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Does mean arterial blood pressure scale with body mass in mammals? – effects of measurement of blood pressure

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Short title: arterial pressure scaling

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Abstract

For at least the last 30 years it has been discussed whether mean arterial blood pressure (MAP) is independent of body mass or whether it increases in accordance with the vertical height between the heart and the brain. The debate has centered on the most appropriate mathematical models for analysing allometric scaling and phylogenetic relationships, there has been preciously little focus on evaluating the validity of underlying physiological data. Currently, the two most comprehensive scaling analyses are based on data from 47 species of mammals, based on 114 references. We reviewed all available references to determine under which physiological conditions MAP had been recorded. In 44 (38.6 %) of the cited references MAP was measured in anaesthetized animals. Data from conscious animals were reported in 59 (51.8%) of references, of these 3 (2.6 %) were radiotelemetric studies. In 5 species, data were reported from both anaesthetized and conscious animals, the mean difference in MAP between these settings was 20 ± 29 mmHg. From a literature search we identified MAP measurements performed by radiotelemetry in 11 of the 47 species included in the meta-analyses. A Bland-Altman analysis showed a bias of 1 mmHg with 95% confidence interval (from -35 to 36 mmHg); i.e. the limits of agreement between radiotelemetric studies and studies in restrained animals was double the supposed difference in MAP between the mouse and elephant. In conclusion, the existing literature does not provide evidence for either a positive or neutral scaling of arterial pressure to body mass across taxa.

Introduction

For the past decades it has been discussed whether mean arterial pressure (MAP) of mammals remains constant or scales positively with body mass (BM). A plethora of comparative studies show that cardiac output (Q) scales proportional to the higher mass-specific metabolism of small animals by virtue of increased heart rate (f_H), whilst stroke volume (Vs) constitutes a constant proportion of body mass [1, 2]. Most authors note that MAP is unaffected by body mass [1, 3-8], such that peripheral vascular resistance decreases proportionally to mass-specific metabolism. Others have argued that MAP does indeed increase with body mass in mammals, albeit with a substantially smaller scaling exponent than f_H (e.g. [2]). It was suggested that the rise in MAP was proportional to the increased vertical distance between the heart and the upper extremeities, such that the scaling effect on MAP could be attributed to the extra work imposed on the heart by gravity [9]. However, the analysis underlying this argument have been critized on mathematical grounds by others [10]. The most recent phylogenetic analysis of MAP is based on data from 47 species of mammals with body mass spanning from 12 g to 4 tons [9]. In support for this view, giraffes clearly rely on a very high MAP to maintain normal cerebral perfusion pressures [11, 12], tall humans appear to have higher MAP than shorter individuals [13], and MAP increases with body length in snakes [14, 15].

Allometric studies build on regression analyses of data pooled from many studies, and any conclusions reached are crucially dependent on the quality of measurements. While much debate has been devoted to discuss the most appropriate mathematical models to analyse allometric scaling, there has been disappointingly little focus on quality of the underlying physiological data. The influence of confinement, disturbance, (post-)operational stress as well as anaesthesia and analgesia, remains important to consider. The *American Heart Association* (AHA) has emphasised

that measurements of blood pressure should be performed "over prolonged periods of time in conscious, unrestrained, unstressed animals" [16]. Obviously, concerns regarding the influence of stress and anaesthesia are particularly pertinent for meta-analyses, where data are being compiled from many different studies to infer general physiological patterns across and between taxa.

In an attempt to provide insight into the intriguing question of allometric scaling of arterial blood pressure, we reviewed the underlying biological data, rather than the mathematical models that laid the foundation for the differing views on allometric scaling of MAP. Furthermore, we conducted a litterature search to identify telemetric blood pressure recordings on as many mammal species as possible. Data from this search was then examined against data from anaesthetized or physically restrained animals. The goal of the present study is to critically examine the physiological conditions during measurements, and to discuss how these conditions may have influenced results.

