Pulmonary vascular resistances during exercise in normal subjects – a systematic review

Gabor Kovacs M.D.*, Andrea Olschewski M.D.**, Andrea Berghold M.Sc.,
PhD***, and Horst Olschewski M.D.*#

Department of Pulmonology*, Department of Anesthesia and Intensiv Care**,
Institute for Medical Informatics, Statistics and Documentation*** at the Medical University
of Graz, Graz, Austria

Ludwig Boltzmann Institute for Lung Vascular Research, Graz, Austria#

First author: Gabor Kovacs MD

Short title: PVR and TPR in healthy subjects

Corresponding Author:

Gabor Kovacs M.D.
Department of Pulmonology, Medical University of Graz, Auenbruggerplatz 20., 8036 Graz,
Austria
e-mail: gabor.kovacs@klinikum-graz.at
Tel: +43 316 385-80748
Fax: +43 316 385-3578

The total word count of the manuscript: 3271
Abstract
The physiological range of pulmonary vascular resistance (PVR) and total pulmonary resistance (TPR) and the impact of exercise, age, and posture have been a matter of debate for many years.

We performed a systematic literature review including all right heart catheterisation data where individual PVR and TPR of healthy subjects both at rest and exercise were available. Data were stratified according to age, exercise level and posture.

Supine resting PVR in subjects <24yr, 24-50yr, 51-69yr, and ≥70yr was 61±23, 69±28, 86±15, and 90±39 dyn*s*cm⁻⁵. Corresponding TPR was 165±50, 164±46, 226±64, and 223±45 dyn*s*cm⁻⁵. During moderate exercise, in subjects ≤50yr, 85% increase in cardiac output (CO) was associated with 25% decrease in TPR (p<0.0001) and 12% decrease in PVR (p<0.01). Between 51-69yr there was no significant TPR and PVR decrease. In individuals ≥70yr TPR even increased by 17% (p=0.01), while PVR did not change significantly. At higher exercise levels, TPR decreased in all age groups. In the upright position, based on a limited number of data, resting TPR and PVR were higher than supine and decreased more prominently during exercise, suggesting the release of resting pulmonary vasoconstriction.

These data may form a basis to define normal pulmonary vascular resistance at rest and exercise.
Introduction

Pulmonary hypertension (PH) has been defined as a resting mean pulmonary arterial pressure (mPAP) ≥ 25 mmHg. [1] The “exercise part” of the earlier hemodynamic definition (mPAP > 30 mmHg during exercise [2]) was abandoned at the last PH world conference in Dana Point, because during exercise mPAP is very much dependent on age and exercise level. [3] The pulmonary pressure response to exercise may, however, provide clinically relevant information where resting hemodynamics do not fully explain the symptoms of the patient. Before we consider reintroducing a hemodynamic definition, we must work on evidence-based ranges for the physiologic hemodynamic response to exercise. This will allow developing criteria for both physiological and pathological exercise hemodynamic patterns.

The available published literature on physiologic hemodynamic responses to exercise in the pulmonary circulation reflects a large variety of theoretic concepts, and offers conflicting results. Previously we analysed the available data of studies with right heart catheter investigations in healthy subjects during exercise with a focus on pulmonary arterial mean pressure. [4] In the present study we aimed to analyse the available individual data focusing on pulmonary vascular resistance during exercise. The changes in total pulmonary resistance (TPR) and pulmonary vascular resistance (PVR) belong to the most important physiologic parameters of the pulmonary circulation. They reflect the anatomic and functional properties of the cardiac chambers and pulmonary vessels. The understanding of physiologic PVR changes during exercise may be helpful to distinguish among a variety of disease conditions associated with exercise intolerance. In fact, recent publications indicate that even a moderate change in PVR may be an early sign of pulmonary vascular disease. [5-7] The goal of this study was to describe the physiologic pattern of TPR and PVR changes in healthy individuals during exercise.

Patients and Methods

We reviewed the available published literature on right heart catheterisation studies with exercise in healthy individuals. For details of the literature research see the description in the Annex. [4] In this review we restricted our research to those studies that provided individual data of mPAP, pulmonary arterial wedge pressure (PAWP), and cardiac output (CO) at rest and during exercise. Only those studies were included which allowed the calculation of individual TPR (mPAP and cardiac output (CO) at rest and at least one exercise level) and/or PVR (mPAP, pulmonary arterial wedge pressure (PAWP) and CO at rest and at least one exercise level). Cardiac output was obtained by the direct Fick method in the
majority of studies, while thermodilution or dye dilution was used in Ref. [8-10]. Studies providing no individual but just mean values of group data, were excluded. Subjects with implausible values (mPAP lower or higher than mean ± 2SD at rest (<8 or >20mmHg) were excluded. Additionally, individuals with a resting PAWP lower or higher than mean ± 2SD (<3 or >13mmHg) and subjects with PAWP values which were not at least 3 mmHg below the corresponding mPAP were excluded from the PVR analysis, as previously suggested. [11]Subjects with extreme obesity were excluded. As body position may significantly influence hemodynamics, data were stratified for the supine vs. the upright position. It has also been shown [4] that exercise hemodynamics in subjects >50yr may follow a different pattern compared to individuals ≤50yr. Therefore data were stratified for these age groups. In order to further explore effects of age, we separated within these strata based on the median age of the subjects. Accordingly, subjects <24yr (<30yr in the upright position), 24-50yr (30-50yr upright), 51-69yr and ≥70yr were analysed separately.

