Effets de la distension thoracique dynamique sur la dyspnée induite par l'exercice physique dans les maladies cardio-pulmonaires

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Résumé en Français

1 - Synthèse des connaissances

1.1 Définition de la dyspnée

La respiration normale est un acte inconscient ne donnant normalement lieu à aucune sensation [1]. Mais dans certaines situations, comme l'exercice physique, ou à l'occasion de certaines pathologies pulmonaires, cardiaques ou neuromusculaires, des perceptions liées à divers phénomènes respiratoires peuvent apparaître, et parfois être ressenties comme inconfortables, ou désagréables, ou gênantes. On parle alors d'essoufflement ou de dyspnée. Ce terme est ambigu, car il peut être utilisé tant pour décrire une sensation "normale" (essoufflement à l'exercice) que pour décrire le symptôme d'une maladie respiratoire, cardiaque, ou neuromusculaire [2]. Pour lever cette ambiguïté, on réserve parfois le terme de dyspnée à "un inconfort respiratoire survenant pour un niveau d'activité usuel qui n'entraîne normalement aucune gêne [3]. Cette définition ne lève que partiellement l'ambiguïté, mais permet de dire que la dyspnée est d'autant plus sévère que l'intensité de l'activité qui la provoque est faible [3]. La pertinence clinique des sensations respiratoires est évidente. En tant que symptôme, la dyspnée constitue fréquemment, au cours des maladies cardiaques ou respiratoires chroniques, une source majeure de handicap. Ce symptôme s'aggrave avec le temps et entraine la cessation progressive de l'activité physique avec, comme conséquence, une altération majeure de la qualité de vie [1]. Une compréhension fine de la physiopathologie des mécanismes de la dyspnée est donc une source de progrès potentiel pour une gestion thérapeutique optimale de ce symptôme.

1.2 Quantification de la dyspnée induite par l'activité physique

La dyspnée d'effort est une plainte essentielle des affections cardiorespiratoires chroniques. L'exercice physique avec une épreuve d'effort progressive et maximale au cyclo-ergomètre constitue un modèle idéal pour étudier la sensation de dyspnée puisqu'à priori, avec l'augmentation de la résistance du cyclo-ergomètre (travail mécanique) et de la ventilation, on pourra évaluer les

variations dans la sensation d'inconfort respiratoire ou dyspnée. Une des plus reconnues et utilisées au cours d'une épreuve d'effort est l'échelle de Borg « modifiée » [4, 5]. L'échelle de Borg « modifiée » associe une échelle numérique - de 1 à 10 - et une échelle catégorielle (**Figure 1**).

0	**rien du tout de dyspnée**
0,5	**très très légère**
1	**très légère**
2	**légère**
3	**modérée**
4	**un peu sévère**
5	**sévère**
6	
7	**très sévère**
8	
9	
10	**très très sévère**

Figure 1 : Exemple d'échelle de Borg modifiée.

Il s'agit de l'adaptation à la mesure de l'intensité de la dyspnée de l'échelle de Borg originale, mise au point pour permettre une description transindividuelle de la perception de l'intensité à un effort [5]. Dans un premier travail, Borg avait établi que la perception à l'effort était liée au travail imposé au sujet par une fonction exponentielle [4]. Les chiffres obtenus avaient une signification relative et ne permettaient pas de comparaisons interindividuelles. Dans un second temps, à partir du postulat que si les gens avaient un langage commun pour décrire leur degré d'effort, les mots placés le long d'une échelle numérique donneraient aux chiffres une signification commune à tous les sujets, Borg a combiné une échelle numérique à une échelle de catégories verbales. En plaçant les mots le long de l'échelle numérique selon une fonction exponentielle, de puissance similaire à celle obtenue par des mesures de la variation de l'intensité perçue sur une échelle ouverte, Borg a donc développé une échelle proportionnelle qui permet une mesure absolue de l'intensité perçue [5]. Cette échelle a été validée pour l'évaluation d'un individu d'une mesure à l'autre et pour comparer des sujets entre eux. Sa validité repose aussi sur le fait que la fonction exponentielle, rendant compte du changement dans la perception de l'intensité de l'exercice, est parallèle à d'autres changements physiologiques survenant pendant l'effort [6] et sur son aptitude à réaliser une mesure proportionnelle à d'autres sensations comme le goût ou l'audition [7].

1.3 Evaluation de la sensation dyspnéique pendant l'effort

L'évaluation de la dyspnée (ou essoufflement) induite par l'exercice physique est réalisée en routine lors de l'épreuve fonctionnelle à l'exercice. La sensation dyspnéique est cotée selon l'échelle de Borg "modifiée", graduée de 0 (« pas d'essoufflement ») à 10 (« l'essoufflement maximal soit que le sujet peut imaginer soit dont il a eu l'expérience ») [5]. Les sujets sont familiarisés avec cette échelle avant l'exercice. L'échelle de Borg est montrée aux patients au repos, puis chaque minute pendant l'exercice et au maximum de l'effort en demandant aux patients de coter la sensation dyspnéique sur l'échelle de Borg avec un doigt, sans parler. A la fin de la séance ils décrivent la raison de l'arrêt de l'exercice : dyspnée, fatigue des membres inférieurs, autre cause.

1.4 Mécanismes de la dyspnée induite par l'activité physique

Contrairement à la plupart des autres sensations comme par exemple la douleur, la nature exacte du stimulus à l'origine de la dyspnée, les voies afférentes et les zones d'intégration centrales impliquées ne sont pas clairement identifiées. On ne connaît pas pour la dyspnée de récepteurs spécifiques. Plusieurs voies afférentes ont été potentiellement mises en cause dans sa genèse. Elles véhiculent des signaux provenant de récepteurs de la paroi thoracique (muscles respiratoires inclus), de récepteurs intrapulmonaires et bronchiques, de chémorécepteurs centraux et périphériques, de barorécepteurs vasculaires et de mécanorécepteurs des voies aériennes supérieures. Ces afférences sont médiées principalement par le nerf vague et le nerf phrénique. Aucune d'elles n'est indispensable à la genèse de la dyspnée, car leur suppression individuelle ne la fait pas disparaître [8]. De nombreuses théories ont été élaborées sur le stimulus à l'origine de la sensation dyspnéique. Une des plus reconnues et la plus classique est la théorie « tension-longueur » de Campbell, selon laquelle la dyspnée serait causée par la perception d'une relation inappropriée entre tension et longueur des muscles respiratoires [9]. Cette théorie, qui attribue aux muscles respiratoires un rôle prépondérant dans la genèse de la dyspnée, peut se traduire au niveau de l'appareil respiratoire dans son ensemble par une altération de la relation pression-volume [3]. En d'autres termes, la dyspnée résulterait de la perception d'une variation de volume pulmonaire inférieure à celle normalement

programmée par les centres nerveux pour une variation de pression donnée. En parallèle à l'hypothèse de Campbell, un autre phénomène impliquant la commande motrice centrale, pourrait aussi expliquer la sensation de dyspnée indépendamment de toute mise en jeu d'afférences périphériques. Il s'agit de la perception anormale de l'intensité de la commande motrice respiratoire, ou de la perception normale d'une commande augmentée, la dyspnée pouvant en première approximation être mise en parallèle à la sensation de fatigue, et la commande respiratoire à l'intensité d'un effort. Dans cet ordre d'idées, il faut se rappeler que des efforts volontaires pour bouger les membres peuvent être ressentis en l'absence de tout mouvement, probablement du fait d'une duplication du signal moteur efférent vers le cortex somesthésique, appelée « décharge corollaire », comme le suggèrent des enregistrements électrophysiologiques chez le chat [10-12]. Chez l'homme, la possibilité de percevoir une sensation d'effort respiratoire sans qu'il n'y ait en réalité d'action respiratoire a été mise en évidence dans des situations de paralysie partielle ou de fatigue des muscles respiratoires. Une sensation d'effort respiratoire intense, désagréable (donc une dyspnée) a ainsi été rapportée par des sujets totalement paralysés à qui l'on demandait de produire une pression inspiratoire maximale [13]. Pour certains qui tentent d'unifier les deux théories, la dyspnée serait finalement le résultat d'une distorsion du triangle reliant tension musculaire, longueur musculaire, et perception de l'intensité de la commande correspondante [3]. En effet, ces auteurs considèrent que l'augmentation de l'effort respiratoire serait la source de la dyspnée via la perception de l'augmentation correspondante de la commande centrale, « copiée » vers le cortex somesthésique (concept de « décharge corollaire ») [10-12]. « L'effort respiratoire » est alors défini comme la relation triangulaire entre l'efficacité des muscles respiratoires (fonction de leur force, de leur longueur, de leur géométrie…), l'impédance thoraco-pulmonaire qui s'oppose à l'action de ces muscles, et le changement de volume thoracique qui en résulte [10-12]. Les muscles respiratoires jouent un rôle fondamental dans ce concept, la relation entre la force développée et leur longueur lors de cette action étant déterminante. Cette théorie rend bien compte de la dyspnée en réponse à l'augmentation de la ventilation (exercice physique ou chémostimulation), à l'application d'une

charge mécanique externe, ou à la réduction de performance musculaire (distension thoracique [14], fatigue musculaire [15]). Il est possible de proposer une théorie unificatrice qui fait du déséquilibre entre la commande ventilatoire et le résultat de cette commande (c'est- à-dire, l'activation des afférences respiratoires) la source principale de la dyspnée [10, 12] (**Figure 2**).

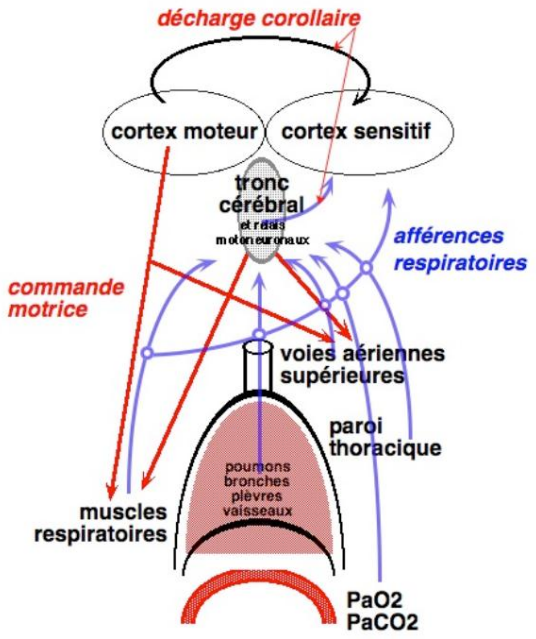

Figure 2 : Représentation schématique du modèle actuellement consensuel au regard des mécanismes des sensations respiratoires. Dans ce modèle, les multiples afférences respiratoires arrivant au niveau du cortex sensitif font l'objet d'une comparaison à une "copie" de l'information motrice respiratoire ("décharge corollaire") qui provient soit des centres respiratoires automatiques du tronc cérébral (dans le cas de la soif d'air en particulier) soit des neurones corticaux impliqués dans la respiration (dans le cas de la sensation d'effort inspiratoire excessif en particulier). Un déséquilibre entre afférences et décharge corollaire fait l'objet d'un traitement affectivo-cognitif négatif, qui est la source de la dyspnée.

Selon ce concept, toute situation au cours de laquelle l'action des muscles ventilatoires sur le système respiratoire dit « passif » n'entraîne pas un retour afférent (« ré-afférence ») proportionnel (en intensité et en cinétique) à la commande ventilatoire efférente originale, est source de dyspnée. Ainsi la dyspnée peut être en rapport avec une faiblesse musculaire inspiratoire (comme par exemple chez les patients atteints d'une maladie neuromusculaire) ou avec une commande ventilatoire excessive ou la combinaison des deux. Ce modèle rend compte de la « sensation d'augmentation d'effort respiratoire » en réponse à l'application d'une charge mécanique, de la « soif d'air » réactionnelle à une hypercapnie lorsque la réponse ventilatoire est insuffisante, et de dyspnées rencontrées dans de nombreuses situations cliniques. Ainsi, au cours de maladies neuromusculaires comme la sclérose latérale amyotrophique, la dyspnée apparaît secondairement à l'atteinte des muscles inspiratoires qui ne sont plus en mesure de répondre à la commande ventilatoire [8]. Au cours de la bronchopneumopathie chronique obstructive (BPCO), le déséquilibre entre la charge mécanique et la performance diaphragmatique liée à la distension thoracique est directement lié à la dyspnée [14]. On peut également appliquer la théorie du déséquilibre entre la commande ventilatoire et le résultat

de cette commande à la dyspnée induite par l'activité physique chez le patients atteints de BPCO au cours d'effort physique [16-18].

La BPCO est une affection caractérisée par la diminution de la capacité des bronches à rester perméables face à une augmentation de la pression transpulmonaire. Ceci se traduit par une réduction disproportionnée du débit expiratoire à mesure que l'expiration s'accomplit, et ce d'autant plus que l'expiration est active (exercice, expiration forcée). La gêne à la vidange pulmonaire qui en résulte implique que le volume de fin d'expiration devient supérieur au volume de relaxation du système respiratoire si la quantité d'air à expirer excède celle qui peut effectivement l'être dans le temps imparti. On parle de distension thoracique dynamique. Celle-ci survient quand le volume courant augmente et/ou que le temps expiratoire diminue. L'hyperventilation liée à l'exercice en est donc un promoteur majeur. La distension est rapidement associée à des contraintes mécaniques qui imposent un effort inspiratoire majoré alors même qu'elles vont rapidement interdire l'augmentation attendue de volume courant en réponse à cet effort[1].

Il se constitue donc un déséquilibre entre la commande ventilatoire, augmentée à la fois par l'exercice et par les anomalies mécaniques du système respiratoire et la réponse afférente du système ventilatoire (limitation du volume courant). Ce déséquilibre est source de dyspnée. On parle de dissociation neuromécanique pour décrire ce phénomène, qui est aggravé par le fait qu'alors même que la charge et la commande augmentent, la capacité du diaphragme à exercer une action inspiratoire sur la cage thoracique s'altère[2]. La distension thoracique dynamique,

Note 1 : La distension dynamique va être à l'origine de la dyspnée par l'élévation de la charge inspiratoire et la réduction des capacités diaphragmatiques. L'équilibre des pressions alvéolaire et atmosphérique qui règne normalement de part et d'autre de la paroi thoracique en fin d'expiration (à la capacité résiduelle fonctionnelle, CRF) est rompu en cas de distension thoracique en raison d'une élévation de la pression alvéolaire télé-expiratoire: le poumon ne revient pas à sa position d'équilibre, de sorte que sa position de fin d'expiration est telle que la pression de recul élastique qui tend à le ramener sur lui-même reste supérieure à la pression d'expansion de la cage thoracique : le différentiel de ces forces, représenté par la pression alvéolaire, est positif, c'est-à-dire supérieur à la pression atmosphérique, alors qu'il est normalement nul à la CRF.
Cette pression expiratoire positive, intrinsèque (PEPi), doit être surmontée par les muscles inspiratoires à chaque cycle avant que leur action ne devienne effectivement motrice d'air vers les alvéoles. Donc, une charge mécanique supplémentaire sera nécessaire en début d'inspiration afin de vaincre cette élévation de pression alvéolaire et revenir au niveau de la pression atmosphérique pour faire entrer un volume d'air dans les voies aériennes. La distension thoracique fait également varier dans un sens défavorable la pente de la courbe pression-volume : à la fin de l'inspiration, il est nécessaire de développer un effort plus grand pour un même incrément de volume inspiré. Ceci va encore majorer la charge mécanique. Le trouble ventilatoire primitivement expiratoire au cours de la BPCO va donc entraîner progressivement une augmentation de charge inspiratoire : commencer à inspirer est plus difficile (surmonter la pression télé-expiratoire positive résiduelle), finir d'inspirer est plus difficile (distendre un poumon moins élastique).

Note 2 : Le diaphragme va, quant à lui, être également dans une situation défavorable, car la distension change sa conformation spatiale : ainsi, a constitution d'une distension dynamique diminue sa capacité à produire une force inspiratoire, car elle entraîne un aplatissement et un raccourcissement du muscle. L'ensemble de ces conséquences de la distension thoracique dynamique va contribuer à rompre l'équilibre entre la capacité musculaire diaphragmatique et la charge mécanique inspiratoire.

conséquence de l'obstruction bronchique et de l'hyperventilation, est donc le mécanisme dominant de la dyspnée d'effort au cours de la BPCO. Ceci explique que, pour un état donné de la fonction respiratoire, la dyspnée survient d'autant plus rapidement que l'hyperventilation est importante.

1.5 Distension thoracique dynamique

L'intérêt pour la distension thoracique dans le contexte de *la BPCO de stade I selon la classification de GOLD, l'insuffisance cardiaque chronique (ICC) et l'hypertension artérielle pulmonaire (HTAP)* (trois situations qui font l'aspect de cette thèse) est lié au fait qu'il a récemment été mis en évidence dans la littérature que les patients atteints de BPCO de stade I [19-21], d'ICC [22, 23] et d'HTAP [24-27] peuvent présenter une atteinte des petites voies aériennes (sous la forme d'une diminution des débits aériens à bas volume pulmonaire sur une courbe débit-volume) qui, au cours d'autres affections comme la BPCO avec atteinte sévère, sont connues comme des déterminants majeurs d'une distension thoracique dynamique particulièrement délétère qui peut contribuer à déterminer ou intensifier la dyspnée induite par l'exercice physique. Chez le sujet normal, sur une courbe débit-volume, les débits expiratoires mobilisés lors de la ventilation de repos au volume courant sont très inférieurs aux débits mobilisés lors de manoeuvres en expiration forcée [28-31] (**Figure 3**). Donc, au cours de l'exercice, l'augmentation des débits, qui est nécessaire à l'accroissement de la ventilation, va se faire sans difficulté, et sans devoir changer le niveau de volume pulmonaire opérationnel auquel la ventilation s'effectue [28-31] (**Figure 3**). En revanche, chez les patients souffrant de maladies obstructives bronchiques avec atteinte sévère, les débits expiratoires sont déjà limités au repos: ils atteignent en effet le niveau des débits en expiration forcée (c'est-à-dire, le volume inspiré ne peut pas être complètement exhalé dans le temps disponible pour l'expiration)[3] [32]. À l'effort, un déplacement du volume opérationnel vers les hauts volumes pulmonaires va donc être nécessaire pour que les débits puissent croître et la ventilation augmenter [32]. Dans toutes les situations dans lesquelles il existe une limitation du débit expiratoire, le temps expiratoire nécessaire à la vidange pulmonaire complète pour arriver à la

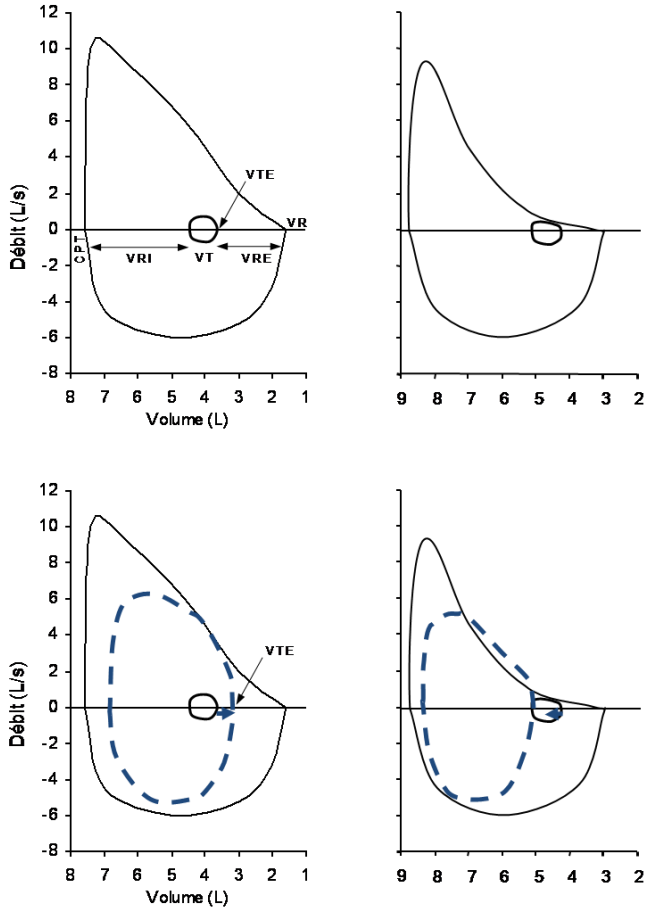

Figure 3 : Comparaison des courbes débit-volume forcée et spontanée au repos (en trait plein) avec la courbe débit-volume spontanée au cours d'un exercice musculaire sous-maximal (trait pointillé), chez un sujet normal (gauche) et chez un malade atteint de BPCO (droite). La grosse flèche indique les variations du volume pulmonaire de fin d'expiration dans le sujet normal et dans le BPCO. (CPT : capacité pulmonaire totale ; VR : volume résiduel) ; VT : volume courant ; VRI : volume de réserve inspiratoire ; VRE : volume de réserve expiratoire ; VTE : volume pulmonaire de fin d'expiration (VRE + VR).

capacité résiduelle fonctionnelle est plus long que chez le sujet sain [32]. Lors de l'exercice, en raison de l'élévation de la fréquence respiratoire et du volume courant, le temps expiratoire est insuffisant pour que la vidange pulmonaire soit complète. Ceci conduit à une élévation progressive, à chaque cycle respiratoire, du volume télé-expiratoire (VTE, ou EELV en anglais) : la distension thoracique dynamique (c'est-à-dire, l'augmentation temporaire et variable du volume de fin d'expiration au-dessus de sa valeur « statique », de relaxation) s'accentue progressivement [32]. Ainsi, à l'exercice, l'élévation du volume courant se fait chez le patient BPCO au prix d'une diminution de la capacité inspiratoire [32].

Note 3 : Chez le sujet normal (Figure 3), au repos comme à l'exercice musculaire, la courbe spontanée n'atteint pas la courbe forcée lors de l'expiration. On dit que le sujet ne présente pas de limitation expiratoire de débit. Pour pouvoir augmenter la ventilation à l'exercice, il faut augmenter les débits tant inspiratoire qu'expiratoire pour produire un volume courant (VT). Augmenter le débit expiratoire est possible parce qu'il y a une « réserve » de débits ; le sujet normal puisera dans le volume de réserve inspiratoire (VRI, à gauche du volume courant) et expiratoire (VRE, à droite du volume courant) de repos pour augmenter son VT et donc le volume pulmonaire de fin d'expiration (VTE, ou EELV en anglais) diminuera [VTE = VRE + volume résiduel (i.e., VR)].

Chez certains malades atteints de BPCO, la situation peut être totalement différente. Même en ventilation spontanée au repos, la courbe spontanée atteint la courbe forcée au cours de l'expiration (Figure 3). Cela signifie que les débits expiratoires maximaux produits par le malade ne sont pas plus élevés que ceux qu'il mobilise au repos en ventilation courante : il n'y a aucune « réserve » de débits expiratoire.

Ainsi à l'exercice, le malade ne peut pas augmenter son débit expiratoire s'il reste au même volume pulmonaire, et l'on parle alors de limitation expiratoire de débit. Quelle est la solution pour le système respiratoire de ces malades lorsque la demande ventilatoire augmente (augmentation du volume courant VT) ? Pour pouvoir augmenter la ventilation, il faut augmenter les débits tant inspiratoire qu'expiratoire. Augmenter le débit expiratoire n'est possible (il n'y a aucune « réserve » de débits expiratoire!) que si le malade respire à plus haut volume pulmonaire, donc en augmentant le VTE, ce qui correspond à une aggravation de la distension thoracique dynamique. Cela revient à dire que, pour être sur une zone plus favorable de la courbe débit-volume, le système respiratoire du malade obstructif chronique "choisit" de se placer à plus haut volume pulmonaire, donc en distension dynamique.

1.6 Evaluation de la distension thoracique dynamique pendant l'effort

La survenue d'une distension thoracique dynamique, c'est-à-dire d'une élévation progressive du volume de fin d'expiration, est habituellement recherchée au cours de l'exercice aux cyclo-ergomètre en demandant aux patients de réaliser à différents niveaux de puissance une manœuvre dite de « capacité inspiratoire » (prendre une inspiration profonde et maximale à partir de la fin d'une expiration) [32]. Il est maintenant clairement démontré que la survenue d'une distension thoracique est associée à la réduction progressive de la capacité inspiratoire, c'est-à-dire au fait que le volume de fin d'expiration se rapproche progressivement de la capacité pulmonaire totale (CPT) [32] (**Figure 4**). Les changements de capacité inspiratoire reflètent donc fidèlement les changements de volume télé-expiratoire à l'exercice si l'on considère que la CPT ne se modifie pas significativement à l'exercice et si les patients réalisent des efforts maximaux lors de la mesure et en l'absence de déficience musculaire inspiratoire intrinsèque. De plus, coupler la mesure de capacité inspiratoire à la mesure du volume de réserve inspiratoire dynamique (capacité inspiratoire moins volume courant) donne des informations supplémentaires sur les contraintes mécaniques qui pèsent sur la ventilation [18, 32] (**Figure 4**). En effet, lorsque la fin de l'excursion du volume courant approche de la limite supérieure possible définie par la

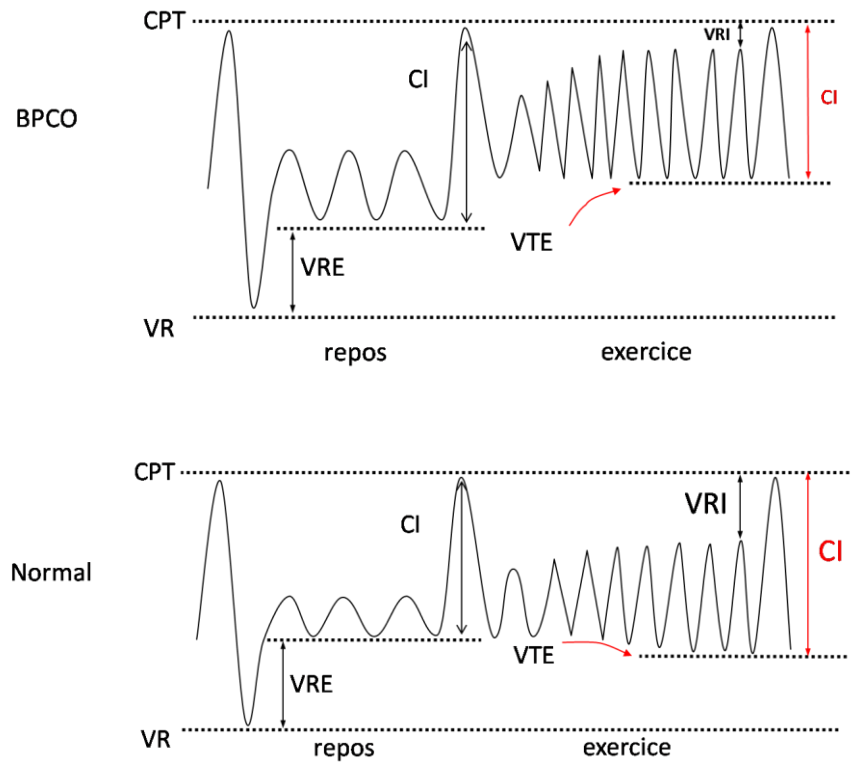

Figure 4 : Les changements de capacité inspiratoire (CI) à l'exercice (flèche rouge) reflètent fidèlement les changements de volume télé-expiratoire (VTE) à l'exercice (flèche rouge) chez les sujets normaux et chez le patients atteints de BPCO.

capacité inspiratoire (et donc que chaque inspiration se termine à proximité de la capacité pulmonaire totale), la relation pression-volume du système respiratoire change de pente: il faut générer davantage de pression pour générer un volume courant donné qu'à un volume pulmonaire inférieur [18, 32].

1.7 Conséquences de la distension thoracique dynamique pendant l'exercice

Une augmentation rapide du volume pulmonaire crée une force de traction radiaire sur les voies aériennes, ce qui a pour effet d'augmenter leur calibre, et s'oppose donc à la survenue de la limitation expiratoire de débit (effet « favorable »). Ainsi, chez des patients atteints de BPCO sévère, la survenue précoce de la distension dynamique lors de l'exercice est « adaptative » en ceci qu'elle autorise une augmentation de la ventilation « sous-maximale » (jusqu'à approximativement 40L/min) et de l'effort inspiratoire correspondant (jusqu'à approximativement 40 % de la valeur maximale) sans que cela ne crée de gêne respiratoire significative (niveau 1 à 2 sur l'échelle de Borg) [18, 21, 32, 33]. Ainsi, la distension dynamique a un bénéfice mécanique lors d'un exercice modéré, à condition que le volume pulmonaire reste inscrit dans la gamme linéaire de la relation pression-volume du système respiratoire (20 à 80 % de la capacité vitale). Cependant, le déplacement du volume opérationnel vers le haut a rapidement des conséquences délétères (il devient « mal-adaptatif »). En effet, l'augmentation du volume télé-expiratoire entraîne une élévation de la pression alvéolaire télé-expiratoire (qui deviens positive), c'est-à-dire supérieur à la pression atmosphérique, alors qu'il est normalement nul à la fin d'expiration (**Figure 5**). Ainsi,

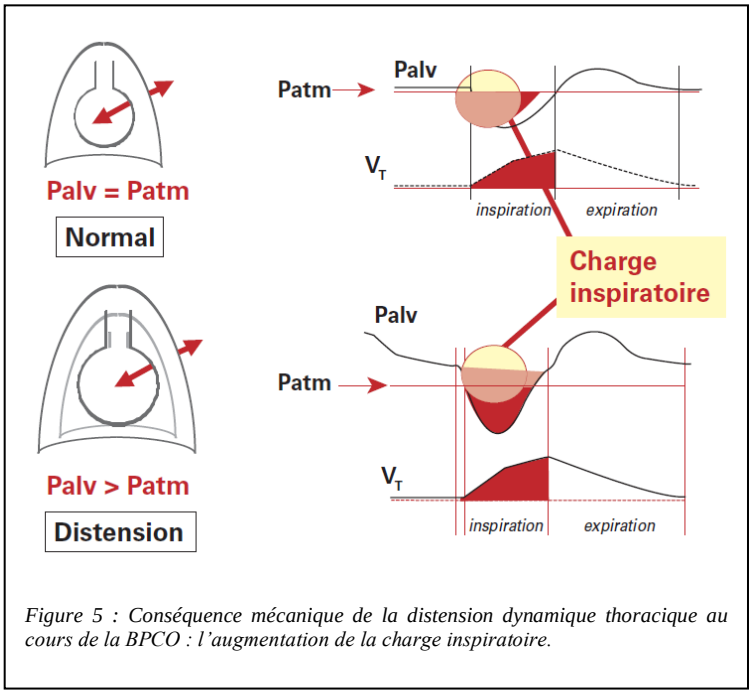

Figure 5 : Conséquence mécanique de la distension dynamique thoracique au cours de la BPCO : l'augmentation de la charge inspiratoire.

une charge mécanique supplémentaire sera nécessaire en début d'inspiration afin de vaincre cette élévation de pression alvéolaire et revenir au niveau de la pression atmosphérique pour faire entrer un volume d'air dans les voies aériennes. La distension thoracique fait également varier dans un sens défavorable la pente de la courbe pression-volume (**Figure 6**) : lorsque le volume de réserve inspiratoire (VRI) s'approche à 0,5 L (ou à 10 % de la CPT prédite), la relation pression-volume s'horizontalise, c'est-à-dire à la fin de l'inspiration il faut développer un effort (pression) plus grand pour un même incrément de volume inspiré. Ceci va encore majorer la charge mécanique.

