



Hypertension

Manuscript Submission and Peer Review System

Disclaimer: The manuscript and its contents are confidential, intended for journal review purposes only, and not to be further disclosed.

URL: <http://hype-submit.aha-journals.org>

Title: Identifying isolated systolic hypertension from upper arm cuff blood pressure compared with invasive measurements

Manuscript number: HYPE/2020/16109

Author(s): James Sharman, University of Tasmania

Dean Picone, University of Tasmania

Martin Schultz, University of Tasmania

Matthew Armstrong, University of Tasmania

J. Andrew Black, Royal Hobart Hospital

Willem Jan Bos, St Antonius Hospital, Nieuwegein

Chen-Huan Chen, Taipei Veterans General Hospital

Hao-Min Cheng, Taipei Veterans General Hospital

Antoine Cremer, University Hospital of Bordeaux, Hôpital St André

Nathan Dwyer, Royal Hobart Hospital

Alun Hughes, University College London

Hack-Lyoung Kim, Boramae Medical Center

Peter Lacy, University College London and the National Institute for
Health Research University College London Hospitals Biomedical
Research Centre, Institute of Cardiovascular Science, London, WC1E 6BT, UK

Esben Laugesen, Aarhus University Hospital

Fuyou Liang, Shanghai Jiao Tong University and Chiba University

International Cooperative Research Centre

Nobuyuki Ohte, Nagoya City University Graduate School of Medical Science

Sho Okada, Chiba University Graduate School of Medicine

Stefano Omboni, Italian Institute of Telemedicine

Christian Ott, University of Erlangen-Nuremberg

Telmo Pereira, Polytechnic Institute of Coimbra, ESTES

Giacomo Pucci, University of Perugia

Roland Schmieder, Friedrich-Alexander-University Erlangen-Nuernberg

Manish Sinha, Guys & St Thomas's NHS Foundation Trust

George Stouffer, University of North Carolina

Kenji Takazawa, Shinanozaka clinic

Philip Roberts-Thomson, University of Tasmania

Ji-Guang Wang, The Shanghai Institute of Hypertension

Thomas Weber, Klinikum Wels-Grieskirchen

Berend Westerhof, University of Twente

Bryan Williams, University College London

1 **Identifying isolated systolic hypertension from upper arm cuff blood pressure**
2 **compared with invasive measurements**

3
4 Dean S. Picone, PhD¹, Martin G. Schultz, PhD¹, Matthew K. Armstrong, BSc(Hons)¹, J.
5 Andrew Black, MBBS(Hons)^{1,2}, Willem J. Bos, MD, PhD^{3,4}, Chen-Huan Chen, MD⁵, Hao-
6 Min Cheng, MD, PhD⁵, Antoine Cremer, MD⁶, Nathan Dwyer, MBBS, PhD^{1,2}, Alun D.
7 Hughes, MBBS, PhD⁷, Hack-Lyoung Kim, MD, PhD⁸, Peter S. Lacy, PhD⁹, Esben Laugesen,
8 MD, PhD¹⁰, Fuyou Liang,¹¹ Nobuyuki Ohte, MD, PhD¹², Sho Okada, MD, PhD¹³, Stefano
9 Omboni, MD^{14,15}, Christian Ott¹⁶, Telmo Pereira, PhD¹⁷, Giacomo Pucci, MD¹⁸, Roland E.
10 Schmieder, MD¹⁶, Manish D. Sinha, PhD¹⁹, George A. Stouffer, MD²⁰, Kenji Takazawa²¹,
11 Philip Roberts-Thomson,^{1,2} Jiguang Wang, MD, PhD²², Thomas Weber, MD²³, Berend E.
12 Westerhof, PhD²⁴, Bryan Williams, MD^{7,9}, James E. Sharman, PhD^{1,2} for the InvaSive blood
13 PressurE ConsortIum

14 ¹Menzies Institute for Medical Research, University of Tasmania, Hobart, Australia

15 ²Royal Hobart Hospital, Hobart, Tasmania

16 ³St Antonius Hospital, Department of Internal Medicine, Nieuwegein, The Netherlands

17 ⁴Department of Internal Medicine, Leiden University Medical Center, Leiden, The
18 Netherlands

19 ⁵Department of Medicine, National Yang-Ming University School of Medicine, Department
20 of Medical Education, Taipei Veterans General Hospital, Taipei, Taiwan

21 ⁶Department of Cardiology/Hypertension, University Hospital of Bordeaux, Bordeaux,
22 France

23 ⁷Institute of Cardiovascular Sciences, University College London, London, United Kingdom

24 ⁸Division of Cardiology, Seoul National University Boramae Hospital, Seoul, South Korea

25 ⁹Institute of Cardiovascular Sciences University College London (UCL) and National
26 Institute for Health Research (NIHR) UCL/UCL Hospitals Biomedical Research Centre,
27 London, United Kingdom

28 ¹⁰Department of Endocrinology and Internal Medicine, Aarhus University Hospital, Aarhus,
29 Denmark

30 ¹¹School of Naval Architecture, Ocean and Civil Engineering, Shanghai Jiao Tong University,
31 Shanghai, China

32 ¹²Department of Cardio-Renal Medicine and Hypertension, Nagoya City University Graduate
33 School of Medical Sciences, Nagoya, Japan

34 ¹³Department of Cardiovascular Medicine, Chiba University Graduate School of Medicine,
35 Chiba, Japan

36 ¹⁴Clinical Research Unit, Italian Institute of Telemedicine, Varese, Italy

37 ¹⁵Scientific Research Department of Cardiology, Science and Technology Park for
38 Biomedicine, Sechenov First Moscow State Medical University, Moscow, Russian
39 Federation

40 ¹⁶Department of Nephrology and Hypertension, University Hospital Erlangen, Friedrich-
41 Alexander University Erlangen-Nürnberg, Erlangen, Germany

42 ¹⁷Polytechnic Institute of Coimbra, ESTES, Department of Physiology, General Humberto
43 Delgado Street 102, Lousã, Portugal