Data selection

All references from the two most exhaustive and comprehensive meta-analyses [2, 9] were obtained through Pubmed, Google or ordered through the Library at Aarhus University. To our knowledge no other extensive meta-analysis of arterial blood pressure scaling have been published since 2014. Each article was carefully reviewed, and the methods used for blood pressure measurement were recorded and allocated in three overall categories: i) telemetry, ii) invasive (i.e. intravascular) or iii) non-invasive (i.e. tail cuff or Doppler). Thereafter, we subdivided the studies into three categories identifying whether animals were freely moving, physically restrained or anesthetized during measurements. For all anaesthtized animals the anaesthetic protocol was recorded. Please confer Figure 1 for an overview of how references were categorised. Furtheremore a litterature seach was conducted in order to identify radiotelemetric recordings of arterial pressure in freely moving

animals beloning to the different species included in the two meta-analyses. We searched MEDLINE via PubMed to identify studies for all of the 47 species.

Data analysis

All values are presented as mean ± standard deviation (SD). The agreement between radiotelemetric recordings and data from animals restrained by any means (*i.e.* including physical and chemical restraint) was assessed by a Bland-Altman analysis [17]. Linear regression was used to calculate slopes, and these were considered significantly non-zero when $p < 0.05$.

Results

A total of 47 different species of mammals were included in the two meta-analyses [2, 9], based on a total of 114 references. A complete overview of all 47 species with original references are presented in Table 1.

Data based on multiple references: In 18 species, arterial pressures had been derived from data reported in more than a single study. No information was provided as to how mean values were generated in these instances. This is also the case for the heart rate (HR) and BM values cited in Table 1.

Comparison of data from conscious and anaesthetized animals: Three of the 114 studies (2.6 %) relied on telemetric recordings of MAP (two studies on giraffes, *Giraffa camelopardalis*[1] and one on

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[1] Please note that the Giraffe was not included in the final allometric analyses of blood pressure in the two meta-analyses due to its long neck.

rabbits, *Oryctolagus cuniculus*). In 44 of the studies, MAP was measured in anaesthetized animals using various dosages of different drugs; in six of the studies the anaesthetic regimen was not stated (Table 1). In 56 studies, the measurements were performed in conscious animals. Of the 18 species for which several references were cited, we found 5 species where MAP had been determined in both conscious and anaesthetized animals. The mean difference in MAP between these two experimental settings was 20 ± 29 (i.e. 104 vs 84) mmHg.

Invasive vs non-invasive: In 79 (69.3 %) of the 114 references blood pressure was measured invasively and in 22 (19.3 %) a non-invasive approach was used. In 4 (3.5 %) of the cited references we were unable to retrieve the relevant information. Finally, in 6 (5.3 %) the articles were deemed irrelevant (i.e. a study performed on Illamas cited under human data, a popular science article with no data, an opinion paper etc.), for overview please cf. Figure 1.

Comparison of results from restrained and freely moving animals: From our own literature search on MEDLINE, we identified radiotelemetric MAP measurements in 11 of the 47 species included in the two meta-analyses [18-27]. For the remaining 36 species we were unable to find similar measures. We compared data on these 11 species with data from the same species (as listed in the meta-analyses) using a Bland-Altman analysis (Figure 2a). This showed a systematic bias of 1 mmHg with 95% Limits of Agreement ranging from -35 to 36 mmHg between radiotelemetry and data from restrained animals. Furtheremore, in restrained animals, there was a positive correlation between MAP and body mass (slope significantly non-zero, p<0.001. $R^2 = 0.292$), but there was no such relationship for telemetry-based MAP measurements (p=0.936. $R^2 = 0.001$) (Figure 2c).

Effects of animal size on methods of restrain during measurements: To examine whether there was a systematic bias in the method of restrain between large (BM > 100 kg) and smaller (BM < 100 kg) animals we examined how frequently chemical vs. physical restrain was used in these two groups. We found no statistically significant difference in the frequence with which chemical restrain was used in large vs. small animals (50 vs 48 %, p = n.s.). The same was true for physical restrain (50 vs. 51 %, p = n.s.). Please see Figure 2d for details.

