Eur Respir J 2009; 34: 888–894
DOI: 10.1183/09031936.00145608

Pulmonary arterial pressure during rest and exercise in healthy subjects: a systematic review

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ABSTRACT: According to current guidelines, pulmonary arterial hypertension (PAH) is diagnosed when mean pulmonary arterial pressure ($\bar{P}$pa) exceeds 25 mmHg at rest or 30 mmHg during exercise. Issues that remain unclear are the classification of $\bar{P}$pa values <25mmHg and whether $\bar{P}$pa >30 mmHg during exercise is always pathological.

We performed a comprehensive literature review and analysed all accessible data obtained by right heart catheter studies from healthy individuals to determine normal $\bar{P}$pa at rest and during exercise. Data on 1,187 individuals from 47 studies in 13 countries were included. Data were stratified for sex, age, geographical origin, body position and exercise level.

$\bar{P}$pa at rest was 14.0±3.3 mmHg and this value was independent of sex and ethnicity. Resting $\bar{P}$pa was slightly influenced by posture (supine 14.0±3.3 mmHg, upright 13.6±3.1 mmHg) and age (<30 yrs: 12.8± 3.1mmHg; 30–50 yrs: 12.9±3.0 mmHg; ⩾50 yrs: 14.7±4.0 mmHg). $\bar{P}$pa during exercise was dependent on exercise level and age. During mild exercise, $\bar{P}$pa was 19.4±4.8 mmHg in subjects aged <50 yrs compared with 29.4±8.4 mmHg in subjects ⩾50 yrs (p<0.001).

In conclusion, while $\bar{P}$pa at rest is virtually independent of age and rarely exceeds 20 mmHg, exercise $\bar{P}$pa is age-related and frequently exceeds 30 mmHg, especially in elderly individuals, which makes it difficult to define normal $\bar{P}$pa values during exercise.

KEYWORDS: Exercise, pulmonary artery pressure, pulmonary hypertension, reference values, review, right heart catheterisation

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Received:
Sept 24 2008
Accepted after revision:
March 06 2009
First published online:
March 26 2009

Under physiological circumstances, the pulmonary circulation is characterised by low pressure and low vascular resistance. Several pathological conditions are associated with increased pulmonary pressure, *i.e.* pulmonary hypertension (PH). PH may be classified as pulmonary arterial hypertension (PAH) or PH due to a variety of causes including left heart diseases, lung diseases or pulmonary thromboembolic disease [1]. PAH is characterised by the absence of the latter causes and may be idiopathic, familial or associated with a number of other conditions.

According to the current European Society of Cardiology guideline, PH has been haemodynamically defined as a mean pulmonary artery pressure ($\bar{P}$pa) >25 mmHg at rest or >30 mmHg during exercise [2]. The available data, however, suggests that normal resting $\bar{P}$pa is considerably lower than 25 mmHg, usually <21 mmHg [3–5]. Several studies in patients with chronic obstructive pulmonary disease or interstitial lung disease have suggested that $\bar{P}$pa values of 15–25 mmHg might be associated with adverse events and impaired outcome [6–8].

Although exercise haemodynamics have been included in the haemodynamic definition of PH, it does not account for factors such as exercise level, exercise method, position and age that may have an impact on $\bar{P}$pa.

This literature review was conducted to summarise the available data that have been obtained from healthy individuals to define normal values of $\bar{P}$pa during rest and exercise. We considered factors that might have an impact on $\bar{P}$pa, such as posture, workload, age, geographic origin and sex. We found that the normal range of resting $\bar{P}$pa is considerably lower than 25 mmHg, while

For editorial comments see page 790.
This article has supplementary material accessible from www.erj.ersjournals.com

European Respiratory Journal
Print ISSN 0903-1936
Online ISSN 1399-3003

exercise values, particularly in individuals aged >50 yrs, often exceed 30 mmHg.

METHODS: SEARCH STRATEGY, SELECTION CRITERIA AND STRATIFICATION

Publications examining pulmonary arterial pressure values during both rest and physical exercise in healthy volunteers were identified by a Medline search using the keywords ''pulmonary arterial pressure and exercise'', ''right heart catheterisation and exercise'' and ''right heart catheter and exercise''. The search was restricted to papers available in the English, German or French languages. A secondary search reviewed the reference lists of relevant papers (mostly not available in Medline). This secondary hand search identified the majority of included studies. Two reviewers (G. Kovacs and H. Olschewski) independently screened the studies identified by the two searches. Differences over inclusion of studies were resolved by consensus reached after discussion.

