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# Pulmonary vascular resistances during exercise in normal subjects: a systematic review

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**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 aged <24 yrs, 24–50 yrs, 51–69 yrs and ⩾70 yrs was 61±23, 69±28, 86±15 and 90±39 dyn·s·cm$^{-5}$, respectively. Corresponding TPR was 165±50, 164±46, 226±64 and 223±45 dyn·s·cm$^{-5}$, respectively. During moderate exercise in subjects aged ⩽50 yrs, an 85% increase in cardiac output was associated with a 25% decrease in TPR (p<0.0001) and a 12% decrease in PVR (p<0.01). At 51–69 yrs of age there was no significant decrease in TPR and PVR. In individuals aged ⩾70 yrs 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 in the supine position and decreased more prominently during exercise, suggesting the release of resting pulmonary vasoconstriction.**

**These data may form a basis to define normal PVR at rest and exercise.**

**KEYWORDS: Exercise, haemodynamics, pulmonary circulation, pulmonary vascular resistance**

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Pulmonary hypertension (PH) has been defined as a resting mean pulmonary artery pressure ($\bar{P}_{pa}$) ⩾25 mmHg [1]. The ''exercise part'' of the earlier haemodynamic definition ($\bar{P}_{pa}$ >30 mmHg during exercise [2]) was abandoned at the last PH world conference in Dana Point (CA, USA) because during exercise $\bar{P}_{pa}$ is very much more dependent on age and exercise level [3]. The pulmonary pressure response to exercise may, however, provide clinically relevant information where resting haemodynamics do not fully explain the symptoms of the patient. Before we consider reintroducing a haemodynamic definition, we must work on evidence-based ranges for the physiological haemodynamic response to exercise. This will allow for the development of criteria for both physiological and pathological exercise haemodynamic patterns.

The available published literature on physiological haemodynamic responses to exercise in the pulmonary circulation reflects a large variety of theoretical 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 $\bar{P}_{pa}$ [4]. In the present study we aimed to analyse the available individual data focusing on pulmonary vascular resistance (PVR) during exercise. The changes in total pulmonary resistance (TPR) and PVR belong to the most important physiological parameters of the pulmonary circulation. They reflect the anatomic and functional properties of the cardiac chambers and pulmonary vessels. The understanding of physiological 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 aim of this study was to describe the physiological

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pattern of TPR and PVR changes in healthy individuals during exercise.

## MATERIALS AND METHODS

We reviewed the available published literature on right heart catheterisation studies with exercise in healthy individuals. For details of the literature research refer to the Annex in the online supplementary material [4]. In this article we restricted our research to those studies that provided individual data on $\bar{P}_{pa}$, pulmonary arterial wedge pressure ($P_{paw}$) and cardiac output (CO) at rest and during exercise. Only those studies which allowed the calculation of individual TPR ($\bar{P}_{pa}$ and CO at rest and at least one exercise level) and/or PVR ($\bar{P}_{pa}$, $P_{paw}$ and CO at rest and at least one exercise level) were included. Cardiac output was obtained by the direct Fick method in the majority of studies, while thermodilution or dye dilution was used [8–10]. Studies providing no individual values but just mean values of group data were excluded. Subjects with implausible values ($\bar{P}_{pa}$ lower or higher than mean$\pm$2SD at rest; <8 or >20 mmHg) were excluded. Additionally, individuals with a resting $P_{paw}$ lower or higher than mean$\pm$2SD (<3 or >13 mmHg) and subjects with $P_{paw}$ values which were not at least 3 mmHg below the corresponding $\bar{P}_{pa}$ were excluded from the PVR analysis, as previously suggested [11]. Subjects with extreme obesity were excluded. As body position may significantly influence haemodynamics, data were stratified for the supine *versus* the upright position. It has also been shown that exercise haemodynamics in subjects aged >50 yrs may follow a different pattern compared to individuals aged $\leqslant$50 yrs [4]. 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 aged <24 yrs (<30 yrs in the upright position), 24–50 yrs (30–50 yrs in the upright position), 51–69 yrs and $\geqslant$70 yrs 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 differentiated. 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: 100–115 beats·min$^{-1}$; submaximal: 130–140 beats·min$^{-1}$; maximal: 160 beats·min$^{-1}$); and 3) work rate (slight: 50 W; submaximal: 100 W; maximal: 150–200 W). 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, two-sided paired t-tests were performed in an exploratory way.

## RESULTS

According to the selection criteria, 237 subjects from 24 different studies with individual $\bar{P}_{pa}$ and corresponding CO values were available at rest and at least one exercise level (fig. 1) [8–10, 12–31]. After the exclusion of individuals with prospectively defined implausible data, 222 subjects (147 males, 33 females, 42 sex not available) were analysed. Out of these, 17 subjects had both supine and upright data at rest and at least one exercise level. Consequently, we analysed the data of 176 subjects in the supine (72 aged <24 yrs, 72 aged 24–50 yrs, 13 aged 51–69 yrs, 12 aged $\geqslant$70 yr and seven with no age data) and 63 in the upright position (29 aged <30 yrs, 25 aged 30–50 yrs, four aged 51–69 yrs and five aged $\geqslant$70 yrs). The determination of TPR was possible in all these subjects. However, the evaluation of PVR was possible only in 88 subjects in the supine (42 aged <24 yrs, 26 aged 24–50 yrs, seven aged 51–69 yrs, nine aged $\geqslant$70 yrs and four no age data) and seven subjects in the upright position (five aged <30 yrs, one aged 30–50 yrs and one aged 51–69 yrs). Furthermore, we analysed the haemodynamics of subjects with $\bar{P}_{pa}$ and CO with/without $P_{paw}$ at more than one exercise level. This was possible in 95 subjects for TPR and 64 subjects for PVR in the supine position and in 48 subjects for TPR and six subjects for PVR in the upright position (fig. 1).

### *Resting $\bar{P}_{pa}$, $P_{paw}$, TPR and PVR*

The analysis of resting $\bar{P}_{pa}$ and $P_{paw}$ data confirmed previously published results [4]. In the supine position, subjects aged <24 yrs and 24–50 yrs had similar resting $\bar{P}_{pa}$ (mean$\pm$SD 14.3$\pm$2.7 *versus* 13.9$\pm$2.9 mmHg), $P_{paw}$ (9.0$\pm$2.7 *versus* 8.0$\pm$2.7 mmHg), TPR (165$\pm$50 *versus* 164$\pm$46 dyn·s·cm$^{-5}$) and PVR (61$\pm$23 *versus* 69$\pm$28 dyn·s·cm$^{-5}$). Subjects aged >50 yrs had slightly higher resting $\bar{P}_{pa}$, TPR and PVR compared to subjects aged $\leqslant$50 yrs, while the subgroups among subjects aged >50 yrs (51–69 *versus* $\geqslant$70 yrs) showed almost no difference in resting haemodynamics ($\bar{P}_{pa}$ 15.7$\pm$1.6 *versus* 15.4$\pm$2.5 mmHg, $P_{paw}$ 9.6$\pm$2.0 *versus* 9.2$\pm$1.6 mmHg, TPR 226$\pm$64 *versus* 223$\pm$45 dyn·s·cm$^{-5}$, and PVR 86$\pm$15 *versus* 90$\pm$39 dyn·s·cm$^{-5}$) (table 1).