44 ¹⁸Unit of Internal Medicine at Terni University Hospital, Department of Medicine, University
45 of Perugia, Perugia, Italy

46 ¹⁹Department of Clinical Pharmacology and Department of Paediatric Nephrology, Kings
47 College London, Evelina London Children's Hospital, Guy's and St. Thomas' NHS
48 Foundation Trust, London, United Kingdom

49 ²⁰Division of Cardiology, University of North Carolina at Chapel Hill, Chapel Hill,

50 North Carolina

51 ²¹Center for Health Surveillance and Preventive Medicine, Tokyo Medical University

52 Hospital, Tokyo, Japan

53 ²²Centre for Epidemiological Studies and Clinical Trials, Shanghai Key Laboratory of

54 Hypertension, The Shanghai Institute of Hypertension, Department of Hypertension, Ruijin

55 Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China

56 ²³Cardiology Department, Klinikum Wels-Grieskirchen, Wels, Austria

57 ²⁴Cardiovascular and Respiratory Physiology, Faculty of Science and Technology, Technical

58 Medical Centre, University of Twente, Enschede, The Netherlands

59

60 **Running title:** Measuring ISH from cuff and invasive BP

61 **Word count:** 5619

62

63 **Address for correspondence:**

64 Professor James E. Sharman

65 Menzies Institute for Medical Research

66 University of Tasmania

67 Private Bag 23

68 Hobart, 7000 Australia

69 Telephone: +61 3 6226 4709

70 Fax: +61 3 6226 7704

71 Email: James.Sharman@utas.edu.au

72

73

74

Abstract

75
76 Isolated systolic hypertension (ISH) is the most common form of hypertension and is highly
77 prevalent in older people. We recently showed differences between upper-arm cuff and
78 invasive blood pressure (BP) become greater with increasing age, which could influence
79 correct identification of ISH. This study sought to determine the difference between
80 identification of ISH by cuff BP compared with invasive BP. Cuff BP and invasive aortic BP
81 were measured in 1695 subjects (median 64 years, interquartile range [55 to 72], 68% male)
82 from the INvaSive blood PressurE ConsorTium (INSPECT). Data was recorded during
83 coronary angiography among 29 studies, using 21 different cuff BP devices. ISH was defined
84 as $\geq 130 / < 80$ mmHg using cuff BP compared with invasive aortic BP as the reference. The
85 prevalence of ISH was 24% (n=407) according to cuff BP, but 38% (n=642) according to
86 invasive aortic BP. There was fair agreement (Cohen's Kappa 0.36) and 72% concordance
87 between cuff and invasive aortic BP for identifying ISH. Among the 28% of subjects (n=471)
88 with misclassification of ISH status by cuff BP, 20% (n=96) of the difference was due to
89 lower cuff SBP compared with invasive aortic SBP (mean -16.4 mmHg 95%CI -18.7 to -
90 14.1), whereas 49% (n=231) was from higher cuff DBP compared with invasive aortic DBP
91 (+14.2 mmHg 95%CI 11.5 to 16.9). In conclusion, compared with invasive BP, cuff BP fails
92 to identify ISH in a sizeable portion of older people, and demonstrates the need to improve
93 cuff BP measurements.

94

95 **Keywords:** catheterization; pulse wave analysis; blood pressure measurement/monitoring;
96 artery

97

98

Introduction

99 Isolated systolic hypertension (ISH) is the most common form of hypertension¹ and is
100 strongly associated with increased cardiovascular disease morbidity and mortality.^{2,3} In
101 clinical practice, hypertension is invariably diagnosed and managed based on blood pressure
102 (BP) readings taken from an upper-arm cuff BP method.^{4,5} However, recent evidence showed
103 that cuff BP was not the same as invasive (intra-arterial) BP, either at the aortic or brachial
104 artery level.^{6,7} Specifically, cuff systolic BP (SBP) was variably higher or lower than
105 invasive aortic SBP, whereas cuff SBP was systematically lower than invasive brachial SBP.
106 On the other hand, cuff diastolic BP (DBP) was systematically higher than both invasive
107 brachial and aortic DBP.

108 The above cuff measurement differences from invasive BP were of such a magnitude to
109 significantly influence the hypothetical classification of hypertension.⁶ Of note, increasing
110 age was related to progressively greater underestimation of cuff SBP and pulse pressure (PP)
111 compared with invasive aortic BP values.⁷ On the other hand, as age increased, cuff DBP was
112 progressively overestimated compared with invasive aortic DBP. These observations suggest
113 that cuff BP may particularly lack precision for identifying ISH among older people. This has
114 never been examined but is an important consideration for correct identification and best-
115 practice management of ISH.³ The aim of this study was to determine the difference between
116 identification of ISH by cuff BP compared with a reference invasive BP.

117

Methods

118 The data, analytical methods, and study materials will be made available on request to other
119 researchers for purposes of reproducing the results or replicating the procedure. Requests for
120 data should be made to the corresponding author.

121 **Overview and study design.** Data used in the analysis was derived from the international
122 INvaSive blood PressurE ConsorTium (INSPECT), which includes studies with cuff BP

123 (automated methods; Online-only Table 1) and invasive BP (fluid-filled or solid-state
124 micromanometer catheters).^{6,7} INSPECT was developed to improve the understanding of
125 cuff BP as an estimate of invasive BP. Comparisons between cuff and invasive aortic BP
126 were made because cuff BP was designed to measure aortic BP⁸ (that which the organs are
127 exposed to),^{6,9-11} as others have suggested.^{12,13} However, for completeness, sensitivity
128 analysis for the comparison of cuff BP and invasive brachial BP for identification of ISH was
129 also conducted (more details below). The Health and Medical Human Research Ethics
130 Committee of Tasmania approved this analysis (reference: H0015048).