All publications working up original data based on right heart catheterisation were included. Studies were excluded when they were referring to and interpreting previous examinations, or when the original data were not clearly identifiable, as well as when they did not provide detailed descriptions of the applied methods or complete haemodynamic data, or when drug-induced changes of pulmonary pressure were investigated. From studies examining pulmonary haemodynamics at high altitude or under hypoxic conditions, only the control measurements performed at sea level and under normal oxygen tension were considered. All subjects in all studies were described as entirely free of clinical symptoms, or had minor medical conditions that, according to the authors, had no influence on pulmonary haemodynamics.

The Medline search identified a total of 1,932 studies. According to the selection criteria, 138 studies were retrieved for more detailed evaluation and 16 studies were ultimately found to be eligible for inclusion. The reasons for exclusion were as follows: not only healthy subjects (38 studies); no original data (10 studies); no right heart catheterisation or no pulmonary arterial pressure measurements (72 studies); case report (two studies). After the secondary hand search, 31 further studies were found to be eligible and were included in the final analysis. Altogether data from 47 studies published in the English, German and French literature between 1947 and 2003 were reviewed, which included 72 separate study populations [9–58].

The majority of studies used cycle ergometry, but some studies used treadmill exercise, leg or arm presses in the supine or upright position. The investigations were performed in different populations (younger or older, untrained or trained, female or male preponderance) in different countries. Data were stratified upon predefined criteria including sex, age (<30 yrs, 30–50 yrs, ⩾50 yrs), origin (USA, Europe), body position (supine, upright) and exercise level. Three exercise levels were distinguished (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: 100–110 min^{-1}, submaximal: 130–135 min^{-1}, maximal: 160–170 min^{-1}); 3) work-rate (slight: ~50 W, submaximal: ~100 W, maximal: ~150–200 W); 4) peak oxygen uptake (slight: ~1,000 $mL \cdot min^{-1}$, submaximal: ~1,400–1,600 $mL \cdot min^{-1}$, maximal: ~2,100–2,400 $mL \cdot min^{-1}$); and 5) cardiac output (slight: ~12–14 $L \cdot min^{-1}$, submaximal: ~16 $L \cdot min^{-1}$, maximal: ~19–20 $L \cdot min^{-1}$). Owing to variations between study protocols, not all subjects were examined at all stages of exercise. Time points 2–3 min after start of a certain workload were considered for this analysis.

In some protocols, light sedation was applied before right heart catheterisation. These studies were included, as a previous review of a large database showed that such pre-medication may decrease systemic arterial pressure values, but has no significant impact on pulmonary haemodynamics [5].

Studies performed in the supine position were evaluated separately from studies in the upright position (sitting/exercising on the cycle ergometer, standing/walking on the treadmill). Few investigations involved the same subjects in the supine and upright positions. The comparison of haemodynamics depending on posture in these studies was analysed separately.

The association between sex and $\bar{P}_{Pa}$ was examined in studies in which both females and males were included and the results given according to sex.

Data originating from Europe, the USA and other parts of the world were compared to exclude bias due to geographical location.

In most studies, the zero level was set at 10 cm above the table (or 5 cm below the level of the sternum). For a few subjects (~10% of all subjects) a slightly different levelling was used (*e.g.* the mid-axillary line).

The recorded data were not reported uniformly in the original publications. Some authors gave the mean values and the standard deviation of parameters for the whole group (~70% of all subjects), with or without describing individual results; in other studies, only individual data were presented (~30% of all subjects). In these cases, the present authors calculated the mean values and standard deviations. The number of study populations (*e.g.* males and females, different age groups, when independently evaluated) and subjects examined for each particular variable at the given exercise level are indicated.

For the final analysis, the weighted mean and the weighted standard deviation values for the whole population reviewed were calculated. To evaluate the effect of position, sex and age at rest and during exercise, subgroup analysis was performed using only those studies in which the results were given according to these variables. A random effects model was used for the meta-analysis (StataCorp, College Station, TX, USA). To further describe the impact of age on pulmonary arterial pressure during exercise, a meta-regression analysis was performed comparing the haemodynamic data for all subjects aged <50 yrs with those aged ⩾50 yrs. To explore the robustness of the results, pre-planned sensitivity analysis of geographical location and exercise method was performed. Upper limits of normal (ULN) were calculated as mean+2SD.