Le trouble ventilatoire primitivement expiratoire au cours de la BPCO va donc entraîner progressivement une augmentation de charge inspiratoire : commencer à inspirer est plus difficile (surmonter la pression télé-expiratoire positive résiduelle), finir d'inspirer est plus difficile (distendre un poumon moins élastique) [18, 21, 32, 33]. Même si les muscles inspiratoires, et particulièrement le diaphragme, s'adaptent remarquablement à la distension thoracique chronique [34], les variations rapides du volume pulmonaire induites par l'exercice ne peuvent pas faire l'objet d'une telle adaptation et, du fait de la relation force-longueur des muscles squelettiques, elles provoquent ce qu'il est convenu d'appeler une « faiblesse fonctionnelle » du diaphragme [35]. Il faut à cet égard noter que la présence d'une

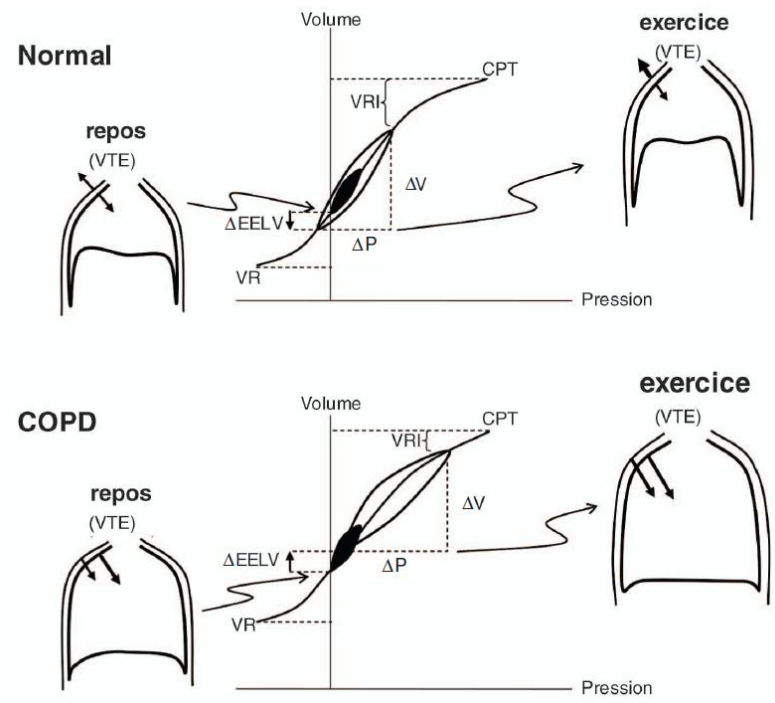

Figure 6 : Relations pression-volume (P-V) du système respiratoire à l'état normal et en cas de BPCO, avec la représentation de la zone du volume courant (en noir) et de son augmentation à l'exercice (en blanc). En cas de BPCO, en raison de l'existence d'une distension tant statique que dynamique (majoration à l'exercice du volume télé-expiratoire, VTE), le volume courant pendant l'exercice s'approche voire atteint la zone alinéaire de la courbe pression-volume, correspondant à une majoration disproportionnée de la charge élastique (il faut générer plus de pression pour produire un volume donné). Ceci limite la possibilité d'augmenter le volume courant, et correspond à un volume de réserve inspiratoire réduit. Contrairement à ce que l'on observe chez le sujet sain, le rappel élastique du poumon et celui de la cage thoracique ont la même direction, tant au repos qu'à l'exercice. Ceci correspond à une charge à seuil pour les muscles inspiratoires.
Abréviations : VTE, volume télé-expiratoire ; VTI, volume télé-inspiratoire ; VR, volume résiduel ; CPT, capacité pulmonaire totale.

charge inspiratoire chronique pourrait, théoriquement, prédisposer les patients atteints de BPCO à une fatigue inspiratoire, mais il n'y a pas de preuve que cela soit réellement le cas [34-36]. Et, de fait, des travaux récents n'ont pas permis de mettre en évidence une fatigue musculaire inspiratoire au maximum d'un l'exercice « épuisant » au cours de la BPCO [37-39].

À mesure que la distension dynamique se constitue, la respiration devient de plus en plus superficielle et rapide. Chez les patients atteints de BPCO modérée à sévère, on observe à l'exercice un véritable plafonnement: le volume courant et le volume télé-inspiratoire n'augmentent plus, et il n'est plus possible d'augmenter la ventilation qu'en augmentant la fréquence respiratoire [18, 21, 33, 40]. Plus grande est la distension dynamique, plus bas est le niveau de ventilation (et de travail respiratoire) auquel ce plateau de volume courant apparaît [18, 21, 33, 40]. Dans des cas extrêmes, l'impossibilité d'augmenter le volume courant à cause d'anomalies sévères du rapport ventilation-perfusion peut conduire à une hypoventilation alvéolaire avec les anomalies gazométriques correspondantes [41].

Chez les sujets sains, le rapport entre l'effort inspiratoire (pression pour faire entrer un volume d'air dans les voies aériennes) et le volume courant correspondant est quasi-constant au cours de l'exercice, ce qui indique que le volume pulmonaire à l'exercice reste inscrit dans la partie linéaire de la courbe pression-volume du système respiratoire (**Figure 6**). Au contraire, chez les patients atteints de BPCO, l'effort inspiratoire nécessaire pour mobiliser un volume donné (et donc le rapport effort/volume courant) augmente progressivement au cours de l'exercice. Ceci reflète le changement des conditions mécaniques qui prévalent à haut volume pulmonaire, et est une conséquence directe de la distension dynamique [32, 42-44]. Lorsque le volume courant ne peut plus augmenter, augmenter la ventilation passe forcément par une accélération de la fréquence respiratoire, et donc de la vitesse de raccourcissement des muscles respiratoires [32, 42-44]. Du fait de la relation force-vitesse des muscles striés, ceci entraîne, comme la diminution de longueur, une faiblesse musculaire fonctionnelle [32, 42-44]. La polypnée est aussi associée à une réduction

progressive de la compliance pulmonaire dynamique, qui dépend de la fréquence exagérée en cas de BPCO [32, 42-44].

1.8 Distension thoracique dynamique et dyspnée

Un certain nombre d'études ont mis en évidence des liens statistiques entre l'intensité de la dyspnée, les capacités de marche, et la distension dynamique mesurés à l'exercice [16-18, 21, 33, 40, 45-48]. Les mécanismes par lesquels la distension dynamique conduit à la dyspnée sont vraisemblablement multiples, mais ils incluent certainement des signaux produits au niveau du système nerveux central par le déséquilibre entre la charge excessive à laquelle les muscles inspiratoires sont soumis alors même qu'ils sont atteints d'une faiblesse fonctionnelle [10, 12, 44]. L'intensité de la dyspnée est fortement corrélée à l'augmentation du rapport effort/volume au cours de l'exercice, ce dernier constituant un index de dissociation neuromécanique [10, 12, 18, 33, 42, 44]. Ainsi, la sensation dyspnéique change avec l'effort et ceci peut témoigner de la dissociation neuromécanique. La sensation dyspnéique dominante que rapportent les patients en fin d'exercice est une impression de ne pas pouvoir faire entrer assez d'air dans le thorax [10, 12, 18, 33, 42, 44]. Elle pourrait représenter la discordance entre une commande ventilatoire augmentée et un retour afférent atténué du fait du plafonnement du volume courant qui représente la conséquence directe de la distension thoracique dynamique [10, 12, 18, 33, 40, 42, 44]. Le corollaire de ces constatations est que des interventions thérapeutiques qui réduisent ou retardent la survenue du plafonnement du volume courant liée à la distension thoracique au repos ou à l'effort devraient diminuer la dyspnée d'effort et améliorer la tolérance à l'exercice. Et en effet, il existe deux façons validées cliniquement de réduire la dyspnée induite par la distension thoracique chez le BPCO [43] qui sont de :

1. diminuer le volume pulmonaire ou ralentir son augmentation à intensité donnée : bronchodilatateurs, chirurgie de réduction de volume pulmonaire;

2. diminuer le niveau de ventilation générée par une intensité d'exercice donné : réentrainement à l'effort.

Cette thèse se focalise surtout sur des interventions qui peuvent diminuer le volume pulmonaire opérationnel ou ralentir son augmentation à intensité donnée.

2 - Objectif général de la thèse

L'objectif de cette thèse est d'étudier la contribution de la distension thoracique dynamique dans la genèse de la dyspnée au cours d'affections qui peuvent entrainer une limitation du débit expiratoire, même si ce n'est pas leur caractéristique principale. Des anomalies évocatrices d'une mécanique anormale des petites voies aériennes ont aussi été mise en évidence à partir des courbes débit-volume, sous la forme d'une réduction disproportionné des débits expiratoires à bas volumes pulmonaires (aspect concave en dehors du bras expiratoire de la courbe débit-volume forcée) au cours de la BPCO stade I [19-21], mais aussi de l'ICC [22, 23] et de l'HTAP [24-27].

L'intérêt pour cette distension thoracique se justifie par son accessibilité potentielle à des interventions pharmacologiques et non-pharmacologiques, qui en fait un objectif thérapeutique "raisonnable".

3 - Hypothèses

Nous avons formulé, et testé, les hypothèses suivantes:

Hypothèse 1: au cours de la BPCO à un stade précoce, l'atteinte des petites voies aériennes est responsable d'une diminution des débits aériens à bas volume pulmonaire qui peut être recherchée sur la courbe débit-volume [19-21]. Les anomalies des voies aériennes distales et des rapports ventilation-perfusion, qui sont essentiellement une conséquence de l'inflammation distale avec remodelage, parfois associées à un déconditionnement musculaire, contribuent à une réponse ventilatoire anormale à l'effort et de la survenue d'une distension thoracique dynamique qui limite

l'exercice et contribue également à la dyspnée induite par l'exercice physique [19-21]. La présence d'une maladie des petites voies aériennes sans obstruction spirométrique majeure (BPCO Gold I) suffit à induire une distension thoracique à l'exercice qui peut être modifiée par les bronchodilatateurs; si c'est le cas, la réduction de la distension thoracique à l'exercice induite par les bronchodilatateurs pourra améliorer la dyspnée d'exercice et avoir un impact majeur soit sur la capacité d'exercice soit sur la qualité de vie des patients ayant une BPCO à un stade précoce.

Pour vérifier cette hypothèse, nous avons conduit une étude interventionnelle chez des patients atteints de BPCO à un stade précoce.

Hypothèse 2: il a été mis en évidence dans la littérature que les patients atteints d'ICC peuvent aussi présenter une atteinte des petites voies aériennes qui peut se manifester comme une diminution des débits aériens à bas volume pulmonaire qui peut être recherchée sur la courbe débit-volume [22, 23, 49]. La nature de l'atteinte des voies aériennes distales n'est pas encore connue mais pourrait être dûe à l'œdème de la muqueuse bronchique, à l'hyperréactivité des voies aériennes, ou à l'effet du vieillissement, du tabagisme ou de la combinaison de l'ensemble ces facteurs [49-53]. Indépendamment de la cause de l'atteinte, les anomalies des petites voies aériennes et des rapports ventilation-perfusion, souvent associées à un déconditionnement musculaire, contribuent à une réponse ventilatoire anormale à l'effort et de la survenue d'une distension thoracique dynamique qui limite l'exercice et contribue à la dyspnée [22, 23]. L'amélioration de la fonction cardiaque et des rapports ventilation-perfusion grâce à une stimulation cardiaque bi-ventriculaire pourrait diminuer la réponse ventilatoire à l'exercice ainsi qu'améliorer la fonction bronchique en diminuant la congestion de la muqueuse bronchique (comme a été mis en évidence dans une étude qui a explorée les effets de la methoxamine -un vasoconstricteur de la muqueuse bronchique qui peut entrainer une augmentation des débits expiratoires - sur la tolérance à l'effort chez certains patients atteints d'ICC [54]). Ceux-ci pourraient, à leur tour, contribuer à la diminution de la distension thoracique à l'exercice. La réduction de la distension thoracique

pourrait améliorer la dyspnée d'exercice et avoir un impact majeur soit sur la capacité d'exercice soit sur la qualité de vie des patients ayant une ICC.

Pour vérifier cette hypothèse, nous avons conduit une étude interventionnelle chez des patients atteints d'ICC qui remplissaient les critères d'implantation d'un stimulateur cardiaque bi-ventriculaire.

Hypothèse 3: il a récemment été mis en évidence dans la littérature que les patients atteints d'HTAP peuvent présenter des anomalies de la mécanique respiratoire (sous la forme d'une diminution des débits aériens à bas volume pulmonaire, évocatrice d'une atteinte des petites voies aériennes) [24-26]. Ainsi, la diminution des débits aériens à bas volume pulmonaire peut entraîner à l'effort une distension thoracique dynamique [27] particulièrement délétère qui peut également contribuer à déterminer ou intensifier la dyspnée induite par l'exercice physique.

Pour vérifier cette hypothèse, nous avons conduit une étude observationnelle chez les patients atteints d'HTAP.

4 - Étude interventionnelle nº 1: évaluation d'une réversibilité aigue aux bronchodilatateurs chez les patients ayant une BPCO de stade I selon la classification de GOLD.

Comme cela a été exposé précédemment, au cours de la BPCO à un stade précoce, les anomalies des voies aériennes distales sans obstruction spirométrique majeure et des rapports ventilation-perfusion, contribuent à une réponse ventilatoire anormale à l'effort et de la survenue d'une distension thoracique dynamique qui limite l'exercice et contribue également à la dyspnée induite par l'exercice physique [19-21]. Chez ces patients, l'impact d'un traitement avec des bronchodilatateurs à courte durée d'action sur la mécanique respiratoire et sur la dyspnée est inconnu.

Nous avons étudié les effets de 500 microgrammes d'ipratropium nébulisé et d'un placebo sur la fonction pulmonaire au repos et sur le profil ventilatoire à l'exercice et la dyspnée d'effort

(selon l'échelle de Borg) lors d'une épreuve fonctionnelle à l'exercice sur cyclo-ergomètre à charge constante chez 16 patients atteints de BPCO de stade I selon la classification de GOLD après 2h de l'administration d'ipratropium ou de placebo. La charge constante correspondant à une puissance égale à 80-85% de la puissance maximale développée lors d'une épreuve fonctionnelle à l'exercice initiale à charge croissante.

Par rapport à placebo, l'ipratropium améliore le volume expiratoire maximal seconde (VEMS), diminue le volume résiduel et les résistances spécifiques des voies aériennes de façon très significative ($p<0.05$) après IB. L'ipratropium augmente la capacité inspiratoire et le volume courant significativement ($p<0.05$) à un temps standardisé lors de l'épreuve fonctionnelle à l'exercice, tandis que il réduit significativement ($p<0.05$) l'intensité de la dyspnée et le rapport dyspnée/ventilation minute. Une forte corrélation entre la réduction de l'intensité de la dyspnée et la réduction de la distension thoracique à l'effort a été observée ($p<0.05$) après l'ipratropium.

Les résultats de cette étude montrent que même chez les patients atteints de BPCO sans obstruction spirométrique majeure (Gold I), la présence d'une maladie des petites voies aériennes suffit à induire une distension thoracique à l'exercice qui peut être modifiée par l'ipratropium. La réduction de la distension thoracique à l'exercice induite par l'ipratropium améliore la dyspnée d'exercice et peut donc théoriquement avoir un impact majeur sur la capacité d'exercice et sur la qualité de vie des patients ayant une BPCO à un stade précoce.

Les données issues de ce premier travail ont fait l'objet d'une publication scientifique dans la revue Thorax (*O'Donnell DE, Laveneziana P, Ora J, Webb KA, Lam YM, Ofir D. Evaluation of acute bronchodilator reversibility in patients with symptoms of GOLD stage I COPD. Thorax. 2009 Mar;64(3):216-223*).

5 - Étude interventionnelle nº 2: effets d'un stimulateur **cardiaque bi-ventriculaire sur la réponse ventilatoire et la dyspnée induite par l'exercice physique chez les patients atteints d'insuffisance cardiaque chronique stable.**

Comme cela a été exposé précédemment, les patients atteints d'ICC peuvent aussi présenter une atteinte des petites voies aériennes qui peut se manifester comme une diminution des débits aériens à bas volume pulmonaire qui peut être recherchée sur la courbe débit-volume [22, 23] et ainsi des anomalies des rapports ventilation-perfusion liées a la dysfonction cardiaque qui contribuent à une réponse ventilatoire anormale à l'effort [22, 23, 49, 51, 53]. Les mécanismes par lesquelles une amélioration aigüe de la fonction cardiaque aboutit à une amélioration de la dyspnée d'effort sont toujours inconnus.

Nous avons émis l'hypothèse que l'amélioration aigüe de la fonction cardiaque et des rapports ventilation-perfusion grâce à l'aide d'un stimulateur cardiaque bi-ventriculaire pourrait diminuer la réponse ventilatoire à l'exercice qui pourrait, à son tour, contribuer à la diminution de la distension thoracique à l'exercice et a la réduction concomitante de la contrainte d'expansion du volume courant. Ceux-ci devraient améliorer la dyspnée d'exercice et avoir un impact positif sur la capacité d'exercice des patients ayant une ICC.

Au cours d'une étude randomisée, menée selon un schéma croisé en double aveugle, nous avons comparé le profil cardiovasculaire, métabolique et ventilatoire, la distension thoracique à l'exercice (mesure de la capacité inspiratoire) et l'intensité de la dyspnée (échelle de Borg) lors d'une épreuve fonctionnelle à l'exercice sur cyclo-ergomètre à charge croissante chez sept patients atteints d'ICC stable. Ils étaient étudiés dans deux conditions: stimulateur cardiaque bi-ventriculaire actif ("ON") et stimulateur cardiaque bi-ventriculaire non-actif ("OFF").

Avec le stimulateur cardiaque bi-ventriculaire actif ("ON"), la consommation d'oxygène était augmentée ($p<0.05$), et l'intensité de la dyspnée était réduite pour un niveau d'exercice standardisé de 40 watts et pour un niveau de ventilation minute standardisé de 31 l/min de façon très significative ($p<0.05$). De la même façon, la réponse cardiovasculaire, métabolique et ventilatoire, étaient significativement améliorée ($p<0.05$), et la capacité inspiratoire et le volume courant étaient significativement augmentes ($p<0.05$) lorsque le stimulateur cardiaque bi-ventriculaire était actif ("ON").

La mise en route du stimulateur bi-ventriculaire a donc abouti à une amélioration aigüe de la fonction cardiaque et des rapports ventilation-perfusion lors d'une épreuve fonctionnelle à l'exercice sur cyclo-ergomètre à charge croissante. Ceci a abouti à une diminution de la réponse ventilatoire à l'exercice qui, à son tour, a contribué à la diminution de la distension thoracique à l'exercice et a la réduction concomitante de la contrainte d'expansion du volume courant. Il s'agit des facteurs clefs de la dyspnée d'exercice chez ces patients ayant une ICC stable.

Les données issues de ce deuxième travail ont fait l'objet d'une publication scientifique dans la revue Journal of Applied Physiology (*Laveneziana P, O'Donnell DE, Ofir D, Agostoni P, Padeletti L, Ricciardi G, Palange P, Duranti R, Scano G. Effect of biventricular pacing on ventilatory and perceptual responses to exercise in patients with stable chronic heart failure. J Appl Physiol. 2009 May;106(5):1574-1583*).

6 - Étude observationelle: contrainte d'expansion du volume courant et dyspnée induite par l'exercice physique chez les patients atteints d'hypertension artérielle pulmonaire.

La troisième des études qui constituent cette thèse est un travail expérimental mené à Paris (collaboration équipes Pr Similowski-Pr Humbert). L'article correspondant est en cours de révision par l'ERJ.

Cette étude montre que, chez des patients atteints d'HTAP idiopathiques (n=25) non fumeurs et dont le VEMS/CV est normal, on peut observer, dans 60% des cas (n=15), une diminution des débits aériens à bas volume pulmonaire (évocatrice d'une atteinte des petites voies aériennes). Ces patients (n=15) ont également une distension thoracique à l'effort (0.50±0.15L) qui contribue à augmenter leur dyspnée. En particulier, chez ces patients qui présentent une distension thoracique à l'effort, nous avons détecté une différence significative de 2.3 unités d'intensité de la dyspnée mesurée à un travail mécanique standardisé de 60watts (iso-WR) et à un niveau de ventilation de ~40L/min (iso-V'_E) lors d'une épreuve fonctionnelle à l'exercice sur cyclo-ergomètre à charge croissante, ceci par rapport aux patients HTAP qui ne présentent pas une diminution des

débits aériens à bas volume pulmonaire sur la courbe débit-volume et, par conséquent, ne présentent pas une distension thoracique à l'effort (n=10). Une forte corrélation entre l'intensité de la dyspnée, la réponse ventilatoire et la distension thoracique à l'effort a été mise en évidence.

La distension dynamique et la ventilation minute excessive lors de l'épreuve fonctionnelle à l'exercice semblent contribuer à l'augmentation de l'intensité de la dyspnée chez certains patients atteints d'HTAP idiopathique. Du point de vue thérapeutique, la mise en évidence d'une propension à la distension thoracique induite par l'exercice chez certains patients atteints d'HTAP (c'est- à-dire, chez qui présente une nette diminution des débits aériens à bas volume pulmonaire sur la courbe débit-volume), pourrait fournir une base théorique à l'adjonction des bronchodilatateurs aux traitements à visée hémodynamique, en sachant qu'une réduction de la distension thoracique devrait diminuer la dyspnée d'effort, améliorer la tolérance à l'exercice, et avoir théoriquement un impact majeur sur la qualité de vie de certains patients atteints d'HTAP qui représente une situation clinique et physiopathologique où les anomalies de la mécanique respiratoire ne sont a priori pas le *primum movens* de la maladie.

Ce troisième travail a été accepté avec révision pour faire l'objet d'une publication scientifique dans la revue European Respiratory Journal (*Pierantonio Laveneziana, Gilles Garcia, Fadia Nicolas-Jilwan, Toufik Brahimi, Louis Laviolette, Olivier Sitbon, Gérald Simonneau, Marc Humbert, Thomas Similowski. Tidal volume constraints and dyspnoea during exercise in pulmonary arterial hypertension. Eur Respir J 2012, accepté avec révision*).

7 - Discussion, Conclusions et Perspectives futures.

Les données issues des travaux regroupés au sein de cette thèse contribuent à une meilleure connaissance de la physiopathologie de la dyspnée d'exercice dans le contexte de la BPCO à un stade précoce, de l'insuffisance cardiaque chronique et de l'hypertension artérielle pulmonaire, en mettant en évidence le rôle d'un mécanisme pathogénétique connu qui n'avait pas été décrit et tant que tel auparavant. En effet, il apparaît sans ambiguïté que la diminution des débits aériens à bas

volume pulmonaire (évocatrice d'une atteinte des petites voies aériennes) recherchée sur la courbe débit-volume, est un facteur favorisant à l'effort de la survenue d'une distension thoracique dynamique particulièrement délétère. De plus, cette distension thoracique est elle-même impliquée dans la dyspnée d'exercice, par le biais d'une réduction critique du volume de réserve inspiratoire dynamique qui génère une contrainte mécanique (impossibilité d'augmenter le volume courant qui plafonne) qui pèse sur la ventilation.

Nos travaux montrent de façon très claire une association entre les deux phénomènes. Le corollaire de ces constatations est que des interventions thérapeutiques qui réduisent la distension thoracique devraient diminuer la dyspnée d'effort et améliorer la tolérance à l'exercice. En effet, la réduction de la dyspnée d'effort est bien corrélée avec la réduction du volume pulmonaire induite directement par des interventions pharmacologiques (bronchodilatateurs à courte duré d'action, première étude interventionelle) ou indirectement (par diminution de la réponse ventilatoire à l'exercice qui, à son tour, contribue à la diminution de la distension thoracique à l'exercice) par des interventions non-pharmacologiques (stimulateur cardiaque bi-ventriculaire, deuxième étude interventionelle).

Avoir observé dans l'ICC et l'HTAP, qui représentent des situations cliniques et physiopathologiques où les anomalies de la mécanique respiratoire ne sont à priori pas le *primum movens* de ces maladies, qu'une partie de la variabilité de la dyspnée d'exercice est expliquée par des facteurs « non liés à la maladie sous jacente », nous permet de lancer la problématique du traitement « non physiopathologique » de la dyspnée. Même si il est contre intuitif en apparence de donner des traitements à visée « respiratoire » à des malades dont la dyspnée est due à d'autres causes, ces traitements peuvent être bénéfiques vu la nature multifactorielle et exponentielle de la sensation dyspnéique chez ces patients.

Par exemple, la mise en évidence d'une propension à la distension thoracique dynamique chez certains patients atteints d'HTAP et d'ICC stable (c'est-à-dire, chez ceux qui présentent une nette diminution des débits aériens à bas volume pulmonaire sur la courbe débit-volume), pourrait fournir

une base théorique à l'adjonction des bronchodilatateurs aux traitements à visée hémodynamique, en sachant qu'une réduction de la distension thoracique devrait diminuer la dyspnée d'effort, améliorer la tolérance à l'exercice, et avoir théoriquement un impact majeur sur la qualité de vie des ces patients chez lesquels les anomalies de la mécanique respiratoire ne sont a priori pas le *primum movens* de la maladie.

De plus, l'amélioration de la fonction bronchique par l'inhalation de la methoxamine (un vasoconstricteur de la muqueuse bronchique qui peut, en diminuant la congestion de celle-ci, entrainer une augmentation des débits expiratoires, comme cela a été mis en évidence chez certains malades atteints d'ICC stable [54]) chez certains patients atteints d'HTAP qui présentent une nette diminution des débits aériens à bas volume pulmonaire sur la courbe débit-volume (évocatrice d'une mécanique anormale des petites voies aériennes) pourrait, à son tour, contribuer à la diminution de la distension thoracique et de la dyspnée d'exercice et avoir théoriquement un impact majeur sur la capacité d'exercice et sur la qualité de vie des ces patients.

Une limitation de nos études tient au fait que nous n'avons pas mesuré directement la force et la fonction des muscles respiratoires. Il sera important dans le futur de mieux quantifier et de mieux décrire la fonction des muscles respiratoires, en sachant que des anomalies de la fonction des muscles respiratoires peuvent contribuenr à la dyspnée induite par l'exercice physique chez les patients attaints de BPCO, d'ICC et d'HTAP.

En conclusion, nos résultats constituent une avancée majeure dans la compréhension des mécanismes de la dyspnée et dans le domaine du traitement de la dyspnée à l'effort, surtout en ce qui concerne les maladies cardiovasculaires, qui représente une approche multidirectionnelle et pas forcément basée sur la physiopathologie cardiovasculaire de ces maladies.

INTRODUCTION

Dyspnoea is a complex, multifaceted and highly personalized sensory experience, the source and mechanisms of which are incompletely understood.

Activity-related dyspnoea is usually the earliest and most troublesome complaint for which patients with cardio-pulmonary diseases seek medical attention**.** This symptom progresses relentlessly as the disease advances leading invariably to avoidance of activity with consequent skeletal muscle deconditioning and an impoverished quality of life. The effective management of exertional dyspnoea remains a major challenge for caregivers, and modern treatment strategies that are based on attempts to reverse the underlying chronic condition are only partially successful.

A growing body of evidence indicates that patients with cardio-pulmonary diseases present with abnormalities in respiratory mechanics. Among these, dynamic lung hyperinflation commonly accompanies a reduction of expiratory flows at low lung volumes or an overt expiratory flow-limitation in patients with GOLD stage I-III chronic obstructive pulmonary disease (COPD) [18-21, 33, 47, 48], chronic heart failure (CHF) [22, 23] and pulmonary arterial hypertension (PAH) [27].

Dynamic lung hyperinflation occurs during exercise in the majority of flow-limited patients with COPD and may have serious sensory and mechanical consequences. This proposition is supported by several studies, which have shown a close correlation between indices of dynamic lung hyperinflation and measures of exertional dyspnoea [10-12, 17-19, 21, 32, 33, 42-45, 47, 48, 55]. The strength of this association has been further confirmed by studies that have therapeutically manipulated this dependent variable by showing that relief of exertional dyspnoea correlates well with pharmacological and/or non-pharmacological reduction of lung hyperinflation [14, 33, 56-60]. The mechanisms by which dynamic lung hyperinflation gives rise to exertional dyspnoea are complex. However, recent mechanistic studies suggest that dynamic lung hyperinflation-induced volume restriction and consequent neuromechanical uncoupling of the respiratory system are key mechanisms [10-12, 18, 33]. The objective of the present thesis is, therefore, to determine whether the association between lung hyperinflation and exertional dyspnoea exists in patients with PAH

(study 3) and whether therapeutic manipulations that reduce lung hyperinflation contribute to the amelioration of exertional dyspnoea in patients with GOLD stage I COPD (study 1) and CHF (study 2). After a short synthesis of the current knowledge on the physiological mechanisms of lung hyperinflation during physical exertion and its negative mechanical and sensory consequences, this thesis presents, in three chapters, three different works, two of which has already been published in scientific journals while the third one is being given full consideration for publication (revision submitted).

The first work, interventional in nature, has been conducted at the Respiratory Investigation Unit, Queen's University, Kingston, Ontario, Canada under the supervision of Prof. Denis O'Donnell. The second work, also interventional in nature, has been conducted at the Department of Internal Medicine, Section of Clinical Immunology, Allergology and Respiratory Disease, Policlinico di Careggi, University of Florence, Italy under the supervision of Prof. Giorgio Scano and at the Respiratory Investigation Unit, Queen's University, Kingston, Ontario, Canada under the supervision of Prof. Denis O'Donnell. The third work, observational in nature, have been conducted at the Pulmonary Function Laboratory (Service des Explorations Fonctionnelles Respiratoires), Antoine Béclère Hospital, Clamart, France, under the supervision of Prof. Thomas Similowski (Paris 6 University, ER10 UPMC, "Biology and Physiology of cardiopulmonary and neurorespiratory interactions"), in collaboration with the director of the Pulmonary Function Laboratory, Dr. Gilles Garcia, and the director of INSERM U999 "Pulmonary Hypertension: pathophysiology and therapeutic innovation" (Paris XI University) of the National Reference Centre for Pulmonary Hypertension (Antoine Béclère Hospital, Clamart, France), Prof. Marc Humbert.

For the candidate, this thesis has provided the unique opportunity to extend his previous work on the pathophysiology of exertional dyspnoea in moderate and severe COPD to the GOLD stage I COPD, as well as to CHF and PAH. Moreover, the results of this work have important clinical implications which can potentially improve the therapeutic management of these devastating and disabling diseases.

SYNTHESIS OF THE CURRENT KNOWLWDGE AND BACKGROUND

The vast majority of the literature on the association between lung hyperinflation and exertional dyspnoea has focused on COPD, and this is the reason why the present thesis will refer essentially to it. On the other hand, this thesis examines, in some detail, the derangements of ventilatory mechanics that are peculiar to CHF and PAH and attempts to provide a mechanistic rationale for the attendant respiratory discomfort.

1.1. Pathophysiology of Dynamic Lung Hyperinflation

Recent evidence have indicated that patients with GOLD stage I COPD [19-21], CHF [22, 23] and PAH [24-27] may exhibit either reduced expiratory flows at low lung volumes at spirometry (namely instantaneous forced expiratory flows measured after 50% and 75% of the FVC has been exhaled [$FEF_{50\%}$ and $FEF_{75\%}$] lower than predicted) or overt expiratory flow-limitation. Expiratory flow-limitation occurs when the flows generated during spontaneous tidal expiration represent the maximal possible flows that can be generated at that operating lung volume [61]. The reduced expiratory flows at low lung volumes as well as the expiratory flow-limitation are well known factors that contribute to promote dynamic lung hyperinflation [defined as a *temporary and variable increase in end-expiratory lung volume (EELV) above its baseline value*] under conditions of increased ventilatory demand, such as in response to physical exercise [29-31, 42].

In health, ventilation (V'_E) increases during exercise by a progressive expansion of V_T to approximately 60% of the vital capacity (VC) or 75% of total lung capacity (TLC). At this operating volume, the diaphragm muscle fibres are maximally shortened and further increases in V'_E may be accomplished solely through increases in breathing frequency which leads to significant reductions in dynamic lung compliance. The expiratory muscles are activated even in mild exercise to reduce dynamic end-expiratory lung volume (EELV); the magnitude of EELV reduction varies with the type and intensity of exercise - with average reductions between 0.3-1.0L below relaxation volume of the respiratory system (V_r) [62-66]. Expiratory muscle recruitment offers several

advantages in health, in fact it allows inspiratory muscles to be lengthened to near optimal levels for force generation during the subsequent inspiration and allows V_T to expand to a maximum of 50 to 60% of the VC by encroaching almost equally on the expiratory and inspiratory reserve volumes (ERV and IRV, respectively) (**Figure 3**, French version) [66]. This ensures that V_T expands within the most compliant (linear) portion of the respiratory system's sigmoid pressure-volume (P-V) relationship (i.e., 20 to 80% of VC) throughout exercise [66], where there is no need of generating high pressure for expanding V_T (i.e., small pressure to generate a high V_T over this range) and the relationship between contractile respiratory muscle effort and thoracic volume displacement is preserved. In this way V_T by encroaching on IRV and ERV (decreasing EELV) may increase without end-inspiratory lung volume (EILV = EELV + V_T) encroaching on the "stiffer" upper portion of respiratory system's P-V relationship, where there is increased elastic loading (**Figure 5**, French version).