131 **Data handling.** The consortium database was developed from separate studies with quality
132 control measures in place, as previously described.^{6,7} Briefly, studies were included where
133 the cuff and invasive BPs were measured at rest (i.e. not during any hemodynamic shifts),
134 either simultaneously, or within an immediate period of each other. A quality score relating to
135 the rigour of methods used was applied to each study.⁶ The present analysis was conducted
136 on subjects ≥ 13 years because adult hypertension cut points apply beyond this age.^{5,14} ISH
137 was defined as SBP ≥ 130 mmHg and DBP < 80 mmHg for both cuff and invasive BP.^{5,15} PP
138 was calculated as SBP minus DBP and any measures less than 20 mmHg were excluded
139 (n=12). The database for cuff BP compared with invasive aortic BP included 25 subjects with
140 manual cuff BP measurements, but these were excluded because there was insufficient data
141 for a separate comparison with the automated BP methods. The database for cuff BP and
142 invasive brachial BP contained sufficient data for separate analyses for automated (n=381)
143 and manual (n=219) cuff BP methods.

144 **Different cut points for defining isolated systolic hypertension.** In addition to the
145 $\geq 130 / < 80$ mmHg ISH threshold, the following cut points were also assessed for concordance
146 of cuff BP and invasive BP: 1) $\geq 160 / < 95$ mmHg, as used in early trials targeted at reducing

147 SBP^{16, 17}; 2) $\geq 140 / < 90$ mmHg, according to the 2018 European Society of
148 Cardiology/European Society of Hypertension guidelines⁴; 3) a PP of ≥ 60 mmHg.⁴

149 **Sensitivity analyses.** Several sensitivity analyses were also conducted for completeness and
150 included: 1) a comparison of cuff BP and invasive brachial BP, in which data were stratified
151 according to the type of cuff device (automated methods (n=381) versus manual cuff BP
152 (n=219)); 2) the type of catheter used for invasive BP measurement (fluid-filled versus solid-
153 state); 3) the study quality score (maximum versus non-maximum rated).

154 **Statistical analysis.** Clinical characteristics and BP for the sample are presented as mean \pm
155 standard deviation, or if non-normally distributed, median [interquartile range (IQR)] for
156 continuous variables and number (%) for categorical variables. To determine the concordance
157 between cuff and invasive aortic or brachial BP for classification of ISH, the proportion of
158 data in each of the following categories was reported: no ISH from both cuff and invasive BP;
159 ISH from both cuff and invasive BP; ISH only from invasive BP; ISH only from cuff BP.

160 The cause of ISH misclassification for subjects with invasive ISH only or cuff ISH only was
161 determined by stratifying the cuff and invasive BP data at the ISH threshold using every
162 possible permutation of cuff and invasive SBP and DBP. For example, for subjects with ISH
163 only from invasive BP, there were three possible cuff BP categories: 1) $\geq 130 / \geq 80$ mmHg; 2)
164 $< 130 / < 80$ mmHg; or 3) $< 130 / \geq 80$ mmHg. The proportion of subjects within each category
165 and the difference between cuff and invasive aortic BP was also analysed. The same analysis
166 was also conducted in reverse (i.e. for subjects with ISH only from cuff BP).

167 Differences in BP were assessed using linear mixed models with a random effect term to
168 account for within study clustering of subjects. Data were analysed using R version 3.5.1 (R:
169 A language and environment for statistical computing. R Foundation for Statistical

170 Computing, Vienna, Austria. URL [https://www.R-project.org/.](https://www.R-project.org/)) The linear mixed models
171 were generated using the lme4 package.¹⁸

172 **Results**

173 **Clinical characteristics.** Overall, subjects were typical of patients undergoing coronary
174 angiography, with a median age of 64 years IQR [55 to 72], 68% were male and body mass
175 index was on average in the overweight range (26.1 kg/m² IQR [23.4 to 29.1]). Seven
176 hundred and ninety-seven (47%) of the cuff BP measurements were the average of at least
177 two readings and 1111 (66%) cuff BP and invasive BP readings were taken simultaneously,
178 whereas the remaining readings were sequential, with either cuff BP just prior to invasive
179 aortic BP or invasive aortic BP taken just prior to cuff BP.

180 **Cuff and invasive aortic BP defined isolated systolic hypertension.** According to cuff BP,
181 407 subjects (24%) had ISH, whilst 642 subjects (38%) were identified with ISH from
182 invasive aortic BP. The agreement between ISH from cuff versus invasive aortic BP
183 according to Cohen's kappa was 0.36, which is classified as 'fair' agreement.¹⁹ Overall, there
184 was 72% concordance between cuff BP and invasive aortic BP for classification of patients
185 with or without ISH ($\geq 130 / < 80$ mmHg; Figure 1). The clinical characteristics of subjects with
186 or without ISH were not different when ISH was defined by cuff or invasive aortic BP (Table
187 1). In 353 subjects (21%), ISH was only identified from invasive BP (Figure 1 and Table 2).
188 In 118 subjects (7%), ISH was misidentified by cuff BP. Thus, ISH was misclassified by cuff
189 BP compared to the invasive reference aortic BP in 471 subjects (28%).

190 **Blood pressure variables causing misclassification of isolated systolic hypertension**

191 The potential BP related causes of misclassification of ISH are shown in Figure 1. The
192 principal BP parameters driving misclassification were lower cuff SBP and higher cuff DBP
193 compared with invasive aortic SBP and DBP. Specifically, 96 subjects (20% of the 471

194 subjects misclassified) with ISH based on invasive aortic BP had cuff SBP readings that were
195 substantially lower than invasive aortic SBP (Online-only results). Conversely, 231 subjects
196 (49%) with ISH based on invasive aortic BP had cuff DBP readings that were substantially
197 higher than invasive aortic DBP. Lower cuff SBP and higher cuff DBP accounted for the
198 misclassification of ISH in 69% of subjects. Full detail of the remaining causes of
199 misclassification are detailed in Figure 1 and the online-only supplement.