We distinguished between studies reporting only on TPR and studies describing both TPR and PVR values. Additionally, studies with a single exercise level (only exercise 1) and those with at least two exercise levels (exercise 1 and 2) were distinguished. As an alternative, three exercise levels were defined (slight, submaximal and maximal exercise) and the data were assigned to these categories, according to the following hierarchical criteria: 1. the original assessment by the authors; 2. heart rate (slight: ca. 100-115/min, submaximal: ca. 130-140/min, maximal: ca. 160/min), 3. work rate (slight: ca. 50W, submaximal: ca. 100W, maximal: ca. 150-200W). In this alternative stratification, due to different study protocols, not all subjects were examined at all stages of exercise.

To describe changes of TPR and PVR during rest and exercise and between the upright and supine position, 2-sided paired t-tests were performed in an exploratory way.

Results

According to the selection criteria, n=237 subjects from 24 different studies with individual mPAP and corresponding CO values were available at rest and at least one exercise level. (Table 1) [8-10,12-31]After the exclusion of individuals with prospectively defined implausible data, n=222 subjects (n=147 male, n=33 female, n=42 gender not available) were analysed. Out of these, n=17 subjects had both supine and upright data at rest and at least one exercise level. Consequently we analysed the data of n=176 subjects in the supine (<24yr: n=72, 24-50yr: n=72, 51-69yr: n=13, ≥70yr: n=12, no age data: n=7) and n=63 in the upright position (<30yr: n=29, 30-50yr: n=25, 51-69yr: n=4, ≥70yr: n=5). The determination of TPR
was possible in all these subjects. However, the evaluation of PVR was possible only in n=88 subjects in the supine (<24yr: n=42, 24-50yr: n=26, 51-69yr: n=7, ≥70yr: n=9, no age data: n=4) and n=7 subjects in the upright position (<30yr: n=5, 30-50yr: n=1, 51-69yr: n=1). Furthermore, we analysed the hemodynamics of subjects with mPAP, CO +/- PAWP at more than one exercise level. This was possible in n=95 subjects for TPR and n=64 subjects for PVR in the supine position and in n=48 subjects for TPR and n=6 subjects for PVR in the upright position. (Table 1)

Resting mPAP, PAWP, TPR, PVR

The analysis of resting mPAP and PAWP data confirmed previously published results. [4] In the supine position, subjects <24yr and between 24-50yr had similar resting mPAP (14.3±2.7 vs. 13.9±2.9 mmHg), PAWP (9.0±2.7 vs. 8.0±2.7 mmHg), TPR (165±50 vs. 164±46 dyn s cm⁻¹) and PVR (61±23 vs. 69±28 dyn s cm⁻¹). Subjects >50yr had slightly higher resting mPAP, TPR and PVR compared to subjects ≤50yr, while the subgroups among subjects >50yr (51-69yr vs. ≥70yr) showed almost no difference in resting hemodynamics (mPAP: 15.7±1.6 vs. 15.4±2.5 mmHg, PAWP: 9.6±2.0 vs. 9.2±1.6 mmHg, TPR: 226±64 vs. 223±45 dyn s cm⁻¹, PVR: 86±15 vs. 90±39 dyn s cm⁻¹) (Table 2).

In the upright position, based on a limited number of data, resting mPAP and PAWP were generally somewhat lower compared to the supine position (mPAP: <30yr: 13.7±2.9, 30-50yr: 13.5±3.1, 51-69yr: 14.0±2.9, ≥70yr: 11.4±3.4 mmHg; PAWP: <30yr: 7.4±2.9, other age groups not available). Resting TPR values were similar in all age groups (<30yr: 190±49, 30-50yr: 210±49, 51-69yr: 180±45, ≥70yr: 185±55 dyn). Resting PVR was only available in a small cohort of younger subjects and appeared higher as compared to the supine position (100±31 dyn s cm⁻¹) (Table 3).

mPAP, TPR and PVR changes during exercise

In the supine position, subjects <24yr and 24-50yr showed a similar response to exercise with respect to mPAP, TPR and PVR. Generally, in subjects ≤50yr a 85% increase in CO was associated with a 41% increase in mPAP, a 25% decrease in TPR (p<0.0001) and a 12% decrease in PVR (p<0.01). In subjects with multiple exercise levels, a further increase in CO appeared almost linearly related to the further mPAP and PAWP increase. (Figure 1) TPR showed a minor further decrease (p>0.0001) and PVR was more or less unchanged (NS). (Figure 2)
In contrast, subjects >50yr showed different mPAP, TPR and PVR responses to exercise as compared to subjects ≤50yr. In subjects between 51-69yr an initial increase in CO by 71% was associated with a 66% mPAP increase, while TPR was virtually unchanged (NS) and PVR decreased by 19%. (NS) (Table 2) During higher levels of exercise, mPAP increased only slightly, while TPR decreased much stronger than PVR (p=0.01 vs NS). (Fig 1, 2)

In subjects ≥70yr an initial increase in CO by 88% was associated with a 119% mPAP increase, and a slight increase in TPR by 17% (p=0.01), while PVR decreased slightly by 11% (NS) (Table 2). At higher exercise levels, mPAP increased only moderately, while TPR returned to the initial values (p<0.001) and PVR was merely unchanged, corresponding to the younger subjects (NS).

An initial increase of TPR was rare in younger subjects, but was more often observed with increasing age (<24yr: 18%, 24-50yr: 25%, 51-69yr: 62%, >70yr: 78%). During further exercise, TPR decreased in almost all (93%) of these subjects.

Supine vs. upright position

At rest, individual hemodynamic data were available in n=34 subjects in both the supine and upright position, allowing the most reliable comparison of hemodynamics between these body positions. These data confirmed that in all age groups both mPAP and CO were slightly higher in the supine vs. the upright position (see also Table 4). TPR was higher in the upright position in younger individuals (p<0.01), while it was similar in subjects >50yr (difference NS). Unfortunately, PAWP was only available in 2 subjects in both positions, therefore the direct comparison of PVR was not possible at rest and during exercise.