Healthy young subjects are able to increase their V_T during exercise by encroaching on the ERV below the EELV because they have available expiratory flow reserve at that lung volume to accommodate their V_T within the ERV available [66]. In other words, the flow rates and the volume changes seen during maximal exercise are well within the maximal flow-volume loops obtained at rest (**Figure 3**, French version), showing no significant expiratory flow-limitation (i.e. impingement of tidal flow-volume loops onto the maximal flow-volume loop) [66].

In health, the relaxation volume (V_r) of the respiratory system is dictated by the balance of forces between the inward elastic recoil pressure of the lung and the outward recoil pressure of chest wall. With advancing age, changes in the connective tissue matrix of the lung result in a reduction of the lung elastic recoil pressure, and the equilibrium point (where the net elastic recoil of the total respiratory system is zero) therefore occurs at a higher lung volume than in youth [42, 43]. In COPD, the increased compliance of the lung, as a result of destructive emphysema, leads to a resetting of the respiratory system's relaxation volume to a higher level than in age-matched

healthy individuals [42, 43] **(Figure 6**, French version**)**. This has been termed "static" lung hyperinflation.

The volume of air remaining in the lung at the end of spontaneous expiration (i.e., end-expiratory lung volume [EELV]) is increased in COPD compared with health. EELV is synonymous with the more conventional term functional residual capacity (FRC). While in health the EELV during relaxed resting breathing corresponds with the actual equilibrium position of the respiratory system, this is often not the case in COPD [42, 43]. During spontaneous resting breathing in patients with expiratory flow-limitation, EELV is also "dynamically" determined and is maintained at a level above the statically-determined relaxation volume of the respiratory system. In flow-limited patients, the mechanical time-constant for lung emptying (i.e., the product of compliance and resistance, "τ") is increased in many alveolar units, but the expiratory time available (as dictated by the respiratory control centers) is often insufficient to allow EELV to return to its normal relaxation volume, and gas accumulation and retention (often termed "air trapping") ensues. In other words, lung emptying during expiration becomes incomplete because it is interrupted by the next inspiration and EELV therefore exceeds the natural relaxation volume of the respiratory system (dynamic hyperinflation) (**Figure 6**, French version). Consequently, the inspiratory muscles have to offset a threshold load - termed auto or intrinsic positive end-expiratory pressure (PEEP) - before inspiratory flow can begin [42, 43]. This situation is further aggravated during times of increased ventilatory demand, such as exercise, where an increase in respiratory rate results in a further decrease in the amount of time available for expiration. Importantly, even in CHF [22, 23], PAH [24-27] and COPD patients with less severe disease [19-21] who may not have evidence of overt expiratory flow-limitation at rest but only a reduction of expiratory flows at low lung volumes at spirometry (i.e., reduced $FEF_{50\%}$ and $FEF_{75\%}$), increases in V'_E during exercise can lead to dynamic increases in EELV above the baseline resting value. In this way, EELV becomes a dynamic variable that fluctuates widely between rest and activity, dependent on such factors as the

degree of flow limitation and breathing pattern, the extent of dynamic airway compression during expiration and the pattern of recruitment of ventilatory muscles.

1.2. Measurement of Dynamic Lung Hyperinflation during Exercise

The measurement of EELV during exercise is cumbersome, so surrogate measurements are often used. The rate and magnitude of dynamic lung hyperinflation during exercise is generally measured in the laboratory setting by serial inspiratory capacity (IC) measurements [18, 21, 33, 42, 44, 46-48, 67]. The IC is *the maximal volume of air that can be inhaled after a spontaneous expiration to EELV*. Since TLC does not change during physical activity [23, 68, 69], the change (decrease) in IC reflects the change (increase) in dynamic EELV, or the extent of dynamic lung hyperinflation (**Figure 4**, French version). This simple method has been shown to be reliable and recent multi-centre clinical trials have confirmed its reproducibility and responsiveness [48, 58, 70, 71].

The use of change in IC to track dynamic lung hyperinflation is further validated by studies that have used oesophageal manometry to demonstrate that even severely dyspnoeic COPD patients are capable of generating maximal inspiratory pressures at the end of exhaustive exercise [16, 72]. This implies that the reductions in IC seen during exercise in COPD are not due to submaximal efforts, and indeed reflect changes in underlying EELV.

1.3. Consequences of Chronic Lung Hyperinflation

Patients with COPD not only have an increased load on the respiratory muscles, but the capacity of their respiratory muscles to generate pressure is also decreased [73]. Hyperinflation impairs the capacity of the respiratory muscles to generate negative intrathoracic pressure through several mechanisms: worsening of the length-tension relationship, decrease in the zone of apposition, decrease in the curvature of the diaphragm, change in the mechanical arrangement of

costal and crural components of the diaphragm, and increase in the elastic recoil of the thoracic cage [73].

Hyperinflation decreases the resting length of the diaphragm and, less so, of the rib cage muscles. The shortening is due to a decrease in the length of the zone of apposition, which causes a decrease in the pressure generated by the diaphragm [73]. The zone of apposition normally constitutes 60% of the diaphragm's total area, but only 40% in patients with COPD. The smaller zone of apposition means that less of the rib cage is exposed to the positive abdominal pressure produced by diaphragmatic contraction, and this further limits the capacity of the diaphragm to produce rib cage expansion.

Hyperinflation has limited effect on the length-tension relationship of the intercostal muscles [73]. As lung volume increases from FRC to TLC, the parasternal intercostals shorten only by 2 to 8% and the external intercostals shorten by no more than 11%. In contrast, the diaphragm shortens by 25% over the same change in volume [73]. The influence of lung volume on the ability to generate pressure, however, is greater for the rib cage muscles than for the diaphragm [74]. On going from a low lung volume to TLC, the rib cage muscles experience an 80% decrease in inspiratory pressure generation, contrasted with a 60% decrease for the diaphragm [74]. The rib cage muscles are less effective because of a shift in the ribs from their usual oblique orientation to a more horizontal position [74]. This shift increases the impedance to rib cage expansion, and the disadvantage is greater for the rib cage muscles than for the diaphragm [74].

Hyperinflation has traditionally been thought to cause flattening of the diaphragm and to increase its radius of curvature. According to Laplace's law, an increase in the radius of curvature causes an increase in the passive tension of the diaphragm and a decrease in the efficiency of transdiaphragmatic pressure generation. At resting FRC, however, the curvature of the diaphragm (coronal plane) is only 3.5% smaller in patients with severe COPD than in healthy subjects [73]. The radius of curvature also changes little over the range of inspiratory capacity in either patients with severe COPD or in healthy subjects [73]. As such, a change in curvature is likely to be less

important than a change in length of diaphragmatic fibers in determining contractile force at either FRC or over the range of IC. When the EELV of dogs is increased by applying PEEP, the costal and crural diaphragms change from a parallel to a series arrangement [73]. The series arrangement decreases the ability of the diaphragm to generate force, and the diaphragm has an expiratory rather than inspiratory action on the rib cage [73]. The same limitation may apply in patients with COPD who are hyperinflated.

As explained above, EELV is usually determined by the static equilibrium between inwardly directed elastic recoil of the lungs and outwardly directly recoil of the thoracic cage (relaxation volume). The outwardly directed forces help the inspiratory muscles to inflate the lungs. When EELV lies above 70% of predicted TLC [73], thoracic elastic recoil is directed inward. With such dynamic hyperinflation, the inspiratory muscles have to work not only against the elastic recoil of the lungs but also against that of the thoracic cage [73].

Nonetheless, the insidious development of flow-limitation and hyperinflation over many years allows for several adaptive mechanisms to come into play to preserve the functional strength of the overburdened inspiratory muscles, particularly the diaphragm [34]. A number of studies have shown several structural adaptations to chronic intrinsic mechanical loading, which include: *1)* reduction in sarcomere length, which improves the ability of the muscle to generate force at higher lung volumes [37]; *2)* an increase in the relative proportion of Type I fibres, which are slow-twitch and fatigue resistant [38, 75]; and *3)* an increase in mitochondrial concentration and efficiency of the electron transport chain, which improves oxidative capacity [37]. It is believed that the function of intercostal and sternomastoid muscles is less disadvantaged than that of the diaphragm in the presence of severe lung hyperinflation [76, 77]. However, despite this temporal adaptation, the presence of severe hyperinflation means that the ability to increase ventilation, when this demand arises, is greatly limited in COPD.

1.4. Negative Effects of Acute Dynamic Lung Hyperinflation during Exercise

Mechanically, the resting IC and, in particular, the dynamic IC during exercise represent the true operating limits for inspiratory V_T expansion. Therefore, when V_T approximates the peak dynamic IC during exercise, or the dynamic end-inspiratory lung volume (EILV) approaches the TLC envelope, further volume expansion is impossible, even in the setting of increasing central drive and inspiratory muscle activation (**Figure 4**, French version). The consequence of this "saturation" of V_T (which occurs when IRV has declined to a critically low value of approximately one half of a litre below TLC) is that further increases in V'_E must rely on increases in breathing frequency [18, 19, 21, 33, 40]. Unfortunately, in flow-limited patients, increases in breathing frequency may further aggravate dynamic lung hyperinflation in a vicious cycle and, in addition, contribute to reduced dynamic lung compliance and increased flow-resistive work.

Although dynamic lung hyperinflation serves to optimise expiratory flow rates by avoiding expiratory flow-limitation at lower lung volumes, it has the deleterious effect of forcing V_T to operate on the upper, flatter part of the respiratory system's compliance curve where increases in pressure no longer generate significant incremental volume change (**Figure 5**, French version). In essence, dynamic lung hyperinflation reduces the ability of V_T to expand appropriately during exercise thus imposing "restrictive" mechanics on the respiratory system and leading to early mechanical limitation of V'_E [18, 19, 21, 33, 40]. In some patients, the mechanical constraint on V_T expansion, in the setting of severe ventilation-perfusion abnormalities (i.e., high fixed physiological dead space), leads to carbon dioxide retention and arterial oxygen desaturation during exercise [41].

Dynamic lung hyperinflation reduces the capacity of the respiratory muscles to generate pressure and increases their mechanical load (both elastic and threshold loads on the inspiratory muscles). Dynamic lung hyperinflation results also in increased intrinsic PEEP: the increase in intrinsic PEEP is overcome by contraction of the diaphragm, commencing before the start of inspiratory flow, thus resulting in a wasted inspiratory effort [73].

The inspiratory threshold load reflects the force that the inspiratory muscles must generate to counterbalance the inward (expiratory) recoil of the lung and chest wall at end-expiration and can

be substantial in COPD [16]. Dynamic lung hyperinflation results in functional inspiratory muscle weakness by maximally shortening the muscle fibers in the diaphragm [14, 34, 35]. The combination of excessive mechanical loading and increased velocity of shortening of the inspiratory muscles can also predispose them to fatigue [35, 78]. However, there is little evidence that inspiratory muscle fatigue actually occurs during incremental cycle exercise even in patients with severe COPD. In fact, there is increasing evidence to the contrary and a suggestion that structural adaptations in the inspiratory muscles, particularly in the diaphragm, render them resistant to fatigue [37-39].

Finally, dynamic lung hyperinflation adversely affects dynamic cardiac function by contributing to pulmonary hypertension, by reducing right ventricular pre-load (reduced venous return) and, in some cases, by increasing left ventricular afterload [56, 79-82]. In the absence of cardiac disease, cardiac output has been found to increase normally as a function of $V'O_2$ during submaximal exercise in COPD, although stroke volume is generally smaller and heart rate correspondingly higher than in health [80, 83]. Of note, peak cardiac output reaches a lower maximal value during exercise in COPD, which may be due, in part, to the abnormal ventilatory mechanics [80, 83].

It has recently been postulated that competition between the overworked ventilatory muscles with the active peripheral muscles for a reduced cardiac output may compromise blood flow and oxygen delivery to the latter, with negative consequences for exercise performance [84-86]. However, the impact of dynamic lung hyperinflation on cardiac output and ventilatory/locomotor muscle competition during exercise needs further study.

All of the above factors are clearly interdependent and contribute in a complex, integrated manner to dyspnoea in patients with COPD.

1.5. Lung Hyperinflation and Exertional Dyspnoea

Dyspnoea, or the perception of respiratory discomfort, is a complex multifaceted and highly personalized sensory experience, the source and mechanisms of which are incompletely understood. Several studies, however, have demonstrated an association between dyspnoea intensity during exercise and indices of lung hyperinflation [16-18, 45-48]. For example, using multiple regression analysis, subjective Borg ratings of dyspnoea intensity were found to be most strongly correlated with changes in EILV (expressed as %TLC) during cycle exercise in 23 patients with advanced COPD (average FEV_1 = 36% predicted) [17]. Furthermore, the measured change in EELV, and the subsequent constraint of V_T expansion, also emerged as independent significant contributors to exertional breathlessness in these patients [17]. In another study by O'Donnell et al. [16], exertional Borg dyspnoea ratings measured at a standardized submaximal work rate correlated well with the concurrent ratio of EELV to TLC. Similarly, Puente-Maestu et al. [45] found that dyspnoea at the end of constant work rate cycle exercise correlated significantly with EELV as a percentage of TLC. In a larger study of 105 patients with moderate-to-severe COPD [47], the V_T/IC ratio, as an index of V_T constraint, emerged as the strongest predictor of exertional dyspnoea. Dyspnoea intensity has also been shown to correlate significantly with the extent of dynamic lung hyperinflation (decrease in IC) during the 6-minute-walk test [46].

1.6. Evaluation of dyspnoea during exercise

The study of dyspnoea within clinical populations under conditions of measured physiological stress (i.e., exercise) is an attempt to circumvent some of the interpretative difficulties of simulated loading in healthy volunteers. Such studies have been facilitated by the development of reliable instruments to measure dyspnoea intensity during exercise. The Borg scale [5], a category scale with ratio properties, has been shown to be reproducible and responsive and ideal for the purpose of dyspnoea assessment during CPET [48].

The key to successful utilization of the Borg scale is, first, precision concerning the specific respiratory sensation that the participant is being asked to rate (e.g., breathing effort, inspiratory

difficulty, air hunger, etc.). Second, the magnitude of respiratory sensation should, a priori, be anchored at both extremes of the scale such that a rating of "10" represents the maximal breathing difficulty that the patient has experienced (or could imagine) and "0" represents no breathing difficulty [87] (**Figure 1**, French version). Though somewhat less popular, the visual analogue scale is another dyspnoea measuring instrument with proven construct validity used during CPET [88, 89].

In accordance with the principals of psychophysical measurement, comparisons of dyspnoea intensity within and between patients should be undertaken at a *standardized* work-rate (WR), $V'O_2$ or V'_E during exercise. Stimulus-response relations can be analysed as slopes of dyspnoea intensity (Borg) over WR or $V'O_2$ (each expressed as %predicted) and compared in clinical populations and in age-matched healthy controls.

CPET allows systematic analysis of the physiological source(s) of exertional dyspnoea in the individual patient [90]. For example, CPET will help identify abnormal ventilatory responses (slopes of V'_E over carbon dioxide output ($V'CO_2$) are invariably increased in pulmonary disease) and the underlying cause of increased ventilatory drive (i.e., metabolic or pulmonary gas exchange abnormalities). The nature and degree of the mechanical abnormality can be assessed by measurement of dynamic operating lung volumes, while cardiovascular impairment can be recognized by indirect measurements (e.g., heart rate, oxygen pulse, anaerobic threshold, etc.) [48, 72].

1.7. Qualitative Aspects of Exertional Dyspnoea

Further insights into the link between dyspnoea and dynamic lung hyperinflation (in COPD) have arisen from studies that have explored the qualitative aspects of respiratory discomfort at a point where it reaches intolerable levels at the break-point of cycle exercise. Measurement of dynamic operating lung volumes (by serial IC measurements) and the ratio of contractile respiratory muscle effort to volume displacement [i.e., tidal esophageal pressure relative to maximum

inspiratory pressure (Pes/P_{Imax}): tidal volume expressed as % predicted vital capacity (V_T/VC)] throughout exercise allow an exploration of the contribution of mechanical factors to dyspnoea causation [18, 33, 91].

1.7.1. *Dyspnoea and Perceived Increased Respiratory Effort*

Recent theories on the mechanisms of dyspnoea have emphasized the central importance of the perception of increased contractile inspiratory muscle effort [10, 12, 92-99]. When skeletal muscles are mechanically loaded, weakened or fatigued, increased electrical activation of the muscle is required to generate a given force, and motor output to these muscles is amplified.

In all cardiopulmonary disorders, dyspnoea intensity rises during exercise as V'_E increases as a fraction of MVC. In fact, the V'_E/MVC ratio is the original dyspnoea "index" [100]. It is reasonable to suggest that dyspnoea intensity rises as a function of the amplitude of central motor command output that originates in the brainstem (automatic) and/or in cortical (voluntary) motor areas in the brain [10, 12]. Voluntary increases in isocapnic V'_E in healthy volunteers to mimic the hyperpnea of exercise are associated with substantially less perceived respiratory discomfort than during actual exercise, suggesting that efferent output from the brainstem is crucially important in inducing dyspnoea [101, 102]. It is reasonable to assume that in patients with cardio-pulmonary diseases, in whom cardiovascular and metabolic derangements drive the increase in ventilation, the brainstem is an important locus of unpleasant respiratory sensation [10-12]. It is postulated that central corollary discharge, which provides efferent copy of information from the brainstem respiratory centers to the somatosensory cortex, may be instrumental in dyspnoea perception, but this lacks definitive experimental verification in humans [10-12, 93, 94] (**Figure 2**, French version). In this regard, it is hypothesized that increased motor output is accompanied by increased corollary discharge to the sensory cortex where it is directly perceived as a heightened sense of effort [10, 12, 93-95, 103, 104] (**Figure 2**, French version).

In health, if the sensory information related to the motor act of breathing is attended to, a conscious determination will generally be made that perceived breathing effort is appropriate for the specific physical task been undertaken [10-12]. Increased respiratory muscular effort in health is appropriately rewarded by increased ventilatory output, even at high exercise intensities. Thus, this perception of increased effort or work of breathing need not be unpleasant and, therefore, need not elicit an affective "distress" response (limbic system activation) to perceived threat with corresponding behavioral compensation [10-12]. Perceived heightened inspiratory effort is pervasive in respiratory disease but is more intense and occurs at lower levels of exercise than in health.

In COPD all of the physiological adaptations that optimize neuromechanical coupling (and that presumably minimize breathing discomfort) in health are seriously disrupted. In this disease, respiratory muscular effort is substantially increased, reflecting increased ventilatory demand. Moreover, respiratory muscle contractile effort is increased for any given ventilation compared with health as a result of the increased loading and functional weakening of inspiratory muscles [16-18, 91]. Studies in cardiopulmonary diseases have shown that during CPET there is a close correlation between the magnitude (and duration) of respiratory effort (measured by tidal esophageal pressure relative to maximum) and the intensity of dyspnoea (measured by the Borg scale) [105]. Altered afferent information from activated mechanoreceptors in the overworked and shortened inspiratory muscles (secondary to dynamic lung hyperinflation) in COPD may contribute to an increased sense of work or effort, but this remains conjectural [12, 104]. Beyond a certain threshold, increased effort may be consciously registered as respiratory discomfort [92, 93, 96-99]. Qualitative descriptors at end-exercise that allude to increased effort or work of breathing are pervasive across health and disease and increased corollary discharge remains a plausible mechanistic explanation for this [12, 16].

However, it must be remembered that increased sense of effort is only one component of this multi-dimensional symptom, and it is acknowledged that dyspnoea can rise to severe levels

even in the absence of increases in contractile muscle effort [10, 12, 91, 106-111]. Mechanical ventilation, which successfully unloads the ventilatory muscles (thereby reducing effort), may not fully alleviate dyspnoea [112, 113]. Chemoreceptor stimulation (by adding carbon dioxide) can induce breathing discomfort, described as air hunger, even in the absence of ventilatory muscle activation [10, 12]. Finally, increasing breathing effort to a high fraction of the maximal possible effort is not necessarily perceived as discomfort in all circumstances [10, 12].

1.7.2. *Dyspnoea and Perceived Unsatisfied Inspiration*

In many respects, the sensory experience in COPD differs fundamentally from that of age-matched healthy individuals at peak $V'O_2$ [16]. While the sense of increased effort, work or heaviness of breathing is common to both groups, only COPD patients consistently select descriptors that allude to unsatisfied inspiration (ie, "can't get enough air in"), and it is reasonable to assume that these different qualitative dimensions of exertional dyspnoea in COPD reflect different underlying mechanisms [16, 18]. There appears to be considerable semantic overlap in the terms "air hunger" (the uncomfortable urge to breathe) described in the original hypercapnic experiments [114] and the qualitative descriptor cluster "unsatisfied inspiration" selected by patients with pulmonary disease at end-exercise [16, 18, 33].

The physiological events that occur at the end of exercise, when dyspnoea becomes intolerable, are well understood. The neural drive to breathe reaches near maximal values, driven by the elevated $V'CO_2$ that accompanies exercise and the early metabolic acidosis that may occur in many deconditioned COPD patients. In some patients, critical arterial oxygen desaturation, sympathetic nervous system over-activation and altered feedback from peripheral muscle metaboreceptors may additionally stimulate ventilation. As already outlined, however, the ventilatory output in response to the increased drive is often markedly diminished because of derangements of dynamic ventilatory mechanics. It is noteworthy that, in contrast to health, the effort-displacement ratio [the ratio of inspired effort Pes/P_{Imax}) to volume displacement (V_T/VC)]

continues to rise in COPD as exercise proceeds. This increased ratio, which crudely reflects the position of the operating tidal volume on the respiratory system's pressure-volume relation (and thus the degree of neuromechanical dissociation), correlates well with perceived intensity of inspiratory difficulty. For example, in 12 patients with severe COPD (FEV_1 = 37% predicted), the effort-displacement ratio was the strongest correlate of dyspnoea intensity during exercise (r=0.86, p<0.001), and also correlated strongly with dynamic hyperinflation (EELV/TLC; r=0.78, p<0.001) [16].

Two recent mechanistic studies has attempted to reconcile the beneficial effects of dynamic lung hyperinflation in early exercise with its deleterious sensory effects that ultimately contribute to exercise limitation [18, 33]. Thus, dynamic lung hyperinflation early in exercise allowed flow-limited patients to increase V'_E while minimizing respiratory discomfort [18, 33]. As a result of this early dynamic lung hyperinflation, the airways are maximally stretched at the higher lung volumes (close to TLC) and expiratory flow-limitation is attenuated allowing patients to maximize expiratory flow rates. Thus, patients with severe COPD could abruptly increase V'_E commensurate with increased metabolic demand, to approximately 40L/min and generate tidal inspiratory pressures exceeding 40% of the maximal possible pressure generation while experiencing minimal increases in dyspnoea (modified Borg ratings 1-2). Effort-displacement ratios are therefore well maintained early in exercise even in advanced COPD. However, this advantage of dynamic lung hyperinflation was quickly negated when V_T expanded to reach a critically low IRV of approximately 0.5L (or 10 % predicted TLC) below TLC [18, 33]. At this "threshold", V_T becomes fixed on the upper less compliant extreme of the respiratory system's sigmoid-shaped pressure-volume relation, where there is increased elastic loading of the inspiratory muscles. At this operating volume, the diaphragm muscle fibers are maximally shortened and the increased breathing frequency leads to increased velocity of shortening and significant reductions in dynamic lung compliance. After reaching this minimal IRV, dyspnoea (described as unsatisfied inspiration) soon rose to intolerable levels and reflected the widening disparity between inspiratory effort

(reaching near maximal central neural drive) and the simultaneous V_T response, which becomes essentially fixed, i.e., increased effort-displacement ratio [18, 33]. Consistent with a previous study [16], dyspnoea intensity again correlated well with the increase in this effort-displacement ratio during exercise in COPD [18, 33].

1.8. Neurophysiology of Exertional Dyspnoea

As outlined above, measurement of dynamic operating lung volumes (by serial IC measurements) and the ratio of contractile respiratory muscle effort to volume displacement [i.e., Pes/P_{Imax} : V_T/VC] throughout exercise allow an exploration of the contribution of mechanical factors to dyspnoea causation [18, 33, 91].

In health, during resting spontaneous breathing and during exercise, the mechanical output of the respiratory system, measured as V'_E, changes in accordance with the level of central neural drive. Complex proprioceptive information (obtained from muscle spindles, Golgi tendon organs, and joint receptors), as well as sensory information pertaining to respired airflows and volume displacement (from mechanosensors located in the lung parenchyma and airways), provide simultaneous feedback to the central nervous system that ventilatory output is appropriate for the prevailing drive [103, 104, 115-118]. Several physiological adaptations during exercise [which include precise control of operating lung volumes and airway (intra- and extra-thoracic) resistance together with breathing pattern adjustments] ensure that the expanding V_T during exercise is accommodated within the most compliant, linear portion of the respiratory system's pressure-volume (P-V) relation (**Figure 6**, French version). The operating position of V_T on this sigmoidal P-V curve dictates the relationship between central respiratory neural drive and the dynamic mechanical/muscular response of the respiratory system during exercise [119]. In health, the effort-displacement ratio is maintained relatively constant during exercise [16, 91]. This indicates optimal positioning of V_T on the P-V curve where harmonious neuro-mechanical coupling is preserved and perceived dyspnoea is avoided (or attenuated) even at high ventilations. Although the perceived

effort of breathing may increase as V'_E increases during exercise, medullary output remains appropriately rewarded, and participants generally do not describe inspiratory difficulty or unsatisfied respiratory effort, even at peak exercise [16].

The situation is markedly different in COPD, where dynamic lung hyperinflation during exercise constrains V_T expansion (**Figure 4**, French version) and results in maximal shortening of the inspiratory muscles [18, 33]. Once V_T expands to reach a critical IRV ceiling, further increases in neural output to the respiratory system are unrewarded in terms of increased mechanical output. It has been argued that this mechanical (volume) restriction is a primary mechanism by which dynamic lung hyperinflation induces exertional dyspnoea and its dominant qualitative dimension of unsatisfied inspiration [16, 18, 21, 33, 40]. It is possible, therefore, that sensory feedback from a multitude of mechanoreceptors throughout the respiratory system (in the muscles, chest wall, airways and lung parenchyma) collectively convey the information to consciousness that the mechanical output achieved is inadequate for the prevailing respiratory drive. In the final phase of exercise, central drive had likely reached near maximal levels yet the V_T response was essentially fixed at only 30% of the predicted vital capacity [18, 21, 33, 40]. Respiratory mechanoreceptors are ideally placed to detect any disparity between the volume displacement achieved and that which is expected [120].

HYPOTHESES

A growing body of evidence indicates that patients with GOLD stage I COPD [18-21, 33, 47, 48], chronic heart failure (CHF) [22, 23] and pulmonary arterial hypertension (PAH) [27] present with either a reduction of expiratory flows at low lung volumes or an overt expiratory flow-limitation. These two factors are known to promote dynamic lung hyperinflation under condition of increased ventilatory demand such as physical exercise. Dynamic lung hyperinflation has been clearly shown to have serious sensory and mechanical consequences in patients with COPD. This proposition is supported by several studies, which have pointed out a close correlation between indices of dynamic lung hyperinflation and measures of exertional dyspnoea [10-12, 17-19, 21, 32, 33, 42-45, 47, 48, 55]. The strength of this association has been further confirmed by studies that have therapeutically manipulated dynamic lung hyperinflation by showing that relief of exertional dyspnoea correlates well with pharmacological and/or non-pharmacological reduction of dynamic lung hyperinflation [14, 33, 56-60].

We therefore tested the following hypotheses:

Hypothesis 1: patients with symptoms of GOLD stage I COPD can have significant abnormalities of ventilatory mechanics (dynamic lung hyperinflation) with greater exertional symptoms and exercise limitation than age-matched healthy subjects [19-21]. In such patients it is reasonable to believe that bronchodilator therapy would be expected to be associated with improvements in airway function, operating lung volumes and dyspnoea intensity during exercise.

To test this hypothesis we undertook an interventional study. In a randomised double-blind crossover study, we assessed the acute effects of nebulised ipratropium bromide 500 microg (IB) on resting pulmonary function and on dyspnoea and ventilatory parameters during symptom-limited constant work rate cycle exercise in 16 patients with milder but symptomatic COPD.

Hypothesis 2: patients with CHF may present with significant abnormalities of ventilatory mechanics (expiratory flow-limitation and dynamic lung hyperinflation) [22, 23] that can lead to increased dyspnoea intensity during exercise and exercise limitation. Despite the growing evidence supporting the use of biventricular cardiac resynchronization therapy (CRT) in patients with CHF, the mechanisms whereby acute hemodynamic improvements lead to improved exertional dyspnoea are not precisely known. We hypothesized that improved cardiac function and ventilation-perfusion relations following CRT would reduce ventilatory demand, thereby improving dynamic operating lung volumes and enhancing tidal volume expansion during exercise. This, in turn, would be expected to reduce perceived exertional dyspnoea and contribute to improved exercise performance. To test this hypothesis we undertook an interventional study. In a randomized, double-blind, crossover study, we compared cardiovascular, metabolic, ventilatory responses (breathing pattern, operating lung volumes, pulmonary gas exchange) and exertional symptoms in seven stable CHF patients who undertook incremental cardiopulmonary cycle exercise test with CRT switched to the "on" (CRT(on)) or "off" (CRT(off)) modality.

Hypothesis 3: patients with PAH may exhibit reduced expiratory flows in tidal operating range [24-27], which could promote exercise-induced dynamic lung hyperinflation [27]. This study aimed at examining the impact of potential dynamic lung hyperinflation-induced critical mechanical constraint on the intensity of dyspnoea in patients with PAH undergoing symptom-limited incremental cardiopulmonary cycle exercise testing (CPET). We undertook an observational study in which twenty-five young non-smoking PAH patients with no evidence of spirometric obstruction and 10 age-matched non-smoking healthy subjects performed a CPET to the limit of tolerance. Ventilatory pattern, operating lung volumes (derived from IC measurements), and dyspnoea intensity (by Borg scale) were assessed throughout CPET.

CHAPTER I

Evaluation of acute bronchodilator reversibility in patients with symptoms of GOLD stage I chronic obstructive pulmonary disease

Patients with symptoms of GOLD stage I chronic obstructive pulmonary disease (COPD) can have significant abnormalities of ventilatory mechanics with greater exertional symptoms and exercise limitation than age-matched healthy subjects. In such patients the impact of bronchodilator therapy remains unknown and is difficult to evaluate.

The acute effects of nebulised ipratropium bromide 500 microg (IB) on resting pulmonary function and on dyspnoea and ventilatory parameters during symptom-limited constant work rate cycle exercise were measured. In a randomised double-blind crossover study, 16 patients with COPD (mean (SD) post-bronchodilator forced expiratory volume in 1 s (FEV(1)) 90 (7)% predicted, FEV(1)/forced vital capacity (FVC) 59 (7)%) with a significant smoking history (mean (SD) 44 (16) pack-years) inhaled either IB or placebo on each of two separate visits. Pulmonary function tests and cycle exercise at 80-85% of each subject's maximal work capacity were performed 2 h after dosing.

Compared with placebo, FEV(1) increased 5 (9)% predicted, residual volume decreased 12 (20)% predicted and specific airway resistance decreased 81 (93)% predicted (all $p<0.05$) after IB. At a standardised time during exercise, dynamic inspiratory capacity and tidal volume significantly increased in tandem by 0.12 and 0.16 litres, respectively (each $p<0.05$), dyspnoea fell by 0.9 (1.8) Borg units ($p = 0.07$) and dyspnoea/ventilation ratios fell significantly ($p<0.05$). The fall in dyspnoea intensity at higher submaximal ventilations correlated with the concurrent decrease in end-expiratory lung volume ($p<0.05$).

In patients with symptoms of GOLD stage I COPD, IB treatment is associated with modest but consistent improvements in airway function, operating lung volumes and dyspnoea intensity

during exercise. These results provide a physiological rationale for a trial of bronchodilator therapy in selected patients with milder but symptomatic COPD.

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Evaluation of acute bronchodilator reversibility in patients with symptoms of GOLD stage I COPD

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► Additional Methods data are published online only at http://thorax.bmj.com/content/vol64/issue3

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ABSTRACT

Background: Patients with symptoms of GOLD stage I chronic obstructive pulmonary disease (COPD) can have significant abnormalities of ventilatory mechanics with greater exertional symptoms and exercise limitation than age-matched healthy subjects. In such patients the impact of bronchodilator therapy remains unknown and is difficult to evaluate.