Conclusion and perspectives

For at least 30 years, it has been discussed whether MAP increases with body mass or remains unaffected and hence constant within mammals. Our analysis clearly shows that when data are limited to telemetric measurements performed in unrestrained animals, there is no indication of a positive correlation with body mass. We caution that our findings do not necessarily refute that MAP may indeed increase with body mass in mammals, but rather indicates that the quality of the available data does not allow for such a discrimination to be made.

We recognize the difficulties in obtaining good reliable blood pressure measurements in large exotic mammals such as giraffes, elephants and bears, and that standardized conditions are virtually impossible to attain. However, we wish to address a number of issues that may explain the variability of pressure measurements between species.

Impact of anaesthesia: Anaesthesia exerts profound influence of blood pressure due to central inhibition of the barostatic regulation as well as direct vascular effects of the anaesthetics that alter vascular resistances [28]. For example, in white rabbits implanted with telemetric pressure sensors,

MAP of unstressed individuals decreased in a dose-dependent manner from 88 mmHg prior to anaesthesia to 76 mmHg when receiving 2.7% isoflurane[29]. Similarly, Cabrel et al [30] noted that MAP decreased from 144.3 mmHg in conscious to 97.5 mmHg in anaestehtized sloths. Average blood pressure changes following anaesthesia in guinea pigs depends on anaesthetic regimen, such that ketamine decreased MAP by 14 mmHg, whilst fentanyl-citrate increased MAP by 30 mmHg, and fentanyl-droperidol did not cause a significant change (Flynn & Wright, 1988). Likewise, in dogs MAP have been shown to decrase from 163 mmHg prior to induction of anaesthsia to 99 mmHg following isoflurane [31]. A similar decline in systolic pressure has been observed with the use halothane [32]. Not only is the anaesthetic agent important to consider, the choice of induction agent is also of interest. Kojima et al. noted that while induction with medetomidine-midazolam produced "relatively large cardiovasvular changes" during a 120 min anaesethetic period only small changes were observed with midazolam-butorphanol [33]. In five of the species included in the two meta-analyses [2, 9], MAP was measured in both conscious and anaesthetized animals. The mean difference between these two states was 20 ± 29 mmHg. As pointed out by Bie [34], studies on integrative cardiovascular function should be limited to conscious animals due to the plethora of cardiovascular and renal effects of various anaesthetic regimens. A point also raised by the AHA guideline stating that "systemic anaesthesia should be avoided whenever feasible because of the well-documented effects of anaesthetics on cardiovascular function" [16].

Freely moving or restrained: Restraint is likely to cause stress and elevate MAP by increased sympathetic tone. Indeed, restrained macaque monkeys (*Macaca mulatta*) have an elevation of MAP of 27 mmHg compared to when they are allowed to move freely [35]. Our comparison of telemetric measurements performed on unrestrained animals with those obtained on restrained animals show differences ranging from -35 to 36 mmHg with a systematic bias of 1 mmHg (the 95% limits of agreement simply describe the possible error in estimate due to sampling error). In other

words, a blood pressure recording of a restrained mammal will be somewhere within -35 to 36 mmHg of the telemetrically measured MAP. We argue that telemtric measurements are most likely to reflect the biologically relevant MAP. Given that the previous meta-analyses [2, 9] argue for a difference in MAP of roughly 30 mmHg between a 25 g mouse and a 4 tonne elephant, it is clear that influence of restraint easily surpasses this difference, and that the influence of stress can have large consequences on the scaling relationships derived from meta-analyses. It should be noted that if restraint was used more frequently among large animals, this could skew measurements towards an overall increase in large animals. However, this appears not to be the case when we assessed the included data (Figure 2d).