Out of the 34 subjects, n=17 subjects exercised both supine and upright (n=9 ≤50yr, n=8 >50yr). In subjects ≤50yr, the TPR decrease during exercise was more prominent in the upright, as compared to the supine position: a CO increase of 124% was accompanied by a TPR decrease of 29% in the upright, while a 86% CO increase merely by a 6% TPR decrease in the supine position. (Table 4) This observation was supported by the comparison of all the available supine and upright TPR data (dTPR/dCO was -8.6 dyn s cm⁻⁵/ l/min in the upright and -6.1 dyn s cm⁻⁵/l/min in the supine position). (Figure 3)

In subjects >50yr with both supine and upright data, an initial rise of TPR was found in the supine position followed by its return to the resting values during further exercise. On the contrary, a continuous slight decrease of TPR may be observed in the upright position. (Table 4)
Based on the available data, the initial PVR response to exercise appeared more pronounced (p<0.005) in the upright position, as compared to the very small changes found in the supine position. (Figure 4, Table 2) During the later stages of exercise, the behaviour of PVR was similar in both positions.

**Discussion**

Since the introduction of right heart catheterisation in humans [32] and the description of a detailed technique for this procedure [33] allowing to examine the hemodynamics of the pulmonary circulation, several concepts have been suggested to describe physiological changes of the pulmonary arterial pressure (PAP), the pulmonary arterial wedge pressure (PAWP) and the pulmonary vascular resistances during exercise. Some of these concepts could not be confirmed by later studies but broadly influenced medical thinking. In this review we describe the observed hemodynamic changes, with a main focus on vascular resistance. As TPR and PVR are composite parameters, we decided only to rely on individual hemodynamic data. In order to assess hemodynamic parameters at different exercise levels, we described changes at two exercise levels (exercise 1 and 2) as derived from the reviewed studies and alternatively after stratification into three exercise levels based on its intensity. The hemodynamic patterns obtained through both methods were very similar. (Table 2 and Annex Table 1, Figure 4, 6 and Annex Figure 1, 2)

**PAP vs. CO**

In the initial studies performed in healthy volunteers by right heart catheter at rest and during exercise, a marked increase in pulmonary flow was observed with just a minor increase in PAP. [31] This suggested a dramatic drop of both TPR and PVR during exercise. Other studies, however, showed a different pattern. In pneumectomy patients Cournand et al described relatively constant PAP values at lower pulmonary flow but a sharp increase of PAP when the pulmonary flow reached a value of about three and a half times the resting flow. [34]

Another concept described an initial increase of PAP but a failure to evoke a further rise in PAP when the pulmonary blood flow reached the double of the resting value. [18] According to the authors, the reason for such a reaction may be the widening of patent pulmonary vessels (dilatation) by the increased ventilatory efforts during exercise and the accelerated flow through the center of vessels of unchanged size or potentially the opening of new vessels (recruitment). This „flattening out“ of the PAP vs. CO curve has also been
described in the first guidelines on primary pulmonary hypertension (PPH) [35] as the typical response to exercise.

With the growing number of clinical studies, however, it seemed as if PAP had been linearly related to CO. Although most studies confirmed this linear association for the mean values, this was not true for all individuals. [27] Indeed, the data suggest a large individual variability in the relation between CO and PAP and its change with exercise.

Our analysis of individual values confirmed a linear or almost linear relationship between mPAP and CO during exercise in subjects ≤50yr. (Figure 1) Some individual data appeared not plausible, for instance when increasing workload resulted in an increasing cardiac output but a decreasing pulmonary pressure. However, the vast majority of slopes showed a linear CO-PAP relationship and the higher the resting PAP, the steeper was the dPAP/dCO relation. (Figure 5)

The pattern of PAP change during exercise may be different in subjects >50yrs. The initial PAP increase appears steeper in subjects between 50-70yr (dPAP/dCO: 2.85mmHg/l/min) compared to individuals ≤50yr (1.06mmHg/l/min) and the dPAP/dCO is even higher in subjects ≥70yrs (3.94mmHg/l/min). This finding is in accordance with previous studies [36] and may be explained by a loss of pulmonary vascular compliance on the one hand (suggested by higher resting PVR values) and by a decreased left ventricular filling compliance during exercise on the other [36] (suggested by a sharp increase of PAWP during low exercise levels). The contribution of the left ventricular filling may gain relevance with increasing age. The linear PAP/CO relationship observed in individuals ≤50yr may not be so common in subjects >50yr and especially >70yr due to a biphasic change in left ventricular filling resistance.

\[PAWP \text{ vs. } CO\]

Similar to PAP, several concepts exist explaining the change in PAWP during exercise. The physiologic range of PAWP and its upper limit of normal during exercise are still a field of scientific debate. Furthermore, the measurement of PAWP during exercise may be technically difficult and may not necessarily represent the left ventricular end diastolic pressure. [37]

According to an early concept, the left ventricular end diastolic pressure and PAWP remains stable or even falls during exercise. [38,39] This speculation has been included in the first guidelines on pulmonary hypertension[35]. As alternative concepts, slight [40] and a more prominent [41] increase in PAWP at increasing pulmonary flow during exercise were described. In the PPH guidelines, based on invasive data, [40] the upper limit of normal was
suggested to be 20mmHg. However, it was added that much more prominent increases in pulmonary pressures were observed in athletes at very high exercise levels. [42] PAWP values >20mmHg were also measured in normal subjects [43] and these results were confirmed by Reeves et al [11,30] suggesting that the 20mmHg threshold may not be relevant. West also argues against this threshold suggesting that left ventricular filling pressures can rise greatly during maximal exercise in normal subjects with perfectly healthy left ventricles. [44] However, a strong increase in PAWP during exercise may also be due to left ventricular disease such as isolated diastolic dysfunction. Such changes should be distinguished from normal individuals presenting with high PAWP at very high pulmonary flow.