Methods: The acute effects of nebulised ipratropium bromide 500 μg (IB) on resting pulmonary function and on dyspnoea and ventilatory parameters during symptom-limited constant work rate cycle exercise were measured. In a randomised double-blind crossover study, 16 patients with COPD (mean (SD) post-bronchodilator forced expiratory volume in 1 s (FEV_1) 90 (7)% predicted, FEV_1/forced vital capacity (FVC) 59 (7)%) with a significant smoking history (mean (SD) 44 (16) pack-years) inhaled either IB or placebo on each of two separate visits. Pulmonary function tests and cycle exercise at 80–85% of each subject's maximal work capacity were performed 2 h after dosing.

Results: Compared with placebo, FEV_1 increased 5 (9)% predicted, residual volume decreased 12 (20)% predicted and specific airway resistance decreased 81 (93)% predicted (all $p<0.05$) after IB. At a standardised time during exercise, dynamic inspiratory capacity and tidal volume significantly increased in tandem by 0.12 and 0.16 litres, respectively (each $p<0.05$), dyspnoea fell by 0.9 (1.8) Borg units ($p = 0.07$) and dyspnoea/ventilation ratios fell significantly ($p<0.05$). The fall in dyspnoea intensity at higher submaximal ventilations correlated with the concurrent decrease in end-expiratory lung volume ($p<0.05$).

Conclusion: In patients with symptoms of GOLD stage I COPD, IB treatment is associated with modest but consistent improvements in airway function, operating lung volumes and dyspnoea intensity during exercise. These results provide a physiological rationale for a trial of bronchodilator therapy in selected patients with milder but symptomatic COPD.

Patients with chronic obstructive pulmonary disease (COPD) who have relatively preserved measurements of forced expiratory flow rates may have extensive small airway dysfunction.[1–4] Such patients report greater intensity of exertional dyspnoea than healthy age-matched controls as a result of the combined effects of abnormal dynamic ventilatory mechanics and higher ventilatory requirements during exercise.[5] This physiological impairment of the respiratory system may explain, at least in part, reports of poor perceived health status in subpopulations of patients with apparently mild airway obstruction.[6] Successful smoking cessation is the only proven intervention that has been shown to improve small airway function in patients with mild COPD.[2 4] However, the optimal clinical management of these smokers with symptoms of mild COPD is not established and remains largely unstudied. It is not known, for example, whether inhaled bronchodilator therapy, which has established efficacy in moderate to severe COPD,[7–10] is effective in alleviating activity-related dyspnoea in those with milder disease. Moreover, it remains uncertain whether traditional spirometric criteria for bronchodilator reversibility, based on arbitrary improvement in the forced expiratory volume in 1 s (FEV_1), are applicable in mild COPD. This information becomes important for clinical practice and for the design of future clinical trials to evaluate the efficacy of therapeutic interventions in early COPD.

The purpose of the present study was therefore to evaluate the acute effects of an anticholinergic bronchodilator on airway function and exertional dyspnoea in patients with mild COPD, as defined by GOLD stage I criteria.[10] Based on the results of a previous mechanistic study in patients with symptoms of mild COPD,[5] we hypothesised that inhaled bronchodilator therapy would improve airway function and lung volumes at rest and reduce the rate of dynamic pulmonary hyperinflation during exercise, thus permitting greater tidal volume expansion and reduced dyspnoea intensity at higher submaximal ventilations. To test this hypothesis we undertook a randomised placebo controlled study in 16 well characterised patients with mild COPD symptoms. We compared the acute effects of nebulised ipratropium bromide and placebo on detailed resting pulmonary function measurements as well as dyspnoea ratings, operating lung volumes, breathing pattern and gas exchange during constant work cycle exercise. To explore potential mechanisms of dyspnoea relief, we also measured oesophageal pressure (Pes)-derived indices of dynamic ventilatory mechanics in a small subsample of patients who consented to undertake these more invasive measurements.

METHODS

Subjects

Sixteen patients with symptoms of GOLD stage I COPD (post-bronchodilator FEV_1 ≥80% predicted and FEV_1/forced vital capacity (FVC) ratio <0.7)[10] who were referred to the COPD Centre at our institution were studied. Patients were excluded if they had (1) other medical conditions which could cause or contribute to breathlessness (ie, metabolic, cardiovascular, asthma or other respiratory diseases) or (2) other disorders which could interfere

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with exercise testing such as neuromuscular diseases or musculoskeletal problems.

Study design

This randomised, double-blind, placebo controlled, crossover study was approved by the Queen's University and Affiliated Hospitals research ethics board. After informed consent and screening of medical history, patients completed four visits conducted approximately 7 days apart. At visit 1, subjects completed pulmonary function tests and a symptom-limited incremental cycle exercise test followed, after 60 min of rest, by a familiarisation constant-load cycle endurance test at 80–85% of their maximal achieved work rate (Wmax). At visit 2 the constant-load cycle test was repeated and, after 60 min of recovery, subjects performed pulmonary function tests before and 20 min after administration of salbutamol (400 μg). At visits 3 and 4, subjects were randomised (sequence) to receive either nebulised ipratropium bromide 500 μg (IB) or a placebo (PL). Subjects performed pulmonary function tests before and 60 min after nebulisation, followed by a constant-load exercise test. All series of pulmonary function tests included spirometry, body plethysmography, transfer factor and respiratory muscle strength measurements. All symptom-limited constant-load exercise tests were conducted at the same work rate for each subject. Withdrawal of bronchodilators before each visit included short-acting β_2 agonists (8 h), short-acting anticholinergics (8 h), long-acting β_2 agonists (48 h) and long-acting anticholinergics (72 h). Subjects avoided caffeine, alcohol and heavy meals for 4 h before visits and avoided major physical exertion entirely on visit days.

Interventions

A 3.5 ml solution containing either 500 μg IB or sterile 0.9% saline (PL) was administered by nebuliser (Parimaster Compressor with Pari LC Jet+nebuliser; PARI Respiratory Equipment, Richmond, Virginia, USA) over a 15–20 min period in a double-blind fashion.

Procedures

Routine spirometry, body plethysmography (ie, functional residual capacity (FRC) and specific airway resistance (sRaw)), transfer factor for carbon monoxide (T_{LCO}) and maximum inspiratory and expiratory mouth pressures (MIP and MEP; measured at FRC and total lung capacity (TLC), respectively) were performed using an automated system (6200 Autobox DL or Vmax229d; SensorMedics, Yorba Linda, California, USA) in accordance with recommended techniques.[11–16] Measurements were expressed as percentages of predicted normal values;[17–19] predicted normal inspiratory capacity (IC) was calculated as predicted TLC minus predicted FRC.

Symptom-limited exercise tests were conducted on an electronically braked cycle ergometer as previously described.[5 20 21] The incremental test consisted of 2 min increments of 20 W to the point of symptom limitation; Wmax was defined as the greatest work rate that the subject could maintain for at least 30 s. Constant-load tests at 80–85% Wmax were performed during all four visits; endurance time was defined as the duration of loaded pedalling. At end-exercise, subjects were asked why they needed to stop exercising. *Rest* was the steady-state period after at least 3 min of breathing on the mouthpiece before exercise began; *peak* was the last 30 s of loaded pedalling; and *isotime* was the duration of the shortest post-treatment test rounded down to the nearest full minute (ie, highest equivalent isotime).

Cardiopulmonary and breathing pattern measurements were collected in a breath-by-breath fashion while subjects breathed through a mouthpiece with nasal passages occluded by a noseclip using a cardiopulmonary exercise testing system (SensorMedics Vmax229d). Pulse oximetry, electrocardiography and blood pressure measurements were also performed. Subjects rated the intensity of their "breathing discomfort" and "leg discomfort" at rest, every minute during exercise and at end-exercise using the modified 10-point Borg scale.[22] Operating lung volumes were derived from IC measurements performed at rest, every second minute during exercise and end-exercise, as previously described.[5] Maximal flow-volume loops were obtained at rest and at end-exercise. Tidal flow-volume curves at rest, every 2 min during exercise and at peak exercise were placed within their respective maximal flow-volume loops using coinciding IC measurements; expiratory flow limitation was estimated as the percentage of tidal volume (V_T) encroaching on the maximal flow envelope.[23] In six subjects, oesophageal pressure (Pes) was recorded continuously during constant-load exercise tests using an integrated data acquisition set-up as described elsewhere (see online supplement).[20] Inspiratory sniff manoeuvres were performed before exercise at rest and immediately at end-exercise to obtain maximum values for Pes (PImax).

Table 1 Subject characteristics

	Enrolled subjects (n = 16)	Subjects with complete mechanical measurements (n = 6)
Gender	63% male	83% male
Age (years)	63 (8)	67 (8)
Body mass index (kg/m^2)	27.8 (4.6)	26.4 (3.8)
Cigarette smoking history (pack-years)	44 (16)	43 (18)
BDI focal score (0–12)	8.3 (2.0)	8.3 (1.9)
MRC dyspnoea scale (1–5)	1.8 (0.7)	1.5 (0.5)
CHAMPS (kcal/week consumed at moderate activities)	2123 (2221)	1736 (1974)
Symptom-limited peak exercise (% predicted maximum)		
Work rate (W)	121 (39), (72%)	119 (30), (74%)
$\dot{V}o_2$ (l/min)	1.84 (0.58), (79%)	1.79 (0.58), (79%)
Pulmonary function (% predicted)		
FEV_1 post-bronchodilator (l)	2.50 (0.58), (90%)	2.44 (0.64), (86%)
FVC post-bronchodilator (l)	4.25 (1.08), (108%)	4.39 (1.18), (108%)
FEV_1/FVC post-bronchodilator (%)	59 (7), (84%)	56 (8), (80%)
IC (l)	3.01 (0.97), (103%)	3.34 (1.13), (106%)
FRC (l)	4.10 (0.91), (122%)	4.45 (0.71), (126%)
TLC (l)	7.11 (1.50), (113%)	7.79 (1.32), (117%)
RV (l)	2.83 (0.48), (129%)	3.08 (0.32), (131%)
MIP (cm H_2O)	95 (32), (115%)	87 (23), (95%)
MEP (cm H_2O)	149 (59), (83%)	139 (44), (100%)
T_{LCO} (ml/min/mm Hg)	21.2 (5.9), (95%)	22.4 (4.5), (106%)
sRaw (cm H_2O.s)	12.3 (4.0), (294%)	13.3 (2.9), (303%)

Values are shown as mean (SD), (% predicted normal values).
BDI, baseline dyspnoea index; MRC, Medical Research Council; CHAMPS, Community Healthy Activities Model Program for Seniors; FEV_1, forced expiratory volume in 1 s; FRC, functional reserve capacity; FVC, forced vital capacity; IC, inspiratory capacity; MIP, maximal inspiratory mouth pressure; MEP, maximal expiratory mouth pressure; RV, residual volume; sRaw, specific airway resistance; TLC, total lung capacity; T_{LCO}, carbon monoxide transfer factor; $\dot{V}o_2$, oxygen consumption.

Table 2 Effect of placebo (PL) and ipratropium bromide (IB) on pulmonary function tests in patients with GOLD stage I COPD

	Post-PL	Post-IB
FEV_1 (l)	2.30 (0.60), (83%)	2.46 (0.59), (88%)*
ΔFEV_1 (l)	0.07 (0.09), (3%)†	0.26 (0.19), (9%)†‡
FVC (l)	4.07 (1.13), (103%)	4.20 (1.17), (106%)*
ΔFVC (l)	0.02 (0.18), (1%)	0.23 (0.21), (6%)†‡
FEV_1/FVC (%)	57 (7), (81%)	59 (7), (83%)
ΔFEV_1/FVC (%)	1.3 (2.0), (2%)†	2.9 (3.2), (4%)†
T_{LCO} (ml/min/mm Hg)	21.0 (6.2), (94%)	20.2 (6.5), (90%)
ΔT_{LCO} (ml/min/mm Hg)	−0.1 (1.4), (−1%)	−1.1 (2.3), (−5%)
MIP (cm H_2O)	96 (20), (120%)	98 (21), (121%)
ΔMIP (cm H_2O)	−1 (11), (−2%)	1.6 (7.7), (1%)
MEP (cm H_2O)	148 (54), (82%)	148 (48), (83%)
ΔMEP (cm H_2O)	1 (12), (1%)	−6 (13), (−10%)
TLC (l)	7.16 (1.49), (114%)	7.04 (1.42), (112%)
ΔTLC (l)	−0.03 (0.26), (−1%)	−0.15 (0.20), (−3%)†
RV (l)	2.73 (0.34), (125%)	2.49 (0.47), (113%)*
ΔRV (l)	−0.14 (0.19), (−6%)†	−0.38 (0.22), (−19%)†‡
FRC (l)	4.05 (0.71), (121%)	3.90 (0.82), (115%)*
ΔFRC (l)	−0.07 (0.17), (−2%)	−0.27 (0.29), (−9%)†‡
IC (l)	3.10 (1.01), (106%)	3.15 (0.86), (109%)
ΔIC (l)	0.04 (0.19), (1%)	0.12 (0.32), (4%)
sRaw (cm H_2O.s)	12.7 (4.3), (301%)	9.3 (4.6), (220%)*
ΔsRaw (cm H_2O.s)	−0.6 (1.7), (−15%)	−4.7 (3.5), (−111%)†‡

Values are mean (SD), (% predicted normal values).
*p<0.05, post-IB vs post-PL.
†p<0.05 post-dose vs pre-dose within treatment.
‡p<0.05 IB vs PL post-dose minus pre-dose differences.
Δ, post-dose minus pre-dose difference; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; IC, inspiratory capacity; MIP, maximal inspiratory pressure; MEP, maximal expiratory pressure; PEF, peak expiratory flow; RV, residual volume; sRaw, specific airway resistance; SVC, slow vital capacity; TLC, total lung capacity; T_{LCO}, carbon monoxide transfer factor.

Table 3 Post-dose peak of symptom-limited constant-load exercise at 80–85% Wmax (99 (32) W)

	Placebo	Ipratropium bromide
Exercise time (min)	8.2 (5.3)	8.2 (4.8)
Dyspnoea (Borg scale)	7.8 (2.9)	7.7 (2.5)
Leg discomfort (Borg scale)	8.6 (1.9)	8.4 (2.2)
Reason for stopping, n (%):		
Breathing	3 (19%)	2 (13%)
Legs	6 (37%)	9 (56%)
Breathing and legs	7 (44%)	5 (31%)
$\dot{V}O_2$ (l/min)	1.88 (0.64)	1.81 (0.56)
$\dot{V}CO_2$ (l/min)	1.73 (0.55)	1.75 (0.58)
$\dot{V}_E$ (l/min)	69.4 (18.2)	73.5 (23.9)
F (breaths/min)	39.6 (7.9)	39.1 (7.3)
V_T (l)	1.81 (0.56)	1.91 (0.58)*
IC (l)	2.46 (0.70)	2.59 (0.70)
IRV (l)	0.65 (0.26)	0.67 (0.32)
V_T/T_E (l/s)	2.10 (0.59)	2.24 (0.80)
V_T/T_I (l/s)	2.56 (0.63)	2.68 (0.80)
T_I/T_{TOT}	0.45 (0.03)	0.45 (0.03)
P_{ETCO_2} (mm Hg)	34.4 (4.7)	33.0 (5.4)
Heart rate (beats/min)	142 (16)	140 (17)
Spo_2 (%)	95 (3)	95 (2)

Values are mean (SD).
*p<0.05 ipratropium bromide versus placebo.
IC, inspiratory capacity; IRV, inspiratory reserve volume; P_{ETCO_2}, partial pressure of end-tidal CO_2; Spo_2, oxygen saturation; T_I/T_{TOT}, inspiratory duty cycle, inspiratory time over total breath time; $\dot{V}O_2$, oxygen uptake; $\dot{V}CO_2$, carbon dioxide production; $\dot{V}_E$, minute ventilation; *F*, breathing frequency; V_T, tidal volume; V_T/T_E and V_T/T_I, mean inspiratory and expiratory tidal flows.

Statistical analysis

A sample size of 16 was used to provide the power (80%) to detect a significant difference in dyspnoea intensity (Borg scale) measured at a standardised work rate during incremental cycle exercise based on a relevant difference in Borg ratings of ±1, an SD of 1 for changes in Borg ratings found in our laboratory ($\alpha = 0.05$). Results were expressed as mean (SD). A $p<0.05$ level of statistical significance was used for all analyses.

Although unlikely in this single-dose study, the possibility of a carryover effect was tested using paired *t* tests to evaluate pre-dose (pre-treatment) pulmonary function measurements. Period effects were evaluated using the two-sample *t* test.[24] Treatment comparisons were made using paired *t* tests with appropriate Bonferroni adjustments for multiple comparisons. Responses at rest and at different time points and/or intensities during exercise were also compared. Repeated measures ANOVA (with treatment, time and interaction as fixed effects and subject as a random effect) was applied to compare the overall treatment effects. Dyspnoea descriptors were analysed as frequency statistics and compared using the Fisher exact test. Physiological contributors to exertional dyspnoea intensity were determined by multiple regression analysis: Borg dyspnoea ratings at a standardised exercise work rate (dependent variable) were analysed against concurrent relevant independent variables (ie, exercise measurements of ventilation, breathing pattern, operating lung volumes, cardiovascular and metabolic parameters, and baseline pulmonary function measurements).

RESULTS

Subjects

Subject characteristics are summarised in table 1. All subjects were had symptoms and had a diagnosis of COPD; the majority (11/16) had a diagnosis made within the previous 5 years. Seven subjects did not use any respiratory medications, two only used a short-acting β_2 agonist bronchodilator on an "as needed" basis and seven used inhalers on a regular basis. Of these latter seven subjects, all used short-acting β_2 agonists, five used a long-acting β_2 agonist, five used an anticholinergic (one short-acting, four long-acting) and six used an inhaled corticosteroid (five in combination with a long-acting β_2 agonist). Comorbidities included stable coronary artery disease (n = 2), well-controlled diabetes mellitus type 2 (n = 1), treated hypertension (n = 1) and varying degrees of osteoarthritis (n = 4). All subjects had a smoking history of ⩾15 pack-years (range 15–63 pack-years, table 1); four subjects were current smokers and 12 were ex-smokers who had stopped smoking at least 2 years before the study.

Chronic activity-related dyspnoea was assessed with the baseline dyspnoea index (BDI)[25] and the Medical Research Council (MRC) dyspnoea scale.[26] BDI focal scores ranged from 5 to 12; nine subjects reported a BDI ⩽8 and seven subjects reported a BDI ⩾9. The majority of subjects (11/16) had a rating of ⩾2 on the MRC dyspnoea scale.

All subjects had a normal post-bronchodilator FEV_1 and an FEV_1/FVC ratio <70%. Lung volumes indicated mild static lung hyperinflation (mean FRC and RV >120% predicted) with a preserved vital capacity and inspiratory capacity (IC) (table 1). Symptom-limited incremental exercise testing showed reduced peak oxygen consumption ($\dot{V}O_2$) and work rate. The subgroup of subjects with Pes-derived measurements had comparable baseline characteristics to the group as a whole (table 1). There

were also no significant differences in the baseline characteristics or in the magnitude of the treatment responses between patients who were using respiratory medication and those who were not.

There were no significant differences between predose measurements of pulmonary function on treatment days (ie, no significant carryover effect). No significant period effects were found when examining pulmonary function or exercise test outcomes.

Pulmonary function responses

Differences in pulmonary function after IB compared with PL are shown in table 2. Subjects with the worst baseline prebronchodilator specific airway resistance (sRaw) had the greatest IB-induced improvements in sRaw ($r = -0.595$, $p = 0.015$) and IC ($r = 0.594$, $p = 0.015$); improvements in sRaw and IC were also strongly interrelated ($r = -0.680$, $p = 0.004$). Maximal expiratory flows measured at FRC after PL were compared with the maximal flow at the same absolute volume after IB within each individual: these isovolume flows improved from a mean (SD) of 0.27 (0.18) l/s to 0.43 (0.30) l/s after PL and IB, respectively ($p = 0.006$).

Responses to constant-load exercise

Post-dose exercise endurance time at 99 (32) W (60 (11)% predicted maximum; 82 (9)% Wmax) did not change significantly after IB compared with PL (table 3): six subjects improved endurance time by ⩾30 s, three subjects decreased endurance time by ⩾30 s and the rest had less than a 30 s difference in endurance time. The distribution of reasons for stopping exercise was not different between treatments. In both visits, leg discomfort was reported as the primary reason for stopping exercise, 2–3-fold more than breathing discomfort (table 3).

Exertional symptoms

Compared with PL, there was no change in peak Borg ratings of breathing or leg discomfort after IB (table 3). However, ratings of breathing and leg discomfort at the highest equivalent isotime (6.8 (4.5) min) during exercise were lower after IB compared with PL by 0.88 (1.83) Borg units ($p = 0.073$) and 0.81 (1.28) Borg units ($p<0.05$), respectively (table 4, fig 1). Ten of the 16 patients decreased the intensity of their breathing discomfort at isotime by at least 1 Borg unit, while the remaining subjects increased (n = 4) or did not change (n = 2) ratings of breathing discomfort after IB compared with PL. Dyspnoea/$\dot{V}_E$ ratios were evaluated to account for the potential effects of IB-induced alterations in $\dot{V}_E$ on exertional dyspnoea intensity: dyspnoea/$\dot{V}_E$ ratios were significantly lower ($p<0.05$) at isotime after IB than after PL (table 4, fig 1). By repeated measures ANOVA, there were no significant interactions between treatment and time during exercise for exertional symptom ratings (ie, the treatment effect did not vary at different times); however, a significant treatment effect was found for dyspnoea/$\dot{V}_E$ ratios ($p = 0.075$) and leg discomfort ratings ($p = 0.021$).

Table 4 Post-dose values at isotime (6.8 (4.5) min) during constant-load exercise

	Placebo	Ipratropium bromide	p Value
Dyspnoea (Borg)	7.4 (2.4)	6.6 (2.4)	0.07
Dyspnoea/$\dot{V}_E$ (Borg/l/min)	0.12 (0.05)	0.10 (0.05)*	
Leg discomfort (Borg)	8.3 (1.7)	7.5 (2.1)*	
$\dot{V}_{O_2}$ (l/min)	1.72 (0.54)	1.82 (0.66)	
$\dot{V}_{CO_2}$ (l/min)	1.67 (0.56)	1.71 (0.62)	
Heart rate (beats/min)	137 (19)	136 (19)	
Spo_2 (%)	96 (3)	96 (2)	
$\dot{V}_E$ (l/min)	65.7 (19.6)	69.0 (24.9)	
F (breaths/min)	36.7 (8.3)	35.3 (8.2)	
V_T (l)	1.83 (0.57)	1.99 (0.65)*	
IC (l)	2.51 (0.70)	2.63 (0.66)*	
ΔIC isotime-rest (l)	−0.55 (0.40)	−0.49 (0.33)	
IRV (l)	0.68 (0.31)	0.64 (0.30)	
T_I (s)	0.77 (0.20)	0.81 (0.21)	
T_E (s)	0.93 (0.20)	0.98 (0.23)	0.06
T_I/T_{TOT}	0.45 (0.03)	0.45 (0.03)	
V_D/V_T estimated (%)	30 (7)	29 (8)*	
$PETCO_2$ (mm Hg)	35.4 (5.1)	34.3 (5.5)	
EFL (% of V_T overlapping maximal flow-volume curve)	78 (13)	62 (20)*	

Values are mean (SD).
*$p<0.05$ ipratropium bromide vs placebo.
EFL, expiratory flow limitation; IC, inspiratory capacity; IRV, inspiratory reserve volume; $PETCO_2$, partial pressure of end-tidal CO_2; Spo_2, oxygen saturation; T_I/T_{TOT}, inspiratory duty cycle, inspiratory time over total breath time; $\dot{V}_{O_2}$, oxygen uptake; $\dot{V}_{CO_2}$, carbon dioxide production; $\dot{V}_E$, minute ventilation; *F*, breathing frequency; VC, vital capacity; V_D, estimated dead space; V_T, tidal volume.

Ventilatory responses

Ventilatory responses to exercise after IB and PL are shown in fig 2. Tidal volume (V_T) was greater after IB compared with PL

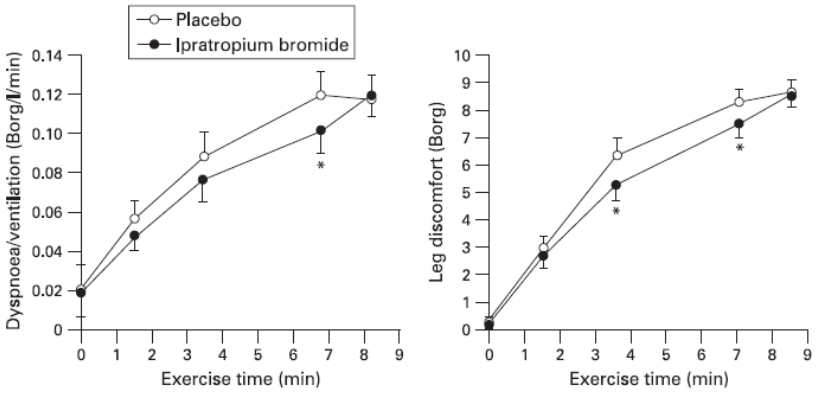

Figure 1 Ratings of dyspnoea intensity, expressed relative to ventilation, and ratings of intensity of leg discomfort plotted against exercise time during constant-load cycle testing at 80–85% of the maximum work rate achieved during incremental testing. *$p<0.05$ ipratropium bromide vs placebo at a given time point. Values are mean (SEM).

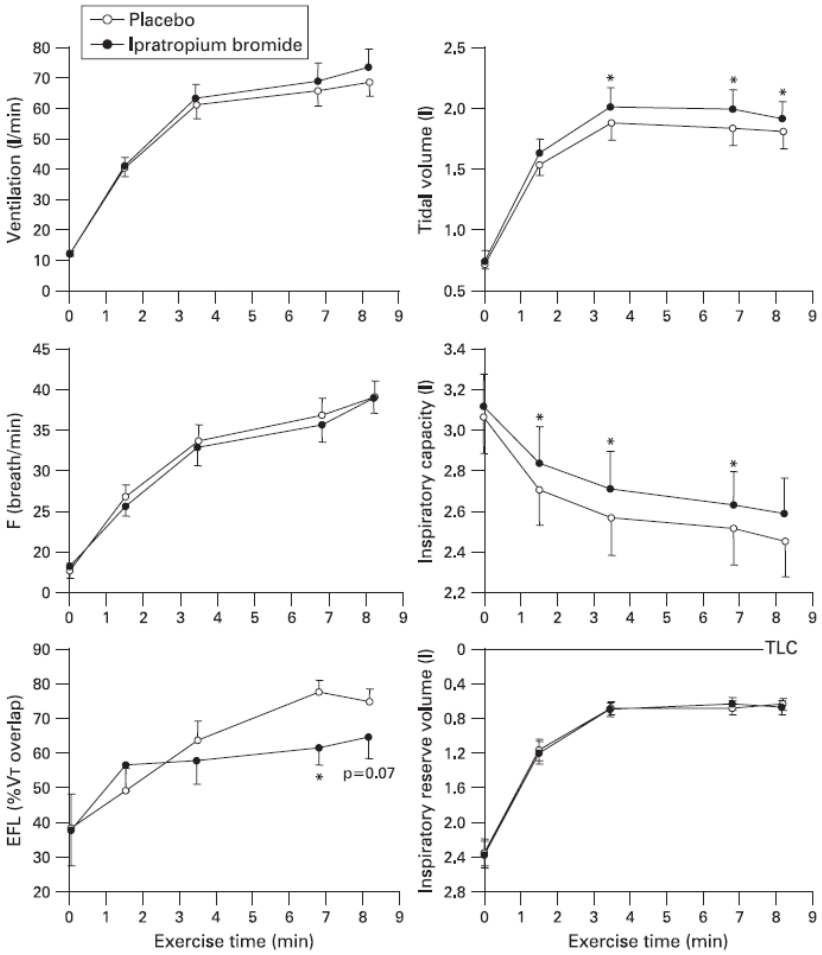

Figure 2 Ventilatory responses to constant-load cycle testing against exercise time after ipratropium bromide (IB) compared with placebo (PL) in 16 subjects with mild chronic obstructive pulmonary disease. Tidal volume (V_T) and inspiratory capacity were greater, and estimates of expiratory flow limitation (EFL) were lower after IB than after PL; minute ventilation, breathing frequency (*F*) and inspiratory reserve volume were not different between treatments. TLC, total lung capacity. *p<0.05 ipratropium bromide vs placebo at a given time point or at peak exercise. Values are mean (SEM).

from minute 4 in exercise to peak exercise by 0.10–0.16 l (p<0.05); increases in V_T were accommodated by concurrent increases in IC of 0.12–0.15 l (p<0.05). Inspiratory reserve volume (IRV) was not different at rest or throughout exercise across treatments. Estimates of expiratory flow limitation were reduced at isotime and at peak exercise by 10% and 17% (p<0.05), respectively, after IB compared with PL. Repeated measures ANOVA also showed a significant treatment effect for V_T (p = 0.012), IC (p = 0.001) and expiratory flow limitation (p = 0.014), with no significant interactions between treatment and exercise time.

Ventilatory mechanics

The pressure-time integral and its surrogate, the calculated tension-time index ($P_{es}/P_{Imax} \times T_I/T_{TOT}$), were not different in response to treatment. However, lung resistance was reduced after IB compared with PL in the order of 0.7–0.8 cm H_2O/l/s at standardised time points throughout exercise (ie, a reduction of ~20% (p<0.05), fig 3). Total work of breathing expressed as J/l fell significantly (p<0.05) during exercise but not at rest after IB compared with PL, primarily due to significant (p<0.05) decreases in the inspiratory threshold load and the elastic work performed against this load. Repeated measures ANOVA showed a significant treatment effect for resistance (p = 0.007), the inspiratory threshold load (p<0.001), total work of breathing (p = 0.002) and elastic work of breathing (p = 0.001), with no significant interactions between treatment and exercise time. Work of breathing measurements were not different when expressed as J/min, so differences were offset by increases in V_E.

Correlates of dyspnoea

The best predictors of the IB-induced decrease in dyspnoea ratings at isotime were the baseline (prebronchodilator) pre-exercise resting IC expressed as percentage predicted (r = 0.637, p = 0.008), the end-inspiratory lung volume (EILV)/TLC ratio (r = −0.561, p = 0.024) and the IRV expressed as percentage predicted TLC (r = 541, p = 0.030); no other baseline pulmonary function parameters correlated. The best correlates of the IB-induced decrease in dyspnoea/V_E ratios at isotime were also the prebronchodilator pre-exercise resting IC expressed as percentage predicted (r = 0.714, p = 0.002), the EILV/TLC ratio (r = −0.637, p = 0.008) and the IRV expressed as percentage predicted TLC (r = 0.549, p = 0.028). When dyspnoea was

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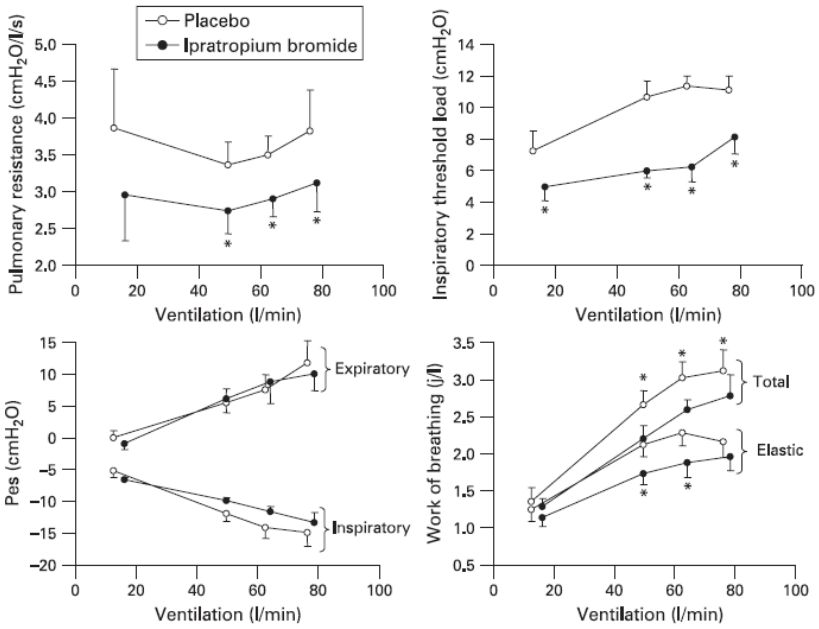

Figure 3 Respiratory mechanical measurements in six subjects during constant-load exercise after ipratropium bromide compared with placebo. Pulmonary resistance, inspiratory threshold load, total work of breathing and the elastic work of breathing component all decreased during exercise after ipratropium bromide compared with placebo. However, peak tidal inspiratory and expiratory oesophageal pressure (Pes) did not change in response to treatment. *$p<0.05$ (one-tailed) ipratropium bromide vs placebo at a given time point or at peak exercise. Values are mean (SEM).

expressed as a ratio against $\dot{V}_E$ (Borg/(l/min)), the strongest correlate of this treatment difference at isotime was the concurrent difference in EELV/TLC ($r = 0.585$, $p<0.05$).