Invasive versus non-invasive measurements: For some species, such as dogs, there is good agreement between invasive and non-invasive techniques for blood pressure measurement [36, 37]. In goats and sheep, reported Bland-Altman 95% limits of agreement are -31 to +31 mmHg, and for large cattle (i.e. weight >150 kg) the limits are -81 to +45 mmHg (Aarnes 2014). In giraffes, oscillometric blood pressure measurements have been reported to give a systematic bias of 27 mmHg for MAP, i.e. a systematic error of more than 10% [38]. In light of such studies it seems pertinent to address the methods used for recording arterial pressure. But, intravascular catheters and conscious animals are not sufficient to guarantee adequate measurements of arterial pressure. Honeyman et al. recorded invasive pressures from the auricular artery in standing conscious elephants, but did not describe any correction for the vertical difference between the heart and auricular artery [39] potentially leading to underestimation of the arterial pressure at heart level. Furthermore, in some of the studies, where invasive pressures were reported, the measurements were not only performed under general anaesthesia, but blood pressures were measured following thoracotomy [40-42], far from a normal physiological state.

Diet: As previously emphasised [43], rodents are traditionally fed at least an order of magnitude more sodium (when normalized to body mass) than other species. MAP of normal Sprague-Dawley rat is salt-sensitive even down to very low levels of sodium intake [44], a phenomenon not present in for instance Wistar rats [45], humans [46, 47] and dogs [48]. The consequence is that when extrapolating data between species the sodium content of the diet provided for the experimental animals should preferrably be similar. This is obviously difficult, but the effects of diet should at least be acknowledged. In the meta-analyses examined in the present paper one of the human references is a case report from a single obese subject undergoing a 34-day long fast to induce weight loss [49]. It is questionable whether data from such an experiment can be incorporated into a meaningful mathematical analysis of normal physiological blood pressure across species.

Scaling of the cardiovascular system: the influence of body size and mass (scaling) among similarly organized animals has been a subject of interest in biology for decades [7, 50]. For instance, the classic work of Kleiber showed that rates of oxygen consumption vary with BM raised to the power of ¾ [51]. So as BM increases, the metabolic rate per gram tissue decreases, which is then supported by a lower capillary density as animals become larger [52]. Blood volume is directly proportional to BM [53]. Heart rate in mammals varies essentially with BM raised to the -1/4 power [54], while stroke volume proves a constant fraction of BM, so cardiac output scales to BM raised to 2/3 [55], while systolic and diastolic pressures are independent of BM [4, 56]. The essential argument here is that blood pressure remains constant across species because the lower mass-specific metabolism in larger animals can be sustained by a lower capillary density resulting in fewer restistance arteries per mass – such that peripheral vascular resistance increases proportionally to the relative decrease in cardiac output. This argument does not consider the shape of the animals, and Seymour and colleagues have logiclly argued that gravity may impose additional demands on MAP [2, 9]. They have therefore suggested that although MAP may not be influenced by BM *per se*, it is reasonable to expect MAP to increase

proportionally to the increased vertical distance between the heart and the upper extremities as animals get larger. We are not contending this view, and it is obvious for example that giraffes require a higher MAP to perfuse the brain [11, 12, 57]. However, as shown in our analysis, the MAP measurements that have been obtained on freely moving and unanaesthetised mammals do not demonstrate that MAP is higher in larger versus small mammals (Figure 2b).

Is a mean value of MAP a mathematical abstraction with little or no physiological meaning? It is common practice, in the clinical as well as in the experimental setting, to summarize long-term blood pressure measurements into a single value. While this approach obviously facilitates comparisons between species or conditions, a single value for MAP should not be regarded as representative for the various behaviours that an animal may display on a daily basis (e.g. eating, sleeping, spontaneous physical activity, mating etc.). This simple point is illustrated in Figure 3 depicting a 24-h blood pressure recording from a small and a large mammal (mouse and human). Blood pressure has a circadian rhythm, which peaks when the animal is awake and nadirs during sleep. As illustrated in Figure 3, the noctural mouse has the highest MAP at night, whereas humans nadir during nightime. Ideally daytime values for diurnal mammals should be compared to night-time values for nocturnal animals. However, the circadian blood pressure rhythm can be affected by a plethora of factors, including physical activity, autonomic function and salt intake (for reviews cf., [58-60] all of which potentially complicates interspecies comparison of a single MAP value.

In conclusion, the existing literature does not provide evidence to distinguish between a positive or neutral scaling of MAP in relation to body mass amongst mammals. We suggest that more focus be directed at obtaining high quality measurements to lay the foundation for fertile discussions on allometric scaling of MAP. Furthermore, we argue that the use of a single value for MAP in a given

species ignores the tremendous biological variation that is present both within individual animals and within each species.

