In other words, the percentage of false negatives is much higher for the same TPG at lower CO_{TD} until it reaches a PVR of 2 WU. TPG: transpulmonary gradient; CO_{TD}: Cardiac output measured by thermodilution; mPAP: mean pulmonary arterial pressure; PAWP: pulmonary artery wedge pressure; PH: pulmonary hypertension; PVR_{TD}: pulmonary vascular resistance calculated using CO_{TD}.

Table 3. Examples of patients diagnosed with PcPH using TD and corresponding DgDis+ probability.

TPG	CO_{TD}	PVR_{TD}	DgDis+
6	2.5	2.4	45.4%
7	2.5	2.8	23.8%
7	3	2.3	37.3%
8	3	2.7	19.6%
8	3.5	2.3	33.6%
9	3	3	8.5%
9	4	2.3	32.0%
10	3	3.3	3.0%
10	4	2.5	16.8%
11	4	2.75	7.3%
11	5	2.2	31.3%

DgDis+ (diagnosis disagreement+) refers to the probability of being categorised as having unclassified PH using DF for a patient diagnosed with PcPH using TD (false positive). The TPG is equal to the difference between the mPAP and the PAWP. For example, a TPG of 11 corresponds to a mPAP of 21 mmHg and a PAWP of 10 mmHg or a mPAP of 22 mmHg and PAWP of 11 mmHg. The percentage of DgDis+ is higher when PVR is close to 2. In other words, the percentage of false positives is higher for the same TPG at higher CO_{TD} until it reaches a PVR of 2 WU. TPG: transpulmonary gradient; CO_{TD}: Cardiac output measured by thermodilution; mPAP: mean pulmonary arterial pressure; PAWP: pulmonary artery wedge pressure; PcPH: precapillary pulmonary hypertension; PVR: pulmonary vascular resistance.