DISCUSSION

The novel findings of this study are as follows: (1) treatment with IB was associated with consistent improvements in forced expiratory flow rates, sRaw and RV in patients with GOLD stage I COPD symptoms; (2) during exercise, IB treatment was associated with significant increases in dynamic IC and V_T in the absence of an increase in cycle exercise endurance time; and (3) improvement in dynamic EELV was linked to a reduction in ratings of exertional dyspnoea intensity at higher levels of ventilation.

Changes in resting pulmonary function

Our patients had extensive physiological impairment and long-term activity-related dyspnoea as measured by validated questionnaires. More than half of the group was already receiving empirical bronchodilator therapy. Our results confirm that release of cholinergic smooth muscle tone improved airway function both at rest and during exercise in these patients. In general, changes in resting spirometry and lung volumes were in the same direction but more modest than those previously reported following a similar dose of IB in moderate to severe COPD.[7–9] Airway resistance, corrected for the lower resting operating volume, decreased after IB by 33% of baseline values while isovolume maximal flow rates in the effort-independent range also consistently improved.

In contrast to previous studies of the acute effects of IB in more advanced disease, resting IC did not increase significantly in our cohort with milder COPD. Thus, FRC and TLC fell in tandem and to a similar extent, such that the change in IC underestimated the extent of IB-induced lung deflation. Small but consistent bronchodilator-associated decreases in TLC have previously been reported in COPD, but the precise mechanisms are unknown.[27 28] Decreases in the plethysmographically-determined TLC may reflect measurement artefact, since mouth pressure during panting could potentially underestimate true alveolar pressure in patients with airflow limitation. A reduction in this disparity after a bronchodilator may result in an artifactual reduction in TLC. We tried to minimise this effect by controlling panting frequency at ~1 Hz. It is unlikely that changes in (regional) lung compliance can explain the observed reductions in TLC; lung compliance curves were superimposed before and after IB in our small subsample with mechanical measurements.

The lack of increase in resting IC in our patients is not surprising. Based on the study of Tantucci *et al*,[29] bronchodilator-induced increases in IC are only expected in patients with COPD who have more extensive expiratory flow limitation and lung hyperinflation (ie, IC <80% predicted) at rest.

Altered ventilatory responses to exercise after bronchodilator

Exercise endurance time did not increase after bronchodilator compared with placebo. Possible explanations for this are: (1) the study was powered to detect an improvement in dyspnoea at a standardised work rate and not a change in exercise endurance time; and (2) intolerable leg discomfort and not dyspnoea was the dominant exercise-limiting symptom in the majority of this group.

IC diminished by 0.55 l from rest to peak exercise, confirming the presence of air trapping due to expiratory flow limitation and high ventilatory demand in patients with mild COPD. Compared with placebo, IB treatment was associated with a significant increase in IC by 0.12–0.15 l throughout exercise, despite slightly greater levels of ventilation (~3 l/min). However, the magnitude of acute change in IC from pre-exercise resting levels at each time point and at peak exercise remained similar (fig 2). We also found consistent reductions in our estimate of expiratory flow limitation at higher exercise levels after IB. Moreover, pulmonary resistance and

conductance were significantly improved during exercise in the subsample who consented to oesophageal balloon measurements. The most likely explanation for lung deflation is therefore improvement in the time constant for lung emptying as a result of reduced airway resistance rather than minimal changes in expiratory time (prolongation) and static lung recoil pressure. The improved dynamic IC allowed greater V_T expansion throughout exercise without further encroachment on the dynamic IRV.

Mechanisms of dyspnoea relief

Standardised ratings of exertional dyspnoea intensity as measured by the Borg scale were not statistically different ($p = 0.07$) after IB compared with placebo, probably due to small concomitant increases in $\dot{V}_E$ with IB. However, when IB-induced alterations in $\dot{V}_E$ were taken into account by examining dyspnoea/$\dot{V}_E$ ratios, these changes reached statistical significance ($p<0.05$). Compared with placebo, the decrease in the dyspnoea/$\dot{V}_E$ ratio after IB correlated best with the concurrent decrease in the dynamic EELV/TLC ratio. In a small subset of patients the measured work of breathing and the pressure-time product (reflecting the oxygen cost of breathing) was not increased after IB despite significantly greater V_T expansion. The work associated with overcoming the inspiratory threshold load (the intrinsic PEEP effect) was significantly reduced at standardised times during exercise. We have argued that increased threshold loading of the inspiratory muscles as a result of dynamic pulmonary hyperinflation plays an important role in dyspnoea causation in asthma during bronchoconstriction and in more advanced COPD during exercise.[30–32] Reduction of the inspiratory threshold load by lung deflation should relieve dyspnoea by reducing the disparity between efferent motor output (sensed by increased corollary discharge) and afferent inputs from mechanosensors in the respiratory muscles, chest wall and lungs (ie, neuromechanical coupling).[33] Thus, dyspnoea relief was related to improved inspiratory muscle function as a result of a reduced dynamic EELV as well as the recruitment of an increased dynamic IC which allowed greater V_T displacement for the same inspiratory effort.

It is noteworthy that patients who derived the greatest reduction in exertional dyspnoea with IB treatment were those with the most severe lung hyperinflation at baseline. In fact, of all the resting physiological parameters that we measured, only the resting prebronchodilator IC and IRV (percentage predicted) correlated with improved dyspnoea intensity ratings during exercise. Previous studies have shown that, when the normal spontaneous V_T response to increasing central respiratory drive is constrained (either volitionally or by imposition), dyspnoea quickly escalates to intolerable levels.[34 35] It follows that release of V_T restriction (ie, IC recruitment) should improve dyspnoea.[21 36]

In summary, traditional spirometric measurements reliably detected modest but consistent improvements in airway function after bronchodilator treatment in patients with symptoms of mild COPD. Bronchodilator administration was associated with improved dynamic IC and a deeper breathing pattern throughout exercise. Dyspnoea intensity ratings fell only at the higher levels of ventilation with IB treatment, in association with reduced dynamic EELV. Mechanical and subjective improvements during exercise after IB treatment were most pronounced in those with the smallest resting IC (and IRV) and therefore the greatest mechanical constraints on tidal volume expansion.

This study highlights the challenges involved in the assessment of bronchodilator efficacy in milder COPD where no evidence-based guidelines for pharmacotherapy currently exist. Our results provide a sound physiological rationale for consideration of a trial of bronchodilator therapy in selected patients with GOLD stage I COPD who experience troublesome activity-related dyspnoea.

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CHAPTER II

Effect of biventricular pacing on ventilatory and perceptual responses to exercise in patients with stable chronic heart failure

Despite the growing evidence supporting the use of biventricular cardiac resynchronization therapy (CRT) in patients with chronic heart failure (CHF), the mechanisms whereby acute hemodynamic improvements lead to improved exertional dyspnoea are not precisely known. We hypothesized that improved cardiac function and ventilation-perfusion relations following CRT would reduce ventilatory demand, thereby improving dynamic operating lung volumes and enhancing tidal volume expansion during exercise. This, in turn, would be expected to reduce perceived exertional dyspnoea and contribute to improved exercise performance.

In a randomized, double-blind, crossover study, we compared cardiovascular, metabolic, ventilatory responses (breathing pattern, operating lung volumes, pulmonary gas exchange) and exertional symptoms in seven stable CHF patients who undertook incremental cardiopulmonary cycle exercise test with CRT switched to the "on" (CRT(on)) or "off" (CRT(off)) modality.

Following CRT(on), peak oxygen uptake was significantly increased by 15%, and dyspnoea ratings were lower for a given work rate (at work rate of 40 W, dyspnoea = 1 +/- 0.4 vs. 2.5 +/- 0.9 Borg units, $P < 0.05$) and ventilation (at ventilation of 31 l/min, dyspnoea = 2 +/- 0.7 vs. 3.3 +/- 1.1 Borg units, $P < 0.05$). CRT(on) was associated with improvements in ventilatory threshold, oxygen pulse, and oxygen uptake/work rate relationships (10.2 +/- 1 vs. 7.9 +/- 1.3 ml.min(-1).W(-1), $P < 0.05$). CRT(on) reduced the ventilatory requirement during exercise as well as the steepness of ventilation-CO(2) production slope (35 +/- 4 vs. 45 +/- 7, $P < 0.05$). Changes in end-expiratory lung volume during exercise were less with CRT(on) than with CRT(off) (0.12 vs. 0.37 liter, $P < 0.05$), and breathing pattern was correspondingly slower and deeper.

Biventricular pacing improved all noninvasive indexes of cardiac function and oxygen delivery during exercise. The decreased ventilatory demand, improved dynamic operating lung volumes, and the increased ability to expand tidal volume during exercise are potential factors in the reduction of exertional dyspnoea.

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Effect of biventricular pacing on ventilatory and perceptual responses to exercise in patients with stable chronic heart failure

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Laveneziana P, O'Donnell DE, Ofir D, Agostoni P, Padeletti L, Ricciardi G, Palange P, Duranti R, Scano G. Effect of biventricular pacing on ventilatory and perceptual responses to exercise in patients with stable chronic heart failure. *J Appl Physiol* 106: 1574–1583, 2009. First published February 26, 2009; doi:10.1152/japplphysiol.90744.2008.—Despite the growing evidence supporting the use of biventricular cardiac resynchronization therapy (CRT) in patients with chronic heart failure (CHF), the mechanisms whereby acute hemodynamic improvements lead to improved exertional dyspnea are not precisely known. We hypothesized that improved cardiac function and ventilation-perfusion relations following CRT would reduce ventilatory demand, thereby improving dynamic operating lung volumes and enhancing tidal volume expansion during exercise. This, in turn, would be expected to reduce perceived exertional dyspnea and contribute to improved exercise performance. In a randomized, double-blind, crossover study, we compared cardiovascular, metabolic, ventilatory responses (breathing pattern, operating lung volumes, pulmonary gas exchange) and exertional symptoms in seven stable CHF patients who undertook incremental cardiopulmonary cycle exercise test with CRT switched to the "on" (CRT_{on}) or "off" (CRT_{off}) modality. Following CRT_{on}, peak oxygen uptake was significantly increased by 15%, and dyspnea ratings were lower for a given work rate (at work rate of 40 W, dyspnea = 1 ± 0.4 vs. 2.5 ± 0.9 Borg units, $P < 0.05$) and ventilation (at ventilation of 31 l/min, dyspnea = 2 ± 0.7 vs. 3.3 ± 1.1 Borg units, $P < 0.05$). CRT_{on} was associated with improvements in ventilatory threshold, oxygen pulse, and oxygen uptake/work rate relationships (10.2 ± 1 vs. 7.9 ± 1.3 $ml \cdot min^{-1} \cdot W^{-1}$, $P < 0.05$). CRT_{on} reduced the ventilatory requirement during exercise as well as the steepness of ventilation-CO_2 production slope (35 ± 4 vs. 45 ± 7, $P < 0.05$). Changes in end-expiratory lung volume during exercise were less with CRT_{on} than with CRT_{off} (0.12 vs. 0.37 liter, $P < 0.05$), and breathing pattern was correspondingly slower and deeper. Biventricular pacing improved all noninvasive indexes of cardiac function and oxygen delivery during exercise. The decreased ventilatory demand, improved dynamic operating lung volumes, and the increased ability to expand tidal volume during exercise are potential factors in the reduction of exertional dyspnea.

heart failure; dyspnea; dynamic lung hyperinflation; ventilation; resynchronization

CHRONIC HEART FAILURE (CHF) is a common and disabling syndrome, affecting 2.5% of the North American population (45). Despite optimal modern pharmacological treatment, many CHF patients experience severe and persistent symptoms, and their prognosis remains poor (12, 28). In selected patients who present with severe left ventricular systolic dysfunction with intra- and interventricular conduction delays, biventricular cardiac resynchronization therapy (CRT) has been found to improve symptoms, exercise tolerance, and quality of life (1, 10, 23, 44, 57).

Despite the growing evidence supporting the use of CRT, the potential mechanisms by which acute hemodynamic improvements lead to improved exertional dyspnea and exercise performance remain uncertain. Previous studies lasting up to 6 mo have found that long-term CRT was associated with improvements in indirect indexes of cardiovascular function and ventilatory efficiency during exercise (51, 54). However, these studies did not examine the impact of CRT on detailed dynamic respiratory function during exercise or on the intensity of the exertional symptoms.

Comparison of physiological responses to CRT with patients randomized acutely to the "on" and "off" modality (CRT_{on} and CRT_{off}, respectively) provides a unique opportunity to elucidate the downstream effects of acutely improving cardiac output on respiratory function and dyspnea intensity during exercise. The present study is the first to explore this approach.

The mechanisms of exertional dyspnea in CHF are multifactorial, but we have previously postulated that a combination of increased ventilatory demand [secondary to increased ventilation ($\dot{V}_E$)-perfusion mismatching, and to chemo- and metaboreflexes] and abnormal dynamic ventilatory mechanics/muscle function may be important contributory factors (37). Previous studies have demonstrated expiratory flow limitation (EFL), dynamic lung hyperinflation (DH), and "restrictive" ventilatory mechanics during exercise, even in nonsmoking patients with CHF (3, 37). In other words, in the presence of EFL, progressive reduction in dynamic inspiratory capacity (IC) may precipitate an early plateau of tidal volume (V_T) and of inspiratory reserve volume (IRV) at a relatively low $\dot{V}_E$ and oxygen uptake ($\dot{V}_{O_2}$) compared with health. We have proposed that this inability to expand V_T appropriately in the face of increasing inspiratory muscle contractile effort can lead to perceived respiratory difficulty earlier in exercise in patients with CHF (37). However, no study to date has established whether partial reversal of these mechanical abnormalities (i.e., decreased dynamic IC, V_T, and IRV) leads to alleviation of exertional

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dyspnea in CHF, a result that would support the role of such mechanical factors in dyspnea causation.

The main objective of this study was, therefore, to determine the acute effects of CRT on cardioventilatory and subjective responses to incremental cycle exercise in patients with stable CHF. Our hypothesis was, first, that improved cardiac function following CRT would reduce ventilatory demand (by improving ventilatory efficiency and delaying metabolic acidosis). Thus reduced reflexic central ventilatory drive (and central corollary discharge) would be associated with improved respiratory sensation. Second, the reduced $\dot{V}_E$ in the setting of EFL should increase dynamic IC, thereby enhancing the ability to expand V_T during exercise. Collectively, reduced ventilatory drive with improved thoracic volume displacement should improve neuromechanical coupling of the respiratory system and, therefore, improve perceived respiratory difficulty during exercise.

MATERIALS AND METHODS

Subjects. Seven consecutive, normoxemic CHF patients in regular sinus rhythm, meeting strict inclusion criteria (below), with a cardiac-resynchronization device implanted since at least 6 mo, completed the study. Eligible patients were in stable New York Heart Association functional class III–IV, have received individually optimized medical therapy for ≥6 mo after implantation of the cardiac-resynchronization device (including angiotensin-converting enzyme inhibitors, β-blockers, and diuretics), and have presented with a left ventricular ejection fraction of no more than 35%, dilated cardiomyopathy of any etiology, sinus rhythm, and QRS interval of at least ≥120 ms on the electrocardiogram. All of the patients were included in the study without knowing a priori whether they were responders or nonresponders to CRT in terms of exercise performance. Patients were excluded if they had showed: *1*) a major cardiovascular event in the previous 6 wk; *2*) a heart failure requiring continuous intravenous therapy; *3*) resting oxygen saturation (Sp_{O_2}) < 90% or a sustained decrease of > 4% during exercise; *4*) other medical conditions, i.e., respiratory diseases and primary pulmonary hypertension, which could cause or contribute to breathlessness and exercise intolerance; or *5*) other problems that could interfere with carrying out of exercise testing, i.e., neuromuscular diseases, orthopedic diseases, etc. Also excluded were patients with atrial fibrillation or severe cardiac arrhythmias, since, in such patients, CRT benefits are less clear (9, 14, 13).

The biventricular CRT device was programmed with the lower heart rate (HR) limit set at 30 beats/min, to limit the amount of continuous atrial pacing that might compromise mechanical function of the left heart in patients with CHF. All implanted devices were programmed to the active mode with the upper rate limit at 85% of the maximal predicted HR, according to the age and sex of the patient. Each patient underwent Doppler echocardiography to determine the optimal atrioventricular delay (electrical delay between atrial and ventricular excitation) during atriobiventricular pacing (10).

Study design. This was a randomized, double-blind, crossover study. The research was carried out in accordance with the principles outlined in the Declaration of Helsinki. The study was approved by the local ethics committee, and all subjects signed written, informed consent at the time of their first assessment. Subjects were tested on 3 consecutive days. The first visit was considered as a "learning session" to let patients familiarize with symptom scales; afterwards, each subject underwent careful clinical evaluation, assessment of resting pulmonary function, and a symptom-limited incremental cycle exercise to make them feel comfortable with all of the testing procedures. During the subsequent two visits (*visits 2* and *3*), participants completed baseline pulmonary function tests, followed by an incremental cycle exercise testing under different pacing modalities, in a random order. It means that, at the end of each visit, the CRT device was programmed, in a random order, to allow a different pacing modality for the subsequent visit (the day after) (see Supplemental Fig. 1). (The online version of this article contains supplemental data.) The pacing modalities were as follows: biventricular pacing modality "off" (CRT_{off}, i.e., with no stimulation of both right and left heart catheters), and biventricular pacing modality "on" (CRT_{on}). In this way, all of the patients underwent the first visit while they had their biventricular pacing active. At the end of *visit 3*, we ensured that all participants had their biventricular pacing modality back to "on". Subjects were asked to avoid caffeine or heavy meals at least 4 h before testing and avoid major physical exertion entirely on each visit day. Visits were conducted at the same time of day for each subject.

Procedures. Baseline spirometry and lung volumes were assessed in accordance with recommended techniques (34, 35, 52) using an automated pulmonary function testing system (Vmax29c, SensorMedics, Yorba Linda, CA). Measurements were standardized as percentages of predicted normal values; predicted normal values for IC were calculated as predicted total lung capacity (TLC) minus predicted functional residual capacity.

Symptom-limited incremental cardiopulmonary cycle exercise testing was conducted on an electronically braked cycle ergometer (Ergometrics 800, Sensors Medics, Yorba Linda, CA) using the Vmax29c Cardiopulmonary Exercise Testing System (SensorMedics). The equipment was calibrated before each test. All exercise tests consisted of a steady-state resting period of 6 min and a 3-min warm-up of unloaded pedaling, followed by an incremental test in which the work rate (WR) was increased in 1-min intervals by increments of 10 W until the point of symptom limitation (peak exercise). Patients were instructed to maintain the pedaling rate between 50 and 70 revolutions/min.

Breath-by-breath data were collected while subjects breathed through a facemask (dead space, 70 ml) with attached low-resistance flow transducer: $\dot{V}_E$, $\dot{V}_{O_2}$, carbon dioxide production ($\dot{V}_{CO_2}$), end-tidal carbon dioxide partial pressure ($P_{ET_{CO_2}}$), V_T, respiratory frequency (f), inspiratory and expiratory time (T_I and T_E, respectively), duty cycle (T_I/total breath time), and mean inspiratory (V_T/T_I) and expiratory flow (V_T/T_E) were calculated. Electrocardiographic monitoring of HR, rhythm, ST-segment changes, blood pressure (by indirect sphygmomanometry), and Sp_{O_2} by ear lobe sensor pulse oximetry (RAD-9; Masimo, Irvine, CA) were carried out continuously at rest and throughout exercise testing. The patients were strongly encouraged to perform a maximal test, but they determined when their symptoms were so severe that it was necessary to stop cycling. Exercise variables were measured continuously and averaged over the last 30 s of each minute and at peak exercise. When the IC maneuver was performed during exercise, all variables were averaged over the first 30 s of that minute-step to avoid the possible influence that the performance of an IC maneuver might have on exercise variables measurements. Peak WR, peak $\dot{V}_{O_2}$ ($\dot{V}_{O_{2peak}}$), and peak $\dot{V}_E$ were defined, respectively, as the highest level of exercise and the highest $\dot{V}_{O_2}$ and $\dot{V}_E$ that could be sustained for at least 30 s during the last stage of exercise. Metabolic and cardioventilatory variables were reported in absolute units, after correction of body weight, and as a percentage of predicted normal values, accounting for age, weight, and sex (27). $\dot{V}_E$ was compared with the maximal ventilatory capacity that was estimated by multiplying the measured forced expiratory volume in 1 s by 35 (17). Breathing pattern was evaluated by examining individual Hey plots (22).

The anaerobic ventilatory threshold (VTh) was detected individually using the V-slope method (53) and verified against other points, i.e., the $\dot{V}_{O_2}$ at which the ventilatory equivalent for oxygen ($\dot{V}_E/\dot{V}_{O_2}$) begins to increase systematically without an increase in the ventilatory equivalent for carbon dioxide ($\dot{V}_E/\dot{V}_{CO_2}$), and where end-tidal oxygen partial pressure begins to increase without a decrease in $P_{ET_{CO_2}}$ (55). Iso-WR was defined as the highest equivalent exercise WR achieved by all participants during all the tests, whereas iso-$\dot{V}_E$ and iso-$\dot{V}_{O_2}$ represented, respectively, the 90% of the lowest peak values for $\dot{V}_E$ and $\dot{V}_{O_2}$ achieved during both incremental exercise tests in each

subject. Exercise capacity was assessed by measuring the $\dot{V}O_2$ at VTh and peak, and by calculating the $\dot{V}O_2$/WR relationship as an index of cardiovascular performance. The $\dot{V}O_2$/WR relationship was evaluated throughout the entire incremental cycle exercise, after elimination of the increase in WR during the first 45–60 s to account for the time constant for the $\dot{V}O_2$ response to the WR increase (20). Mismatching of the heart and lungs was evaluated via the ventilatory efficiency measure $\dot{V}E/\dot{V}CO_2$ slope, i.e., the slope of the linear relationship between $\dot{V}E$ and $\dot{V}CO_2$ from 1 min after the beginning of loaded exercise to the end of the isocapnic buffering period. The dead space volume of the facemask was subtracted from the total $\dot{V}E$ before calculating $\dot{V}E/\dot{V}CO_2$ slopes and ratios. Two experts independently read each test, and the results were averaged.

Exertional symptoms evaluation. Dyspnea, or breathlessness, was defined as "the unpleasant sensation of laboured or difficult breathing" and leg discomfort as "the level of leg discomfort experienced during exercise." Before exercise testing, subjects were familiarized with the Borg scale (5), and its end points were anchored such that "0" represented "no breathlessness (and leg discomfort)" and "10" represented maximum breathlessness or "the most severe breathlessness (and leg discomfort) that they had ever experienced or could imagine experiencing." By pointing to the Borg scale, subjects rated the magnitude of their perceived breathlessness and leg discomfort at rest, every minute, and at peak exercise. Symptom ratings preceded IC maneuvers by at least five breaths to avoid interference with pre-IC breathing patterns, and to avoid the possible influence that the performance of an IC maneuver might have on dyspnea intensity.

Immediately after exercise cessation, subjects were also asked to verbalize their main reason(s) for stopping exercise (i.e., breathlessness, leg discomfort, both, or others).

Operating lung volumes and ventilatory constraints. Since TLC does not change significantly during the exercise (3), the change (decrease) in IC reflects the change (increase) in dynamic end-expiratory lung volume (EELV), or the extent of DH. Therefore, IC was gathered at rest, every 2 min during exercise, and at peak exercise to estimate changes in EELV. The IRV was calculated as IC minus V_T; likewise, changes in IRV (IRV = IC − V_T) reflect changes in end-inspiratory lung volume (EILV) (EILV = TLC − IRV). Techniques for performing and accepting IC measurements have been previously described (40). At each visit, the correct conduct of IC maneuvers was fully explained to the patient and then practiced at rest until consistently reproducible efforts were made (i.e., within ±5% or ±100 ml, whichever was larger). Subjects were given a few breaths of warning before an IC maneuver, a prompt for the maneuver (i.e., "At the end of the next normal breath out, take a deep breath all the way IN" or "at the end of this breath out, take a big breath all the IN"), and then strong verbal encouragement to make a maximal effort (i.e., "in. . ., in. . ., in. . ."). before returning to their regular breathing. The resting IC was recorded as the mean of the two best reproducible efforts. Satisfactory technique and repeatability of maneuvers was ensured before proceeding with exercise testing. During the incremental cycle exercise tests, IC maneuvers were performed at 2-min intervals during the last 30-s period of each interval. When subjects indicated the desire to terminate exercise, an "end-exercise" IC maneuver was performed within 15 s, and the subjects were permitted to cool down, or, if an acceptable IC had been performed within the preceding 30 s and the breathing pattern had not restabilized, then the value for that IC was used as the end-exercise value. If an exercise IC maneuver was found to be unacceptable (i.e., submaximal effort or anticipatory changes in breathing pattern immediately preceding the IC maneuver), it was not repeated and was excluded from the analysis.

Tidal flow-volume curves at rest, every 2 min during exercise, and at peak exercise were constructed for each patient and placed within their respective maximal flow-volume envelopes, according to coinciding IC measurements. Maximal flow-volume loops were performed only at rest for this analysis. The presence or absence of flow limitation was then determined by comparing tidal expiratory flows with those of the maximal envelope at isovolume: we looked at the shape and limits of the maximal flow-volume curve in the tidal operating range [forced expiratory flow at 50% and 75% of the forced vital capacity ($FEF_{50\%}$ and $FEF_{75\%}$, respectively)], as well as the extent of EFL by evaluating the percentage of V_T that encroached on the maximal flow-volume envelope (26).

Statistical analysis. Results are expressed as means ± SE. Metabolic, cardioventilatory, and perceptual responses at iso-$\dot{V}E$ and iso-$\dot{V}O_2$ were calculated by linear interpolation between adjacent measurement points for each subject. All group responses (CRT_{on} vs. CRT_{off}) were compared at rest, iso-WR, iso-$\dot{V}E$, iso-$\dot{V}O_2$, and peak exercise by using paired *t*-tests with appropriate Bonferroni adjustments for multiple comparisons. Repeated-measures ANOVA (with treatment, times/points, and interaction as fixed effects, and subject as a random effect) was applied to compare the overall treatment effects over the course of the exercise test (i.e., rest vs. iso-WR vs. peak). A $P < 0.05$ level of statistical significance was used for all analyses. All statistical procedures were carried out using Intercooled Stata 6.0 for Windows (Stata, College Station, TX) and Statgraphics Plus 5.1 for Windows (Manugistics, Rockwille, MD).

RESULTS

Comparisons are shown by only applying paired *t*-tests with appropriate Bonferroni adjustments for multiple comparisons (see Tables 2 and 3).

By repeated-measures ANOVA, there were significant interactions between treatment and time points during exercise (rest vs. iso-WR vs. peak for both conditions) for exertional symptom ratings, $\dot{V}E$ (except for peak), f (except for peak), V_T (in absolute value and as percentage of either VC predicted or IC predicted), T_I and T_E (except for resting T_I), IC (either in absolute value or as percent predicted), EELV (except for iso-WR vs. peak), HR, $\dot{V}O_2$, and O_2 pulse (i.e., the treatment effect did vary at different time points).

Repeated-measures ANOVA showed a significant treatment effect for $\dot{V}E/\dot{V}O_2$ and $\dot{V}E/\dot{V}CO_2$ ratios, with no significant interactions between treatment and exercise time points.

Pulmonary function and baseline characteristics. Subject characteristics and resting pulmonary function at *visit 1* (familiarization visit) are summarized in Table 1. There were

Table 1. *Subjects characteristics and resting pulmonary function testing during the first visit*

Sex (male/female)	5/2
Age, yr	71±2
Height, cm	171±3
Weight, kg	78±3
Body mass index, kg/m^2	26.5±0.7
Cigarette smoking history (smoker/nonsmoker)	4/3
FVC, %predicted	91±8
FEV_1, %predicted	97±9
FEV_1/FVC, %	73±5
FEV_1/SVC, %	70±4
TLC, %predicted	100±6
SVC, %predicted	90±6
IC, %predicted	90±8
FRC, %predicted	104±8
RV, %predicted	115±8
RV/TLC, %	44±3

Values are means ± SE. FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 s; TLC, total lung capacity; SVC, slow vital capacity; IC, inspiratory capacity; FRC, functional residual capacity; RV, residual volume; FEV_1/FVC, FEV_1/SVC, and RV/TLC are ratios.

Table 2. *Metabolic and cardiorespiratory responses to cardiopulmonary cycle exercise testing in patients with chronic heart failure*

Variables	Rest		iso-WR		Peak	
	CRT_{off}	CRT_{on}	CRT_{off}	CRT_{on}	CRT_{off}	CRT_{on}
Work rate, W (%pred)			40 (29±3)	40 (29±3)	66±8 (46±6)	72±9*(51±6)*
$\dot{V}O_2$, l/min (% pred)	0.266±0.02 (15±1)	0.274±0.02 (16±1)	0.601±0.06 (35±5)	0.684±0.05* (40±5)*	0.766±0.06 (45±4)	0.987±0.07* (58±7)*
$\dot{V}O_2$/kg	3.4±0.2	3.5±0.2	7.7±0.8	8.9±0.6*	9.9±0.9	13±1.4*
HR, beats/min (%pred)	75±6 (46±3)	69±6* (42±3)*	93±10 (57±6)	83±8* (51±5)*	110±11 (68±7)	102±9* (63±5)*
O_2 pulse, ml/beat	3.6±0.3	4.1±0.3*	6.6±0.6	8.5±0.6*	7.7±1.4	10.2±1.2*
$\dot{V}E$, l/min (%MVC)	12.3±1.2 (15±2)	9.7±1.5* (12±2)*	27±3.4 (36±8)	25±2.8* (32±7)*	36±3 (45±7)	39±2 (49±7)
f, breaths/min	17±1	14±2*	26±4	21±3*	30±4	28±2
VT, liters (%VC pred)	0.718±0.05 (19±2)	0.709±0.04 (18±1)	1.07±0.07 (27±1)	1.19±0.05* (31±1)*	1.26±0.11 (32±1)	1.43±0.10* (37±2)*
VT, %IC pred	25±2	25±2	37±1	42±1*	43±2	50±2*
IC, liters (%pred)	2.24±0.3 (78±9)	2.34±0.3 (82±10)	1.99±0.3 (68±8)	2.27±0.3* (79±8)*	1.83±0.2 (64±7)	2.19±0.2* (76±8)*
EELV, liters (%TLC pred)	4±0.4 (63±6)	3.9±0.4 (62±6)	4.3±0.4 (68±6)	4.0±0.4* (63±6)*	4.37±0.4 (70±6)	4.01±0.4* (64±6)*
$\dot{V}E/\dot{V}O_2$	46±2	35±3*	46±4	36±2*	47±3	40±3*
$\dot{V}E/\dot{V}CO_2$	52±3	40±4*	52±4	43±3*	49±3	42±3*
Dyspnea (Borg units)	0	0	2.5±0.9	1±0.4*	4.6±1.2	2.7±0.9*
Leg discomfort (Borg units)	0	0	3.1±0.9	0.7±0.4*	6.7±0.7	4.7±1.1*

Values are means ± SE. WR, work rate; CRT_{off}, cardiac resynchronization therapy (CRT) switched to "off" modality; CRT_{on}, CRT switched to "on" modality; pred, predicted; $\dot{V}O_2$, O_2 uptake; HR, heart rate; $\dot{V}E$, ventilation; MVC, maximal ventilatory capacity; f, respiratory frequency; VT, tidal volume; VC, vital capacity; IC, inspiratory capacity; EELV, end-expiratory lung volume; TLC, total lung capacity; $\dot{V}CO2$, CO_2 production. *$P < 0.05$.

absolutely no changes between resting pulmonary function at *visit 1* and those obtained in the two subsequent visits. See the online data supplements for more detail.