In the upright position, based on a limited number of data, resting $\bar{P}_{pa}$ and $P_{paw}$ were generally somewhat lower compared to the supine position ($\bar{P}_{pa}$: 13.7$\pm$2.9, 13.5$\pm$3.1, 14.0$\pm$2.9 and 11.4$\pm$3.4 mmHg at <30 yrs, 30–50 yrs, 51–69 yrs and $\geqslant$70 yrs, respectively; $P_{paw}$: 7.4$\pm$2.9 at <30 yrs; other age groups were not available). Resting TPR values were similar in all age groups (190$\pm$64, 210$\pm$49, 180$\pm$45 and 185$\pm$55 dyn·s·cm$^{-5}$ at <30 yrs, 30–50 yrs, 51–69 yrs and $\geqslant$70 yrs, respectively). Resting PVR was only available in a small cohort of younger subjects and appeared higher compared to the supine position (100$\pm$31 dyn·s·cm$^{-5}$) (table 2).

### *$\bar{P}_{pa}$, TPR and PVR changes during exercise*

In the supine position, subjects aged <24 yrs and 24–50 yrs showed a similar response to exercise with respect to $\bar{P}_{pa}$, TPR and PVR. Generally, in subjects aged $\leqslant$50 yrs an 85% increase in CO was associated with a 41% increase in $\bar{P}_{pa}$, 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 $\bar{P}_{pa}$ and $P_{paw}$ increase (figs 2 and 3). TPR showed a minor further decrease ($p>0.0001$) and PVR was more or less unchanged (NS) (fig. 4).

In contrast, subjects aged >50 yrs showed different $\bar{P}_{pa}$, TPR and PVR responses to exercise compared to subjects aged $\leqslant$50 yrs. In subjects 51–69 yrs of age, an initial increase in CO by 71% was associated with a 66% increase in $\bar{P}_{pa}$, while TPR was virtually unchanged (NS) and PVR decreased by 19% (NS) (table 1). During higher levels of exercise, $\bar{P}_{pa}$ increased only slightly, while TPR decreased much more strongly than PVR ($p=0.01$ *versus* NS) (figs 2 and 4).

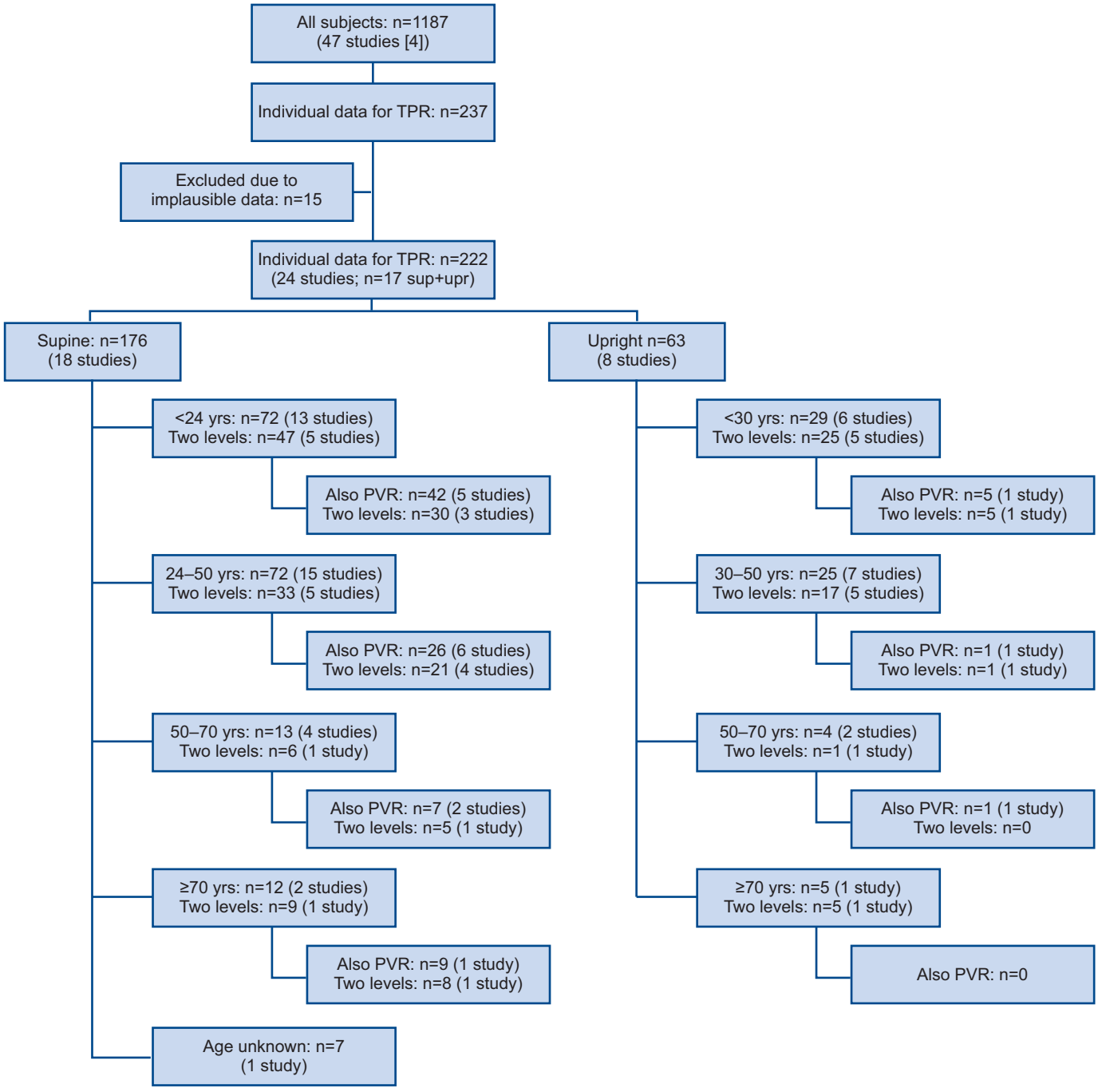


**FIGURE 1.** Subjects reviewed for their individual pulmonary vascular resistance (PVR) and total pulmonary resistance (TPR) data in the upright (upr) and supine position (sup). Levels refer to exercise levels.