200 **Examination of different cut points for defining isolated systolic hypertension.**

201 *ISH cut points of $\geq 160 / < 95$ mmHg and $\geq 140 / < 90$ mmHg.* According to the ISH cut point of
202 $\geq 160 / < 95$ mmHg, 147 subjects (9%) had ISH from cuff BP, whilst 276 subjects (16%) were
203 identified with ISH from invasive aortic BP. Using the $\geq 140 / < 90$ mmHg cut point, 422
204 subjects (25%) had ISH from cuff BP, whilst 638 subjects (38%) had ISH based on invasive
205 aortic BP. The clinical characteristics of subjects with or without ISH were not different
206 when defined by cuff or invasive aortic BP using either cut point (Online-only Tables 2-3).
207 Concordance between cuff and invasive aortic BP classification of ISH was 88% when the
208 $\geq 160 / < 95$ mmHg cut point was used (Figure 2 and Online-only Table 4). Concordance based
209 on the $\geq 140 / < 90$ mmHg ISH cut point was 76%, similar to the primary analysis (Figure 2 and
210 Online-only Table 5).

211 *PP cut point of ≥ 60 mmHg.* According to cuff BP, high PP was identified in 680 subjects
212 (40%) while, 965 subjects (57%) were identified with high PP from invasive aortic BP. The
213 clinical characteristics of subjects with or without high PP from the ≥ 60 mmHg cut point
214 were not significantly different when defined by cuff or invasive aortic PP (Online-only
215 Table 6). Concordance between cuff and invasive aortic PP for identifying high PP was 75%
216 (Figure 2 and Online-only Table 7).

217 **Sensitivity analyses.**

218 *Comparisons with invasive brachial BP.* According to the data for automated cuff BP, 115
219 subjects (30%) had ISH, whilst 212 subjects (56%) were identified with ISH from invasive
220 brachial BP. From the data with manual cuff BP, 35 subjects (16%) had ISH, whilst 44
221 subjects (20%) were identified with ISH from invasive brachial BP. The clinical
222 characteristics of subjects with or without ISH were not different when defined by automated
223 cuff or invasive brachial BP (Online-only Table 8) or from manual cuff BP or invasive
224 brachial BP (Online-only Table 9). Concordance between automated cuff BP and invasive
225 brachial BP for identifying ISH was 66%, whilst concordance between manual cuff BP and
226 invasive brachial BP was 86% (Figure 2).

227 *Fluid-filled versus solid-state catheter.* Concordance of the ISH classification was similar for
228 fluid-filled or solid-state catheters used for the measurement of invasive aortic or brachial BP
229 (Online-only Table 10).

230 *Maximum versus non-maximum rated studies.* Concordance of the ISH classification was
231 similar for maximum versus non-maximum rated study methods (Online-only Table 10).

232 **Discussion**

233 The key new findings from this study were that there was a greater prevalence of ISH
234 classified from invasive aortic BP than from upper-arm cuff measured BP (38% versus 24%).
235 As expected, differences between cuff BP and invasive aortic BP classification of ISH were
236 mostly related to lower cuff SBP and higher cuff DBP. Together, these two differences
237 accounted for 69% of the potential BP related causes of misclassification of ISH by cuff BP
238 compared with invasive aortic BP. Altogether, these findings show that although ISH is
239 appropriately detected by cuff BP in many people, there is a sizeable element of potential
240 error in identifying the true risk related to ISH - in this study, just over one quarter of the

241 study population. Since ISH is the most common form of hypertension further improvements
242 to non-invasive cuff BP measurement could help to achieve greater clinical precision.

243 It is commonly believed that SBP rises with ageing in most humans.²⁰ On the other hand,
244 DBP generally increases up to midlife before a plateau and eventual drop in later life. The
245 higher SBP and lower DBP (thus widened PP) characterises the ISH phenotype and explains
246 why it is the most common form of hypertension, particularly in older age.¹ A widened PP is
247 a hallmark of vascular ageing, in which stiffening of the aorta is associated with increased
248 SBP.²¹ In the current study, those classified with ISH (from either cuff BP or invasive aortic
249 BP) were older and had higher SBP, but similar DBP compared to those not classified with
250 ISH. Our previous work has illustrated that in older age cuff SBP underestimated invasive
251 aortic SBP,⁷ thus leading us to hypothesise that a diagnosis of ISH may be significantly
252 underappreciated by cuff BP. Of equal importance to correctly identifying ISH is the age-
253 related drop in aortic DBP (according to invasive BP) that is not fully detected by cuff BP
254 methods due to systematic overestimation of cuff DBP across all ages.⁷

255 It was reassuring that 72% of the study population were appropriately classified with respect
256 to ISH based on cuff BP compared with invasive aortic BP because it suggests that a majority
257 of people will have the opportunity to receive appropriate clinical care based on correct
258 diagnosis using standard cuff BP.⁴ Nonetheless, there was only fair agreement between cuff
259 and invasive BP methods for identifying ISH, with almost one quarter of the subjects being
260 misclassified with or without ISH. As indicated in Figure 1, the ISH misclassification was
261 attributable to several differences between cuff BP and invasive aortic SBP and DBP. Firstly,
262 when cuff SBP was lower than invasive aortic SBP (in the ISH range), the correct
263 classification of ISH was missed. A practical outcome of this ‘false negative’ ISH
264 classification may be that appropriate treatment would not be initiated, and a heightened level
265 of cardiovascular risk related to ISH would remain. Secondly, when cuff DBP was higher

266 than invasive aortic DBP, a correct classification of ISH was not made. This ‘false negative’
267 ISH classification may have less clinical ramifications, since individuals would still be
268 classified with hypertension and possibly receive the same medical care as if identified with
269 ISH. Nonetheless, due to systematically higher cuff DBP compared with invasive aortic DBP,
270 some individuals with DBP <70 mmHg could be at risk of overtreatment. This is of particular
271 relevance to those with established coronary artery disease, where there is the potential of
272 conferring harm.^{4,22}