Our data showed a moderate increase of PAWP during exercise in subjects ≤50yr. At a CO of about 18 l/min, PAWP usually remained <15mmHg and rarely reached values >20mmHg. (Figure 1) The individual data from subjects >50yr suggest that during exercise, PAWP may more frequently exceed 20mmHg and that this is quite common in individuals >70yr. (Figure 1) Similar age-dependent changes of PAWP have been described in studies, where only group data were available. [36]

**TPR and PVR vs. CO**

The changes in TPR and PVR reflect important hemodynamic mechanisms of the pulmonary circulation during exercise. Their responses may be the key to distinguish early pathologic changes of the pulmonary vessels from left heart dysfunction. While PVR is mainly determined by the resistance of the precapillary pulmonary arteries, TPR is composed of PVR + left ventricular filling resistance.

The first published studies suggested a marked decrease of PVR during exercise. [45] This was explained by an increase in the cross-sectional area of the vascular bed, both by dilatation of vessels and by recruitment of previously unperfused vessels. According to this concept, even early stages of pulmonary vasculopathy would impair the ability of the pulmonary blood vessels to increase their calibre and decrease their resistance during exercise.

However, already at the time of the first world conference on PPH, a much more modest PVR decrease was suggested. [35] This shift was based on studies performed in Sweden describing a PVR decrease of just 27% during exercise. [19,20,46] Some studies found no PVR change at all during exercise. [47] Our review supports these results and suggests a very modest PVR decrease during exercise-induced CO increase which is in the range of 0.95 - 1.45 dyn s cm⁻⁵/l/min in individuals ≤50yr.
In contrast, the reviewed individual data suggest a more pronounced decrease in TPR during exercise (5 - 7 dyn s cm$^{-5}$/l/min) in individuals $\leq$50yr. The different magnitude of TPR and PVR changes indicate that during exercise the pulmonary vascular resistance is nearly constant while the left ventricular filling resistance decreases considerably.

In subjects $>50$yr, similarly to younger individuals, a very modest PVR decrease was observed. The missing decrease and even an increase in TPR after the beginning of exercise which is seen rarely in subjects $\leq$50, but more often between 50-70yr and almost always in individuals $\geq$70yr (Figure 2) may indicate a failure or initial difficulty to decrease left ventricular filling resistance with increasing cardiac output. Interestingly, in practically all of the subjects with initial TPR increase the TPR decreased during further exercise stages suggesting the delayed decrease of the left ventricular filling resistance. This might represent a means to identify latent left heart dysfunction, which may be highly prevalent in older subjects. [48] Correspondingly, previous studies comparing subjects $\leq$50yr and $>50$yr found similar PAWP values in both groups at rest (7.1±2.3mmHg vs. 7.0±2.9mmHg), but higher PAWP values in the older group during exercise (10.6±3.6mmHg vs. 15.1±5.8mmHg). [4]

The resistive properties of pulmonary arteries may be characterized by multi-point pressure-flow curves generated from PAP or transpulmonary gradient (TPG = mean PAP – mean PAWP) values at several levels of flow. This method may be superior over single-point PVR measurements, [49-51] particularly if PVR is strongly flow dependent. Hemodynamic measurements at a large number of different flow levels during exercise were only available in a minority of the reviewed studies preventing the depiction of multi-point pressure-flow curves in a large number of subjects. The pressure-flow plot of those 51 subjects who provided at least 3-point measurements (Annex Figure 3) suggested that the TPG-flow relation is nearly linear and the regression line may cross the y axis virtually at zero. These observations suggest that single-point PVR may give a valuable estimate of the pulmonary resistance characteristics.

**Supine vs. upright data**

The hemodynamic differences at rest and during exercise between the supine and upright positions have been described in previous studies. [20,27,42,46,52,53] Generally, after transition from supine to upright position at rest, the increase of heart rate, systemic blood pressure, systemic vascular resistance, PVR and AVDO2, and the decrease of PAP, PAWP, left ventricular end systolic volume, left ventricular end diastolic volume, stroke volume and cardiac index can be observed.
The behaviour of PVR and its different patterns during supine and upright exercise were most extensively reviewed by Reeves et al. [11] and their findings are comparable with the results of our analysis. At supine exercise they described a minimal PVR decrease, in the upright position, however, they found higher resting PVR values which fell in a non-linear way at the transition from rest to moderate exercise. Following the initial drop, PVR behaved very similarly to that observed in the supine position, showing just a minimal, further decrease. The suggested explanation for the increased resting PVR in the upright position was a smaller amount of perfused lung vessels due to vascular collaps in West Zone I. [54] During mild exercise these vessels would reopen [55,56] leading to a fall in PVR. An alternative explanation is that vasoconstrictive mechanisms are activated at rest in the upright position that allow for a relatively even perfusion of all parts of the lung and leads to an elevated PVR. This vasoconstriction would be released during exercise resulting in a PVR decrease. Since it has never been shown in humans that West Zone I was present in healthy subjects, we favour the second explanation.

Unfortunately, there are very few individual PVR data available on upright exercise in healthy subjects to give a reliable description of the PVR changes. The available group data comparing the hemodynamics of the same subjects in the supine and upright position [52,57,58] suggest a higher transpulmonary gradient and a lower cardiac output and thus a higher PVR in the upright position at rest compared to the supine position. During mild exercise, a more pronounced decrease in PVR and TPR may be expected in the upright compared to the supine position, however, the low number of direct comparisons of both positions precludes reliable conclusions.