Conflict of interest

None declared.

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Table 1: Overview of the various anaesthetic regimes used in the cited studies. All species are listed in alphabetical order and according to latin names. Doses stated are intravenous unless stated otherwise. All reported values are cited from [2, 9], for those where no values were reported, we sought the original references to obtain values. All species included in figure 2 are marked with bold. Abbreviations: mean artterial pressure (MAP); body mass (BM); heart rate (HR); number of animals studied in the cited reference (n); intra muscular (i.m.); intraperitoneal (i.p.); not applicable (n/a); not specified (n.s.). Notes: 1) The authors have not stated any other dosing than 5% w/v; 2) An opinion paper that cites data from various other studies. No information specied as to how data was obtained.; 3) A textbook from 1935 that summarizes what we assume is data from several different studies. No detailed information is given with regard to methods.; 4) A biology data textbook from 1975 that summarizes physiological data from multiple species. No information is provided as to how data was recorded.; 5) Data from a table in a textbook from 1935, from the table it can be read that data was collected under local anaesthesia. No further information is provided except that the

data is unpublished.; 6) We are uncertain as to whether the two papers by van Citters [12, 61] are data from the same two animals or rather separate experiments on different animals.; 7) This is not a scientific paper, but an article from a popular science magazine.; 8) A study not on humans but on llamas.; 9) Data from a single obese subject undergoing a 34-day long fast.; 10) The concentration of the solution is not stated in the article.; 11) This is not a paper, but an abstract from a conference. Only limited information is provided with regards to methods and data. Direct arterial pressure in the unanesthetised rabbit. Am J Physiol. **129**. P448 (abstr)".; 12) Authors used a laboratory rat belonging to the rattus norvegicus species, not rattus rattus.

Tables

Table 1

Animal species	MAP (mmHg)	BM (kg)	HR (bpm)	n	References	Anaesthetic protocol
Acinoyx jubatus	102.30	41.1	112	13	[62]	Telazol (2.63–4.29 mg kg^{-1}, i.m.) and isoflurane
Aepyceros melampus	122	29.6	n/a	44	[63]	A-3080 (20-90 µg kg^{-1}) or carfentanil (27-83 µg kg^{-1})
Arctictis binturong	123.90	20.8	80	34	[64]	Ketamine (8 mg kg^{-1}). medetomidine (0.02 mg kg^{-1}) and butorphanol (0.4 mg kg^{-1}) or ketamine (4 mg kg^{-1}) medetomidine (0.04 mg kg^{-1}) and butorphanol (0.4 mg kg^{-1}). If needed additional drugs were

						administered (not specified in paper).
Bos taurus	130	508	57	12	[65]	Conscious, catheters placed under local anaesthesia (not specified)
				3	[66]	Conscious
Bradypus tridactylus	115	3.73	85	9	[30]	Either conscious or pentobarbital (20 mg kg^{-1})
				13	[67]	Conscious
				8	[68]	Conscious
				10	[40]	Pentobarbital (30 mg kg^{-1})
				7	[69]	Alpha-cloralose (50mg kg^{-1}) or reserpine (0.35 mg kg^{-1}, i.p.)
Camelus bactrianus	145	400	n/s	2	[70]	Xylazine (1.25 mg kg^{-1}) and thimylal (6.25 mg kg^{-1}), followed byhalothane

						(3%) and succinylcholine (800 mg) or gallamine (0.09 mg kg^{-1})
Camelus dromedarius	149.70	369	62	1	[71]	Pentothal sodium (dosing not stated)
				12	[72]	Local followed by pentobarbitone sodium (5% w/v)[1]
				11	[73]	Triflupromazine hydrochloride 2 mg kg^{-1} i.m
				12	[74]	Thiopentone (7.4 +/- 0.33 mg kg^{-1}) and halothane (1-2%)
Canis aureus	126.50	11.0	90	22	[75]	Medetomidine (113 µg kg^{-1}) and ketamine (2 mg kg^{-1}) or medetomidine (88 µg kg^{-1}) and midazolam (0.5 mg kg^{-1}, i.m.)