RESULTS

Tables 1–2 and figures 1–3 contain the most important results from the 47 publications included, describing 72 individually

TABLE 1 Haemodynamics at rest (supine)

$\bar{P}_{pa}$ mmHg	14.0±3.3
Systolic P_{pa} mmHg	20.8±4.4
Diastolic P_{pa} mmHg	8.8±3.0
P_{paw} mmHg	8.0±2.9
Heart rate min^{-1}	76±14
Cardiac output L·min^{-1}	7.3±2.3
Cardiac index L·min^{-1}·m^{-2}	4.1±1.3
PVR dyn·s·cm^{-5}	74±30

Data are presented as weighted mean±weighted SD. $\bar{P}_{pa}$: mean pulmonary arterial pressure; P_{pa}: pulmonary arterial pressure; P_{paw}: pulmonary arterial wedge pressure; PVR: pulmonary vascular resistance. n=882 healthy volunteers.

evaluated populations, altogether comprising 1,187 subjects (225 females, 717 males, no sex data for 245 subjects). The short description of all included studies (table A) and further haemodynamic analysis (tables B–K) are provided in the online data supplement.

Mean and systolic pulmonary arterial pressure at rest: upper limit of normal

$\bar{P}_{pa}$ and the most important haemodynamic variables at rest are shown in table 1. Data from the upright measurements and exercise data from all studies are shown in the online data supplement (tables B and C).

Based on the reviewed studies, resting $\bar{P}_{pa}$ is 14.0±3.3 mmHg in the supine (based on data from 882 subjects) and 13.6±3.1 mmHg in the upright position (n=301) (fig. 1). Consequently, the ULN would be 20.6 mmHg in the supine and 19.8 mmHg in the upright position.

The corresponding resting systolic pulmonary arterial pressure is 20.8±4.4 mmHg in the supine (n=625, ULN 29.6 mmHg), and 20.9±4.4 mmHg in the upright position (n=241, ULN 29.7 mmHg).

Pulmonary arterial pressure during exercise

As a response to exercise, $\bar{P}_{pa}$, heart rate and cardiac output increased. As the studies used different exercise protocols, $\bar{P}_{pa}$ during exercise was evaluated by analysing those studies in which the subjects were examined at rest and at least two different exercise levels [10, 26, 32, 47, 52, 53, 55]. According to these studies, $\bar{P}_{pa}$ increase during exercise corresponded to the increase in cardiac output (fig. 2).

TABLE 2 Haemodynamics during upright exercise

	Rest	Slight	Maximal
$\bar{P}_{pa}$ mmHg	13.8±3.1	20.8±4.0	25.6±5.6
P_{paw} mmHg	5.9±2.8	9.1±4.2	14.9±7.9
Heart rate min^{-1}	82±16	103±14	170±14
Cardiac output L·min^{-1}	7.4±2.2	14.9±3.9	20.0±3.8

Data are presented as weighted mean±weighted SD. $\bar{P}_{pa}$: mean pulmonary arterial pressure; P_{paw}: pulmonary arterial wedge pressure. n=193 healthy volunteers.

Based on this group of patients, the ULN of $\bar{P}_{pa}$ in the upright position was 28.8 mmHg during slight and 36.8 mmHg during maximal exercise (table 2). In studies where individual values were available, a total of 20 out of 97 (21%) subjects (aged <50 yrs) reached $\bar{P}_{pa}$ values >30 mmHg during maximal exercise.

The influence of age on $\bar{P}_{pa}$ at rest and during exercise

Several studies have addressed the effect of age on pulmonary arterial pressure during rest and exercise by comparing different age groups (<30 yrs, 30–50 yrs, >50 yrs) (fig. 3) [42, 48, 50].

Although the differences were small at rest, $\bar{P}_{pa}$ was significantly higher in subjects aged ⩾50 yrs compared with younger subjects ($p<0.001$). The mean values were 14.7±4.0 mmHg, 12.9±3.0 mmHg and 12.8±3.1 mmHg in subjects aged ⩾50 yrs, 30–50 yrs and <30 yrs, respectively. There was no significant difference ($p=0.64$) between the <30-yr-old and 30–50-yr-old age-groups.