Limitations

There are certain limitations of this analysis. Despite our effort to review all available studies for individual data, some published data may have been missed. We have especially little information on PVR in the upright position. The small number of subjects in the higher age groups emphasizes the need for a well designed prospective analysis. Therefore, our results for PVR in the higher age groups particularly in the upright position should be considered with caution. Additionally, there is no standardised location of zero reference level in the upright position, which may have caused minor differences between studies. We accepted the statements in the reviewed studies that the volunteers were healthy, or their diseases did not influence pulmonary hemodynamics, yet we cannot exclude that unidentified diseases influenced pulmonary pressure and especially that an undiagnosed diastolic
dysfunction of the left ventricle influenced hemodynamic changes particularly in subjects > 50yrs and more so in individuals >70yr. Echocardiographic assessment and thus the echocardiographic evaluation of diastolic dysfunction was not available in most studies. Some of these individuals had increased systemic blood pressure values at rest, but according to our analysis this did not cause a significant change in resting or exercise TPR and PVR. Finally, male subjects were over-represented compared to females in the reviewed studies. This may have had practical reasons like the availability of subjects.

**Conclusion**

Based on the available published data, an age- and exercise-dependent increase in PAP and PAWP, a moderate decrease in TPR and a minor decrease in PVR may be expected during exercise in healthy subjects. These physiologic changes might form a basis for the definition of early pulmonary vasculopathy and early left ventricular diastolic dysfunction.
Table legends:

Table 1. Subjects reviewed for their individual PVR and TPR data
(PVR: pulmonary vascular resistance, TPR: total pulmonary resistance)

Table 2. Hemodynamic data of subjects in the supine position at rest and during exercise
(PVR: pulmonary vascular resistance, TPR: total pulmonary resistance, mPAP: mean pulmonary arterial pressure, PAWP: pulmonary arterial wedge pressure, CO: cardiac output, TPG: transpulmonary gradient, ex1: exercise level 1, ex2: exercise level 2)

Table 3. Hemodynamic data of subjects in the upright position at rest and during exercise
(PVR: pulmonary vascular resistance, TPR: total pulmonary resistance, mPAP: mean pulmonary arterial pressure, PAWP: pulmonary arterial wedge pressure, CO: cardiac output, ex1: exercise level 1, ex2: exercise level 2)

Table 4. Hemodynamic data of subjects exercising both in the supine and upright position
(TPR: total pulmonary resistance, mPAP: mean pulmonary arterial pressure, CO: cardiac output, HR: heart rate, ex1: exercise level 1, ex2: exercise level 2)

Annex Table 1. Hemodynamic data of subjects in the supine position at rest and during exercise based on predefined exercise levels (slight, submaximal, maximal)
(PVR: pulmonary vascular resistance, TPR: total pulmonary resistance, mPAP: mean pulmonary arterial pressure, PAWP: pulmonary arterial wedge pressure, CO: cardiac output, HR: heart rate)

Annex Table 2. Hemodynamic data of subjects in the supine position at rest and during exercise
(PVRI: pulmonary vascular resistance index, TPRI: total pulmonary resistance index, mPAP: mean pulmonary arterial pressure, PAWP: pulmonary arterial wedge pressure, CI: cardiac index, TPG: transpulmonary gradient, ex1: exercise level 1, ex2: exercise level 2)

Figure legends:

Figure 1. mPAP (full lines) and PAWP (broken lines) vs. CO in subjects <24yr (red), 24-50yr (green), 51-69yr (blue), ≥70yr (yellow) in the supine position (SD shown in Table 2)
(mPAP: mean pulmonary arterial pressure, PAWP: pulmonary arterial wedge pressure, CO: cardiac output)

Figure 2. TPR (full lines) and PVR (broken lines) vs. CO in subjects <24yr (red), 24-50yr (green), 51-69yr (blue), ≥70yr (yellow) in the supine position (SD shown in Table 2)
(PVR: pulmonary vascular resistance, TPR: total pulmonary resistance, CO: cardiac output)

Figure 3. TPR supine (blue, n=144) vs. upright (red, n=54) ($\leq$50yr)
(TPR: total pulmonary resistance, CO: cardiac output)
Figure 4. TPR (full lines) and PVR (broken lines) vs CO (supine (blue, n=51) vs. upright (red, n=6))

(TPR: total pulmonary resistance, PVR: pulmonary vascular resistance, CO: cardiac output)

Figure 5. mPAP vs CO in subjects with at least 2 exercise levels (≤50yr, supine, n=80)

(mPAP: mean pulmonary arterial pressure, CO: cardiac output)

Annex Figure 1. mPAP (full lines) and PAWP (broken lines) vs. CO in subjects <24yr (red), 24-50yr (green), 51-69yr (blue), ≥70yr (yellow) in the supine position based on predefined exercise levels (slight, submaximal, maximal) (SD shown in Annex Table 1)

(mPAP: mean pulmonary arterial pressure, PAWP: pulmonary arterial wedge pressure, CO: cardiac output)

Annex Figure 2. TPR (full lines) and PVR (broken lines) vs. CO in subjects <24yr (red), 24-50yr (green), 51-69yr (blue), ≥70yr (yellow) in the supine position based on predefined exercise levels (slight, submaximal, maximal) (SD shown in Annex Table 1)

(PVR: pulmonary vascular resistance, TPR: total pulmonary resistance, CO: cardiac output)

Annex Figure 3. TPG vs. CO in subjects ≤50yr with values at rest and at least 2 exercise levels (n=51, SD shown in Table 2)

(TPG: transpulmonary gradient, CO: cardiac output)
References


Table 1

- All subjects: 1107 [47 studies] (see [4])
  - individual data for TPR: 237
    - Excluded due to implausible data: 15
      - individual data for TPR: 222 [24 studies, n=17 sup-up]