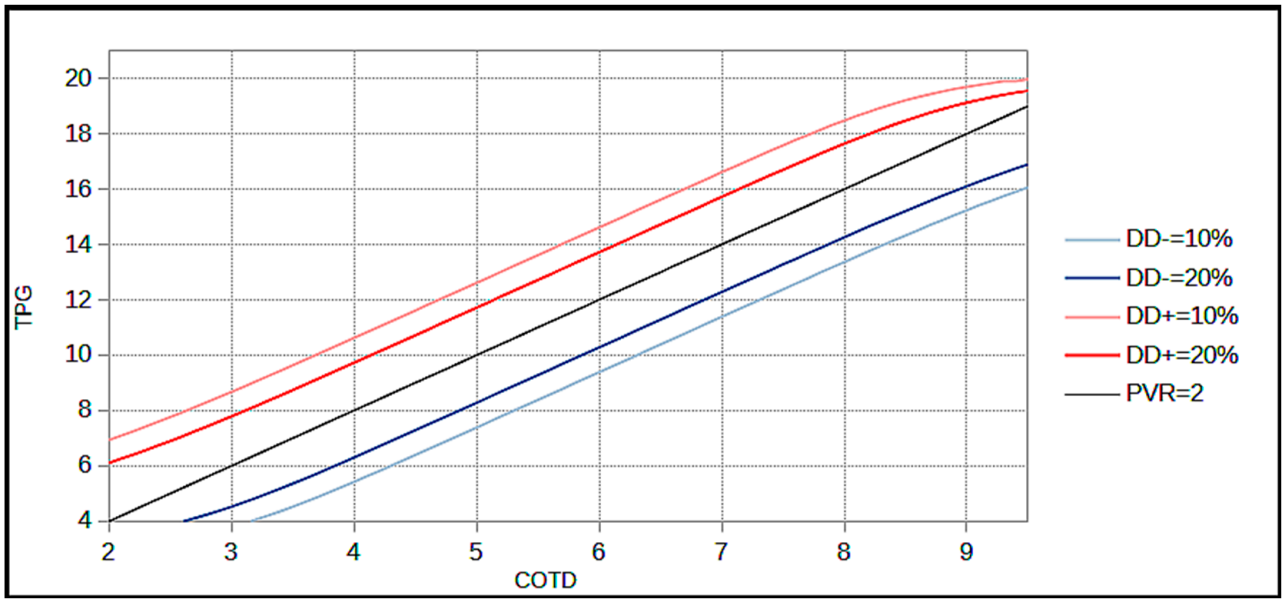

Figure 3. IsoDgDis (diagnosis disagreement) graph: IsoDgDis (DD) lines are represented on the TPG/CO_{TD} graph. The limits of the models are with physiological CO in between 1.3 L/min to 10.2 L/min, 1.96 SD of the bias of 2 L/min and bias of 0 L/min. The isoPVR line of 2 is the diagnosis line (patients above this line are diagnosed with precapillary PH and patients under this line are diagnosed with unclassified PH). COTD: Cardiac Output using Thermodilution; DgDis (DD): diagnosis disagreement (DgDis (DD)+ corresponds to false positive diagnosis using TD; DgDis (DD)− corresponds to false negative diagnosis using TD); PVR: pulmonary vascular resistance; TPG: transpulmonary gradient.

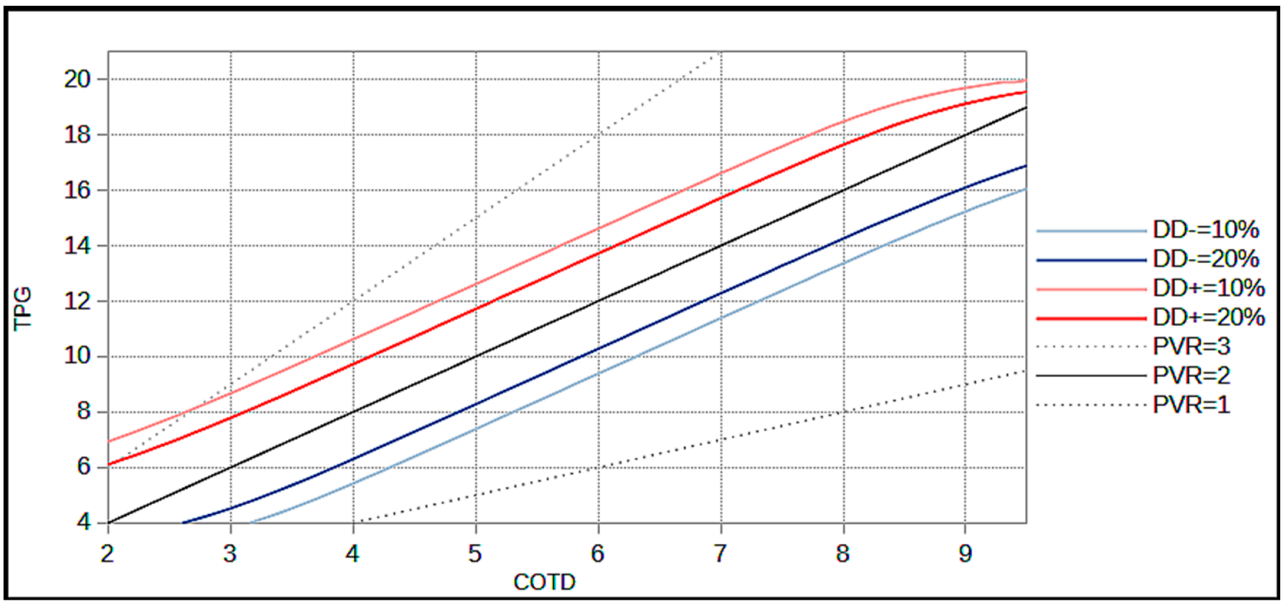

Figure 4. IsoDgDis and isoPVR graph. The same graph as above is shown with the addition of isoPVR line at 1 WU and 3 WU. This highlights the impact of CO and PVR values on diagnosis disagreement. COTD: Cardiac Output using Thermodilution; DgDis (DD): diagnosis disagreement (DgDis (DD)+) corresponds to false positive diagnosis using TD; DgDis (DD)− corresponds to false negative diagnosis using TD); PVR: pulmonary vascular resistance; TPG: transpulmonary gradient.