During slight exercise, $\bar{P}_{pa}$ was significantly higher in subjects aged ⩾50 yrs compared with younger subjects ($p<0.001$). The mean values were 29.4±8.4 mmHg, 20.0±4.7 mmHg and 18.2±5.1mmHg in subjects aged ⩾50 yrs, 30–50 yrs and <30 yrs, respectively (fig. 3) The combined $\bar{P}_{pa}$ of the <30-yr-old and 30–50-yr-old age-groups was 19.4±4.8mmHg, so the ULN for $\bar{P}_{pa}$ in individuals aged <50 yrs would be 29.0 mmHg, while in subjects aged ⩾50 yrs it would be 46.2 mmHg. As only a few subjects aged ⩾50 yrs were examined at higher exercise levels, reliable statistical analysis was not possible.

Pulmonary arterial wedge pressure, cardiac output and pulmonary vascular resistance

Although the primary objective of this study was pulmonary arterial pressure, other haemodynamic parameters were also

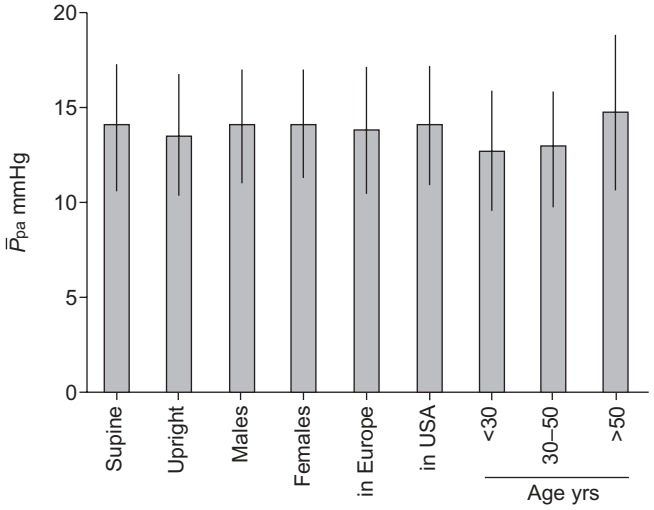

FIGURE 1. Mean pulmonary arterial pressure ($\bar{P}_{pa}$) of healthy subjects at rest according to different strata. Data are presented as mean±SD.

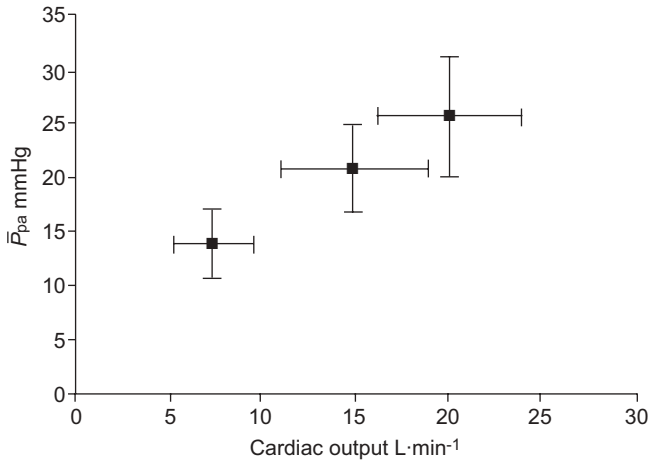

FIGURE 2. Mean pulmonary arterial pressure ($\bar{P}_{pa}$) and cardiac output in healthy subjects at rest, slight exercise and maximal exercise in an upright position. Data are presented as mean±SD. n=193.

reviewed. Resting pulmonary arterial wedge pressure (P_{paw}) was independent of age (7.7±3.0 mmHg for individuals aged ⩾50 yrs *versus* 8.0±2.8 mmHg for subjects aged <50 yrs; p=0.61), but similarly to $\bar{P}_{pa}$, P_{paw} showed an age dependency during exercise, when individuals younger (10.9±3.9 mmHg at supine slight exercise) and older than 50 yrs (16.8±6.5 mmHg with supine slight exercise) were compared (p<0.001) (online data supplement, tables E and F). Data on cardiac output and pulmonary vascular resistance were not always available and might not follow a Gaussian distribution. The mean±SD values given in table 1 should be interpreted with caution.