Cardiovascular response to exercise. The highest equivalent standardized exercise WR (iso-WR) achieved by all participants during all the tests corresponded to 40 W. Measurements at rest, at iso-WR, and at peak exercise are shown in Table 2. Measurements at iso-$\dot{V}O_2$ are shown in Table 3. CRT_{off} patients stopped exercise at lower $\dot{V}O_{2peak}$, WR, and O_2 pulse, but at higher HR compared with CRT_{on} patients (Fig. 1). An improvement in the $\dot{V}O_{2peak}$ was seen in five of seven patients with CRT_{on} compared with CRT_{off}, in line with the existent literature (51). The change (Δ) in $\dot{V}O_2/\Delta WR$ relationship was upwards shifted and increased from the value of 7.9 ± 1.3 $ml \cdot min^{-1} \cdot W^{-1}$ during CRT_{off} session to normal value of 10.2 ± 1 $ml \cdot min^{-1} \cdot W^{-1}$ during CRT_{on} session (by ~24%, $P < 0.05$). See the online data supplements for more detail.

Ventilatory response to exercise. Compared with the CRT_{on} session, $\dot{V}E$ was significantly increased at rest and at any submaximal $\dot{V}O_2$ and exercise intensity during CRT_{off} session (Fig. 2 and Table 2).

During CRT_{on} session, f was significantly lower at rest and throughout the entire exercise, with the exception of peak (Fig. 3). Rest-to-peak changes in VT ranged from 0.54 liter during CRT_{off} session to 0.72 liter during CRT_{on} session ($P < 0.05$).

Upon evaluation of individual Hey plots (22), the average $\dot{V}E$ at the VT inflection point was similar at 32 and 29 l/min in CRT_{on} and CRT_{off} patients, respectively; however, this inflection occurred at a significantly ($P < 0.05$) lower $\dot{V}O_2$ and WR in CRT_{off} patients.

Differences were also noted in the timing components of the breathing pattern. Both TI and TE were higher during CRT_{on} session throughout the exercise (Fig. 3) compared with CRT_{off} session, excepted for the value of resting TI, which did not

Table 3. *Significant change in metabolic and cardiorespiratory variables at iso-$\dot{V}O_2$ and iso-$\dot{V}E$ during cardiopulmonary cycle exercise testing in patients with chronic heart failure*

Variables	iso-$\dot{V}O_2$		iso-$\dot{V}E$	
	CRT_{off}	CRT_{on}	CRT_{off}	CRT_{on}
Work rate, W (%pred)	47±6 (34±5)	41±6 (29±3)	53±7 (37±4)	57±6* (41±4)*
$\dot{V}O_2$, l/min (% pred)	0.694±0.06 (41±4)	0.694±0.06 (41±4)	0.692±0.05 (40±4)	0.852±0.05* (50±5)*
$\dot{V}O_2$/kg	9±0.8	9±0.8	9.0±0.7	11.1±0.9*
HR, beats/min (%pred)	97±9 (60±5)	84±7* (51±4)*	99±8 (61±5)	92±7* (56±4)*
O_2 pulse, ml/beat	7.6±1.2	8.6±1.1*	7.4±1.1	9.7±1.1*
$\dot{V}E$, l/min (%MVC)	30±3 (38±6)	25±3* (32±5)*	31±2 (40±6)	31±2 (40±6)
f, breaths/min	27±3	22±2*	27±3	24±3*
VT, liters (%VC pred)	1.16±0.09 (30±1)	1.19±0.08 (30±1)	1.21±0.10 (31±1)	1.31±0.08* (34±1)*
VT, %IC pred	40±1	41±1	42±2	46±1*
IC, liters (%pred)	2±0.3 (80±9)	2.3±0.3* (69±8)*	1.94±0.2 (67±8)	2.23±0.2* (78±8)*
EELV, liters (%TLC pred)	4.24±0.4 (68±6)	3.94±0.4* (62±6)*	4.3±0.4 (68±6)	4.01±0.4* (64±6)*
IRV, liters (%TLC pred)	0.84±0.2 (13±3)	1.11±0.3* (18±4)*	0.73±0.2 (12±3)	0.91±0.2* (15±3)*
$\dot{V}E/\dot{V}O_2$	44±3	36±2*	46±3	37±3*
$\dot{V}E/\dot{V}CO_2$	48±3	43±2*	49±3	41±3*
Dyspnea (Borg score)	2.7±0.9	1.1±0.4*	3.3±1.1	2.0±0.7*
Leg discomfort (Borg score)	3.3±0.8	1.1±0.6*	4.1±1	2.5±0.9*

Values are means ± SE. IRV, inspratory reserve volume. *$P < 0.05$.

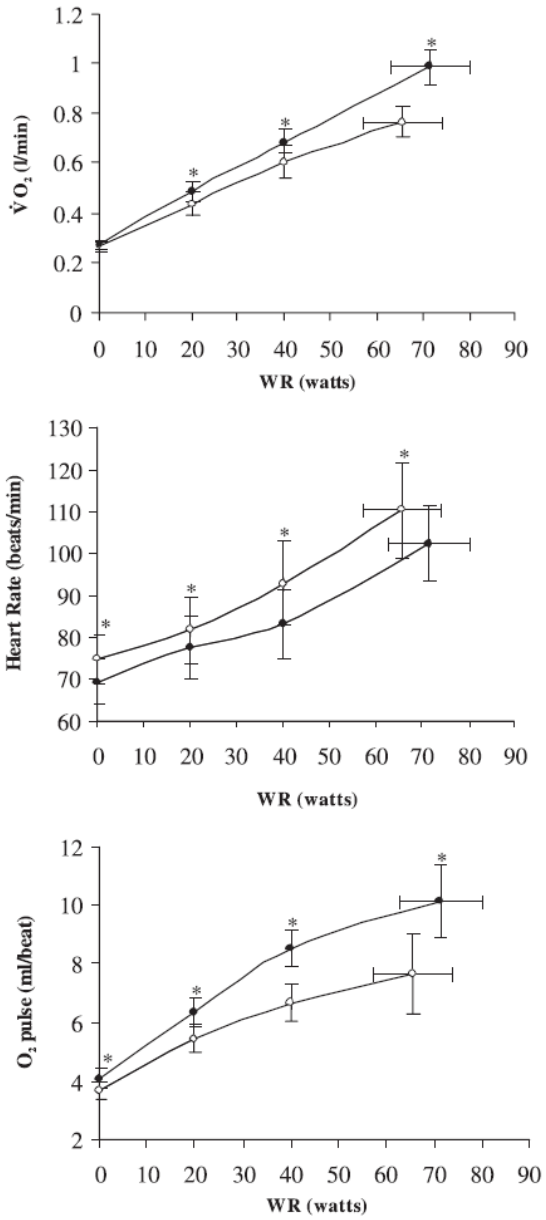

Fig. 1. Oxygen uptake ($\dot{V}O_2$), heart rate, and O_2 pulse are shown in response to increasing work rate (WR) during symptom-limited incremental cycle exercise in patients with cardiac resynchronization therapy (CRT) switched to the "on" (CRT_{on}; ●) and CRT switched to the "off" modality (CRT_{off}; ○). Graphs represent mean ± SE values at rest, at 20 and 40 W during exercise, and at peak exercise. *$P < 0.05$, CRT_{on} vs. CRT_{off}.

reach statistical significance ($P = 0.08$). Consequently, the total time allowed to breathe (T_T) was greater in CRT_{on} patients throughout the exercise.

The $\dot{V}E/\dot{V}O_2$ and $\dot{V}E/\dot{V}CO_2$ ratios were significantly lower ($P < 0.05$) during CRT_{on} sessions compared with CRT_{off} sessions at rest and throughout the entire exercise (Tables 2 and 3). The $\dot{V}E/\dot{V}CO_2$ slope, a strong CHF prognostic indicator independent of $\dot{V}O_{2peak}$ (11, 29, 43), was significantly elevated during CRT_{off} session (45 ± 7) and improved significantly by ~20% during CRT_{on} session (35 ± 4, $P < 0.05$). See the online data supplements for more detail.

Operating lung volume response to exercise. In the present study, all of the CHF subjects presented with resting EFL, which was not abolished by CRT_{on}.

EELV was significantly higher ($P < 0.05$) in CRT_{off} patients at any submaximal exercise intensity (Tables 2 and 3). Rest-to-peak changes in EELV ranged from 0.12 liter during CRT_{on} session to 0.37 liter during CRT_{off} session (Fig. 4, $P < 0.05$). Of note, six out of seven CHF patients improved their dynamic IC in response to active cardiac pacing. See the online data supplements for more detail.

Dyspnea and leg discomfort. Dyspnea intensity was higher in CRT_{off} patients during exercise at a given WR, as well as at iso-$\dot{V}O_2$ and iso-$\dot{V}E$ and at peak (Fig. 5, Tables 2 and 3). Dyspnea/$\dot{V}E$ and dyspnea/$\dot{V}O_2$ slopes were also greater in CRT_{off} patients than CRT_{on} patients by 50 and 47%, respectively ($P < 0.05$).

Leg discomfort intensity was higher in CRT_{off} patients during exercise at a given WR, as well as at iso-$\dot{V}O_2$ and at peak (Fig. 5, Tables 2 and 3). Leg discomfort/WR and leg discomfort/$\dot{V}O_2$ slopes were also greater in CRT_{off} patients

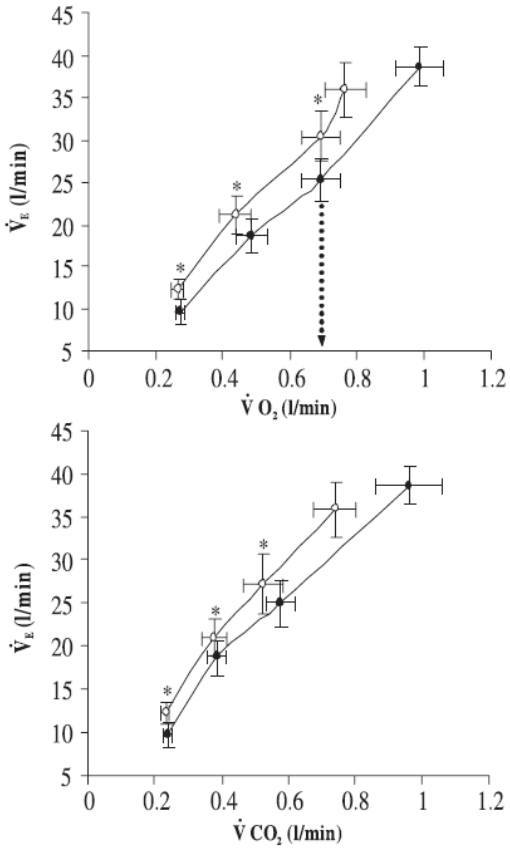

Fig. 2. Minute ventilation ($\dot{V}E$) is shown in response to increasing $\dot{V}O_2$ and carbon dioxide production ($\dot{V}CO_2$) during symptom-limited incremental cycle exercise in patients with CRT_{on} (●) and with CRT_{off} (○). Vertical dotted arrow represents iso-$\dot{V}O_2$ point. Values are means ± SE. *$P < 0.05$, CRT_{on} vs. CRT_{off}.

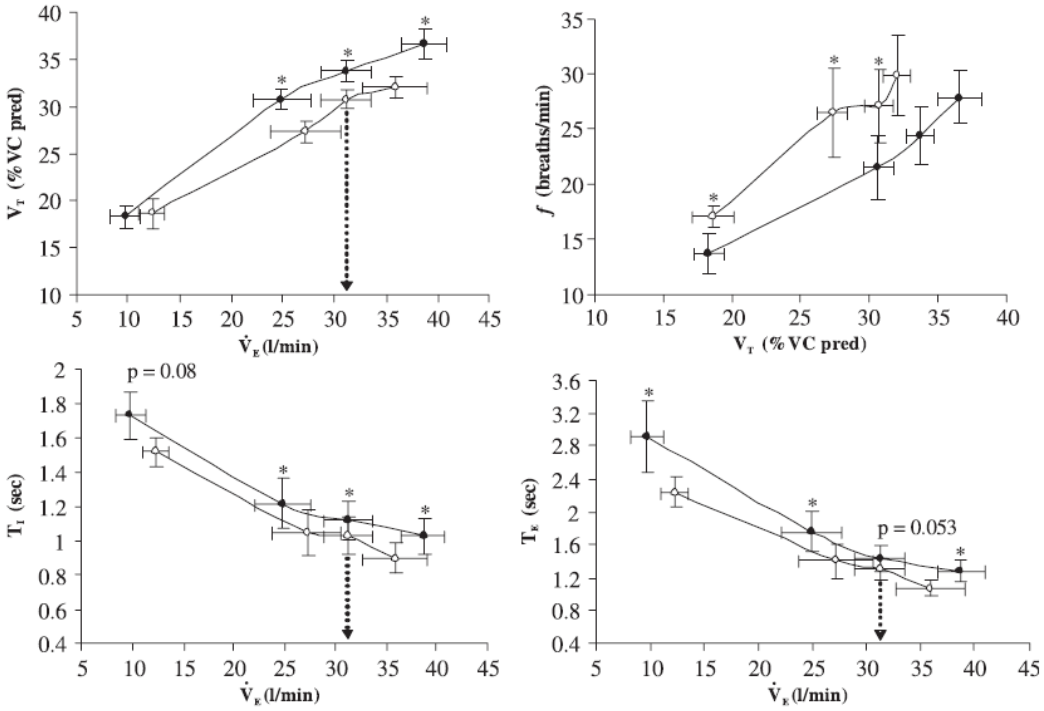

Fig. 3. Tidal volume (V_T) expressed as percentage of predicted vital capacity (V_T %VCpred) and inspiratory (T_I) and expiratory time (T_E) are shown in response to increasing $\dot{V}_E$ during symptom-limited incremental cycle exercise in patients with CRT_{on} (●) and with CRT_{off} (○). Respiratory frequency (f) is shown in response to expansion of V_T %VCpred. Breathing pattern was deeper and slower with CRT_{on} compared with CRT_{off}. Vertical dotted arrows represent iso-$\dot{V}_E$ points. Values are means ± SE. *$P < 0.05$, CRT_{on} vs. CRT_{off}.

than CRT_{on} patients by 66 and 57% ($P < 0.05$). See the online data supplements for more detail.

DISCUSSION

The main findings of this study are that biventricular pacing was associated with the following: *1*) improved indirect indexes of cardiovascular function; *2*) reduced ventilatory requirements, increased dynamic IC, and a deeper, slower breathing pattern; and *3*) significant reduction in exertional symptoms and increased symptom-limited $\dot{V}O_{2peak}$.

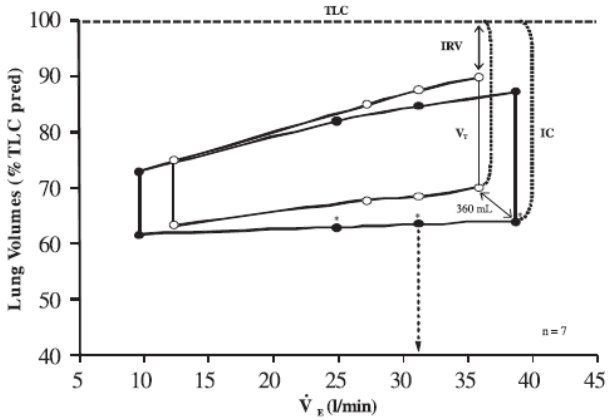

Fig. 4. Average data of changes in operating lung volumes expressed as percentage of predicted total lung capacity (%TLCpred) are shown as $\dot{V}_E$ increases during symptom-limited incremental cycle exercise in patients with CHF ($n = 7$) following CRT_{on} (●) and CRT_{off} (○). "Restrictive" constraints on V_T expansion during exercise are significantly greater with CRT_{off} compared with CRT_{on} from both below [reduced inspiratory capacity (IC)] and above [inspiratory reserve volume (IRV)]. Vertical dotted arrows represent iso-$\dot{V}_E$ points. Values are means ± SE. *$P < 0.05$, CRT_{on} vs. CRT_{off}.

The present is the first study to evaluate, in a crossover fashion, the acute effects of CRT on cardiovascular and respiratory function in patients with severe CHF with an average $\dot{V}O_{2peak}$ of only 9.9 ml·kg^{-1}·min^{-1}. Accordingly, these results may not apply to patients with CRT, but less severe CHF (4, 54). Exercise tolerance was clearly compromised in our patients with CHF: peak symptom-limited $\dot{V}O_2$ was reduced to 55% of the predicted normal value (Table 2). CRT_{on} was associated with consistent increases in $\dot{V}O_{2peak}$ by 15% predicted. Previous hemodynamic studies (24, 48, 50) have confirmed acute and chronically maintained improvements in cardiac output following biventricular pacing in selected patients. Wasserman et al. (54) also reported improvements in cardiovascular indexes in a large series of patients who underwent CRT. In the present study, improvements in cardiovascular function and oxygen delivery are suggested by the following: *1*) the increased $\dot{V}O_2$ at VTh and at peak of exercise; *2*) the greater O_2 pulse at rest and on exertion; *3*) improved HR responses; *4*) the increase in the $\dot{V}O_2$/WR relationship; and *5*) delay in the VTh.

In accordance with the results of previous studies (54), CRT_{on} was associated with consistent reductions in $\dot{V}_E$ at a given $\dot{V}O_2$ (by ~17%) or power output (by ~10%) throughout exercise in the absence of any measurable deterioration in pulmonary gas exchange (both Sp_{O_2} and P_{ETCO_2} were pre-

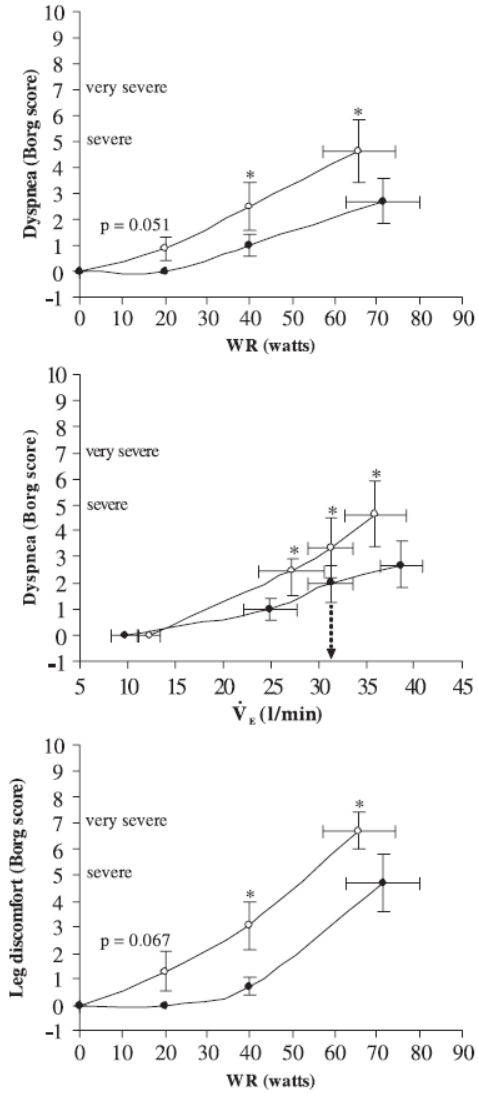

Fig. 5. Exertional dyspnea and leg discomfort intensity (Borg score) are shown in response to increasing WR and/or $\dot{V}_E$ during symptom-limited incremental cycle exercise in patients with CRT_{on} (●) and with CRT_{off} (○). Exertional dyspnea and leg discomfort intensity (Borg score) were lower with CRT_{on} than with CRT_{off}. Dyspnea/WR, Dyspnea/$\dot{V}_E$, and leg discomfort/WR slopes were significantly ($P < 0.05$) steeper with CRT_{off} than with CRT_{on}. Vertical dotted arrow represents iso-$\dot{V}_E$ point. Values are means ± SE. *$P <$ 0.05, CRT_{on} vs. CRT_{off}.

served; see the online data supplements for more detail). This reduced ventilatory requirement, in turn, likely reflected improved $\dot{V}_E$/perfusion relations as a result of improved ability to reduce a higher physiological dead-space during exercise due to improved pulmonary perfusion. Greater expansion of V_T during CRT_{on} could also have contributed to this (Fig. 2, Tables 2 and 3). Ventilatory efficiency improved, as indicated by reduced steepness of $\dot{V}_E/\dot{V}_{CO_2}$ slope (by ~20%) and the lower $\dot{V}_E/\dot{V}_{CO_2}$ and $\dot{V}_E/\dot{V}_{O_2}$ ratios throughout exercise (Fig. 2, Tables 2 and 3). Additionally, a consistent increase in the VTh during CRT_{on} condition suggests delayed onset of metabolic acidosis secondary to improved oxygen delivery, or utilization, or both.

Improvement of dynamic ventilatory mechanics. This study extends the results of previous studies and is the first to examine the impact of improved cardiac function on the ventilatory mechanical parameters relevant to symptom perception. Resting pulmonary function was largely preserved in our CHF patients and was not altered by activation of biventricular pacing. Small airway dysfunction and EFL during exercise have previously been described in CHF (3, 37). The nature of the airway dysfunction in CHF is poorly understood and may reflect bronchial mucosal edema, airway hyperresponsiveness, or the attendant effects of aging or tobacco smoking or various combinations of these factors (8, 15, 16, 18, 30). The reduced resting ERV and the shape and limits of the maximal flow-volume curves in the tidal operating range (showing a reduction of $FEF_{50\%}$ and $FEF_{75\%}$ by 76 and 55%, respectively), as well as the encroachment of V_T upon the maximal flow-volume envelope in our CHF patients, mean that operating V_T was positioned closer to residual volume, thus increasing the propensity for EFL (15) (Table 1). During the accelerated ventilatory response to exercise, IC decreased by an average of 0.37 liter from rest to peak exercise, in keeping with previous reports (37). If we accept that TLC remains stable throughout exercise, and there is good evidence for this from the study of Agostoni and colleagues (3), we can assume that the decreases in dynamic IC reflect increase in the rate of change in EELV (DH). This suggests that the mechanical time constants for lung emptying were delayed in CHF patients to a degree that air trapping was precipitated during the tachypnea of exercise. Of interest, DH in CHF patients was associated with a more rapid, shallow breathing at each stage of exercise, as well as at iso-$\dot{V}_E$ (Fig. 3).

When randomized to CRT_{on}, there were consistent increases in dynamic IC and IRV with corresponding improvements in the volume and timing components of breathing: V_T increased by an average of 0.72 liter (~50% of predicted IC), and f was reduced due to prolongation of both T_I and T_E (Fig. 3). The mechanisms of reduced DH were not fully elucidated: we were unable to demonstrate improved mean expiratory flow rates or reduced EFL during exercise. It is reasonable to assume that the reduced $\dot{V}_E$ (by 10–12%) and reduced f seen in this study would reduce the extent of air trapping in patients with EFL, as it has been demonstrated in COPD patients (38, 47). It is also conceivable that improvement in the time constant for lung emptying of heterogeneous alveolar units may occur in response to improved cardiopulmonary interactions during active cardiac pacing and not be reflected in our estimation of EFL by the flow-volume overlap method.

An alternative explanation for the increase in IC during exercise when patients were randomized to the active cardiac pacing modality is improved inspiratory muscle performance, secondary to improved blood perfusion to muscle (due to the increased cardiac output) (42). Thus, if this is the case, increases in dynamic IC might reflect an increased ability to reach TLC during the IC maneuvers. It is possible that improved cardiac function with CRT_{on}, by improving oxygen delivery and inspiratory muscle regional blood flow, may have reduced respiratory muscle fatigue and/or decrease the competition for blood flow with locomotor muscles (6). Given this scenario, the alterations in breathing pattern following active

cardiac pacing may reflect increased functional strength of the inspiratory muscles. However, the behavior of the inspiratory muscles in CHF during exercise is still debated (32, 42). Mancini et al. (32) showed no fatigue of the diaphragm after incremental exercise using phrenic nerve stimulation in CHF population. Interestingly, there is evidence that rats may protect diaphragm blood flow during exercise, despite severe left ventricle dysfunction (36). Johnson et al. (25) showed that both CHF and healthy subjects achieved inspiratory tidal flows that approached a similar percentage of the maximal available inspiratory flows, suggesting that the inspiratory flow-generating reserve of the inspiratory muscles at peak exercise was similar (but occurred at lower lung volumes in the CHF patients). In the absence of esophageal pressure measurements in this study, we must concede that both mechanisms of dynamic IC recruitment (either singly or in combination) are possible. However, regardless of the underlying mechanisms, improved dynamic IC during exercise is likely to have salutary sensory and mechanical consequences for patients with CHF.

Improved exertional symptoms with biventricular pacing. Although intolerable leg discomfort is usually the primary limiting symptom in patients with CHF, as seen in this study, patients also report severe dyspnea (19, 37). Potential mechanisms include the following: *1*) increased vascular congestion/distension and interstitial edema (41); *2*) DH (37); *3*) excessive loading (due to decreased lung compliance from pulmonary edema or increased airways resistance) of inspiratory muscles (3, 33); *4*) ventilatory muscle weakness (33); and *5*) increased ventilatory demand (secondary to increased $\dot{V}_E$/perfusion mismatching and to chemo- and metaboreflexes) (31, 49). Dyspnea/$\dot{V}_E$ slopes were consistently reduced by ~50% during exercise in response to active cardiac pacing. The attendant reduction in central respiratory drive is likely to ameliorate dyspnea intensity. Improved dynamic IC (either due to reduced DH, or increased inspiratory muscle strength, or both) should reduce the central motor command output (and central corollary discharge to the somatosensory cortex) required to drive the ventilatory muscles, thereby improving dyspnea (39). Reduced f would also reduce the velocity of shortening of the inspiratory muscles and reduce dynamic functional weakness in this manner. Improved cardiopulmonary interaction during active cardiac pacing in patients with CHF may favorably alter activation patterns in mechanosensors in the lung, airways, heart, and pulmonary vasculature and reduce unpleasant respiratory sensation in a manner that is not fully understood (7, 37, 46, 56). The net effect of these changes in ventilatory control, dynamic respiratory mechanics, and ventilatory muscle function is enhanced neuromechanical coupling of the respiratory system.

Perceived leg discomfort was significantly reduced during CRT_{on} (Fig. 5), suggesting that active cardiac pacing improved O_2 transport and the metabolic milieu at the active locomotor muscle level. We previously demonstrated that inspiratory muscle unloading (using pressure support $\dot{V}_E$) during exercise in patients with CHF similarly relieved leg discomfort (37). We postulated that improved cardiopulmonary interactions with reduced ventilatory/locomotor muscle competition were the most plausible mechanism (6, 21). Further mechanical studies are needed to determine whether the reduced leg discomfort, in association with CRT_{on}, is explained by similar mechanical improvements.

LIMITATIONS

In the absence of esophageal pressure measurements, we must concede that improvement in dynamic IC in response to active cardiac pacing may be due either to reduced DH, increased inspiratory muscle contractile strength, or both in combination. Regardless of the mechanism, the consistent increase in dynamic IC in six of the seven patients following CRT is likely to be physiologically and clinically meaningful. Given the small sample size and the heterogenous pathophysiology that is normally characteristic of patients with CHF (many of whom have respiratory comorbidities), we must be careful to avoid any generalization of our findings to the larger CHF population. Although we did not preselect our CHF patients, the majority (5 out of 7) improved their $\dot{V}O_{2peak}$ when randomized to active pacing. Similar high response rates have been reported elsewhere (51). However, further studies that contain a larger sample size (which includes nonresponders to CRT) will be required to definitively elucidate the physiological mechanisms of benefit of this intervention.

In summary, CRT_{on} was associated with consistent improvements of all noninvasive indexes of cardiac function and oxygen delivery during exercise. We suggest that, collectively, the decrease in ventilatory demand, improved dynamic operating lung volumes (due to either reduced DH, improved muscle function, or both), and an increased ability to expand V_T during exercise could have contributed to the impressive reduction in exertional dyspnea. Future controlled studies that utilize CRT in this manner have the potential to offer unprecedented insights into the nature of cardiopulmonary interaction and the origin of intolerable exertional symptoms in patients with CHF.

ACKNOWLEDGMENTS

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CHAPTER III

Tidal volume constraints and dyspnoea during exercise in pulmonary arterial hypertension

Patients with pulmonary arterial hypertension (PAH) may exhibit reduced expiratory flows in tidal operating range, which could promote exercise-induced dynamic lung hyperinflation. This study aimed at examining the impact of potential dynamic lung hyperinflation-induced critical mechanical constraint on the intensity of dyspnoea in patients with PAH undergoing symptom-limited incremental cardiopulmonary cycle exercise testing (CPET).

Twenty-five young (38±12yr old) non-smoking PAH patients with no evidence of spirometric obstruction and 10 age-matched non-smoking healthy subjects performed a CPET to the limit of tolerance. Ventilatory pattern, operating lung volumes [derived from inspiratory capacity (IC) measurements], and dyspnoea intensity (by Borg scale) were assessed throughout CPET.

IC decreased (i.e., dynamic lung hyperinflation) progressively throughout CPET in PAH patients (average 0.15L), whereas it increased in all the healthy subjects (0.45L). Among PAH, 15 patients (60%) exhibited reduced expiratory flows at low lung volumes. In this subgroup decreased the IC decreased throughout exercise by 0.50L, whereas it increased by 0.36L in the remaining 10 patients (40%) increased the IC by 0.36L. Dyspnoea intensity and ventilation were greater whereas inspiratory reserve volume was lower in PAH patients than in controls at any stage of CPET.

This study is the first to examine the impact of potential dynamic lung hyperinflation - induced critical mechanical constraints on the intensity of dyspnoea in young non-smoking patients with idiopathic and heritable PAH undergoing symptom-limited incremental CPET. It confirms that reduced expiratory flows at low lung volumes at spirometry exist in a large proportion of idiopathic and heritable PAH patients (60%) despite a preserved FEV_1/VC ratio. When increased ventilation/perfusion mismatching is superimposed on pre-existing abnormal airway function, greater troublesome exertional symptoms ensue. Dyspnoea causation is multifactorial but our

results clearly indicate that increased ventilatory demand and abnormal dynamic ventilatory mechanics should be considered in PAH patients. The corollary of this is that therapeutic interventions as add-ons to vasodilators, that effectively reduce dynamic lung hyperinflation should theoretically delay the appearance of the mechanical constraint of V_T expansion and the attendant dyspnoea during physical activity in selected patients with stable PAH.

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Tidal volume constraints and dyspnoea during exercise in pulmonary arterial hypertension

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ABSTRACT

Patients with pulmonary arterial hypertension (PAH) may exhibit reduced expiratory flows in tidal operating range, which could promote exercise-induced dynamic hyperinflation (DH). This study aimed at examining the impact of potential DH-induced critical mechanical constraint on the intensity of dyspnoea in patients with PAH undergoing symptom-limited incremental cardiopulmonary cycle exercise testing (CPET).

Twenty-five young (38±12yr old) non-smoking PAH patients with no evidence of spirometric obstruction and 10 age-matched non-smoking healthy subjects performed a CPET to the limit of tolerance. Ventilatory pattern, operating lung volumes [derived from inspiratory capacity (IC) measurements], and dyspnoea intensity (by Borg scale) were assessed throughout CPET.

IC decreased progressively throughout CPET in PAH patients (average 0.15L), whereas it increased in all the healthy subjects (0.45L). Among PAH, 15 patients (60%) exhibited reduced expiratory flows at low lung volumes. In this subgroup IC decreased throughout exercise by 0.50L, whereas it increased by 0.36L in the remaining 10 patients (40%). Dyspnoea intensity and ventilation were greater whereas inspiratory reserve volume was lower in PAH patients than in controls at any stage of CPET.

DH-induced mechanical constraint on tidal volume expansion and excessive ventilatory demand occurred in young non-smoking PAH patients with no spirometric obstruction and contributed to exertional dyspnoea.

Keywords: dynamic lung hyperinflation; dyspnoea; exercise; pulmonary arterial hypertension.