In subjects aged ⩾70 yrs, an initial increase in CO by 88% was associated with a 119% $\bar{P}_{pa}$ increase and a slight increase in TPR by 17% (p=0.01), while PVR decreased slightly by 11% (NS) (table 1). At higher exercise levels, $\bar{P}_{pa}$ 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 (18%, 25%, 62% and 78% at <24 yrs, 24–50 yrs, 51–69 yrs and >70 yrs, respectively). During further exercise, TPR decreased in almost all (93%) of these subjects.

### *Supine* versus *upright position*

At rest, individual haemodynamic data were available in 34 subjects in both the supine and upright positions, allowing reliable comparison of haemodynamics between these body positions. These data confirmed that in all age groups both $\bar{P}_{pa}$ and CO were slightly higher in the supine *versus* the upright

**TABLE 1** Haemodynamic data of subjects in the supine position at rest and during exercise

| | Subjects n | At rest | | | | | | Exercise level 1 | | | | | | Exercise level 2 | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | $\bar{P}_{pa}$ mmHg | $P_{paw}$ mmHg | CO L·min$^{-1}$ | TPR dyn·s·cm$^{-5}$ | PVR dyn·s·cm$^{-5}$ | TPG mmHg | $\bar{P}_{pa}$ mmHg | $P_{paw}$ mmHg | CO L·min$^{-1}$ | TPR dyn·s·cm$^{-5}$ | PVR dyn·s·cm$^{-5}$ | TPG mmHg | $\bar{P}_{pa}$ mmHg | $P_{paw}$ mmHg | CO L·min$^{-1}$ | TPR dyn·s·cm$^{-5}$ | PVR dyn·s·cm$^{-5}$ | TPG mmHg |
| **Age <24 yrs** | | | | | | | | | | | | | | | | | | | |
| TPR (1 level) | 72 | 14.1±2.7 | | 7.1±1.4 | 168±49 | | | 19.3±4.7 | | 12.4±3.3 | 131±34 | | | | | | | | |
| TPR (2 levels) | 47 | 13.8±2.7 | | 7.3±1.5 | 159±51 | | | 19.4±4.7 | | 13.1±3.0 | 123±33 | | | 21.2±5.4 | | 16.8±4.3 | 104±27 | | |
| PVR+ TPR (1 level) | 42 | 14.3±2.7 | 9.0±2.7 | 7.2±1.6 | 165±50 | 61±23 | 5.3±1.7 | 19.2±4.8 | 10.9±4.0 | 13.4±3.1 | 119±35 | 52±19 | 8.3±2.5 | | | | | | |
| PVR+ TPR (2 levels) | 30 | 14.1±2.4 | 9.0±2.4 | 7.3±1.6 | 163±51 | 58±18 | 5.1±1.4 | 19.3±4.7 | 11.3±3.8 | 13.4±3.1 | 118±32 | 49±18 | 8.0±2.6 | 22.0±5.0 | 11.8±4.5 | 17.6±4.5 | 103±23 | 49±17 | 10.2±3.0 |
| **Age 24–50 yrs** | | | | | | | | | | | | | | | | | | | |
| TPR (1 level) | 72 | 13.9±2.7 | | 6.9±1.6 | 168±45 | | | 19.6±5.1 | | 11.7±3.4 | 144±42 | | | | | | | | |
| TPR (2 levels) | 33 | 13.0±2.7 | | 7.1±1.7 | 153±46 | | | 19.6±4.7 | | 12.5±2.9 | 131±40 | | | 21.9±6.1 | | 16.4±4.6 | 113±37 | | |
| PVR+ TPR (1 level) | 26 | 13.9±2.9 | 8.0±2.7 | 7.1±1.9 | 164±46 | 69±28 | 5.9±1.8 | 21.0±4.7 | 10.7±3.9 | 13.4±2.3 | 129±34 | 63±22 | 10.3±3.2 | | | | | | |
| PVR+ TPR (2 levels) | 21 | 13.4±2.7 | 7.7±2.8 | 7.2±2.0 | 157±46 | 67±28 | 5.7±1.6 | 20.3±4.7 | 9.9±3.7 | 13.7±2.4 | 121±30 | 62±19 | 10.4±3.2 | 23.7±6.3 | 12.0±4.6 | 18.2±3.8 | 106±29 | 53±21 | 11.7±4.8 |
| **Age ⩽50 yrs** | | | | | | | | | | | | | | | | | | | |
| PVR+ TPR (2 levels) | 51 | 13.8±2.5 | 8.5±2.6 | 7.3±1.8 | 161±49 | 62±23 | 5.3±1.5 | 19.7±4.7 | 10.7±3.8 | 13.5±2.8 | 119±31 | 55±20 | 9.0±3.1 | 22.7±5.6 | 11.8±4.5 | 17.8±4.2 | 104±25 | 50±19 | 10.9±3.8 |
| **Age 51–70 yrs** | | | | | | | | | | | | | | | | | | | |
| TPR (1 level) | 13 | 15.7±1.7 | | 6.0±1.7 | 222±60 | | | 26.6±9.6 | | 9.8±4.0 | 227±66 | | | | | | | | |
| TPR (2 levels) | 6 | 16.0±1.6 | | 6.0±1.5 | 228±70 | | | 27.3±5.5 | | 10.1±2.1 | 223±64 | | | 28.2±6.9 | | 13.1±2.1 | 174±48 | | |
| PVR+ TPR (1 level) | 7 | 15.7±1.6 | 9.6±2.0 | 5.9±1.4 | 226±64 | 86±15 | 6.1±1.1 | 26.1±5.9 | 17.6±5.8 | 10.1±1.9 | 213±64 | 70±32 | 8.5±3.6 | | | | | | |
| PVR+ TPR (2 levels) | 5 | 15.6±1.3 | 9.2±1.5 | 6.2±1.6 | 212±64 | 85±18 | 6.4±1.1 | 27.2±6.1 | 18.8±4.7 | 9.7±2.2 | 230±69 | 71±37 | 8.4±4.2 | 28.0±7.6 | 19.4±7.1 | 12.7±2.1 | 178±52 | 57±27 | 8.6±3.3 |
| **Age ⩾70 yrs** | | | | | | | | | | | | | | | | | | | |
| TPR (1 level) | 12 | 14.7±2.6 | | 5.6±0.7 | 215±47 | | | 30.8±7.9 | | 9.7±2.0 | 259±57 | | | | | | | | |
| TPR (2 levels) | 9 | 15.4±2.5 | | 5.6±0.6 | 223±45 | | | 33.7±6.7 | | 10.5±1.5 | 260±49 | | | 33.9±6.2 | | 12.9±1.4 | 212±42 | | |
| PVR+ TPR (1 level) | 9 | 15.4±2.5 | 9.2±1.6 | 5.6±0.6 | 223±45 | 90±39 | 6.2±2.5 | 33.7±6.7 | 23.1±6.4 | 10.5±1.5 | 260±49 | 80±21 | 10.6±3.2 | | | | | | |
| PVR+ TPR (2 levels) | 8 | 15.4±2.7 | 9.4±1.6 | 5.6±0.6 | 221±48 | 86±39 | 6.0±2.6 | 33.9±7.1 | 23.3±6.8 | 10.3±1.5 | 264±51 | 81±22 | 10.6±3.5 | 34.6±6.2 | 22.5±8.4 | 12.9±1.5 | 217±42 | 76±33 | 12.1±5.0 |