Canis lupus familiaris	128	19.2	105	5	[76]	Conscious
				10	[77]	Conscious
				5	[41]	Thiopental sodium (0.75 g). morphine (1 mg kg^{-1}) and diphenhydramide (1 mg kg^{-1})
				6	[78]	Conscious
				n/a	[79]	n/a^2
				5	[80]	Conscious
				12	[81]	Conscious
				n.s.	[3]	Data from several references^3; Nembutal or only local anaesthesia.
Canis rufus	113.10	54.4	n.s.	32	[82]	Xylazine (8 mg kg^{-1}) and ketamine (2 mg kg^{-1}) or medetomidine (40 µg kg^{-1})

						and ketamine (2 mg kg^{-1}) or medetomidine (40 µg kg^{-1}), ketamine (2 mg kg^{-1}) and acepromazine (0.01 mg kg^{-1}) or medetomidine (20 µg kg^{-1}), ketamine (2 mg kg^{-1}) and butorphanol (0.2 mg kg^{-1})
Capra hircus	95	31.2	79	n/a	[83]	n/a[4]
Cavia porcellus	61.90	0.52	273	10	[84]	Conscious
				6	[85]	Diazepam (dosing not stated) and fentanyl (dosing not stated)
				24	[86]	Conscious
				20	[87]	Conscious
Ceratotherium dimum	124	2495	39	12	[88]	Conscious

Cevus canadensis	100	275	83	8	[89]	Conscious, physically retrained in squeeze box
Elephas maximus	138	2960	40	8	[39]	Conscious
Equus caballus	127	422	47	117	[90]	Conscious
				6	[91]	Conscious
					[92]	Conscious
				12	[93]	Propiopromazine 50 mg (semi conscious)
				21	[94]	Not clearly stated
				6	[3]	Local anaesthesia[5]
				3	[66]	Conscious
Felis silvestris	124	3.03	179	27	[95]	Medetomidine (0.1 mg kg^{-1}), O$_2$/N$_2$O (40%/60%) and pentobarbital (7 mg kg$^-$

domesticus						^{1} h^{-1})
				20	[40]	Pentobarbital (30mg kg^{-1})
				3	[96]	Conscious
				17	[97]	Urethane (300 mg kg^{-1}) and alpha-chloralose (30 mg kg^{-1})
Leptailurus serval	101.10	13.7	85	7	[98]	Medetomidine (47 µg kg^{-1}), ketamine (1 mg kg^{-1}) and butorphanol (0.2 mg kg^{-1})
Gazella dama	120	48	n/s	16	[99]	Carfentanil citrate (18 µg kg^{-1})
Giraffa camelopardalis	214	651	102	4	[100]	Conscious
				2	[12]	Conscious
				2	[61]	Conscious[6]

				n/a	[101]	n/a[7]
Gorilla gorilla	n/s	83.5	n/s	5	[102]	Phencyclidine (1 mg kg^{-1}), promazine (1 mg kg^{-1}) and ketamine (0.5-1.0 mg kg^{-1} or 1-2 mg kg^{-1} i.m.). 4 of 5 animals also received atropine (0.01 mg kg^{-1})
Homo sapiens	93	68.8	70	n/a	[103]	n/a[8]
				22	[104]	Conscious
				65	[105]	Conscious
				1	[49]	Conscious[9]
				11	[106]	Conscious
				18	[107]	Conscious

Species					Ref	Condition
				n/a	[79]	n/a[2]
				9	[108]	Conscious
Lama glama	132	108	58	3	[103]	Conscious
				5	[109]	Conscious
				5	[110]	Xylazine (0.25 mg kg^{-1}), ketamine (2.5 mg kg^{-1}) and halothane (dose variable, range not specified)
Loxodonta africana	154	4080	40	7	[39]	Conscious
				1	[111]	Etorphine (0.0017 mg kg^{-1}), azaperone (0.06 mg kg^{-1}) and isoflurane
Macaca fascicularis	90	4.6	175	21	[112]	Ketamine (15 mg kg^{-1})
				6	[113]	Conscious