273 Historically, hypertension treatment thresholds were focused on raised DBP,²³ but as
274 evidence evolved the focus shifted towards raised SBP as being more clinically important.^{4,5}
275 Today, most older people are likely to have treatment decisions made on the basis of raised
276 SBP, irrespective of DBP. In the present study we examined other definitions of ISH beyond
277 the 130/80 mmHg threshold (e.g. $\geq 160 / < 95$ mmHg,^{16,17} $\geq 140 / < 90$ mmHg).⁴ Irrespective of
278 the ISH definition, findings were similar, with the exception of ISH defined as $\geq 160 / \geq 95$
279 mmHg, in which only 12% of subjects were misclassified. However, this threshold has since
280 been shown to be too high because increased risk related to ISH is conferred at lower levels
281 of BP.⁴ Indeed, there is a continuous association between higher SBP and/or DBP and
282 increased cardiovascular risk²⁴ and this again demonstrates the importance of high-quality,
283 BP measurement precision irrespective of hypertension thresholds. The differences between
284 cuff BP and invasive aortic BP which become more substantial with increasing age⁷ may
285 adversely impact the optimal management of patients with high cardiovascular risk. This is
286 perhaps of most importance in the context of absolute cardiovascular risk assessment, which
287 is the suggested basis for hypertension management decisions outlined in current clinical
288 guidelines.^{4,5}

289 **Limitations.** Data from INSPECT was compiled from populations undergoing coronary
290 angiography, and so the results may not be generalisable to other populations, such as those

291 having BP assessed in general practice. Moreover, whether these results would remain
292 consistent in younger people is unclear. The invasive data consisted of BP measured by both
293 micro-manometer tipped and fluid-filled catheters, as well as various cuff BP devices. Whilst
294 these methods of BP assessment may not be considered the same, we have previously shown
295 major cuff BP differences from invasive BP, independent of the type of invasive reference
296 measurement and cuff type.⁶ In the present study, manual cuff BP performed better than
297 automated cuff BP for detection of ISH compared with invasive brachial BP (86% versus 66%
298 concordance). Whilst this result suggests manual BP may be superior, there were distinct
299 differences in the clinical characteristics of the subjects in the automated and manual cuff BP
300 datasets which may also have contributed to the differences in ISH concordance (Online
301 Tables 8 and 9). This study was based solely on classification of ISH from BP measures and
302 guideline thresholds. Clinical decisions are generally recommended to be made based on
303 absolute cardiovascular risk assessment,^{4, 5, 25} but we were unable to assess this in the current
304 analysis. Moreover, whether the theoretical misclassification of ISH described in this paper
305 leads to adverse cardiovascular disease outcomes in clinical practice remains unknown.

306 **Perspectives.** Slightly over one quarter of this sample of older people had ISH misclassified
307 by cuff BP compared with invasive aortic BP. This demonstrates a need to improve cuff BP
308 methods for greater precision in identifying ISH. This study expands on previous findings
309 which have shown greater inaccuracy of cuff BP associated with older age⁷ and with
310 heightened vascular stiffness,²⁶ which are characteristics that increase the likelihood of ISH.
311 At least one study has attempted to improve the precision and accuracy of cuff measured BP
312 among older people with stiffer vasculature, by deeper analysis of patient-specific
313 components of the oscillometric BP waveform.²⁷ These investigators established proof-of-
314 concept that such an approach was feasible, and the results of the present study provide

315 further justification for improving the quality of cuff BP measurement to ultimately drive
316 better patient outcomes related to ISH and other forms of hypertension.

For Hypertension Peer Review. Do not distribute.
Destroy after use.

317

Acknowledgements

318 Additional members of the Invasive Blood Pressure Consortium are:

319 Ahmed M. Al-Jumaily: Institute of Biomedical Technologies, Auckland University of
320 Technology, Auckland, New Zealand

321 Sandy Muecke: Department of Critical Care Medicine, Flinders University, Adelaide,
322 Australia

323 Niklas B. Rossen: Department of Endocrinology and Internal Medicine, Aarhus University
324 Hospital, Aarhus, Denmark

325 Ralph Stewart: Green Lane Cardiovascular Service, Auckland City Hospital,
326 University of Auckland, Auckland, New Zealand

327

Funding

328 This work was supported by a Vanguard Grant from the National Heart Foundation of
329 Australia (reference 101836) and Royal Hobart Hospital Research Foundation project grant
330 (reference 19-202).

331

Disclosures

332 James E Sharman: His university has received equipment and research funding from
333 manufacturers of BP devices including AtCor Medical, IEM and Pulsecor (Uscom). He has
334 no personal commercial interests related to BP companies. No disclosures from other authors.

335

- 337 1. Franklin SS, Jacobs MJ, Wong ND, L'Italien GJ, Lapuerta P. Predominance of
338 isolated systolic hypertension among middle-aged and elderly us hypertensives:
339 Analysis based on national health and nutrition examination survey (nhanes) iii.
340 *Hypertension*. 2001;37:869-874
- 341 2. Yano Y, Stamler J, Garside DB, Daviglius ML, Franklin SS, Carnethon MR, Liu K,
342 Greenland P, Lloyd-Jones DM. Isolated systolic hypertension in young and middle-
343 aged adults and 31-year risk for cardiovascular mortality: The chicago heart
344 association detection project in industry study. *J. Am. Coll. Cardiol.* 2015;65:327-335
- 345 3. Staessen JA, Gasowski J, Wang JG, Thijs L, Den Hond E, Boissel JP, Coope J,
346 Ekblom T, Gueyffier F, Liu L, Kerlikowske K, Pocock S, Fagard RH. Risks of
347 untreated and treated isolated systolic hypertension in the elderly: Meta-analysis of
348 outcome trials. *Lancet*. 2000;355:865-872
- 349 4. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, Clement
350 DL, Coca A, de Simone G, Dominiczak A, et al. 2018 esc/esh guidelines for the
351 management of arterial hypertension: The task force for the management of arterial
352 hypertension of the european society of cardiology and the european society of
353 hypertension: The task force for the management of arterial hypertension of the
354 european society of cardiology and the european society of hypertension. *J. Hypertens.*
355 2018;36:1953-2041
- 356 5. Whelton PK, Carey RM, Aronow WS, Casey DE, Jr., Collins KJ, Dennison
357 Himmelfarb C, DePalma SM, Gidding S, Jamerson KA, Jones DW, et al. 2017
358 acc/aha/aapa/abc/acpm/ags/apha/ash/aspc/nma/pcna guideline for the prevention,
359 detection, evaluation, and management of high blood pressure in adults: A report of