  - supine: 176 [19 studies]
    - <24yrs: 72 [13 studies] (2 levels: 47 [5 studies])
      - also PVR: 42 [6 studies] (2 levels: 30 [3 studies])
    - 24-50yrs: 72 [15 studies] (2 levels: 35 [5 studies])
      - also PVR: 26 [6 studies] (2 levels: 21 [4 studies])
    - 50-70yrs: 13 [4 studies] (2 levels: 6 [1 study])
      - also PVR: 7 [2 studies] (2 levels: 5 [1 study])
    - >70yrs: 12 [2 studies] (2 levels: 5 [1 study])
      - also PVR: 9 [1 study] (2 levels: 8 [1 study])
    - Age unknown: 7 [1 study]

  - upright: 63 [9 studies]
    - <30yrs: 28 [4 studies] (2 levels: 25 [5 studies])
      - also PVR: 6 [1 study] (2 levels: 5 [1 study])
    - 30-50yrs: 25 [7 studies] (2 levels: 17 [5 studies])
      - also PVR: 1 [1 study] (2 levels: 1 [1 study])
    - 50-70yrs: 4 [2 studies] (2 levels: 1 [1 study])
      - also PVR: 1 [1 study] (2 levels: 1 [1 study])
    - >70yrs: 9 [1 study] (2 levels: 5 [1 study])
    - also PVR: 0
<table>
<thead>
<tr>
<th>Supine</th>
<th>n</th>
<th>mPAPrest</th>
<th>PAWPrest</th>
<th>COrest</th>
<th>TPRrest</th>
<th>PVRrest</th>
<th>TFGrest</th>
<th>mPAPex1</th>
<th>PAWPex1</th>
<th>COnex1</th>
<th>TPRex1</th>
<th>PVRex1</th>
<th>TFGex1</th>
<th>mPAPex2</th>
<th>PAWPex2</th>
<th>Conex2</th>
<th>TPRex2</th>
<th>PVRex2</th>
<th>TFGex2</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;24yr</td>
<td>72</td>
<td>14±1.7</td>
<td>7.1±1.4</td>
<td>14±5.9</td>
<td>19±2.7</td>
<td>12±2.5</td>
<td>13±3.0</td>
<td>12±2.5</td>
<td>13±3.0</td>
<td>12±2.5</td>
<td>13±3.0</td>
<td>12±2.5</td>
<td>13±3.0</td>
<td>21±2.5</td>
<td>16±2.5</td>
<td>10±2.5</td>
<td>16±2.5</td>
<td>10±2.5</td>
<td>16±2.5</td>
</tr>
<tr>
<td>24-50yr</td>
<td>72</td>
<td>13±1.7</td>
<td>6.9±1.6</td>
<td>16±4.5</td>
<td>19±1.7</td>
<td>11±1.4</td>
<td>12±2.9</td>
<td>11±1.4</td>
<td>12±2.9</td>
<td>11±1.4</td>
<td>12±2.9</td>
<td>11±1.4</td>
<td>12±2.9</td>
<td>21±4.6</td>
<td>15±4.6</td>
<td>11±3.7</td>
<td>15±4.6</td>
<td>11±3.7</td>
<td>15±4.6</td>
</tr>
<tr>
<td>≤50yr</td>
<td>72</td>
<td>13±1.7</td>
<td>6.9±1.6</td>
<td>16±4.5</td>
<td>19±1.7</td>
<td>11±1.4</td>
<td>12±2.9</td>
<td>11±1.4</td>
<td>12±2.9</td>
<td>11±1.4</td>
<td>12±2.9</td>
<td>11±1.4</td>
<td>12±2.9</td>
<td>21±4.6</td>
<td>15±4.6</td>
<td>11±3.7</td>
<td>15±4.6</td>
<td>11±3.7</td>
<td>15±4.6</td>
</tr>
<tr>
<td>&gt;50yr</td>
<td>52</td>
<td>15±2.5</td>
<td>8.5±2.6</td>
<td>7.5±1.8</td>
<td>16±1.49</td>
<td>62±23</td>
<td>5.3±1.5</td>
<td>19±4.7</td>
<td>10.7±3.8</td>
<td>15±2.4</td>
<td>12±1.3</td>
<td>62±19</td>
<td>10.4±3.2</td>
<td>29±0.63</td>
<td>12.0±4.6</td>
<td>18.2±3.8</td>
<td>10±3.9</td>
<td>58±21</td>
<td>11.7±4.8</td>
</tr>
<tr>
<td>24-50yr</td>
<td>72</td>
<td>15±2.7</td>
<td>7.7±2.8</td>
<td>7.2±2.0</td>
<td>16±1.49</td>
<td>62±23</td>
<td>5.3±1.5</td>
<td>19±4.7</td>
<td>10.7±3.8</td>
<td>15±2.4</td>
<td>12±1.3</td>
<td>62±19</td>
<td>10.4±3.2</td>
<td>29±0.63</td>
<td>12.0±4.6</td>
<td>18.2±3.8</td>
<td>10±3.9</td>
<td>58±21</td>
<td>11.7±4.8</td>
</tr>
<tr>
<td>≤50yr</td>
<td>72</td>
<td>15±2.7</td>
<td>7.7±2.8</td>
<td>7.2±2.0</td>
<td>16±1.49</td>
<td>62±23</td>
<td>5.3±1.5</td>
<td>19±4.7</td>
<td>10.7±3.8</td>
<td>15±2.4</td>
<td>12±1.3</td>
<td>62±19</td>
<td>10.4±3.2</td>
<td>29±0.63</td>
<td>12.0±4.6</td>
<td>18.2±3.8</td>
<td>10±3.9</td>
<td>58±21</td>
<td>11.7±4.8</td>
</tr>
<tr>
<td>&gt;50yr</td>
<td>52</td>
<td>15±2.5</td>
<td>8.5±2.6</td>
<td>7.5±1.8</td>
<td>16±1.49</td>
<td>62±23</td>
<td>5.3±1.5</td>
<td>19±4.7</td>
<td>10.7±3.8</td>
<td>15±2.4</td>
<td>12±1.3</td>
<td>62±19</td>
<td>10.4±3.2</td>
<td>29±0.63</td>
<td>12.0±4.6</td>
<td>18.2±3.8</td>
<td>10±3.9</td>
<td>58±21</td>
<td>11.7±4.8</td>
</tr>
<tr>
<td>24-50yr</td>
<td>72</td>
<td>14±2.6</td>
<td>6.5±0.7</td>
<td>21±15.4</td>
<td>32±7.9</td>
<td>13±2.0</td>
<td>32±7.9</td>
<td>13±2.0</td>
<td>32±7.9</td>
<td>13±2.0</td>
<td>32±7.9</td>
<td>13±2.0</td>
<td>32±7.9</td>
<td>23±2.5</td>
<td>15±2.5</td>
<td>10±2.5</td>
<td>23±2.5</td>
<td>15±2.5</td>
<td>10±2.5</td>
</tr>
<tr>
<td>≤50yr</td>
<td>72</td>
<td>14±2.6</td>
<td>6.5±0.7</td>
<td>21±15.4</td>
<td>32±7.9</td>
<td>13±2.0</td>
<td>32±7.9</td>
<td>13±2.0</td>
<td>32±7.9</td>
<td>13±2.0</td>
<td>32±7.9</td>
<td>13±2.0</td>
<td>32±7.9</td>
<td>23±2.5</td>
<td>15±2.5</td>
<td>10±2.5</td>
<td>23±2.5</td>
<td>15±2.5</td>
<td>10±2.5</td>
</tr>
<tr>
<td>&gt;50yr</td>
<td>52</td>
<td>15±2.5</td>
<td>8.5±2.6</td>
<td>7.5±1.8</td>
<td>16±1.49</td>
<td>62±23</td>
<td>5.3±1.5</td>
<td>19±4.7</td>
<td>10.7±3.8</td>
<td>15±2.4</td>
<td>12±1.3</td>