4. Discussion

In this study, we presented the first mathematical model that allows the calculation of the probability of DgDis if CO_{DF} was used rather than CO_{TD} for a given individual with a mPAP > 20 mmHg and a PAWP $\leq$ 15 mmHg.

This work introduces the notion of doubt related to CO determination in the catheterisation laboratory, which results in a systematic questioning concerning the reliability of CO measurement using TD and its influence on the diagnosis of PcPH.

The model can be used both for patients being categorised as having either PcPH (mPAP > 20 mmHg, PAWP $\leq$ 15 mmHg and PVR > 2 WU) or as having unclassified PH (mPAP > 20 mmHg, PAWP $\leq$ 15 mmHg and PVR $\leq$ 2 WU) using CO_{TD} according to the new PH haemodynamic definition [1].

The model's findings highlighted two intuitive rules: the DgDis is high if the patient lies close to a PVR of 2 WU and the DgDis is higher for a given PVR for lower CO or a lower TPG. In other terms, since the PVR is a ratio between the TPG and the CO, the smaller the TPG and CO are in absolute terms, the greater is the impact of a given variability on the calculation of the PVR and thus the diagnosis disagreement.

When considering these rules, one should be particularly aware of patients with a PVR close to 2 WU and with low CO. For example, a patient diagnosed with unclassified PH using TD with a mPAP of 21 mmHg a PAWP of 14 mmHg and a CO_{TD} of 4 L/min (PVR = 1.75 WU) has a 29.4% estimated probability of being diagnosed as having PcPH using CO_{DF} (Table 2, row 2).

On the other hand, it is possible to be confident in the haemodynamic diagnosis using CO_{TD} in a patient with very elevated or very low PVR. For example, a patient diagnosed with PcPH using TD based on a mPAP of 21 mmHg, a PAWP of 11 mmHg and a CO_{TD} of 3 L/min (PVR = 3.3 WU), has a 3% of chance of being diagnosed as having unclassified PH using DF, which is very reassuring (Table 3, row 8).

Based on the model; we propose three distinct situations:

1. For a DgDis < 10%, the clinician can be quite confident of a diagnosis using CO_{TD} and measurement of CO_{DF} is not systematically required.
2. For a DgDis between 10 and 20% the clinician should consider the use of CO_{DF}.
3. For a DgDis > 20% the clinician should use CO_{DF} because the probability that the patient would be classified differently using CO_{DF} is high.

In our model, default settings including no systematic bias, a 1.96 SD of bias of 2 L/min and resting CO in between 1.3 L/min and 10.2 L/min were used. We considered this was the most appropriate subjective default settings considering the actual literature. However, it must be acknowledged that there a paucity of data, with only three studies cumulating a total of 134 patients with 21 CTEPH and 113 PAH patients. As shown in Table 1, the exact bias and 1.96 SD of bias between TD and DF in the context of PcPH is unknown and there is variability in the published studies. Possible explanations for the observed variability include: different severity and characteristics of PcPH patients, with lower mean CO in the study from Hoeper et al. [2], and differences in the protocol of CO measurement using either TD or DF (e.g., average of two to three measurements for TD for Duknic et al. [3], five measurements with deletion of highest and lowest values for TD for Hoeper et al. [2]).

We assumed a normal distribution of the difference, which implies that there is no proportional bias when comparing CO_{TD} and CO_{DF} (i.e., the differences systematically increase or decrease with increasing CO). Reassuringly a proportional bias was not observed in the included studies [2–4]. This is incorrect during exercise with high CO where a proportional bias is often observed using TD and the assumption of a normal distribution between the differences of CO is therefore lost [3,11]. Consequently, the presented mathematical model should not be used in this context.

The resting limits of CO were based on real life data of CO_{TD} and CO_{DF} in PcPH using the lowest mean CO (Hoeper et al. 1.6 L/min) and the highest mean CO (Duknic et al. 8.5 L/min) and adding safety margin of 20% yielding CO limits between 1.3 L/min to

10.2 L/min [2,3]. The consequence of fixing boundaries of possible CO is the creation of a distortion in the linear DgDis line when approaching the limit of the model as seen in Figures 3 and 4. We considered this was the best mathematical representation of the real life where an aberrant CO measurement (e.g., 1 L/min) would probably be rejected by the clinician.