Influence of sex, geographical origin, exercise method and position on $\bar{P}_{pa}$

Sex and the geographical origin of the data did not significantly influence resting and exercise $\bar{P}_{pa}$ values (online data supplement, tables G–I) [13, 14, 16, 18, 19, 29, 35, 39, 43, 47].

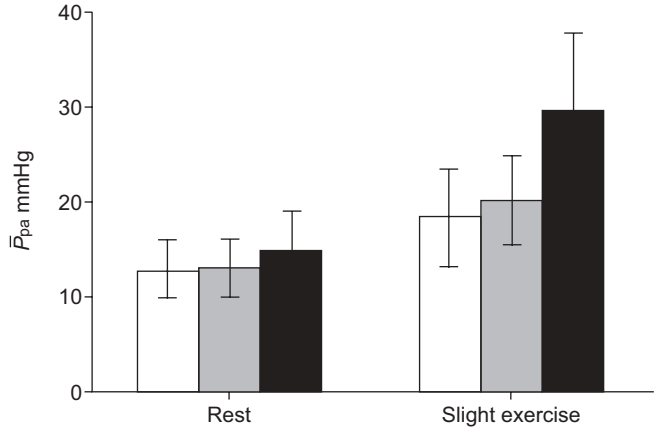

FIGURE 3. Mean pulmonary arterial pressure ($\bar{P}_{pa}$) during rest and slight supine exercise in healthy subjects aged 18–30 yrs (□; n=144), 30–50 yrs (■; n=169) and ⩾50 yrs (■; n=91). Data are presented as mean±SD.

The type of exercise influenced the results. Measured on the treadmill, [26, 32, 46, 55] $\bar{P}_{pa}$ at rest (14.2±4.2 mmHg) and at slight exercise (19.8±4.9 mmHg) was similar to cycle ergometry data, while during submaximal and maximal exercise $\bar{P}_{pa}$ was about 8–13% higher on the treadmill (27.3±6.7 mmHg at maximal exercise resulting in an ULN of 40.7 mmHg; n=41), than on the cycle ergometer (24.0±6.4 mmHg supine and 25.2±5.1 mmHg upright).

Haemodynamic differences observed between the supine and upright position at rest and during exercise showed slightly decreased $\bar{P}_{pa}$ and cardiac output and increased heart rate values in the upright compared with the supine position and were in agreement with previous reports (online data supplement, table J) [59].

DISCUSSION

We reviewed a substantial body of available data on pulmonary pressure values during rest and different levels of exercise in healthy volunteers. Only haemodynamic data obtained from right heart catheterisations were considered. With 1,187 included individuals, this is to our knowledge the largest survey to date of right heart catheterisation data in healthy individuals.

We stratified data for the most important factors, such as level of exercise, posture, sex, age, and geographical origin.

Resting $\bar{P}_{pa}$

Resting $\bar{P}_{pa}$ is virtually independent of sex and geographical origin and is influenced slightly by age and posture. If a definition of mean+2SD is accepted for the ULN, the ULN for resting $\bar{P}_{pa}$ is 20.6 mmHg (20.2 mmHg in individuals aged <50 yrs). Historically, the threshold for PAH was defined as 25 mmHg [60] and this value has been used in the current guidelines. In view of the results of the present analysis, it should be considered that the optimal threshold distinguishing between normal and elevated resting $\bar{P}_{pa}$ may be considerably lower. A $\bar{P}_{pa}$ of 20–25 mmHg may represent clinically relevant pulmonary hypertension. In fact, even values above the 1SD limit (17.3 mmHg) may have prognostic relevance as suggested by studies on patients with chronic obstructive pulmonary disease and lung fibrosis, where patients with $\bar{P}_{pa}$ >17–18 mmHg had an unfavourable prognosis [6–8]. Until now, patients with a $\bar{P}_{pa}$ <25 mmHg were excluded from randomised controlled trials for PAH. Consequently, we do not know whether patients with $\bar{P}_{pa}$ values of 20–25 mmHg would benefit from targeted PAH therapies.