$\bar{P}_{pa}$: mean pulmonary artery pressure; $P_{paw}$: pulmonary arterial wedge pressure; CO: cardiac output; TPR: total pulmonary resistance; PVR: pulmonary vascular resistance; TPG: transpulmonary gradient.

**TABLE 2** Haemodynamic data of subjects in the upright position at rest and during exercise

| | Subjects n | At rest | | | | | Exercise level 1 | | | | | Exercise level 2 | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | $\bar{P}_{pa}$ mmHg | $P_{paw}$ mmHg | CO L·min$^{-1}$ | TPR dyn·s·cm$^{-5}$ | PVR dyn·s·cm$^{-5}$ | $\bar{P}_{pa}$ mmHg | $P_{paw}$ mmHg | CO L·min$^{-1}$ | TPR dyn·s·cm$^{-5}$ | PVR dyn·s·cm$^{-5}$ | $\bar{P}_{pa}$ mmHg | $P_{paw}$ mmHg | CO L·min$^{-1}$ | TPR dyn·s·cm$^{-5}$ | PVR dyn·s·cm$^{-5}$ |
| **Age <30 yrs** | | | | | | | | | | | | | | | | |
| TPR (1 level) | 29 | 13.7±2.9 | | 6.1±1.3 | 190±64 | | 19.5±5.2 | | 13.2±3.8 | 125±44 | | | | | | |
| TPR (2 levels) | 25 | 13.5±2.8 | | 6.0±1.3 | 192±66 | | 19.2±5.4 | | 12.4±3.5 | 130±45 | | 24.1±6.6 | | 18.0±4.4 | 113±42 | |
| PVR+TPR | 5 | 15.0±2.0 | 7.4±2.9 | 6.2±1.3 | 199±44 | 100±31 | 20.6±5.0 | 12.0±4.5 | 13.4±2.8 | 126±31 | 52±17 | 22.0±5.5 | 11.6±5.0 | 18.2±2.3 | 98±26 | 46±8 |
| **Age 31–50 yrs** | | | | | | | | | | | | | | | | |
| TPR (1 level) | 25 | 13.5±3.1 | | 5.2±1.0 | 210±49 | | 22.1±5.2 | | 12.7±4.9 | 151±43 | | | | | | |
| TPR (2 levels) | 17 | 13.5±3.4 | | 5.1±0.9 | 215±48 | | 20.8±4.4 | | 10.1±2.2 | 168±36 | | 25.4±7.7 | | 13.7±2.2 | 149±42 | |
| PVR+TPR | 1 | 19 | 8 | 7.2 | 211 | 122 | 27 | 18 | 16.3 | 133 | 44 | 30 | 22 | 18.1 | 133 | 35 |
| **Age 51–70 yrs** | | | | | | | | | | | | | | | | |
| TPR (1 level) | 4 | 14.0±2.9 | | 6.3±0.4 | 180±45 | | 18.8±7.3 | | 9.7±2.2 | 152±26 | | | | | | |
| TPR (2 levels) | 1 | 16 | | 6.0 | 215 | | 21 | | 9.8 | 171 | | 25 | | 12.3 | 163 | |
| PVR+TPR | 1 | 11 | 3 | 6.1 | 143 | 104 | 14 | 4 | 8.1 | 138 | 99 | | | | | |
| **Age ⩾70 yrs** | | | | | | | | | | | | | | | | |
| TPR (1 level) | 5 | 11.4±3.4 | | 5.1±1.1 | 185±55 | | 20.2±4.6 | | 8.7±1.5 | 186±32 | | | | | | |
| TPR (2 levels) | 5 | 11.4±3.4 | | 5.1±1.1 | 185±55 | | 20.2±4.6 | | 8.7±1.5 | 186±32 | | 22.8±4.9 | | 11.5±1.9 | 158±19 | |
| PVR+TPR | 0 | | | | | | | | | | | | | | | |

$\bar{P}_{pa}$: mean pulmonary artery pressure; $P_{paw}$: pulmonary arterial wedge pressure; CO: cardiac output; TPR: total pulmonary resistance; PVR: pulmonary vascular resistance; TPG: transpulmonary gradient.

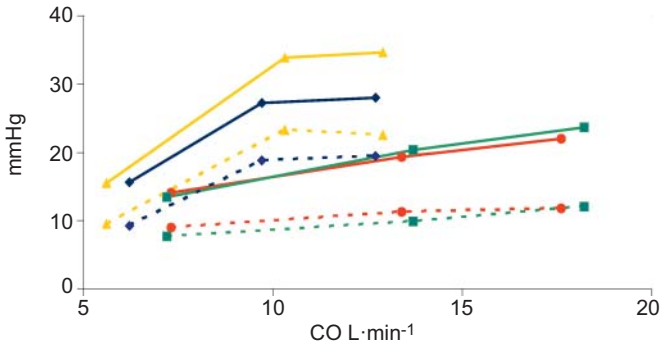


**FIGURE 2.** Mean pulmonary artery pressure (——) and pulmonary arterial wedge pressure (- - - -) *versus* cardiac output (CO) in subjects aged <24 yrs (red), 24–50 yrs (green), 51–69 yrs (blue) and ⩾70 yrs (yellow) in the supine position.