- 360 the american college of cardiology/american heart association task force on clinical
361 practice guidelines. *J. Am. Coll. Cardiol.* 2018;71:e127-e248
- 362 6. Picone DS, Schultz MG, Otahal P, Aakhus S, Al-Jumaily AM, Black JA, Bos WJ,
363 Chambers JB, Chen CH, Cheng HM, et al. Accuracy of cuff-measured blood pressure:
364 Systematic reviews and meta-analyses. *J. Am. Coll. Cardiol.* 2017;70:572-586
- 365 7. Picone DS, Schultz MG, Otahal P, Black JA, Bos WJ, Chen CH, Cheng HM, Cremer
366 A, Dwyer N, Fonseca R, et al. Influence of age on upper arm cuff blood pressure
367 measurement. *Hypertension.* 2020;75:844-850
- 368 8. Zanchetti A, Mancia G. The centenary of blood pressure measurement: A tribute to
369 scipione riva-rocci. *J. Hypertens.* 1996;14:1-12
- 370 9. Booth J. A short history of blood pressure measurement. *Proc. R. Soc. Med.*
371 1977;70:793-799
- 372 10. Karamanou M, Papaioannou TG, Tsoucalas G, Tousoulis D, Stefanadis C,
373 Androutsos G. Blood pressure measurement: Lessons learned from our ancestors.
374 *Curr. Pharm. Des.* 2015;21:700-704
- 375 11. Sharman JE, Marwick TH. Accuracy of blood pressure monitoring devices: A critical
376 need for improvement that could resolve discrepancy in hypertension guidelines. *J.*
377 *Hum. Hypertens.* 2019;33:89-93
- 378 12. Narayan O, Casan J, Szarski M, Dart AM, Meredith IT, Cameron JD. Estimation of
379 central aortic blood pressure: A systematic meta-analysis of available techniques. *J.*
380 *Hypertens.* 2014;32:1727-1740
- 381 13. Davies JJ, Band MM, Pringle S, Ogston S, Struthers AD. Peripheral blood pressure
382 measurement is as good as applanation tonometry at predicting ascending aortic blood
383 pressure. *J. Hypertens.* 2003;21:571-576

- 384 14. Gidding SS, Whelton PK, Carey RM, Flynn J, Kaelber DC, Baker-Smith C. Aligning
385 adult and pediatric blood pressure guidelines. *Hypertension*. 2019;73:938-943
- 386 15. Cheng HM, Chuang SY, Sung SH, Yu WC, Pearson A, Lakatta EG, Pan WH, Chen
387 CH. Derivation and validation of diagnostic thresholds for central blood pressure
388 measurements based on long-term cardiovascular risks. *J. Am. Coll. Cardiol.*
389 2013;62:1780-1787
- 390 16. Staessen JA, Fagard R, Thijs L, Celis H, Arabidze GG, Birkenhager WH, Bulpitt CJ,
391 de Leeuw PW, Dollery CT, Fletcher AE, et al. Randomised double-blind comparison
392 of placebo and active treatment for older patients with isolated systolic hypertension.
393 The systolic hypertension in europe (syst-eur) trial investigators. *Lancet*.
394 1997;350:757-764
- 395 17. Liu L, Wang JG, Gong L, Liu G, Staessen JA. Comparison of active treatment and
396 placebo in older chinese patients with isolated systolic hypertension. Systolic
397 hypertension in china (syst-china) collaborative group. *J. Hypertens*. 1998;16:1823-
398 1829
- 399 18. Bates D, Maechler M, Bolker B, Walker S. Fitting linear mixed-effects models using
400 lme4. *J Stat Softw*. 2015;67:1-48
- 401 19. McHugh ML. Interrater reliability: The kappa statistic. *Biochem. Med. (Zagreb)*.
402 2012;22:276-282
- 403 20. Franklin SS, Gustin Wt, Wong ND, Larson MG, Weber MA, Kannel WB, Levy D.
404 Hemodynamic patterns of age-related changes in blood pressure. The framingham
405 heart study. *Circulation*. 1997;96:308-315
- 406 21. Kaess BM, Rong J, Larson MG, Hamburg NM, Vita JA, Levy D, Benjamin EJ, Vasan
407 RS, Mitchell GF. Aortic stiffness, blood pressure progression, and incident
408 hypertension. *JAMA*. 2012;308:875-881

- 409 22. Vidal-Petiot E, Ford I, Greenlaw N, Ferrari R, Fox KM, Tardif JC, Tendera M,
410 Tavazzi L, Bhatt DL, Steg PG, Investigators C. Cardiovascular event rates and
411 mortality according to achieved systolic and diastolic blood pressure in patients with
412 stable coronary artery disease: An international cohort study. *Lancet*. 2016;388:2142-
413 2152
- 414 23. Report of the joint national committee on detection, evaluation, and treatment of high
415 blood pressure. A cooperative study. *JAMA*. 1977;237:255-261
- 416 24. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R, Prospective Studies
417 Collaboration. Age-specific relevance of usual blood pressure to vascular mortality: A
418 meta-analysis of individual data for one million adults in 61 prospective studies.
419 *Lancet*. 2002;360:1903-1913
- 420 25. National Heart Foundation of Australia. Guideline for the diagnosis and management
421 of hypertension in adults. 2016
- 422 26. Carlsen RK, Peters CD, Khatir DS, Laugesen E, Botker HE, Winther S, Buus NH.
423 Estimated aortic blood pressure based on radial artery tonometry underestimates
424 directly measured aortic blood pressure in patients with advancing chronic kidney
425 disease staging and increasing arterial stiffness. *Kidney Int*. 2016;90:869-877
- 426 27. Liu J, Cheng HM, Chen CH, Sung SH, Hahn JO, Mukkamala R. Patient-specific
427 oscillometric blood pressure measurement: Validation for accuracy and repeatability.
428 *IEEE J Transl Eng Health Med*. 2017;5:1900110

429

430

431

Novelty and significance

432 What Is New?

- 433 • ISH was misclassified by cuff BP measurements in about one quarter of the study
434 sample when compared to invasive BP.