Factors influencing $\bar{P}_{pa}$ during exercise

$\bar{P}_{pa}$ during exercise is affected by workload. According to studies in which subjects were examined at multiple exercise levels (table 2), the increase in $\bar{P}_{pa}$ was comparable from rest to slight exercise and from slight to maximal exercise, and showed a linear relation to the increase in cardiac output. $\bar{P}_{pa}$ values during lower exercise levels almost always remained <30 mmHg (in subjects aged <50 yrs), but 21% of the examined healthy individuals (aged <50 yrs) surpassed the present threshold for PAH (*i.e.* 30 mmHg) during maximal exercise.

Age substantially influences $\bar{P}_{pa}$ values. At rest, the difference between age-groups is negligible. During slight exercise, differences become substantial, and the $\bar{P}_{pa}$ in subjects aged >50 yrs exceed the 30 mmHg threshold in ~47% of all cases.

Consequently, it may not be possible to define a single upper limit of normal $\bar{P}_{pa}$ that fits all individuals and all exercise levels, and so it may be difficult to incorporate exercise haemodynamics in the haemodynamic definition of PH.

Definition of normal ranges for $\bar{P}_{pa}$

With the assumption that the values follow a Gaussian distribution, it seems quite unlikely that a healthy individual aged <50 yrs would surpass the 25 mmHg $\bar{P}_{pa}$ threshold at rest (one person in 5,000), while this can be expected in 1 in 250 healthy subjects aged ⩾50 yrs (online data supplement, table K). However, even in young individuals, a rate of 0.0002 would translate into a prevalence of 200 per million, and would thus by far exceed current estimates of PAH prevalence (15–52 per million) [61, 62]. On the other hand, resting $\bar{P}_{pa}$ values >17 mmHg may indicate pathological conditions [6, 7]. This highlights the importance of clinical assessment as compared with focusing on haemodynamics only. Further prospective studies will be necessary to justify certain pulmonary arterial pressure thresholds for the definition of PH.

The data of this review do not support the current threshold of $\bar{P}_{pa}$ during exercise. According to the reviewed data, nearly half of subjects aged ⩾50 yrs are expected to develop a $\bar{P}_{pa}$ >30 mmHg during slight exercise and about 20% of subjects aged <50 yrs are expected to exceed this value during maximal exercise (online data supplement, table K).

Study limitations

There are certain limitations to this analysis. Despite our effort to review all relevant studies, some published data may have been missed. The interpretation of the results of almost 1,200 subjects examined by right heart catheterisation under controlled conditions should nonetheless allow robust conclusions.

Although studies from three continents (Europe, North America and South America) were included, the population of a large part of the world was not represented. In addition, only studies conducted at sea level with normal oxygen tension were analysed.

There may be an overrepresentation of well-trained subjects due to recruitment bias; however, there was no indication that fitness level has an impact on $\bar{P}_{pa}$. One study examined this question, by applying the same protocol to trained and untrained individuals [49]. It showed differences in heart rate and cardiac output, but not in $\bar{P}_{pa}$ values between the groups, either at rest or during exercise.

Our data originate from normal-weight populations. These results may not apply to overweight subjects [63, 64].

In most studies, the zero level was set either 10 cm above the table level or 5 cm below the level of the sternum. A few studies used the mid-thoracic line for levelling. This might have altered the results slightly.

We accepted the statements in the reviewed studies that the volunteers were healthy, or that their diseases did not influence pulmonary haemodynamics, yet we cannot exclude the possibility that unidentified diseases influenced pulmonary pressure. Of the 72 study populations, five included some subjects with systemic arterial hypertension. $\bar{P}_{pa}$ values at rest and during exercise derived from these five studies showed no significant difference at rest or during exercise compared to those originating from studies excluding all subjects with systemic hypertension. Nevertheless we cannot be sure whether the high $\bar{P}_{pa}$ values during exercise in patients aged ⩾50 yrs might have been related partly to underlying diastolic dysfunction of the left ventricle.

Conclusion

The data from a large number of right heart catheterisations in healthy individuals suggest a normal mean pulmonary arterial pressure of 14.0 ± 3.3 mmHg at rest and an age-dependent increase during exercise that may exceed 30 mmHg, particularly in subjects aged ⩾50 yrs.

STATEMENT OF INTEREST

None declared.

ACKNOWLEDGEMENTS

J. Widimsky (Prague, Czech Republic) kindly provided the summary of a retrospective multicentre WHO study for the authors. We would like to thank E. Lamont (Dept of Pathology, Medical University of Graz, Graz, Austria) for careful linguistic revision of the manuscript.

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