<td>62±19</td>
<td>10.4±3.2</td>
<td>29±0.63</td>
<td>12.0±4.6</td>
<td>18.2±3.8</td>
<td>10±3.9</td>
<td>58±21</td>
<td>11.7±4.8</td>
</tr>
<tr>
<td>24-50yr</td>
<td>72</td>
<td>14±2.6</td>
<td>6.5±0.7</td>
<td>21±15.4</td>
<td>32±7.9</td>
<td>13±2.0</td>
<td>32±7.9</td>
<td>13±2.0</td>
<td>32±7.9</td>
<td>13±2.0</td>
<td>32±7.9</td>
<td>13±2.0</td>
<td>32±7.9</td>
<td>23±2.5</td>
<td>15±2.5</td>
<td>10±2.5</td>
<td>23±2.5</td>
<td>15±2.5</td>
<td>10±2.5</td>
</tr>
<tr>
<td>≤50yr</td>
<td>72</td>
<td>14±2.6</td>
<td>6.5±0.7</td>
<td>21±15.4</td>
<td>32±7.9</td>
<td>13±2.0</td>
<td>32±7.9</td>
<td>13±2.0</td>
<td>32±7.9</td>
<td>13±2.0</td>
<td>32±7.9</td>
<td>13±2.0</td>
<td>32±7.9</td>
<td>23±2.5</td>
<td>15±2.5</td>
<td>10±2.5</td>
<td>23±2.5</td>
<td>15±2.5</td>
<td>10±2.5</td>
</tr>
<tr>
<td>&gt;50yr</td>
<td>52</td>
<td>15±2.5</td>
<td>8.5±2.6</td>
<td>7.5±1.8</td>
<td>16±1.49</td>
<td>62±23</td>
<td>5.3±1.5</td>
<td>19±4.7</td>
<td>10.7±3.8</td>
<td>15±2.4</td>
<td>12±1.3</td>
<td>62±19</td>
<td>10.4±3.2</td>
<td>29±0.63</td>
<td>12.0±4.6</td>
<td>18.2±3.8</td>
<td>10±3.9</td>
<td>58±21</td>
<td>11.7±4.8</td>
</tr>
<tr>
<td>Upright</td>
<td>n</td>
<td>mPAP rest</td>
<td>PAWP rest</td>
<td>CO rest</td>
<td>TPR rest</td>
<td>PVR rest</td>
<td>mPAP ex1</td>
<td>PAWP ex1</td>
<td>CO ex1</td>
<td>TPR ex1</td>
<td>PVR ex1</td>
<td>mPAP ex2</td>
<td>PAWP ex2</td>
<td>CO ex2</td>
<td>TPR ex2</td>
<td>PVR ex2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>---------</td>
<td>----</td>
<td>-----------</td>
<td>-----------</td>
<td>--------</td>
<td>---------</td>
<td>---------</td>
<td>---------</td>
<td>---------</td>
<td>-------</td>
<td>--------</td>
<td>---------</td>
<td>---------</td>
<td>---------</td>
<td>--------</td>
<td>-------</td>
<td>--------</td>
<td>-------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50yr</td>
<td>29</td>
<td>13.7±1.9</td>
<td>5.1±1.3</td>
<td>100±64</td>
<td>19.5±5.2</td>
<td>13.2±3.8</td>
<td>125±44</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 lev, TPR</td>
<td>25</td>
<td>13.5±1.8</td>
<td>5.0±1.3</td>
<td>192±65</td>
<td>19.2±5.4</td>
<td>12.4±3.5</td>
<td>130±45</td>
<td>24.1±6.6</td>
<td></td>
<td></td>
<td></td>
<td>18.0±4.4</td>
<td></td>
<td>113±42</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 lev, TPR</td>
<td>5</td>
<td>15.0±2.0</td>
<td>7.4±2.9</td>
<td>199±44</td>
<td>100±31</td>
<td>20.6±5.0</td>
<td>12.0±4.5</td>
<td></td>
<td>13.4±2.8</td>
<td></td>
<td></td>
<td>126±31</td>
<td>52±17</td>
<td>22.0±5.5</td>
<td>11.8±5.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PVR, TPR</td>
<td></td>
<td>31-50yr</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 lev, TPR</td>
<td>25</td>
<td>19.5±3.1</td>
<td>5.2±1.0</td>
<td>210±49</td>
<td>22.1±5.2</td>
<td>12.7±4.9</td>
<td>151±43</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 lev, TPR</td>
<td>17</td>
<td>13.5±3.4</td>
<td>5.1±0.9</td>
<td>215±48</td>
<td>20.8±4.4</td>
<td>10.1±2.2</td>
<td>168±36</td>
<td>25.4±7.7</td>
<td></td>
<td></td>
<td></td>
<td>13.7±2.2</td>
<td></td>
<td>145±42</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PVR, TPR</td>
<td>1</td>
<td>19</td>
<td>7.2</td>
<td>211</td>
<td>22</td>
<td>16.3</td>
<td>135</td>
<td>44</td>
<td>30</td>
<td>22</td>
<td>18.1</td>
<td>135</td>
<td>35</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>51-70yr</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 lev, TPR</td>
<td>4</td>
<td>14.0±1.9</td>
<td>6.3±0.4</td>
<td>180±45</td>
<td>18.8±7.3</td>
<td>9.7±2.1</td>
<td>152±26</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 lev, TPR</td>
<td>1</td>
<td>16</td>
<td>6.0</td>
<td>215</td>
<td>21</td>
<td>9.8</td>
<td>171</td>
<td>25</td>
<td>12.3</td>
<td>163</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PVR, TPR</td>
<td>1</td>
<td>11</td>
<td>6.14</td>
<td>143</td>
<td>145</td>
<td>8.1</td>
<td>138</td>
<td>99</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥70yr</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 lev, TPR</td>
<td>5</td>
<td>11.4±3.4</td>
<td>5.1±1.1</td>
<td>185±55</td>
<td>20.2±4.6</td>
<td>8.7±1.5</td>
<td>186±32</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 lev, TPR</td>
<td>5</td>
<td>11.4±3.4</td>
<td>5.1±1.1</td>
<td>185±55</td>
<td>20.2±4.6</td>
<td>8.7±1.5</td>
<td>186±32</td>
<td>22.8±4.9</td>
<td></td>
<td></td>
<td></td>
<td>11.5±1.9</td>
<td></td>
<td>156±19</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PVR, TPR</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 4