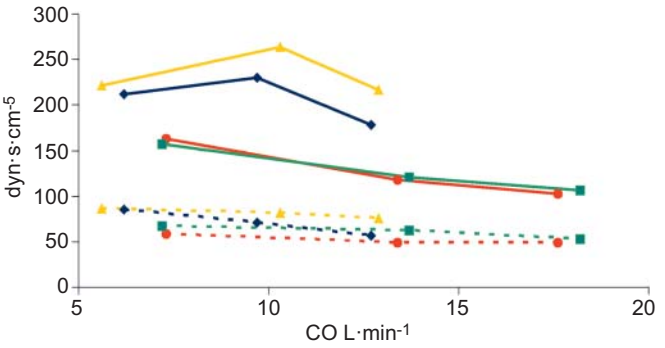


**FIGURE 4.** Total pulmonary resistance (——) and pulmonary vascular resistance (- - - -) *versus* cardiac output (CO) in subjects aged <24 yrs (red), 24–50 yrs (green), 51–69 yrs (blue) and ⩾70 yrs (yellow) in the supine position.

position (table 3). TPR was higher in the upright position in younger individuals ($p<0.01$), while it was similar in subjects aged >50 yrs (NS). Unfortunately, $P_{paw}$ was only available in two subjects in both positions; therefore, direct comparison of PVR was not possible at rest and during exercise.

Out of the 34 subjects, 17 subjects exercised both in the supine and upright position (⩽50 yrs: n=9; >50 yrs: n=8). In subjects aged ⩽50 yrs, the TPR decrease during exercise was more prominent in the upright compared to the supine position. A CO increase of 124% was accompanied by a TPR decrease of 29% in the upright position, while an 86% CO increase accompanied a mere 6% TPR decrease in the supine position (table 3). This observation was supported by the comparison of all the available supine and upright TPR data (the slope of the TPR *versus* CO graph (dTPR/dCO) was -8.6 dyn·s·cm$^{-5}$·L$^{-1}$·min in the upright and -6.1 dyn·s·cm$^{-5}$·L$^{-1}$·min in the supine position) (fig. 5).

In subjects aged >50 yrs 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. Conversely, a continuous slight decrease of TPR may be observed in the upright position (table 3).

Based on the available data, the initial PVR response to exercise appeared more pronounced ($p<0.005$) in the upright position, compared to the very small changes found in the supine position (fig. 6, table 1). During the later stages of exercise, the behaviour of PVR was similar in both positions.

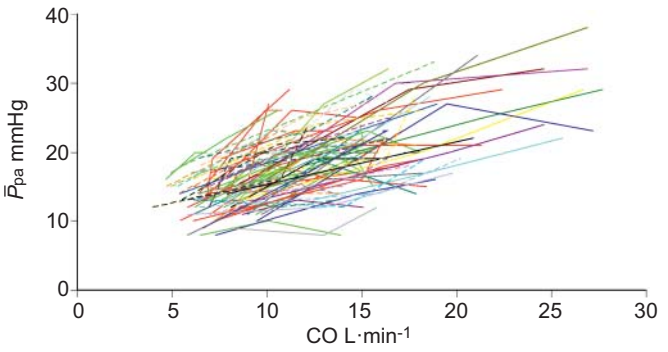


**FIGURE 3.** Mean pulmonary artery pressure ($\bar{P}_{pa}$) *versus* cardiac output (CO) in 80 subjects aged ⩽50 yrs with at least two exercise levels in the supine position.

## DISCUSSION

Since the introduction of right heart catheterisation in humans [32] and the description of a detailed technique for this procedure [33], allowing the examination of the haemodynamics of the pulmonary circulation to be examined, several concepts have been suggested to describe physiological changes of the pulmonary artery pressure ($P_{pa}$), $P_{paw}$ and PVR during exercise. Some of these concepts could not be confirmed by later studies but nonetheless broadly influenced medical thinking. In this article we described the observed haemodynamic changes, with a main focus on vascular resistance. As TPR and PVR are composite parameters, we decided only to rely on individual haemodynamic data. In order to assess haemodynamic parameters at different exercise levels, we described changes at two exercise levels (exercise level 1 and 2) as derived from the reviewed studies and alternatively after stratification into three exercise levels based on its intensity. The haemodynamic patterns obtained through both methods were very similar (table 1 and figs 2 and 4, and table 1 and figs 1 and 2 in the online supplement).

### $P_{pa}$ versus *CO*

In the initial studies performed in healthy volunteers by right heart catheterisation at rest and during exercise, a marked increase in pulmonary flow was observed with only a minor increase in $P_{pa}$ [31]. This suggested a dramatic decrease of both TPR and PVR during exercise. Other studies, however, showed a different pattern. In pneumectomy patients, COURNAND and RILEY [34] described relatively constant $P_{pa}$ values at lower pulmonary flow but a sharp increase of $P_{pa}$ when the pulmonary flow reached a value of approximately 3.5 times the resting flow.

Another concept described an initial increase of $P_{pa}$ but a failure to evoke a further increase in $P_{pa}$ when the pulmonary blood flow reached double 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 centre of vessels of unchanged size or potentially the opening of new vessels (recruitment). This ''flattening out'' of the $P_{pa}$ *versus* CO curve has also been described in the first

**TABLE 3** Haemodynamic data of subjects exercising both in the supine and upright position

| | Subjects n | At rest | | | | Exercise level 1 | | | | Exercise level 2 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | *fc* beats·min$^{-1}$ | $\bar{P}_{pa}$ mmHg | CO L·min$^{-1}$ | TPR dyn·s·cm$^{-5}$ | *fc* beats·min$^{-1}$ | $\bar{P}_{pa}$ mmHg | CO L·min$^{-1}$ | TPR dyn·s·cm$^{-5}$ | *fc* beats·min$^{-1}$ | $\bar{P}_{pa}$ mmHg | CO L·min$^{-1}$ | TPR dyn·s·cm$^{-5}$ |
| **Supine** | | | | | | | | | | | | | |
| Age ⩽50 yrs | 9 | 68±5 | 12.6±3.4 | 8.8±1.2 | 113±21 | 113±9 | 21.8±6.0 | 16.4±2.9 | 106±23 | 155±12 | 24.0±8.0 | 22.6±4.5 | 84±17 |
| Age >50 yrs | 8 | 71±11 | 14.5±1.9 | 6.3±1.1 | 190±41 | 104±9 | 29.5±4.8 | 10.4±1.4 | 229±50 | 129±13 | 32.3±7.7 | 13.3±1.6 | 195±49 |
| **Upright** | | | | | | | | | | | | | |
| Age ⩽50 yrs | 9 | 74±12 | 11.4±2.8 | 6.3±1.0 | 146±30 | 108±9 | 18.4±7.4 | 14.1±3.6 | 103±24 | 151±12 | 23.3±8.3 | 20.5±4.8 | 90±19 |
| Age >50 yrs | 8 | 80±8 | 12.6±3.5 | 5.4±1.0 | 188±48 | 102±11 | 20.5±5.1 | 9.3±1.9 | 177±29 | 127±6 | 23.2±4.5 | 11.6±1.7 | 159±17 |

*fc*: cardiac frequency; $\bar{P}_{pa}$: mean pulmonary artery pressure; CO: cardiac output; TPR: total pulmonary resistance.