INTRODUCTION

Exertional dyspnoea is the most frequent complaint for which patients with pulmonary arterial hypertension (PAH) seek medical attention. It progresses relentlessly as the disease advances, contributing importantly to an impoverished quality of life [1]. Previous studies on the mechanisms of exertional dyspnoea in PAH have largely and mostly focused on the cardiovascular determinants of respiratory discomfort [2-4]. However, respiratory mechanics abnormalities could contribute to exertional dyspnoea in these patients. For instance, PAH patients may exhibit peripheral airway obstruction ("small airway disease") despite a preserved forced expiratory volume in 1 s/forced vital capacity ratio (FEV_1/FVC) [5-7]. This is evidenced by reduced expiratory flows at low lung volumes (namely instantaneous forced expiratory flows measured after 50% and 75% of the FVC has been exhaled [$FEF_{50\%}$ and $FEF_{75\%}$] lower than predicted). Meyer et al. [6] showed that such a finding could be common in certain PAH cohorts. They related it to incidental descriptions of airway wall thickening with lymphocytic infiltration in PAH [8] and proposed several other speculative explanatory mechanisms, either biological or mechanical [6]. Whatever its cause, peripheral airway obstruction implies that the operating tidal volume (V_T) range becomes closer than normally to residual volume (RV) mostly through an increase in RV (elevated residual volume/total lung capacity ratio, RV/TLC). The reduced difference between forced and tidal expiratory flows promotes dynamic lung hyperinflation (i.e., a progressive increase in end-expiratory lung volume) under conditions of increased ventilatory demand. Dynamic lung hyperinflation (DH) increases the mechanical inspiratory load that the respiratory muscles must overcome to produce ventilation (V'_E), places the diaphragm at mechanical disadvantage, and reduces the ability of V_T to expand appropriately during exercise, thus imposing "restrictive" mechanics [9, 10]. Dyspnoea ensues, as clearly shown in flow-limited patients with chronic obstructive pulmonary disease (COPD) and chronic heart failure (CHF) during exercise [10-14].

We hypothesized that this sequence of events would occur in PAH patients exhibiting peripheral airway obstruction. To test these hypotheses, we examined the impact of DH-induced mechanical constraint on V_T expansion on exertional dyspnoea in young non-smoking PAH patients with no evidence of spirometric obstruction with respect to the presence or absence of signs of small airway disease.

MATERIAL AND METHODS

Patients and controls

We studied 25 non-smoking consecutive clinically stable patients with idiopathic or heritable PAH [15], diagnosed according to the current evidence-based clinical practice guidelines [16, 17], with a normal body mass index (BMI) and no spirometric evidence of an obstructive ventilatory defect [18] . This sample size provides a 80% power to detect a significant difference (two-sided α=0.05) in dyspnoea

intensity (Borg scale) measured at a standardized work rate during incremental cardiopulmonary cycle exercise testing (CPET), based on a relevant difference in Borg ratings of ~1.5, a SD of ~1.0 for Borg ratings changes found at our laboratory. Patients were included in the study irrespective of the treatment received, if they had been clinically stable during the 3 preceding months, and if they were scheduled for CPET within the frame of their clinical follow-up at the reference center. A control group of 10 age-matched healthy subjects, all of them lifelong non-smokers and having a normal spirometry [18], was taken from two previous studies [19, 20]. The research was carried out in accordance with the principles outlined in the Declaration of Helsinki. The subjects gave their informed consent to participate, and the study received the approval of the Institutional Review Board of the French learned society for respiratory medicine (*Comité d'Evaluation des Protocoles de Recherche Observationnelle, Société de Pneumologie de Langue Française, CEPRO 2010-020*). Please see the online data supplement for more detail.

Procedures

Pulmonary function tests were performed according to recommended standards [21-23]. Measurements were expressed as percentages of predicted normal values [24-27]; predicted inspiratory capacity (IC) was calculated as predicted total lung capacity (TLC) minus predicted functional residual capacity (FRC). Procedures for conducting symptom-limited incremental CPET have been described previously [10, 11]. The intensity of dyspnoea and of leg discomfort were rated using the modified 10-point Borg scale [28] at rest, every minute during exercise and at peak exercise. Inspiratory flow reserve, an indirect index of inspiratory muscle constraint/fatigue, was assessed using the technique described by Johnson et al [29]. Please see the online data supplement for more detail.

Operating Lung Volumes

Operating lung volumes derived from IC maneuvers were measured at rest, every second minute during exercise and at end-exercise based on the assumption that TLC did not change significantly during the exercise. To ensure that this was actually the case, TLC was measured before and immediately after completion of CPET. DH was defined by any decrease in IC from rest to peak exercise, as previously described [11, 30].

Statistical analysis

Unless otherwise specified, variables are summarized as means ± SD. Statistical procedures were carried out using either Statview 5.0 (Abacus Concepts, SanFrancisco, CA, USA) or Prism 4.0 (GraphPad Software, Inc., San Diego, CA, USA). Comparisons between the PAH group as a whole and the control group, and between the PAH patients who developed DH (PAH-H) and those who did not (PAH-NH) (see

results for details) were performed at rest, at common standardized exercise work-rates (40watts and 60watts), and at peak exercise using unpaired t-tests with appropriate Bonferroni adjustments for multiple comparisons. Pearson correlations were used to establish associations between Borg dyspnoea ratings at a standardized exercise work rate (dependent variable) and concurrent relevant independent variables (i.e., exercise measurements of V'_E, breathing pattern, operating lung volumes, cardiovascular and metabolic parameters, and baseline pulmonary function measurements). Differences were considered significant when the probability P of a type I error was <0.05.

RESULTS

The characteristics of the participants and their resting pulmonary function measurements are summarized in Table 1. Twenty patients were diagnosed with idiopathic PAH and 5 with heritable PAH. Seven patients were in functional class I according to the New York Heart Association (NYHA) classification, 13 in class II, and 5 in class III. Of note, all the patients had received PAH-specific pharmacotherapy according to guidelines [16, 17] and had been clinically stable during the 3 preceding months. PAH-specific pharmacotherapy is summarized in Table 1 of the online data supplement.

Physiological group responses to CPET

The physiological and perceptual responses to CPET are summarized in Table 2. Compared with the control subjects, peak V'_E was significantly reduced in all PAH patients. Yet PAH subjects exhibited significantly increased V'_E, oxygen uptake ($V'O_2$) and carbon dioxide production ($V'CO_2$) at any submaximal work-rate (WR) (Figure 1A). When compared with controls, dyspnoea intensity was higher in the PAH group at any given WR and V'_E (Figure 1B). Dyspnoea/$V'O_2$ and dyspnoea/V'_E slopes were also greater in the PAH patients than in the control subjects (6.9±2.8 and 0.12±0.04 vs 2.0±1.0 and 0.04±0.02, respectively; $p<0.05$). PAH patients presented with a relatively rapid and shallow breathing pattern (Figure 1B). On average, their IC decreased significantly during exercise (rest-to-peak IC change -0.15±0.46L, $p<0.05$) while it consistently increased in the control subjects (0.45±0.16L). The ratio of inspiratory reserve volume (IRV) to TLC [IRV/TLC(%)], taken as an index of the mechanical constraint on V_T expansion, was significantly lower in PAH patients than it was in control subjects at any given WR and V'_E (Table 2 and Figure 1B).

Identification of two subgroups of PAH patients

Both PAH-H and PAH-NH were stable on therapy with a satisfactory hemodynamic and clinical response, as demonstrated by cardiac output at rest, right atrial pressure, NYHA functional class, and 6-minute walk

distance (Table 3). Based on rest-to-peak changes in IC, 15 PAH patients exhibited DH during exercise (PAH-H group, IC= -0.50±0.15L), whereas the remaining 10 patients did not (PAH-NH group, IC= +0.36±0.18L) (Figure 2). Characteristics and pulmonary function tests at rest of the two groups are compared in Table 3. Of note, TLC did not change after CPET, either in the PAH-H group (5.2±1.1 vs 5.3±1.1L, respectively; p=0.4) or in the PAH-NH group (5.6±1.1 vs 5.6±1.0L, respectively; p=0.9). The physiological and perceptual responses to CPET in the PAH-H and the PAH-NH groups are summarized in Table 4. All measurements obtained at rest were similar in both groups, as were the patterns of $V'O_2$ and V'_E responses to exercise expressed relative to WR, $V'O_2$ and $V'CO_2$ (Figure 3A). Response patterns were also similar when measurements of breathing pattern were plotted against V'_E (Figure 3B). In spite of these similarities, the dyspnoea/$V'O_2$ and dyspnoea/V'_E slopes were steeper in PAH-H than in PAH-NH (8.1±2.2 and 0.14±0.04 vs 5.1±2.7 and 0.09±0.03, respectively; $p<0.05$). Operating lung volumes were also different between the two groups throughout exercise. Rest-to-40w and rest-to-60w changes in IC/TLC(%), taken as an index of DH, did significantly differ between PAH-H and PAH-NH (7±3 and 7.2±2 vs -4±2 and -5±3%, respectively; $p<0.05$). In addition, rest-to-40w and rest-to-60w changes in IRV/TLC(%) were significantly different in PAH-H (12±6 and 18±5%) than in PAH-NH (3±4 and 7±5%, $p<0.05$) (Figure 3B). Despite these differences in operating lung volume behavior, inspiratory reserve flow at peak exercise was not statistically different between PAH-H and PAH-NH (1.7±0.3 vs 2.0±0.3, $p<0.05$) (Figure 2). Finally, dyspnoea ratings were significantly greater in PAH-H than in PAH-NH patients at any given WR and V'_E (Table 4 and Figure 3B).

Correlates of exertional dyspnoea

In the PAH patients as whole group (n=25), the best predictors of the rest-to-60w difference (i.e., Δ) in Borg ratings of dyspnoea were the ΔIC/TLC(%) (R=-0.70, 95% confidence interval -0.857 to -0.422, $p<0.05$) and the ΔIRV/TLC(%) (R=-0.78, 95% confidence interval -0.897 to -0.555, $p<0.05$) (Figure 4). Of note, the ΔIRV/TLC(%) was strongly predicted by the ΔIC/TLC(%) (R=0.73, 95% confidence interval 0.466 to 0.871, $p<0.05$). The Δ in Borg ratings of dyspnoea also correlated with the $\Delta V'_E$/MVC(%) (R=0.59, 95% confidence interval 0.257 to 0.799, $p<0.05$). Change in dyspnoea intensity during exercise did not correlate with any of the cardiovascular variables obtained during resting right heart catheterization or with NYHA functional class.

DISCUSSION

The main findings of this study are as follows: 1) exercise capacity was significantly reduced in PAH patients as compared to control subjects, and exertional dyspnoea ratings were higher at any given WR, $V'O_2$ and V'_E; 2) ventilatory abnormalities during exercise in PAH patients included a higher ventilatory

demand, significant DH, and a relatively rapid and shallow breathing pattern; 3) resting pulmonary function tests confirmed that the majority of PAH patients (60%) exhibited signs of significant small airway dysfunction; 4) DH and excessive V'_E contributed to a great extent to increased exertional dyspnoea intensity during cycle exercise in patients with PAH.

Our young non-smoking idiopathic and heritable PAH subjects with normal BMI and with no evidence of spirometric obstruction were stable on therapy with a satisfactory hemodynamic and clinical response, as demonstrated by cardiac output at rest, a right atrial pressure, NYHA functional class, and 6-minute walk distance. These patients had mild-to-moderate exercise limitation, with a peak symptom-limited $V'O_2$ being reduced by 23% on average of the predicted normal value (Table 2), despite PAH-specific pharmacotherapy. We are satisfied that the reduced exercise performance in our PAH patients was not the result of reduced motivational effort: patients reported intolerable exertional symptoms at peak exercise and had a respiratory exchange ratio at peak >1.15. Although exercise limitation was multifactorial and the proximate cause likely varied among individuals, significant ventilatory constraints and attendant respiratory difficulty were evident in the majority of PAH patients.

During exercise, dyspnoea intensity ratings were higher at any given power output, whereas both dyspnoea/$V'O_2$ and dyspnoea/V'_E slopes were steeper in the PAH patients than in the control subjects. Potential contributors to exertional dyspnoea in PAH patients included: 1) higher ventilatory demand as a result of pulmonary gas exchange or cardio-metabolic abnormalities, 2) greater abnormalities of dynamic ventilatory mechanics and muscle function that would cause dyspnoea to increase for any given V'_E compared with health, or 3) a combination of both.

Increased Ventilatory Demand

Our findings of an increased ventilatory demand during cycle exercise in PAH patients confirm previously published studies [2, 5]. Briefly, peak V'_E was diminished, reflecting the reduced peak symptom-limited $V'O_2$. Compared with control subjects, V'_E was significantly increased in PAH patients at any given submaximal WR and $V'O_2$.

The mechanisms of the excessive ventilatory response to exercise were beyond the objectives of the present study and were not, therefore, fully elucidated. Nevertheless, it is conceivable that a combination of reduced oxygen delivery/utilization and ventilation/perfusion abnormalities stimulated V'_E during exercise to a greater extent in PAH patients than in control subjects, as suggested by: 1) the greater $V'_E/V'CO_2$ (slopes and ratios) and $V'_E/V'O_2$; 2) the greater V_D/V_T (in the presence of low $PaCO_2$ that did not significantly fall further during exercise in PAH patients); the earlier occurrence of anaerobic ventilatory thresholds (data not shown); the greater heart rate/$V'O_2$ slopes (data not shown); and the lower

$V'O_2$/ heart rate (i.e., O_2 pulse, data not shown) observed throughout exercise in PAH patients compared with health.

Regardless of the mechanism, the increased V'_E likely contributed to the greater dyspnoea intensity and exercise curtailment. A correlative analysis confirmed an association between dyspnoea intensity ratings and the V'_E/MVC (%) ($R=0.59$, $p<0.05$). The higher V'_E in PAH ultimately reflects a relatively increased central neural drive and contractile muscular effort (relative to the maximal possible value) for the ventilatory muscles.

Abnormal Dynamic Ventilatory Mechanics

Dyspnoea/V'_E slopes were consistently elevated during exercise our PAH patients, suggesting increased intrinsic mechanical loading and/or functional weakness of the ventilatory muscles. Resting pulmonary function tests showed unambiguous mechanical abnormalities in 15/25 PAH patients (i.e., PAH-H). These patients exhibited signs of small airway dysfunction with a consistent and uniform reduction of the maximal expiratory flow rates over the effort-independent portion of the maximum flow-volume curve (MFVC), whilst the FEV_1/VC ratio, TLC and IC were preserved. Small airway dysfunction has previously been described in PAH [6, 8]. Its mechanisms are poorly understood. They could include competition for space between hypertrophied vessels and distal airways within the interstitial space [31], small airway wall thickening, airways mucus plugs, airway hyper-responsiveness, the attendant effects of aging or tobacco smoking or various combinations of these factors [8]. In our study we excluded elderly patients, as well as patients with a tobacco smoking history, asthma, and other cardio-respiratory diseases. In addition, the duration of the disease did not differ between PAH-H and PAH-NH. Pathological studies will be needed to understand the differences in airway morphology between PAH patients who exhibit small airway dysfunction and PAH patients who do not.

Regardless of the mechanisms underlying the PAH-related small airway dysfunction, the reduced resting expiratory reserve volume and the shape and limits of the MFVC in the tidal operating range (showing a reduction of $FEF_{75\%}$) mean that in our PAH-H patients the operating V_T was positioned closer to RV than normally. As a result, our PAH-H patients had an increased propensity to expiratory flow-limitation (EFL). Indeed, although PAH-H patients did not exhibit EFL during resting breathing, they encroached on their maximal expiratory flow reserve relatively early in exercise (Figure 2). Such a phenomenon is known to promote DH under conditions of increased ventilatory demand [9]. During the accelerated ventilatory response to exercise IC decreased by an average of 0.50L from rest to peak exercise in PAH-H. Similar levels of DH have been reported in patients with mild-to-severe COPD and in CHF [9, 12, 14], and clearly associated with dyspnoea.

What does the dynamic decrease in IC reflect in patients with PAH? Since TLC remained stable throughout exercise (see Results), we can assume that the decrease in dynamic IC reflects an increase in the rate of change in end-expiratory lung volume, i.e., DH. An alternative explanation would be a decreased inspiratory muscle performance [32, 33]. We cannot exclude a contribution of inspiratory muscle weakness or fatigue to the decreased IC in our patients, and to the concomitant alterations in breathing pattern. Indeed, respiratory muscle dysfunction has been suspected in PAH patients [32, 33], mostly in severely compromised PAH [34]. However, both PAH-H and PAH-NH achieved inspiratory tidal flows that approached a similar percentage of the maximal available inspiratory flows (i.e., similar inspiratory flow reserve), suggesting that the inspiratory flow-generating reserve of the inspiratory muscles at peak exercise was similar (but occurred at different operating lung volumes), thus making the presence of inspiratory muscle constraint/fatigue unlikely. In addition, we did not observe any decrease in IC (on the contrary) in the 10 PAH-NH patients who did not develop DH during exercise. Therefore, these patients did not suffer from an impairment of inspiratory muscle strength that would have been sufficient to prevent them to reach TLC during a voluntary maneuver. Yet these patients were similar to the PAH-H ones regarding their general characteristics, the severity, the duration and the medical management of the disease. Nevertheless, in the absence of esophageal pressure measurements in this study - a choice justified by the exploratory nature of the study and our concern to keep it as close to observational as possible - we must concede that both mechanisms of dynamic IC decrease (either singly or in combination) are possible.

Irrespective of its cause, the rapid development of DH during exercise observed in our PAH-H patients is likely to have a sensory consequence. DH causes increased elastic loading and functional weakness of the inspiratory muscles thus reducing the ability of V_T to expand appropriately during exercise on a background of progressively increasing central neural drive [9, 10, 35]. This has been well documented in the majority of flow-limited patients with COPD and CHF during exercise [10-14]. It is generally accepted that in this setting dyspnoea results from the conscious awareness of the increasing disparity between respiratory effort (or neural drive to breathe) and simultaneous thoracic volume displacement. We argue that this was the case in our PAH-H patients and, therefore, that the dyspnoea they reported was at least in part due to altered respiratory mechanics [35]. Indeed, at standardized WRs, dyspnoea intensity was significantly higher and dynamic IRV was proportionately lower in the PAH-H group than in the PAH-NH one and in the control subjects. The notion that DH and the subsequent constraint of V_T expansion contributed to exertional dyspnoea is bolstered by the strong inverse correlation between dyspnoea intensity and both the reduced dynamic IC/TLC(%) ($R=-0.70$, $p<0.05$) and the IRV/TLC(%) ($R=-0.78$, $p<0.05$) at a standardized exercise stimulus.

Limitations and Conclusions

This study is the first to examine the impact of potential DH-induced critical mechanical constraint on the intensity of dyspnoea in young non-smoking patients with idiopathic and heritable PAH undergoing symptom-limited incremental CPET. It confirms that small airway dysfunction at spirometry exists in a large proportion of idiopathic and heritable PAH patients (60%) despite a preserved FEV_1/VC ratio. When increased ventilation/perfusion mismatching is superimposed on pre-existing abnormal airway function, greater exercise limitation and troublesome exertional symptoms ensue. Dyspnoea causation is multifactorial but our results clearly indicate that increased ventilatory demand and abnormal dynamic ventilatory mechanics should be considered in PAH patients. The corollary of this is that therapeutic interventions, such as administration of inhaled bronchodilators [36] as add-ons to vasodilators, that effectively reduce DH should theoretically delay the appearance of the mechanical constraint of V_T expansion and the attendant dyspnoea during physical activity even in patients with stable PAH. Further studies that contain a larger sample size and engage esophageal pressure measurements during exercise will be required to definitively elucidate the physiological mechanisms of the altered ventilatory mechanics seen in PAH patients.

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Table 1. Anthropometric characteristics and resting pulmonary function testing in PAH patients and in controls

	PAH	Controls
Female/Male	15/10	5/5
Age, yr	38±12	39±16
Height, cm	168±8	171±9
BMI, kg.m-^{2}	24±3	23±4
FEV_1, L (%pred)	3.0±0.8* (91±16)*	4.0±0.7 (116±11)
FVC, L (%pred)	3.6±1.0* (93±17)*	4.7±0.8 (116±10)
$^\#FEV_1$/VC	115±10	110±5
TLC, L (%pred)	5.3±1.1* (93±10)*	6.4±0.9 (107±9)
VC, L (%pred)	3.7±1.1* (94±17)*	4.7±0.8 (113±10)
FRC, L (%pred)	2.8±0.6 (95±14)	3.2±0.7 (104±16)
IC, L (%pred)	2.5±0.8* (93±20)*	3.2±0.4 (108±18)
RV, L (%pred)	1.6±0.4 (97±23)	1.7±0.5 (95±17)
ERV, L (%pred)	1.2±0.5 (93±36)	1.5±0.6 (115±34)
$FEF_{25\%}$, L/sec (%pred)	6.7±1.7 (100±16)	7.6±1.8 (108±10)
$FEF_{50\%}$, L/sec (%pred)	4.0±1.2* (89±20)*	5.1±1.0 (109±18)
$FEF_{75\%}$, L/sec (%pred)	1.4±0.7* (69±25)*	2.2±0.7 (105±8)

Definition of abbreviations: PAH = pulmonary arterial hypertension; BMI = body mass index; FEV_1 = forced expiratory volume in one second; FVC = forced vital capacity; TLC = total lung capacity; VC = vital capacity; FRC = functional residual capacity; IC = inspiratory capacity; RV = residual volume; ERV = expiratory reserve volume; $FEF_{25\%,50\%,75\%}$ = instantaneous flow measured after 25%, 50% and 75% of the FVC has been exhaled; Raw = airways resistance; Values are mean ± SD (% of predicted normal in parentheses). 1 kPa = 7.5 mm Hg. $^*P<0.05$, overall PAH versus Healthy. $^\#$Spirometric evidence of an obstructive ventilatory defect as defined by a reduced FEV_1/VC ratio $<5^{th}$ percentile of the predicted value [18].

Table 2. Physiological and perceptual responses to cardiopulmonary exercise testing in PAH patients and in controls

	Rest		iso-WR 1		iso-WR 2		Peak	
Variables	**PAH**	**Controls**	**PAH**	**Controls**	**PAH**	**Controls**	**PAH**	**Controls**
Work rate, watts	/	/	40±0	40±0	60±0	60±0	93±26*	179±50
$V'O_2$, L/min (% pred)	0.26±0.03 (14±5)	0.24±0.03 (11±4)	0.64±0.12 (32±10)	0.66±0.12 (32±15)	0.79±0.14 (40±13)	0.86±0.17 (42±21)	1.27±0.31* (62±17)*	2.39±0.70 (106±13)
$V'O_2$/kg	3.9±0.8	3.7±0.4	9.5±1.8	10.0±1.8	11.8±2.3	13.0±2.2	18.8±4.2*	36.1±7.8
$V'CO_2$, L/min	0.23±0.02	0.20±0.03	0.57±0.10	0.52±0.11	0.81±0.11	0.71±0.18	1.45±0.37*	2.63±0.76
V'_E, L/min	11.4±2.2*	9.7±0.9	25.9±4.7*	18.2±2.7	36.7±7.5*	23.1±5.1	67.7±19.1*	108.1±9.9
V'_E, % MVC	11±3*	7±1	27±9*	14±6	38±16*	18±9	67±18*	80±13
F_b (breaths/min)	15±4	14±2	24±4*	18±4	28±7*	19±4	35±7	34±5
V_T, L	0.80±0.19	0.71±0.12	1.11±0.22	1.05±0.16	1.36±0.29	1.21±0.21	1.94±0.47	2.19±0.49
V_T/IC (%)	32±7*	23±6	48±14*	31±8	59±15*	35±9	83±13*	61±12
IC, L	2.6±0.7*	3.2±0.5	2.5±0.8*	3.5±0.5	2.5±0.7*	3.5±0.5	2.4±0.8*	3.6±0.5
IC/TLC (%)	48±6	50±6	45±7*	54±6	45±6*	55±6	44±7*	57±6
IRV, L	1.8±0.6*	2.5±0.5	1.4±0.7*	2.4±0.5	1.1±0.7*	2.3±0.6	0.5±0.5*	1.4±0.5
IRV/TLC (%)	32±6	38±6	24±9*	37±6	19±9*	36±7	8±7*	23±9
Dyspnoea, (Borg units)	0.0±0.0	0.0±0.0	2.0±1.2*	0.2±0.5	3.4±1.7*	0.6±0.6	6.8±1.8*	4.1±1.5
Leg discomfort, (Borg units)	0.0±0.0	0.0±0.0	2.4±1.5*	0.2±0.5	3.8±2.1*	0.6±0.7	6.6±1.8	7.6±1.7
$P_{ET}CO_2$, mmHg	28±4*	42±3	29±5*	44±3	28±6*	45±3	26±6*	40±3

Definition of abbreviations: PAH = pulmonary arterial hypertension; $V'O_2$ = oxygen uptake; $V'CO_2$ = carbon dioxide production; V'_E= ventilation; MVC = maximal ventilatory capacity; F_b = breathing frequency; V_T = tidal volume; IC = inspiratory capacity; TLC = total lung capacity; IRV = inspiratory reserve volume; $P_{ET}CO_2$ = end-tidal partial pressure of carbon dioxide; Values are mean±SD. * P<0.05, PAH versus Healthy group at the same measurement point.

Table 3. Anthropometric characteristics, cardiovascular variables obtained during resting right heart catheterization under pharmacotherapy, and resting pulmonary function testing in PAH-H, in PAH-NH, and in controls

	PAH-H (n=15)	PAH-NH (n=10)	Controls (n=10)
Female/Male	9/6	6/4	5/5
Age, yr	40±11	35±13	39±16
Height, cm	167±8	169±9	171±9
Body mass index, kg/m^2	25±3	22±3	23±4
Duration of disease (months)	70±59	79±78	/
NYHA functional class	2±1	2±1	/
6MWD, meters	523±84	568±113	/
mPAP, mmHg	48±13	50±22	/
Right atrial pressure, mmHg	5±3	7±4	/
PCWP, mmHg	8±4	9±2	/
PAR, Wood units	6.1±2.5	7.3±3.5	/
CO, L/min	6.7±1.2	5.9±1.1	/
CI, $L/min/m^2$	3.7±0.6	3.5±0.7	/
Mixed venous oxygen saturation, %	72±6	71±6	/
Resting pulmonary function:			
FEV_1, L (%pred)	2.8±0.7$^{\$}$ (88±17)$^{\$}$	3.3±0.9 (95±14)$^{\&}$	4.0±0.7 (116±11)
FVC, L (%pred)	3.4±1.0$^{\$}$ (91±17)$^{\$}$	3.9±1.0 (97±17)$^{\&}$	4.7±0.8 (116±10)
FEV_1/VC $^{\#}$	113±11	117±9	110±5
TLC, L (%pred)	5.2±1.1$^{\$}$ (92±11)$^{\$}$	5.6±1.1 (96±10)	6.4±0.9 (107±9)
VC, L (%pred)	3.6±1.1$^{\$}$ (93±18)$^{\$}$	4.0±1.0 (96±16)	4.7±0.8 (113±10)
FRC, L (%pred)	2.6±0.5$^{\$}$ (89±10)$^{*\$}$	3.1±0.6 (103±14)	3.2±0.7 (104±16)
IC, L (%pred)	2.6±0.8 (98±22)	2.5±0.6 (90±17)	3.2±0.4 (108±18)
RV, L (%pred)	1.6±0.5 (93±24)	1.6±0.4 (94±23)	1.7±0.5 (95±17)
ERV, L (%pred)	1.0±0.4$^{*\$}$ (83±31)$^{*\$}$	1.5±0.6 (114±43)	1.5±0.6 (115±34)
$FEF_{25\%}$, L/sec (%pred)	6.5±1.7 (98±18)	7.0±1.9 (102±11)	7.6±1.8 (108±10)
$FEF_{50\%}$, L/sec (%pred)	3.7±0.9$^{\$}$ (85±20)$^{\$}$	4.5±1.4 (95±19)	5.1±1.0 (109±18)
$FEF_{75\%}$, L/sec (%pred)	1.1±0.4$^{*\$}$ (56±15)$^{*\$}$	1.9±0.9 (89±25)	2.2±0.7 (105±8)

Definition of abbreviations: PAH = pulmonary arterial hypertension; PAH-H = PAH patients who developed dynamic lung hyperinflation during exercise; PAH-NH = PAH patients who did not develop dynamic lung hyperinflation during exercise; NYHA = New York Heart Association; 6MWD = six-minute walking distance; mPAP = mean pulmonary artery pressure; PCWP = postcapillary wedge pressure; PAR = pulmonary artery

Table 4. Physiological and perceptual responses to cardiopulmonary exercise testing in PAH-H and in PAH-NH

	Rest		iso-WR 1		iso-WR 2		Peak	
Variables	**PAH-H**	**PAH-NH**	**PAH-H**	**PAH-NH**	**PAH-H**	**PAH-NH**	**PAH-H**	**PAH-NH**
Work rate, watts	/	/	40±0	40±0	60±0	60±0	90±25	98±28
$V'O_2$, L/min (% pred)	0.26±0.03 (14±5)	0.26±0.03 (13±5)	0.62±0.09 (32±10)	0.66±0.16 (32±12)	0.78±0.09 (40±13)	0.81±0.20 (40±14)	1.25±0.25 (63±18)	1.30±0.40 (61±16)
$V'O_2$/kg	3.8±0.7	4.2±0.9	8.8±1.2	10.5±2.3	11.1±1.3	12.9±3.1	17.8±3.0	20.4±5.3
$V'CO_2$, L/min	0.22±0.02	0.23±0.02	0.56±0.08	0.58±0.12	0.80±0.09	0.81±0.15	1.42±0.29	1.50±0.48
V'_E, L/min	11.3±2.2	11.6±2.2	26.1±4.6	25.6±5.1	37.7±7.4	35.1±7.9	67.5±17.5	67.9±22.4
V'_E, % MVC	12±3	11±3	28±9	25±10	41±15	34±16	71±15	62±20
F_b (breaths/min)	15±3	15±5	25±4	22±5	29±7	26±7	37±7	34±7
V_T, L	0.80±0.20	0.80±0.18	1.08±0.21	1.17±0.24	1.33±0.28	1.42±0.32	1.89±0.46	2.02±0.50
V_T/IC (%)	31±6	34±8	51±15	45±12	62±14	54±17	90±9*	72±11
IC, L	2.6±0.7	2.5±0.6	2.3±0.8	2.7±0.7	2.3±0.7	2.7±0.7	2.1±0.7*	2.8±0.7
IC/TLC (%)	50±5*	44±3	43±7*	48±4	43±6*	49±3	40±6*	51±4
IRV, L	1.8±0.6	1.7±0.6	1.2±0.7	1.5±0.7	0.9±0.6	1.3±0.8	0.2±0.3*	0.8±0.5
IRV/TLC (%)	34±6	29±6	22±9	27±7	17±8	23±9	4±5*	14±6
Dyspnoea, (Borg units)	0.0±0.0	0.0±0.0	2.7±0.9*	0.9±0.2	4.3±1.4*	2.0±0.8	7.9±0.9*	5.2±1.6
Leg discomfort, (Borg units)	0.0±0.0	0.0±0.0	2.5±1.6	2.1±1.6	3.9±2.0	3.8±2.4	6.3±1.8	7.1±1.9
PaO_2, mmHg	82.3±8.6	86.0±12.5	/	/	/	/	77.2±12.9	79.0±17.7
$PaCO_2$, mmHg	32.3±4.1	33.6±5.2	/	/	/	/	29.8±3.7	31.5±5.2
$P_{ET}CO_2$, mmHg	28±4	29±4	28±4	29±6	27±5	29±8	25±5	26±7
$P(a\text{-}ET)CO_2$, mmHg	4.8±2.2	4.2±3.4	/	/	/	/	4.9±2.4	5.0±3.9
V_D/V_T	0.43±0.08	0.43±0.09	/	/	/	/	0.39±0.06	0.37±0.09

Definition of abbreviations: PAH = pulmonary arterial hypertension; PAH-H = PAH patients who developed dynamic lung hyperinflation during exercise; PAH-NH = PAH patients who did not develop dynamic lung hyperinflation during exercise; $V'O_2$ = oxygen uptake; $V'CO_2$ = carbon dioxide production; V'_E= ventilation; MVC = maximal ventilatory capacity; F_b = breathing frequency; V_T = tidal volume; IC = inspiratory capacity; TLC = total lung capacity; IRV = inspiratory reserve volume; PaO_2 = arterial partial pressure of oxygen; $PaCO_2$ = arterial partial pressure of carbon dioxide; $P_{ET}CO_2$ = end-tidal partial pressure of carbon dioxide; $P(a\text{-}ET)CO_2$ = the gradient between arterial and end-tidal carbon dioxide partial pressure; V_D/V_T = the physiological dead space-to-tidal volume ratio. Values are mean±SD. * $P<0.05$, PAH-H versus PAH-NH at the same measurement point.