The main limitations of the model are the unknown exact 1.96 SD of bias in PcPH patients and the assumptions that the CO differences followed a normal distribution in all settings. More data are needed to understand the exact 1.96 SD of bias and to assure that CO differences follow a normal distribution in a wide variety of PcPH patients and haemodynamic severities. In addition, patients with the mPAP of 21, 22, 23 or 24 mmHg were not included in the presented studies and the 1.96 SD of bias might be different for patients with low mPAP. Published studies did not, however, find differences in agreement with increasing tricuspid regurgitation, which is linked to an increase mPAP [2,4]. Bearing this in mind, we hypothesized that the agreement between TD and DF would not significantly differ for patients with a lower mPAP.

The strengths of the model are an individualised approach for a given patient and the highlighting of the influence of CO measurements agreement on the diagnosis of PcPH. Additionally, defaults settings of the model could be easily adapted if new evidence on the agreement of TD and DF is published.

Although DF remains the gold standard in measuring CO, its systematic use is difficult to implement due to its complexity and its time-consuming nature. In practice its use is often restricted to situations where TD is known to give false results as for patients with intracardiac shunts. This mathematical model can help to identify patients who would benefit most from DF. Either an incorrect diagnosis of PcPH or an incorrect diagnosis of the absence of PcPH could have serious implications. Our model could aid clinicians to adopt a personalised strategy when evaluating the potential added value of the use of DF and may lead to a more accurate diagnosis.

Cardiac output measurement using indirect Fick is frequently used in clinic. However, the agreement between IF and TD for patients with PH or suspicion of PH is poor with LoA ranging between 1.8 L/min to 4.1 L/min and bias ranging between 0.4 L/min and −0.8 L/min [5,12–14]. Comparisons of indirect Fick with DF in PcPH are lacking [7]. For this reason IF is not recommended anymore in the international guidelines because it is considered less reliable than TD and DF [1]. Other non-invasive methods have been studied in PcPH including inert gas rebreathing, bioimpendance, bioreactance, pulse wave analysis, cardiac magnetic resonance imaging and echocardiography [7]. The most promising method might be cardiac magnetic resonance imaging that showed excellent agreement when compared to TD or DF with LoA close to 1 L/min [15,16]. Since the characteristics of the presented mathematical model were based on the agreement between TD and DF, it cannot be readily used for other methods, such as indirect Fick or cardiac magnetic resonance, that have different agreement with the gold standard DF. However, the mathematical model could be modified to study the influence on diagnosis disagreement of any given CO methods assuming that the LoA and bias are known and that the CO differences of the studied methods have a normal distribution.

The principle of this mathematical model could also be adapted to study the influence on the diagnosis of PcPH of different parameters of the PVR equation. For example, the mPAP can be estimated using cardiac magnetic resonance [17]. The mathematical model could be modified to study the diagnosis influence of the mPAP estimated using cardiac magnetic resonance compared to the mPAP measured during RHC.

5. Conclusions

Using the new haemodynamic definition of PcPH, we created a model that estimated the probability of a different diagnosis (PcPH or unclassified PH) when using CO_{TD} instead of CO_{DF} based on the patient individual haemodynamic characteristics. This model can help the clinician to evaluate the potential benefit of measuring CO_{DF} during the diagnostic

work-up of PcPH in any given patient with a mPAP > 20 mmHg and a PAWP $\leq$ 15 mmHg. Moreover, it emphasises the need to question the reliability of TD over DF for the diagnosis of PcPH for every patient. Such an approach could increase the diagnosis accuracy, and thus be beneficial to patients.

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Institutional Review Board Statement: As neither new real patients, nor new real data were included, permission from the local ethics committee was not necessary in order to create this model.

Informed Consent Statement: Not applicable.

Data Availability Statement: The data that support the findings of this study can be made available from the authors upon reasonable request.

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