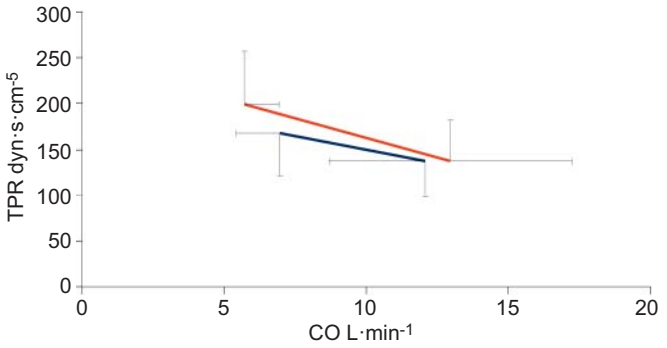


**FIGURE 5.** Total pulmonary resistance (TPR) *versus* cardiac output (CO) in the 144 subjects in the supine position (blue) and 54 subjects in the upright position (red) at age ⩽50 yrs. Error bars represent standard deviation.

guidelines on primary pulmonary hypertension (PPH) [35] as the typical response to exercise.

However, with the growing number of clinical studies it seemed as if $P_{pa}$ were 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 relationship between CO and $P_{pa}$ and its change with exercise.

Our analysis of individual values confirmed a linear or almost linear relationship between $\bar{P}_{pa}$ and CO during exercise in subjects aged ⩽50 yrs (fig. 2). Some individual data appeared implausible; for instance when increasing workload resulted in an increasing CO but a decreasing pulmonary pressure. However, the vast majority of slopes showed a linear CO–$P_{pa}$ relationship and the higher the resting $P_{pa}$, the steeper the d$P_{pa}$/dCO relationship (fig. 3).

The pattern of $P_{pa}$ change during exercise may be different in subjects aged >50 yrs. The initial $P_{pa}$ increase appears steeper in subjects aged 50–70 yrs (d$P_{pa}$/dCO 2.85 mmHg·L$^{-1}$·min) compared to individuals aged ⩽50 yrs (1.06 mmHg·L$^{-1}$·min) and the d$P_{pa}$/dCO is even higher in subjects aged ⩾70 yrs (3.94 mmHg·L$^{-1}$·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]

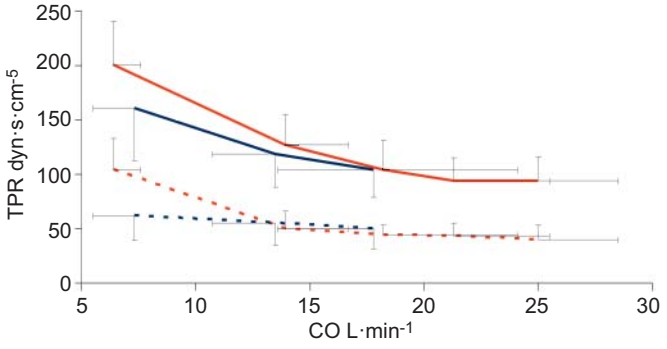


**FIGURE 6.** Total pulmonary resistance (——) and pulmonary vascular resistance (- - - -) *versus* cardiac output (CO) in 51 subjects in the supine position (blue) and six in the upright position (red).

(suggested by a sharp increase of $P_{paw}$ during low exercise levels). The contribution of the left ventricular filling may gain relevance with increasing age. The linear $P_{pa}$–CO relationship observed in individuals aged ⩽50 yrs may not be so common in subjects aged >50 yrs and especially in those aged >70 yrs due to a biphasic change in left ventricular filling resistance.

### $P_{paw}$ versus *CO*

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

According to an early concept, left ventricular end-diastolic pressure and $P_{paw}$ remain stable or even falls during exercise [38, 39]. This speculation was included in the first guidelines on PH [35]. As an alternative concept, a slight [40] and more prominent [41] increase in $P_{paw}$ at increasing pulmonary flow during exercise was described. In the PPH guidelines, based on invasive data [40], the upper limit of normal was suggested to be 20 mmHg. However, it was added that much more prominent increases in pulmonary pressures were observed in athletes at very high exercise levels [42]. $P_{paw}$ values >20 mmHg were also measured in normal subjects [43] and these results were confirmed by REEVES *et al.* [11] and GROVES *et al.* [30] suggesting that the 20 mmHg threshold may not be relevant. WEST [44] also argues against this threshold suggesting that left ventricular filling pressures can increase greatly during maximal exercise in normal subjects with perfectly healthy left ventricles. However, a strong increase in $P_{paw}$ 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 $P_{paw}$ at very high pulmonary flow.

Our data showed a moderate increase of $P_{paw}$ during exercise in subjects aged ⩽50 yr. At a CO of ~18 $L \cdot min^{-1}$, $P_{paw}$ usually remained <15 mmHg and rarely reached values >20 mmHg (fig. 2). The individual data from subjects aged >50 yrs suggest that during exercise, $P_{paw}$ may more frequently exceed 20 mmHg and that this is quite common in individuals aged >70 yrs (fig. 2). Similar age-dependent changes of $P_{paw}$ have been described in studies where only group data were available [36].

### *TPR and PVR* versus *CO*

The changes in TPR and PVR reflect important haemodynamic mechanisms of the pulmonary circulation during exercise. Their responses may be the key to distinguish early pathological changes of the pulmonary vessels from left heart dysfunction. While PVR is mainly determined by the resistance of the pre-capillary pulmonary arteries, TPR is composed of PVR plus 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, 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 $dyn \cdot s \cdot cm^{-5} \cdot L^{-1} \cdot min$ in individuals aged ⩽50 yrs.

In contrast, the reviewed individual data suggest a more pronounced decrease in TPR during exercise (5–7 $dyn \cdot s \cdot cm^{-5} \cdot L^{-1} \cdot min$) in individuals aged ⩽50 yrs. The different magnitude of TPR and PVR changes indicate that during exercise the PVR is nearly constant while the left ventricular filling resistance decreases considerably.

In subjects aged >50 yrs, 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 aged ⩽50 yrs, but more often between 50–70 yrs and almost always in individuals aged ⩾70 yrs (fig. 4), may indicate a failure or initial difficulty to decrease left ventricular filling resistance with increasing CO. Interestingly, in practically all of the subjects with initial TPR increase, the TPR decreased during further exercise stages suggesting a 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 aged ⩽50 yrs and >50 yrs found similar $P_{paw}$ values in both groups at rest ($7.1 \pm 2.3$ mmHg *versus* $7.0 \pm 2.9$ mmHg), but higher $P_{paw}$ values in the older group during exercise ($10.6 \pm 3.6$ mmHg *versus* $15.1 \pm 5.8$ mmHg) [4].