Macaca mulatta	82	4.24	154	14	[35]	Conscious, physically restrained
				13	[114]	Conscious, physically restrained
				14	[115]	Conscious
				4	[116]	Conscious, physically restrained
Macropus robustus	93.30	30.3	90	1	[117]	Dial-urethane-Nembutal (0.75 ml kg^{-1})[10]
Marmota flaviventris	133.40	4	149	9	[118]	Conscious or pentobarbital (40 mg kg^{-1})
Martes pennanti	96	3.95	n/s	13	[119]	Medetomidine (0.4 mg) and ketamine (20 mg) or ketamine (100 mg)
Mesocricetus auratus	101.90	0.12	n/s	Approx100 0	[120]	Hypothermia induced hibernation (cooled to a core body temperature of 5°C)
Mus musculus	111	0.03	580	8	[121]	Consicous (4 hours after recovery after

						recovery from surgery)
				8	[122]	Conscious
				21	[123]	Ketamine (40 mg kg^{-1}, i.p.) and pentobarbital sodium (33 mg kg^{-1}, i.p.)
				12	[4]	Urethane or ether (dosing not stated)
Mustela eversmanni		0.971	n/s	24	[124]	Sevoflurane or isoflurane
Mustela putoris furo	91.20	1.35	274	7	[42]	Sevoflurane
Odocoileus virginianus	101	52	53	11	[125]	Yxlazine (6 mg kg^{-1}, i.m.) and ketamine (7 mg kg^{-1}, i.m.)
Oryctolagus cuniculus	77	2.51	251	6	[126]	Pentobarbitone (30 mg kg^{-1})
				16	[127]	Ketamine (40 mg kg^{-1} bolus, followed by constant infusion)

				18	[128]	Conscious
				23	[29]	Conscious
				46	[129]	Alpha-chloralose (50 mg kg^{-1}) and urethane (500 mg kg^{-1})
				n/a	[130]	n/a[11]
				6	[131]	Not clearly stated in article
Ovis aries	104	47.5	126	4	[132]	Conscious
				8	[133]	Conscious
				13	[3]	Local anaesthesia[5]
				13	[134]	Conscious
Pan troglodytes	96.70	55	n/s	26	[135]	Ketamine (10-15 mg kg^{-1}, i.m.) and diazepam (0.2 mg kg^{-1})

Pelea capreolus		19.4	n/s	12	[136]	Xylazine (0.4 mg kg^{-1}) and either carfetanil (0.01 mg kg^{-1}) or etorphine (0.01 mg kg^{-1})
Phoca vitulina	120	60.3	98	5	[137]	Local anaesthesia
Rattus norvegicus	103.70	0.23	n/s	350	[138]	Pentobarbital sodium (4.5 mg 0.1 kg^{-1})
Rattus rattus	111	0.34	340	13	[139]	Conscious[12]
				6	[140]	Conscious[12]
				10	[141]	Pentobarbital (50 mg kg^{-1}, i.p.)[12]
				25	[142]	Conscious[12]
				46	[143]	Urethane (2.5 - 3 ml 50% kg^{-1}, i.p.)[12]
				14	[144]	Not clearly stated[12]
				n/a	[79]	n/a[2]

				10	[145]	Inactin (120 mg kg^{-1}, i.p.)[12]
				8	[146]	Conscious[12]
Suncus murinus	98.20	0.046	n/s	n.s.	[147]	Urethane (1g kg^{-1}, i.p.)
Sus scrofa	84	102	84	14	[3]	n/a[3]
				Not stated	[83]	Unknown[4]
				18	[148]	Ketamine (20 mg kg^{-1}), atropine (0.02 mg kg^{-1}) and pentobarbital (20 mg kg^{-1})
				4	[149]	Azaperone and halothane followed by chloralose infusion
Tragulus javanicus	99	1.18	n/s	3	[150]	Sodium pentothal (25 mg kg^{-1})

Tursiops truncatus	134	93.1	n/s	4	[151]	Nitrix-oxide
Ursus arctos horribilis	88	58.8	103	6	[152]	Tiletamine and zolazepam (2 or 5 mg kg^{-1})
Ursus maritimus	145.30	145	n/s	11	[153]	Multiple different anaesthetic regimens, please see paper for details.