435 What Is Relevant?

- 436 • ISH is the most prevalent form of hypertension. Irrespective of the ISH threshold,
437 these findings may have implications for the appropriate identification of ISH.

438 Summary

439 This study extends on previous findings which have shown greater inaccuracy of cuff BP in
440 older age and with vascular stiffness. Taken altogether, the data support the need to improve
441 cuff BP methods for better identification of ISH in older people.

442

For Hypertension Peer Review: Do not distribute.
Destroy after use.

443

Figure legends.

444 **Figure 1.** Classification of isolated systolic hypertension (ISH) from cuff and invasive aortic
445 blood pressure (BP n=1695). Details from the misclassified data are presented in the first
446 branches of the flow chart to show which cuff BP variable caused ISH misclassification. For
447 each cause of misclassification, further mechanisms and potential clinical ramifications are
448 detailed in the lower two rows of boxes. ISH was defined as systolic BP (SBP) ≥ 130 /diastolic
449 BP (DBP) < 80 mmHg for both cuff and invasive aortic measurements. Cuff SBP/DBP 'lower'
450 indicates that cuff BP was lower than invasive aortic BP, whilst cuff SBP/DBP 'higher'
451 indicates that cuff BP was higher than invasive aortic BP.

452 **Figure 2.** Classification of isolated systolic hypertension (ISH) based on cuff and invasive
453 blood pressure according to various definitions of ISH. The comparisons of cuff and invasive
454 aortic BP are in 1695 subjects. The comparison for automated cuff BP and invasive brachial
455 BP is in 381 subjects. The comparison for manual cuff BP and invasive brachial BP is in 219
456 subjects. Some column percentages may not add to 100 due to rounding.

Table 1. Clinical characteristics and haemodynamics stratified by the presence or absence of isolated systolic hypertension defined by cuff or invasive aortic blood pressure measurements at a cut point of $\geq 130 / < 80$ mmHg (n=1695).

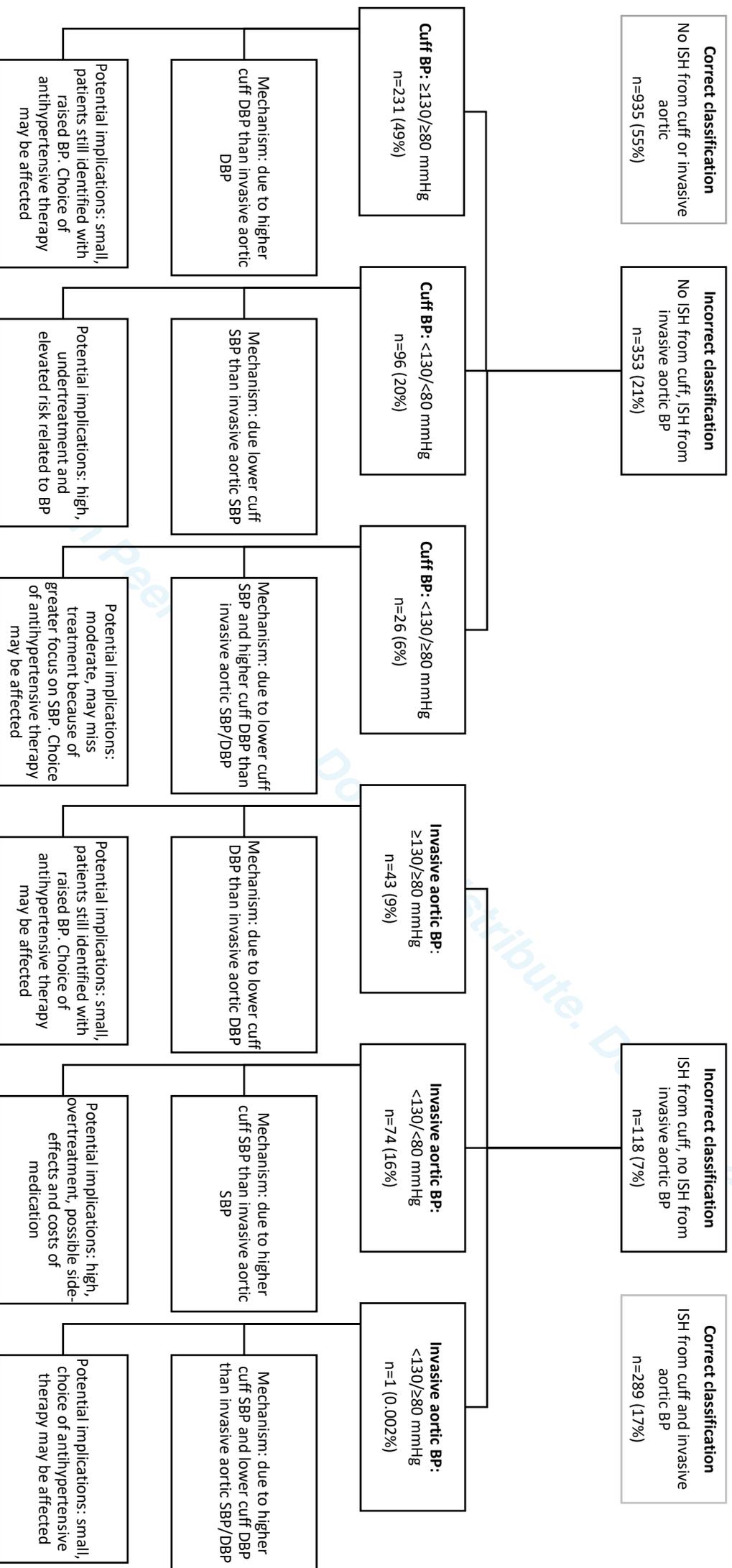
Clinical characteristics	No isolated systolic hypertension (cuff)		Isolated systolic hypertension (cuff)		No isolated systolic hypertension (invasive)		Isolated systolic hypertension (invasive)	
	N	1288	407	1053	642			
Age, years	62 [54 to 70]	69 [62 to 76]	60 [52 to 68]	69 [62 to 76]				
Male sex %	912 (72; n=1264)	226 (56; n=403)	747 (72; n=1032)	391 (62; n=635)				
Body mass index, kg/m ²	26.1 [23.4 to 29.2; n=1178]	26.6 \pm 5 (n=360)	26.3 [23.5 to 29.8; n=959]	26.2 \pm 5 (n=579)				
Height, cm	167 \pm 10 (n=1179)	163 \pm 10 (n=361)	167 \pm 10 (n=960)	163 \pm 10 (n=580)				
Weight, kg	72.0 [62.0 to 85.0; n=1186]	69.0 [58.6 to 80.0; n=363]	73.7 [63.1 to 86.4; n=967]	67.5 [58.0 to 79.9; n=5821]				
Heart rate, beats/min	67 [60 to 76; n=1165]	65 [58 to 73; n=322]	68 [61 to 77; n=957]	64 [58 to 72; n=530]				
Coronary artery disease (%)	610 (67; n=906)	178 (71; n=252)	483 (66; n=734)	305 (72; n=424)				
Blood pressure								
Cuff systolic BP, mmHg	133 \pm 23	141 [134 to 151]	126 [115 to 142]	144 \pm 18				
Invasive aortic systolic BP, mmHg	133 \pm 26	146 [133 to 159]	122 [112 to 141]	147 [138 to 160]				
Cuff – invasive systolic BP, mmHg	-0.8 \pm 14	-2.9 \pm 14	1.8 \pm 13	-6.3 \pm 13				
Cuff diastolic BP, mmHg	80 \pm 13	73 [68 to 76]	78 \pm 14	77 \pm 11				
Invasive aortic diastolic BP, mmHg	71 \pm 13	68 \pm 10	72 \pm 14	70 [63 to 75]				
Cuff – invasive diastolic BP, mmHg	8.5 \pm 11	3.6 \pm 9	6.0 \pm 10	9.5 \pm 12				
Cuff pulse pressure, mmHg	51 [43 to 60]	70 [63 to 82]	50 [41 to 60]	67 \pm 17				
Invasive aortic pulse pressure, mmHg	59 [47 to 74]	78 [66 to 92]	53 [45 to 65]	80 [69 to 93]				
Cuff – invasive pulse pressure, mmHg	-9.3 \pm 15	-6.4 \pm 15	-4.2 \pm 13	-15.8 \pm 15				