The resistive properties of pulmonary arteries may be characterised by multi-point pressure–flow curves generated from $P_{pa}$ or transpulmonary gradient (TPG = $\bar{P}_{pa}$ - mean $P_{paw}$) 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. Haemodynamic 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 three-point measurements (fig. 3 in the online supplement) suggested that the TPG–flow relationship 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* versus *upright data*

The haemodynamic 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 arteriovenous oxygen saturation difference, and the decrease of $P_{pa}$, $P_{paw}$, 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. During 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 collapse in zone 1 [54]. During mild exercise these vessels would re-open [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 lead 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 zone 1 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 provide a reliable description of the PVR changes. The available group data comparing the haemodynamics of the same subjects in the supine and upright position [52, 57, 58] suggest a higher TPG and a lower CO 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 emphasises 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 haemodynamics, yet we cannot exclude the possibility that unidentified diseases influenced pulmonary pressure and especially that an undiagnosed diastolic dysfunction of the left ventricle influenced haemodynamic changes particularly in subjects aged >50 yrs and more so in individuals aged >70 yr. 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 overrepresented compared to females in the reviewed studies. This may have been due to practical reasons, such as the availability of subjects.

### *Conclusion*

Based on the available published data, an age- and exercise-dependent increase in $P_{pa}$ and $P_{paw}$, a moderate decrease in TPR and a minor decrease in PVR may be expected during exercise in healthy subjects. These physiological changes might form a basis for the definition of early pulmonary vasculopathy and early left ventricular diastolic dysfunction.

## STATEMENT OF INTEREST

None declared.

## REFERENCES


1 Galie N, Hoeper MM, Humbert M, *et al.* Guidelines for the diagnosis and treatment of pulmonary hypertension: The Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by the International Society of Heart and Lung Transplantation (ISHLT). *Eur Heart J* 2009; 30: 2493–2537.

2 Galie N, Torbicki A, Barst R, *et al.* Guidelines on diagnosis and treatment of pulmonary arterial hypertension. The Task Force on Diagnosis and Treatment of Pulmonary Arterial Hypertension of the European Society of Cardiology. *Eur Heart J* 2004; 25: 2243–2278.

3 Badesch DB, Abman SH, Ahearn GS, *et al.* Medical therapy for pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. *Chest* 2004; 126: Suppl. 1, 35S–62S.

4 Kovacs G, Berghold A, Scheidl S, *et al.* Pulmonary arterial pressure during rest and exercise in healthy subjects: a systematic review. *Eur Respir J* 2009; 34: 888–894.

5 Kovacs G, Maier R, Aberer E, *et al.* Borderline pulmonary arterial pressure is associated with decreased exercise capacity in scleroderma. *Am J Respir Crit Care Med* 2009; 180: 881–886.

6 Saggar R, Khanna D, Furst DE, *et al.* Exercise-induced pulmonary hypertension associated with systemic sclerosis: four distinct entities. *Arthritis Rheum* 2010; 62: 3741–3750.

7 Tolle JJ, Waxman AB, Van Horn TL, *et al.* Exercise-induced pulmonary arterial hypertension. *Circulation* 2008; 118: 2183–2189.

8 Reeves JT, Groves BM, Sutton JR, *et al.* Operation Everest II: preservation of cardiac function at extreme altitude. *J Appl Physiol* 1987; 63: 531–539.

9 Yu PN, Murphy GW, Schreiner BF Jr, *et al.* Distensibility characteristics of the human pulmonary vascular bed. Study of the pressure–volume response to exercise in patients with and without heart disease. *Circulation* 1967; 35: 710–723.

10 Messin R, Degre S, Demaret B, *et al.* The effect of age on pulmonary circulation in normal subjects. *Prog Respir Res* 1970; 5: 385–394.

11 Reeves JT, Dempsey JA, Grover RF. Pulmonary circulation during exercise. *In:* Weir EK, Reeves JT, eds. Pulmonary Vascular Physiology and Physiopathology. New York, Marcel Dekker, 1989; pp. 107–133.

12 Hickam JB, Cargill WH. Effect of exercise on cardiac output and pulmonary arterial pressure in normal persons and in patients with cardiovascular disease and pulmonary emphysema. *J Clin Invest* 1948; 27: 10–23.

13 Dexter L, Whittenberger JL, Haynes FW, *et al.* Effect of exercise on circulatory dynamics of normal individuals. *J Appl Physiol* 1951; 3: 439–453.

14 Slonim NB, Ravin A, Balchum OJ, *et al.* The effect of mild exercise in the supine position on the pulmonary arterial pressure of five normal human subjects. *J Clin Invest* 1954; 33: 1022–1030.

15 Donald KW, Bishop JM, Cumming G, *et al.* The effect of exercise on the cardiac output and circulatory dynamics of normal subjects. *Clin Sci (Lond)* 1955; 14: 37–73.

16 Freedman ME, Snider GL, Brostoff P, *et al.* Effect of training on response of cardiac output to muscular exercise in athletes. *J Appl Physiol* 1955; 8: 37–47.