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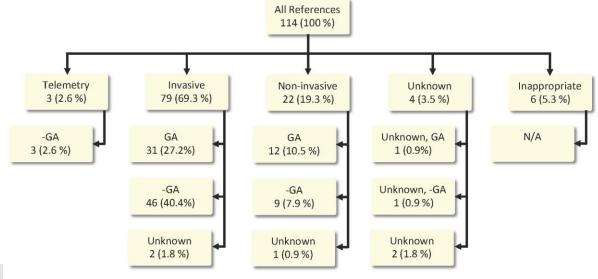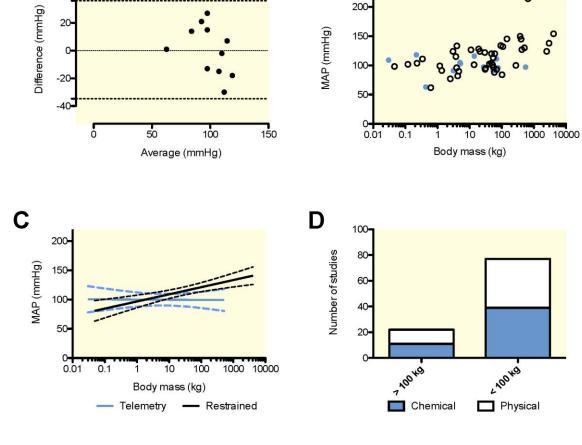**Legends**:

Figure 1: Diagram showing the distribution of references grouped according to the methods used to record blood pressure; and secondly whether or not anesthesia was used. *Telemetry*; radiotelemetry in freely moving animals. *Invasive*; invasive measurements performed in an artery in restrained animals. *Non-invasive*; measurements performed using tail-cuff or Doppler. *Unknown*; method or anesthesia regimen not clearly stated. *Inappropriat*; in our opinion an irrelevant paper. *GA*; general anesthesia. *–GA*; without general anesthesia. *N/A*; not applicable.

Figure 2: Differences in measurements of mean arterial blood pressure (MAP) in the same species in either consicous freely moving animals (telemetry) and during restraint (physical or chemical i.e. anaesthesia). **A**) Bland-Altman analysis showing the difference as a function of the average of measurements in the same species for freely moving or restarined animals. Dotted lines indicate the 95% limits of confidence (-35 and 36 mmHg, respectively). Only species for which data is available for both experimental settings are included. **B)** Semi-logarithmic plot showing MAP as a function of body mass in freely moving animals (blue circles) and restrained animals (black open circles). **C)** Semi-logarithmic plot showing MAP as a function of body mass obtained in freely moving animals (blue line) or during restrained (black line). Please note that for restarined animals there is a significant increase in pressure with body mass (slope significantly non-zero, p<0.001. R^2 = 0.292), whereas for the freely moving animals this is not the case (slope not significantly difference from zero, p=0.936. R^2 = 0.001). Dotted lines indicate 95% limits of confidence. D) Effects of animal seize on methods of restrain during measurements. To examine if there was a systematic bias in the method of restrain between large (BM > 100 kg) and small (BM < 100 kg) animals we examined how frequently chemical vs. physical restrain was used in these two groups. Chemical restrain was used in 11 of 22 studies on large animals (50 %) and in 39 of 78 studies on small animals (51%). Physical

restrain was used in 11 of 22 studies on large animals (50%), and in 38 of 77 studies on small animals (49%).

Figure 3: 24-hour blood pressure recordings. **A)** Oscillometric ambulatory blood pressure recordings from a young healthy man. Shaded black area indicates the night time when the subject was asleep. Please note the nocturnal dipping of arterial pressure that occurs during sleep. **B)** Telemetric blood pressure recording from a mouse. The shaded black area indicates the nocturnal period where the animal is most active and thus has a higher blood pressure.

A

B

C

D