Data are mean \pm standard deviation, median [interquartile range] or n (%). Isolated systolic hypertension was defined as systolic blood pressure (BP) ≥ 130 /diastolic BP <80 mmHg for both cuff and invasive aortic measurements.

Table 2. Clinical characteristics and pressure parameters stratified by the isolated systolic hypertension classification based on cuff and aortic blood pressure at a cut point of ≥ 130 / < 80 mmHg (n=1695).

Clinical characteristics	No ISH (cuff and invasive)	ISH (cuff and invasive)	ISH (invasive only)	ISH (cuff only)
	N	935	289	353
Age, years	60 [52 to 68]	71 [65 to 77]	67 [60 to 74]	64 [56 to 70]
Male sex (%)	679 (74; n=916)	158 (55; n=287)	233 (67; n=348)	68 (59; n=116)
Body mass index, kg/m²	26.3 [23.5 to 29.7; n=855]	26.2 \pm 5 (n=256)	25.6 [23.0 to 27.9; n=323]	27.6 \pm 5 (n=104)
Height, cm	167 \pm 10 (n=856)	161 \pm 10 (n=257)	164 \pm 11 (n=323)	166 \pm 9 (n=104)
Weight, kg	73.4 [63.2 to 86.4; n=861]	68 [57 to 78; n=257]	67.5 [59.6 to 81.0; n=325]	74.4 [62.0 to 86.8; n=106]
Heart rate, beats/min	68 [61 to 77; n=857]	63 [57 to 72; n=222]	65 [59 to 72; n=308]	69 [62 to 75; n=100]
Coronary artery disease (%)	431 (65; n=659)	126 (71; n=177)	179 (72; n=247)	52 (69; n=75)
Blood pressure				
Cuff systolic BP, mmHg	124 [113 to 141]	142 [136 to 154]	142 \pm 20	136 [131 to 142]
Invasive aortic systolic BP, mmHg	121 [110 to 141]	149 [140 to 162]	145 [136 to 158]	126 [122 to 146]
Cuff – invasive systolic BP, mmHg	1.4 \pm 13	-6.0 \pm 12	-6.5 \pm 14	-4.9 \pm 14
Cuff diastolic BP, mmHg	79 \pm 14	72 [67 to 76]	83 \pm 10	74 [70 to 76]
Invasive aortic diastolic BP, mmHg	72 \pm 14	67 [61 to 73]	71 [66 to 76]	73 [63 to 81]
Cuff – invasive diastolic BP, mmHg	6.6 \pm 10	4.7 \pm 8	13.5 \pm 13	0.9 \pm 12
Cuff pulse pressure, mmHg	48 [40 to 57]	73 [65 to 84]	60 \pm 15	65 [59 to 71]
Invasive aortic pulse pressure, mmHg	52 [44 to 64]	85 [73 to 97]	77 [67 to 88]	61 [53 to 73]
Cuff – invasive pulse pressure, mmHg	-5.2 \pm 13	-10.7 \pm 13	-18.0 [-26.7 to -11.0]	4.0 \pm 13

Data are mean \pm standard deviation, median [interquartile range] or n (%). Isolated systolic hypertension (ISH) was defined as systolic blood pressure (BP) ≥ 130 /diastolic BP < 80 mmHg for both cuff and invasive aortic measurements.



For Hypertension

Do not distribute. Do not use.