17 Sancetta SM, Rakita L. Response of pulmonary artery pressure and total pulmonary resistance of untrained, convalescent man to prolonged mild steady state exercise. *J Clin Invest* 1957; 36: 1138–1149.
18 Fishman AP, Fritts HW Jr, Cournand A. Effects of acute hypoxia and exercise on the pulmonary circulation. *Circulation* 1960; 22: 204–215.
19 Holmgren A, Jonsson B, Sjostrand T. Circulatory data in normal subjects at rest and during exercise in recumbent position, with special reference to the stroke volume at different work intensities. *Acta Physiol Scand* 1960; 49: 343–363.
20 Bevegard S, Holmgren A, Jonsson B. The effect of body position on the circulation at rest and during exercise, with special reference to the influence on the stroke volume. *Acta Physiol Scand* 1960; 49: 279–298.
21 Ekelund LG. Circulatory and respiratory adaptation during prolonged exercise in the supine position. *Acta Physiol Scand* 1966; 68: 382–396.
22 Harris P, Segel N, Bishop JM. The relation between pressure and flow in the pulmonary circulation in normal subjects and in patients with chronic bronchitis and mitral stenosis. *Cardiovasc Res* 1968; 2: 73–83.
23 Emirgil C, Sobol BJ, Campodonico S, *et al.* Pulmonary circulation in the aged. *J Appl Physiol* 1967; 23: 631–640.
24 Gurtner HP, Walser P, Faessler B. Normal values for pulmonary hemodynamics at rest and during exercise in man. *Prog Respir Res* 1975; 9: 295–315.
25 Alexander JK, Hartley LH, Modelski M, *et al.* Reduction of stroke volume during exercise in man following ascent to 3,100 m altitude. *J Appl Physiol* 1967; 23: 849–858.
26 Ekelund LG, Holmgren A. Circulatory and respiratory adaptation, during long-term, non-steady state exercise, in the sitting position. *Acta Physiol Scand* 1964; 62: 240–255.
27 Damato AN, Galante JG, Smith WM. Hemodynamic response to treadmill exercise in normal subjects. *J Appl Physiol* 1966; 21: 959–966.
28 Epstein SE, Beiser GD, Stampfer M, *et al.* Characterization of the circulatory response to maximal upright exercise in normal subjects and patients with heart disease. *Circulation* 1967; 35: 1049–1062.
29 Lonsdorfer-Wolf E, Richard R, Doutreleau S, *et al.* Pulmonary hemodynamics during a strenuous intermittent exercise in healthy subjects. *Med Sci Sports Exerc* 2003; 35: 1866–1874.
30 Groves BM, Reeves JT, Sutton JR, *et al.* Operation Everest II: elevated high-altitude pulmonary resistance unresponsive to oxygen. *J Appl Physiol* 1987; 63: 521–530.
31 Riley RL, Himmelstein A, Motley HL, *et al.* Studies of the pulmonary circulation at rest and during exercise in normal individuals and in patients with chronic pulmonary disease. *Am J Physiol* 1948; 152: 372–382.
32 Forssmann W. Die Sondierung des rechten Herzens. *Klin Wochenschr* 1929; 8: 2085.
33 Cournand A, Ranges H. Catheterization of right auricle in man. *Proc Soc Exp Biol Med* 1941; 46: 452.
34 Cournand A, Riley RL. Pulmonary circulation and alveolar ventilation perfusion relationships after pneumonectomy. *J Thorac Surg* 1950; 19: 80–116.
35 Hatano S, Strasser T. Primary Pulmonary Hypertension: Report on a WHO Meeting, Geneva, 15–17 October 1973. Geneva: World Health Organization, 1975.
36 Ehrsam RE, Perruchoud A, Oberholzer M, *et al.* Influence of age on pulmonary haemodynamics at rest and during supine exercise. *Clin Sci (Lond)* 1983; 65: 653–660.
37 Halpern SD, Taichman DB. Misclassification of pulmonary hypertension due to reliance on pulmonary capillary wedge pressure rather than left ventricular end-diastolic pressure. *Chest* 2009; 136: 37–43.
38 Ross J Jr, Gault JH, Mason DT, *et al.* Left ventricular performance during muscular exercise in patients with and without cardiac dysfunction. *Circulation* 1966; 34: 597–608.
39 Milnor WR. Pulmonary haemodynamics. *In:* Bergel DH, ed. Cardiovascular Fluid Dynamics. New York, Academic Press, 1972; pp. 299–340.
40 Ekelund LG, Holmgren A. Central hemodynamics during exercise. *Circ Res* 1967; 20: Suppl. 1, I33–I34.
41 Parker JO, Di Giorgi S, West RO. A hemodynamic study of acute coronary insufficiency precipitated by exercise. With observations on the effects of nitroglycerin. *Am J Cardiol* 1966; 17: 470–483.
42 Bevegard S, Holmgren A, Jonsson B. Circulatory studies in well trained athletes at rest and during heavy exercise. With special reference to stroke volume and the influence of body position. *Acta Physiol Scand* 1963; 57: 26–50.
43 Harris P, Heath D. Normal variations in pressure and flow. *In:* Harris P, Heath D, eds. The Human Pulmonary Circulation: its Form and Function in Health and Disease. Oxford, Churchill Livingstone, 1986; pp. 149–160.
44 West JB. Left ventricular filling pressures during exercise: a cardiological blind spot? *Chest* 1998; 113: 1695–1697.
45 Fishman A. Dynamics of the pulmonary circulation. *In:* Hamilton W, Dow P, eds. Handbook of Physiology. Washington, American Physiological Society, 1963; pp. 1667–1743.
46 Granath A, Jonsson B, Strandell T. Circulation in healthy old men, studied by right heart catheterization at rest and during exercise in supine and sitting position. *Acta Med Scand* 1964; 176: 425–446.
47 Lockhart A, Duhaze P, Polianski J, *et al.* A modified double dye injection method for pulmonary blood volume determination. II. Results in resting and exercising normal subjects. *Cardiovasc Res* 1974; 8: 120–131.
48 Lam CS, Borlaug BA, Kane GC, *et al.* Age-associated increases in pulmonary artery systolic pressure in the general population. *Circulation* 2009; 119: 2663–2670.
49 Naeije R. Pulmonary vascular function. *In:* Peacock A, Rubin LJ, eds. Pulmonary Circulation. 2nd Edn. London, Edward Arnold, 2004; pp. 3–13.
50 Naeije R, Vizza D. Current perspectives modern hemodynamic evaluation of the pulmonary circulation. Application to pulmonary arterial hypertension and embolic pulmonary hypertension. *Ital Heart J* 2005; 6: 784–788.
51 Chesler NC, Argiento P, Vanderpool R, *et al.* How to measure peripheral pulmonary vascular mechanics. *Conf Proc IEEE Eng Med Biol Soc* 2009; 2009: 173–176.
52 Higginbotham MB, Morris KG, Williams RS, *et al.* Regulation of stroke volume during submaximal and maximal upright exercise in normal man. *Circ Res* 1986; 58: 281–291.
53 Kubicek F, Gaul G. Comparison of supine and sitting body position during a triangular exercise test. I. Experiences in healthy subjects. *Eur J Appl Physiol Occup Physiol* 1977; 36: 275–283.
54 West JB. Respiratory Physiology. Baltimore, Williams and Wilkins, 1979.
55 Harf A, Pratt T, Hughes JM. Regional distribution of VA/Q in man at rest and with exercise measured with krypton-81m. *J Appl Physiol* 1978; 44: 115–123.
56 Wagner WW Jr, Latham LP, Capen RL. Capillary recruitment during airway hypoxia: role of pulmonary artery pressure. *J Appl Physiol* 1979; 47: 383–387.
57 Hossack KF, Adair OV, Crowley ST. Atrial natriuretic factor production during upright exercise. *Cardiology* 1990; 77: 433–442.
58 Thadani U, Parker JO. Hemodynamics at rest and during supine and sitting bicycle exercise in normal subjects. *Am J Cardiol* 1978; 41: 52–59.