FIGURE LEGENDS

Figure 1A. Top-left and bottom-left panels: oxygen uptake ($V'O_2$) and ventilation (V'_E) are shown in response to increasing work-rate (WR) during symptom-limited incremental cycle exercise in patients with pulmonary arterial hypertension (PAH) as whole group (n=25; open sign and solid line) and in healthy control subjects (n=10; filled sign and dashed line). Top-right and bottom-right panels: V'_E is shown in response to increasing $V'O_2$ and carbon dioxide production ($V'CO_2$) during symptom-limited incremental cycle exercise in patients with PAH as whole group and in healthy control subjects. Graphs represent mean ± SE values at rest, at 40watts (iso-WR 1), 60watts (iso-WR 2), and at peak exercise. *P<0.05, PAH versus healthy at rest, at common standardized exercise work-rates (40watts and 60watts), or at peak exercise.

Figure 1B. Top-left and bottom-left panels: exertional dyspnea intensity (Borg score) is shown in response to increasing work-rate (WR) and ventilation (V'_E) during symptom-limited incremental cycle exercise in patients with pulmonary arterial hypertension (PAH) as whole group (n=25; open sign and solid line) and in healthy control subjects (n=10; filled sign and dash line). Top-middle and bottom-middle panels: breathing frequency (F_b) and tidal volume (V_T) expressed as percentage of inspiratory capacity (IC) [V_T/IC (%)] are shown in response to increasing V'_E during symptom-limited incremental cycle exercise in patients with PAH as whole group and in healthy control subjects. Top-right and bottom-right panels: IC and inspiratory reserve volume (IRV) expressed both as percentage of total lung capacity (TLC) [IC/TLC (%) and IRV/TLC (%), respectively] are shown in response to increasing V'_E during symptom-limited incremental cycle exercise in patients with PAH as whole group and in healthy control subjects. "Restrictive" constraints on V_T expansion during exercise are significantly greater in the PAH group from both below (reduced IC) and above (reduced IRV) compared with healthy. Graphs represent mean ± SE values at rest, at 40watts (iso-WR 1), at 60watts (iso-WR 2), and at peak exercise. *P<0.05, PAH versus healthy at rest, at common standardized exercise work-rates (40watts and 60watts), or at peak exercise.

Figure 2. Maximal and tidal flow-volume loops (average data) are shown at rest and during incremental cycle exercise in patients with pulmonary arterial hypertension who did hyperinflate (n=15, PAH-H; left panel, open sign) and in those who did not hyperinflate (n=10, PAH-NH; right panel, filled sign). Tidal flow-volume loops are provided at rest (solid line), at a standardized exercise work-rate of 60watts (dotted line), and at peak exercise (dashed line). Note a significant decrease in dynamic inspiratory capacity during exercise in PAH-H compared with PAH-NH.

Figure 3A. Top-left and bottom-left panels: oxygen uptake ($V'O_2$) and ventilation (V'_E) are shown in response to increasing work-rate (WR) during symptom-limited incremental cycle exercise in patients with pulmonary arterial hypertension who did hyperinflate (n=15, PAH-H; open sign) and in those who did not hyperinflate (n=10, PAH-NH; filled sign). Top-right and bottom-right panels: V'_E is shown in response to increasing $V'O_2$ and carbon dioxide production ($V'CO_2$) during symptom-limited incremental cycle exercise in PAH-H and in PAH-NH. Graphs represent mean ± SE values at rest, at 40watts (iso-WR 1), at 60watts (iso-WR 2), and at peak exercise. *P<0.05, PAH-H versus PAH-NH at rest, at common standardized exercise work-rates (40watts and 60watts), or at peak exercise.

Figure 3B. Top-left and bottom-left panels: exertional dyspnea intensity (Borg score) is shown in response to increasing work-rate (WR) and ventilation (V'_E) during symptom-

limited incremental cycle exercise in patients with pulmonary arterial hypertension who did hyperinflate (n=15, PAH-H; open sign) and in those who did not hyperinflate (n=10, PAH-NH; filled sign). Top-middle and bottom-middle panels: breathing frequency (F_b) and tidal volume (V_T) expressed as percentage of inspiratory capacity (IC) [V_T/IC (%)] are shown in response to increasing V'_E during symptom-limited incremental cycle exercise in PAH-H and in PAH-NH. Top-right and bottom-right panels: IC and inspiratory reserve volume (IRV) expressed both as percentage of total lung capacity (TLC) [IC/TLC (%) and IRV/TLC (%), respectively] are shown in response to increasing V'_E during symptom-limited incremental cycle exercise in PAH-H and in PAH-NH. "Restrictive" constraints on V_T expansion during exercise are significantly greater in PAH-H from both below (reduced IC) and above (reduced IRV) compared with PAH-NH. Graphs represent mean ± SE values at rest, at 40watts (iso-WR 1), at 60watts (iso-WR 2), and at peak exercise. *P<0.05, PAH-H versus PAH-NH at rest, at common standardized exercise work-rates (40watts and 60watts), or at peak exercise.

Figure 4. Significant intercorrelations between indices of dyspnea, mechanical constraints on tidal volume expansion and DH during exercise (Δ = rest-to-60watts difference) in patients with pulmonary arterial hypertension (PAH) as whole group (n=25). Dyspnea intensity assessed by the Borg scale correlated significantly with an index of mechanical constraints on tidal volume expansion as assessed by the IRV/TLC (%), where IRV is inspiratory reserve volume expressed as percentage of total lung capacity (TLC). Dyspnea intensity is also significantly predicted by DH, as assessed by the inspiratory capacity (IC) as a proportion of TLC [IC/TLC (%)]. IRV/TLC (%) and IC/TLC (%) are also strongly correlated. Abbreviations: CI = confidence interval.

FIGURES

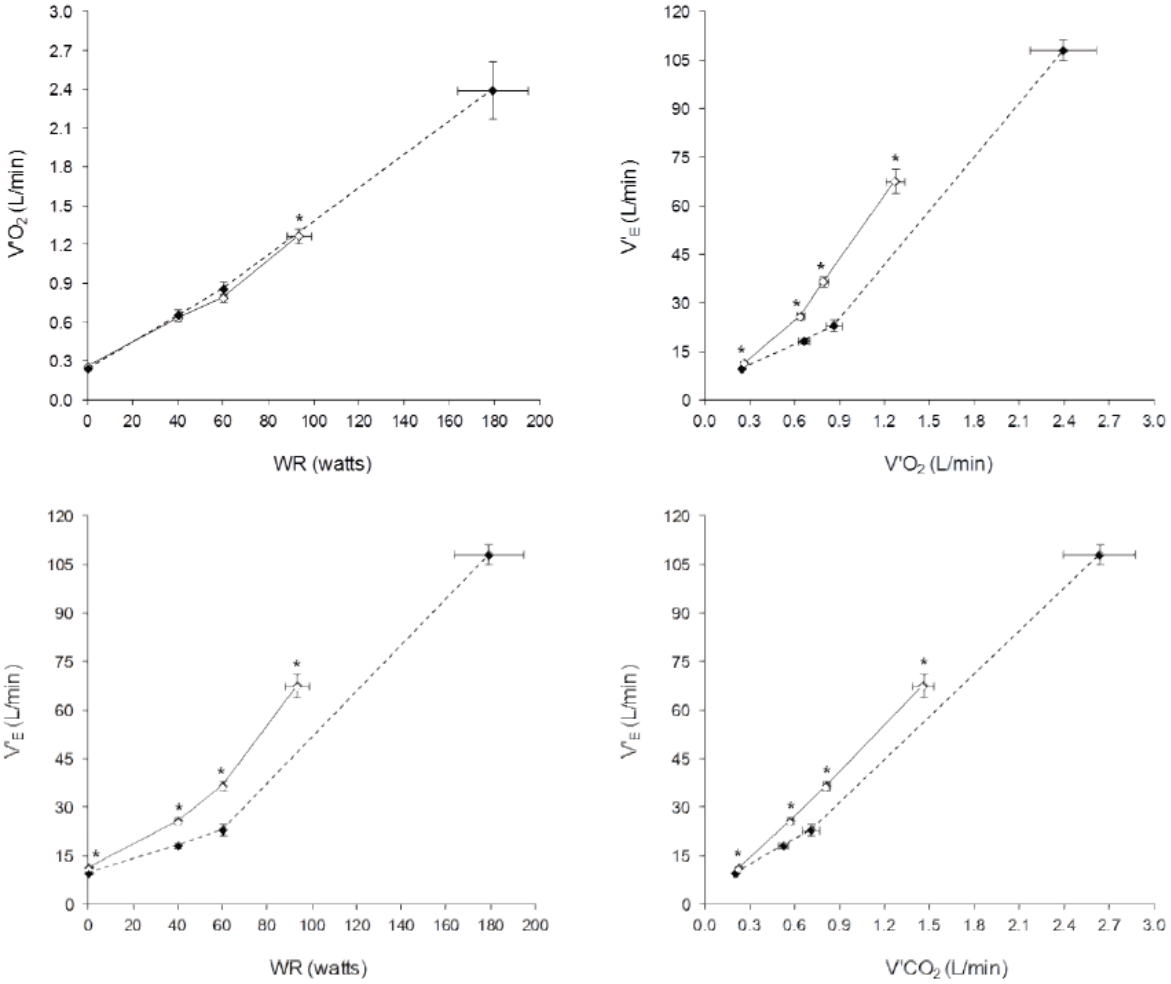

Figure 1A

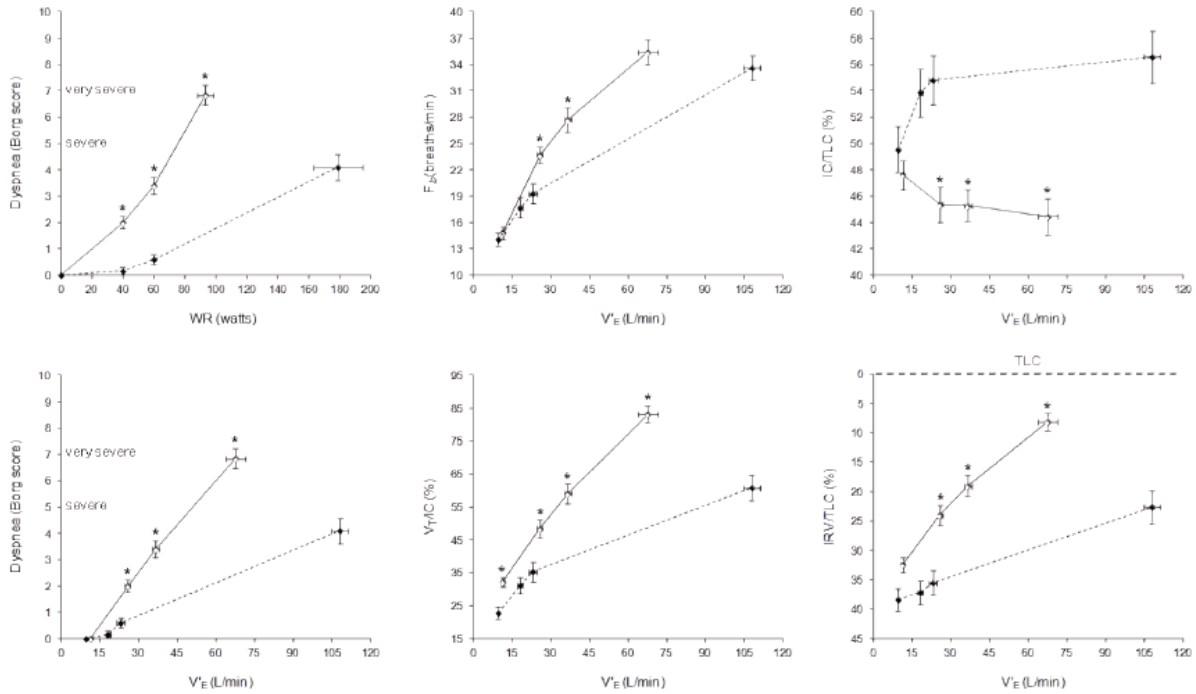
Dyspnea (Borg score)
very severe
severe
WR (watts)
F_R (breaths/min)
V'_E (L/min)
IC/TLC (%)
V_T/IC (%)
TLC
IRV/TLC (%)

Figure 1B

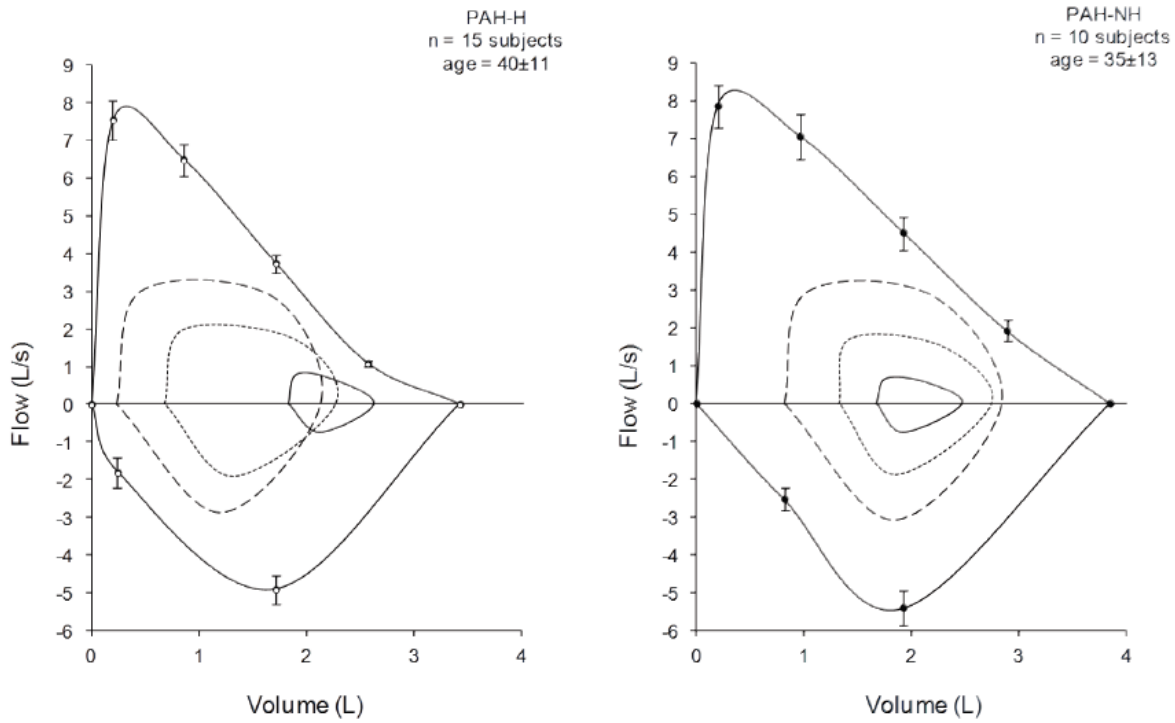
PAH-H
n = 15 subjects
age = 40±11
Flow (L/s)
Volume (L)
PAH-NH
n = 10 subjects
age = 35±13
Flow (L/s)
Volume (L)

Figure 2

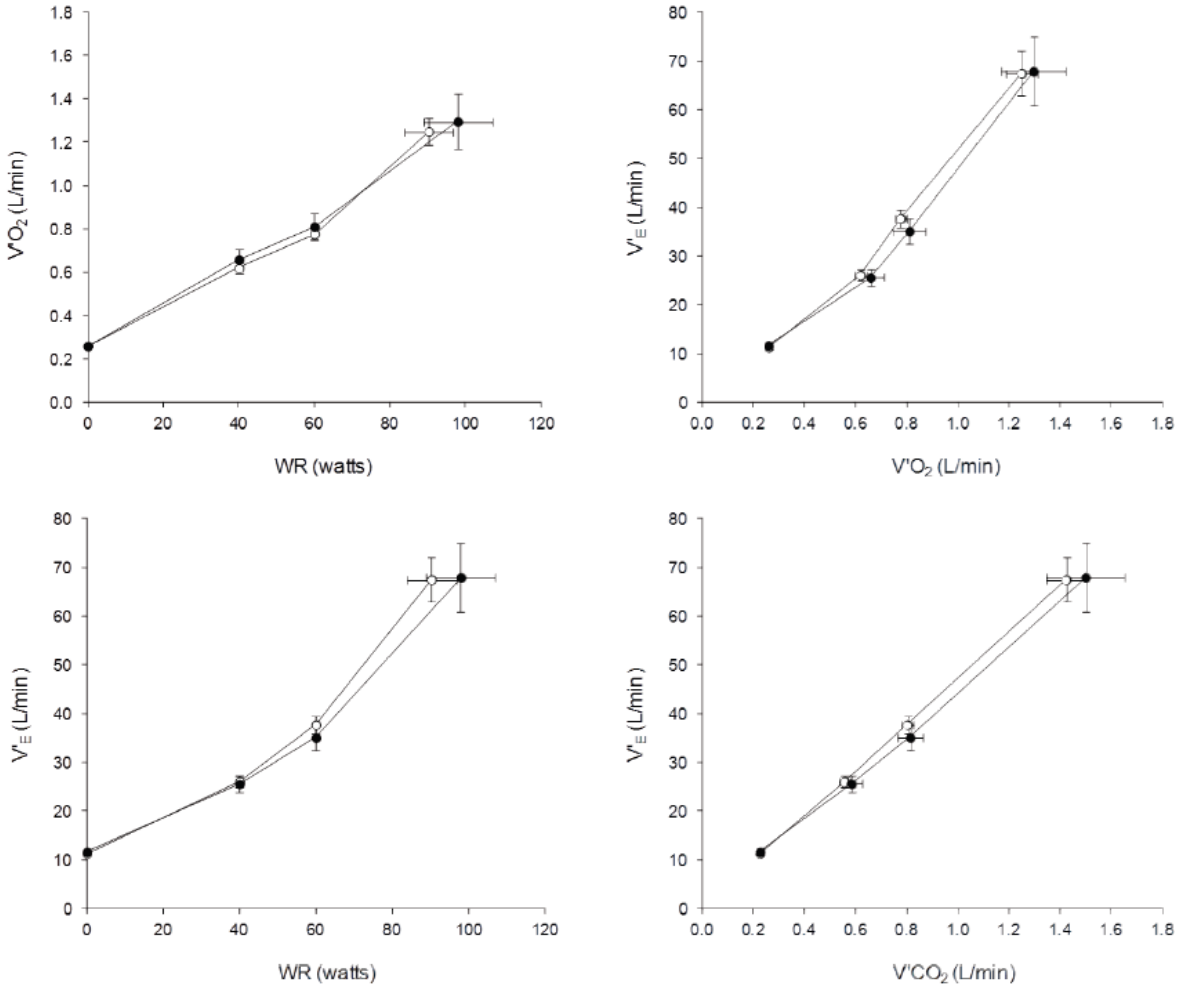
V'O2 (L/min)
WR (watts)
V'E (L/min)
V'O2 (L/min)
V'E (L/min)
WR (watts)
V'E (L/min)
V'CO2 (L/min)

Figure 3A

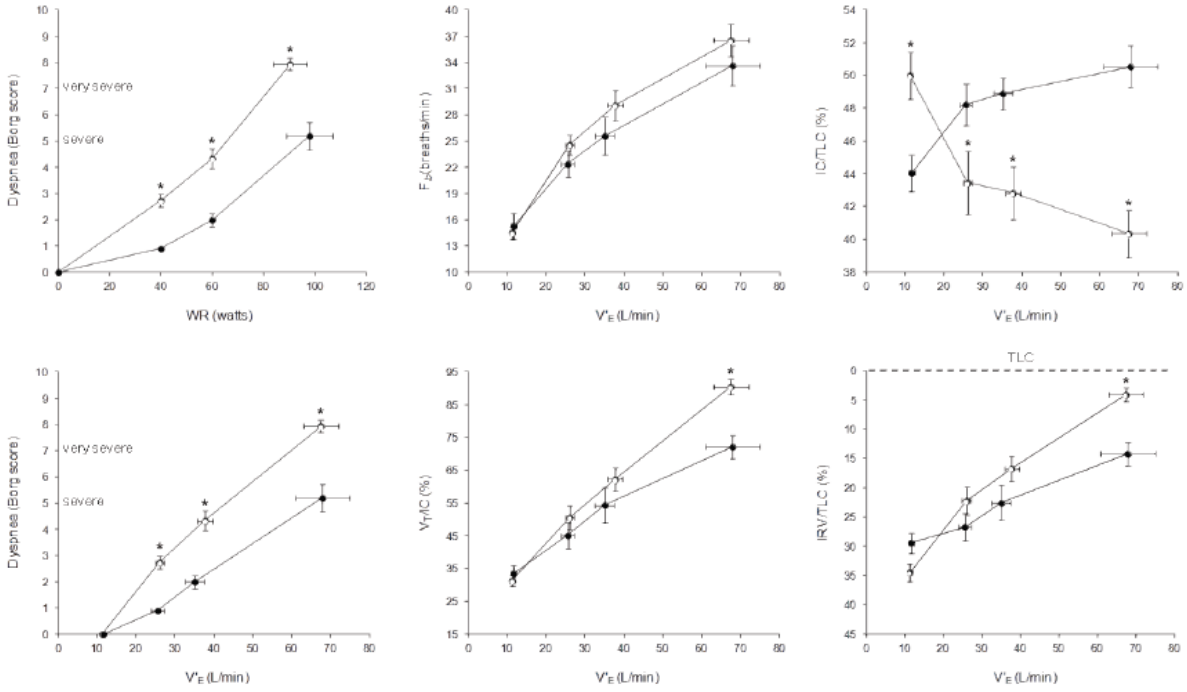
Dyspnea (Borg score)
Very severe
Severe
WR (watts)
F_R (breaths/min)
V'_E (L/min)
IC/TLC (%)
V_T/IC (%)
TLC
IRV/TLC (%)

Figure 3B

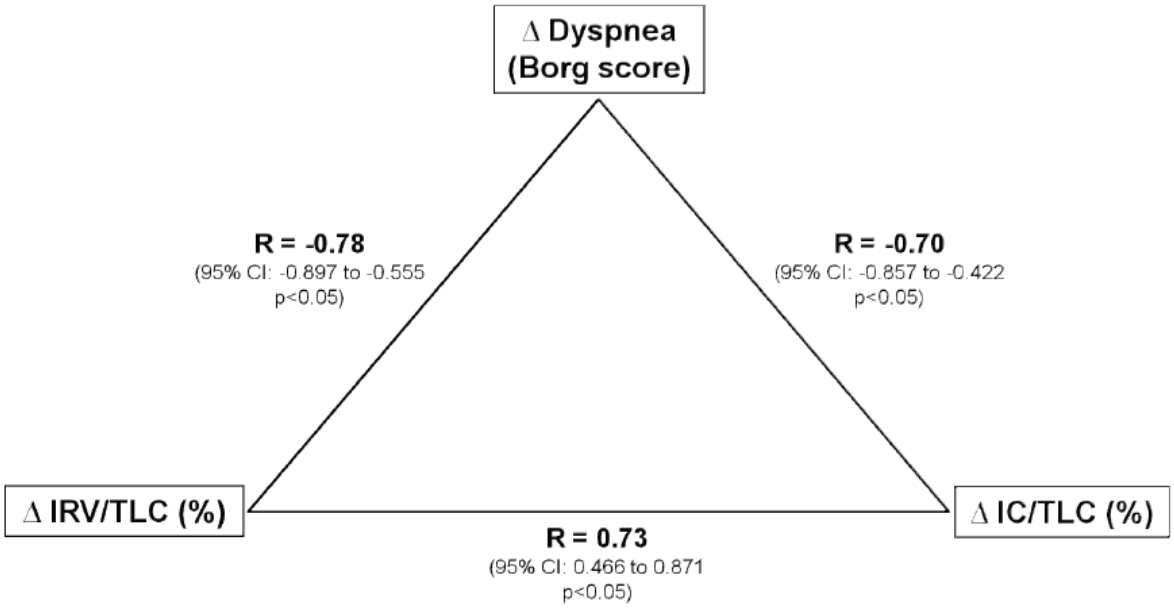
Δ Dyspnea
(Borg score)
R = -0.78
(95% CI: -0.897 to -0.555
p<0.05)
R = -0.70
(95% CI: -0.857 to -0.422
p<0.05)
Δ IRV/TLC (%)
Δ IC/TLC (%)
R = 0.73
(95% CI: 0.466 to 0.871
p<0.05)

Figure 4

CONCLUSIONS AND PERSPECTIVES

The results of the three works presented in this thesis contribute to a better understanding of the pathophysiological mechanisms of exertional dyspnoea in patients with GOLD stage I COPD, CHF and PAH. Moreover, this thesis may have important clinical implications which can potentially improve the therapeutic management of these devastating and disabling diseases.

We have clearly shown that these patients may present with a reduction of expiratory flows at low lung volumes or an overt expiratory flow-limitation that are known to be implicated in promoting exercise-related dynamic lung hyperinflation [10-12, 17-19, 21, 32, 33, 42-45, 47, 48, 55]. The mechanisms by which dynamic lung hyperinflation gives rise to exertional dyspnoea are complex. However, recent mechanistic studies suggest that dynamic lung hyperinflation-induced volume restriction and consequent neuromechanical uncoupling of the respiratory system are key mechanisms [10-12, 18, 33].

When increased ventilation/perfusion mismatching is superimposed on pre-existing abnormal airway function, greater troublesome exertional symptoms ensue. Dyspnoea causation is multifactorial but our results clearly indicate that increased ventilatory demand and dynamic lung hyperinflation-induced constraint of V_T expansion should be considered in patients with GOLD stage I COPD, CHF and PAH.

This proposition is bolstered by the strong correlation between dyspnoea intensity and indices of dynamic lung hyperinflation and mechanical constraints on V_T expansion in patients with PAH (3rd paper). The strength of this association is further confirmed by the 1st and 2nd study that have clearly demonstrated that pharmacological (short-acting bronchodilator in the 1st study) and non-pharmacological (biventricular pace-maker in the 2nd study) manipulation of dynamic lung hyperinflation (directly or indirectly by reducing ventilator demand) is clearly associated with relief of exertional dyspnoea.

What are the clinical perspectives and the future directions of this work? We have discovered that, although exertional dyspnoea is multifactorial, in clinical situations where lung

mechanics is not an intuitive candidate to explain dyspnoea such us in our patients with CHF and PAH, dynamic lung hyperinflation-induced mechanical constraint of V_T expansion does play a significant role. This seems very important from a therapeutic standpoint because it opens up new horizons for research in the "multidirectional" treatment of dyspnoea. It goes without saying that any intervention that improves exertional dyspnoea should be beneficial even when this intervention is not directly related to the main/obvious pathophysiological determinant of the disease.

This way of reasoning is supported by the clinical and scientific observation that the relationship between dyspnoea intensity and the underlying disease' abnormalities is not linear, but rather exponential, especially in cardiac diseases. In other words, when a given disease is already responsible for a very intense dyspnoea, a small additional deterioration directly or indirectly related to the disease (for example, the respiratory mechanics abnormalities) can make dyspnoea intolerable.

In this regard, the results of the 3rd study on PAH are encouraging because it can open up new horizons in the pharmacological management of this population. It follows, therefore, that therapeutic intervention, such as administration of inhaled bronchodilators as add-ons to vasodilators, that effectively reduce dynamic lung hyperinflation should theoretically delay the appearance of the mechanical constraint of V_T expansion and the attendant dyspnoea during physical activity even in selected patients with stable PAH. The same principle can be applied to CHF. In addition, inhalation of methoxamine (a vasoconstrictor that reduces the bronchial mucosal edema thus improving the expiratory flows) by preventing exercise-induced vasodilation of airway vessels could reduce dynamic lung hyperinflation in selected PAH patients who present with a reduction of expiratory flows at low lung volumes (small airways dysfunction?), as demonstrated in selected patients with stable CHF [54]. This could have sensory beneficial effects in terms of reduction of exertional dyspnoea.

This thesis has some limitations. In the absence of oesophageal pressure measurements in the 2nd and 3rd study we must concede that the changes observed in dynamic IC may be due either to

dynamic lung hyperinflation, inspiratory muscle weakness or fatigue, or both in combination. Regardless of the mechanism, the changes in dynamic IC observed in patients with CHF and PAH are likely to be physiologically and clinically meaningful. Given the small sample size of the three studies we must be careful to avoid any generalization of our findings to the larger GOLD I COPD, CHF and PAH populations. Further studies that contain a larger sample size and engage oesophageal pressure measurements during exercise will be required to definitively elucidate the physiological mechanisms of the altered ventilatory mechanics seen in these patients.

In conclusion, we believe that dynamic lung hyperinflation and the attendant mechanical constraint on V_T expansion are key mechanisms in exertional dyspnoea causation in patients with GOLD I COPD, CHF and PAH. Moreover, this thesis may have important clinical implications because it opens up new horizons for research in the "multidirectional" treatment of dyspnoea, especially in patients with cardiac diseases.

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ABSTRACT

Patients with GOLD stage I COPD, CHF and PAH may present with a reduction of expiratory flows at low lung volumes or an overt expiratory flow-limitation. This is known to promote exercise-related dynamic lung hyperinflation, a major determinant of exertional dyspnoea.

Here we show that greater troublesome exertional symptoms ensue when increased ventilation/perfusion mismatching accompanies pre-existing abnormal airway function that promote dynamic lung hyperinflation in response to exercise-related increase in ventilation.

Our results illustrate that dyspnoea is multifactorial. Indeed, we show that in clinical situations where lung mechanics is not an intuitive candidate to explain dyspnoea, dynamic lung hyperinflation-induced constraint of V_T expansion does play a significant role.

This proposition is bolstered by the strong correlation between dyspnoea intensity and indices of dynamic lung hyperinflation and mechanical constraints on V_T expansion in patients with PAH (3rd paper). The strength of this association is further confirmed by the 1st and 2nd study that have clearly demonstrated that pharmacological (short-acting bronchodilator in the 1st study) and non-pharmacological (biventricular pace-maker in the 2nd study) manipulation of dynamic lung hyperinflation (directly or indirectly by reducing ventilatory demand) is associated with relief or attenuation of exertional dyspnoea.

This thesis contributes to a better understanding of the pathophysiological mechanisms of exertional dyspnoea in patients with cardiopulmonary diseases. Its findings open up also new horizons for research in the treatment of dyspnoea, by bearing in mind that every intervention that improves exertional dyspnoea is good even when this intervention is not directly related to the main/obvious pathophysiological determinant of the disease (e.g., bronchodilators in cardiac failure and pulmonary arterial hypertension).

KEY WORDS: chronic obstructive pulmonary disease, chronic heart failure, pulmonary arterial hypertension, dyspnoea, respiratory mechanics, dynamic lung hyperinflation, exercise testing.

RESUME

Les patients atteints de BPCO de stade I, d'ICC et d'HTAP peuvent présenter une diminution des débits aériens à bas volume pulmonaire. Il s'agit d'un déterminant majeur de la distension thoracique dynamique, particulièrement délétère, et facteur important de la dyspnée d'exercice. Nos travaux montrent sans ambiguïté une forte association entre la distension thoracique dynamique (qui génère une contrainte mécanique limitant l'augmentation du volume courant) et la dyspnée à l'effort chez ces patients. Le corollaire de ces constatations est que des interventions thérapeutiques qui réduisent la distension thoracique devraient diminuer la dyspnée d'effort et améliorer la tolérance à l'exercice, et ce y compris dans des situations cliniques où les anomalies de la mécanique respiratoire ne sont a priori pas le *primum movens* de la maladie. Et en effet, la réduction de la dyspnée d'effort est bien corrélée avec la réduction du volume pulmonaire induite directement par des interventions pharmacologiques (bronchodilatateurs a courte duré d'action, premiere étude interventionelle) ou indirectement (par diminution de la réponse ventilatoire à l'exercice) par des interventions non-pharmacologiques (pace maker cardiaque bi-ventriculaire, deuxième étude interventionelle). De plus, du point de vue thérapeutique, la mise en évidence dans la troisième étude d'une propension à la distension thoracique induite par l'exercice chez certains patients atteints d'HTAP qui présentent une nette diminution des débits aériens à bas volume pulmonaire peut elle fournir une base théorique à l'adjonction de bronchodilatateurs aux traitements à visée hémodynamique. En conclusion, cette thèse contribue à une meilleure connaissance de la physiopathologie de la dyspnée d'exercice dans le contexte de la BPCO à un stade précoce, de l'ICC et de l'HTAP, en mettant en évidence le rôle d'un mécanisme pathogénétique qui n'avait pas été décrit auparavant.

MOTS CLE : bronchopneumopathie chronique obstructive, insuffisance cardiaque chronique, hypertension artérielle pulmonaire, dyspnée, mécanique respiratoire, distension thoracique dynamique, exercice.