<table>
<thead>
<tr>
<th>Supine</th>
<th>n</th>
<th>HR rest</th>
<th>mPAP rest</th>
<th>CO rest</th>
<th>TPR rest</th>
<th>HR ex1</th>
<th>mPAP ex1</th>
<th>CO ex1</th>
<th>TPR ex1</th>
<th>HR ex2</th>
<th>mPAP ex2</th>
<th>CO ex2</th>
<th>TPR ex2</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤50yr</td>
<td>9</td>
<td>68±5</td>
<td>12.6±3.4</td>
<td>8.8±1.2</td>
<td>113±21</td>
<td>113±9</td>
<td>21.8±6.0</td>
<td>16.4±2.9</td>
<td>106±23</td>
<td>155±12</td>
<td>24.0±8.0</td>
<td>22.6±4.5</td>
<td>84±17</td>
</tr>
<tr>
<td>&gt;50yr</td>
<td>8</td>
<td>71±11</td>
<td>14.5±1.9</td>
<td>6.3±1.1</td>
<td>190±41</td>
<td>104±9</td>
<td>29.5±4.8</td>
<td>10.4±1.4</td>
<td>129±50</td>
<td>129±13</td>
<td>32.3±7.7</td>
<td>13.3±1.6</td>
<td>195±49</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Upright</th>
<th>n</th>
<th>HR rest</th>
<th>mPAP rest</th>
<th>CO rest</th>
<th>TPR rest</th>
<th>HR ex1</th>
<th>mPAP ex1</th>
<th>CO ex1</th>
<th>TPR ex1</th>
<th>HR ex2</th>
<th>mPAP ex2</th>
<th>CO ex2</th>
<th>TPR ex2</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤50yr</td>
<td>9</td>
<td>74±12</td>
<td>11.4±2.8</td>
<td>6.3±1.0</td>
<td>145±50</td>
<td>108±9</td>
<td>18.4±7.4</td>
<td>14.1±3.6</td>
<td>103±24</td>
<td>151±12</td>
<td>25.3±8.5</td>
<td>20.5±4.8</td>
<td>90±19</td>
</tr>
<tr>
<td>&gt;50yr</td>
<td>8</td>
<td>80±8</td>
<td>12.6±3.5</td>
<td>5.4±1.0</td>
<td>188±48</td>
<td>101±11</td>
<td>20.5±5.1</td>
<td>9.3±1.9</td>
<td>177±29</td>
<td>127±6</td>
<td>29.2±4.5</td>
<td>11.6±1.7</td>
<td>150±17</td>
</tr>
</tbody>
</table>
Figure 2

Graph showing the relationship between CO (l/min) and PVR, TPR (dyn s cm⁻⁵).
Figure 4
Figure 5