Method specificity of non-invasive blood pressure measurement: oscillometry and finger pulse pressure vs acoustic methods

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- 1 The agreement of blood pressure measurements by stethoscope auscultation (SBP_a , DBP_{a-IV} and DBP_{a-V}), oscillometry (Dinamap®; SBP_o , and DBP_o) and digital photoplethysmography (Finapres®; SBP_f , and DBP_f) with the graphical analysis of the analogue microphone signals of vascular wall motion sound (SBP_g and DBP_g) was evaluated in eight healthy subjects in the presence of responses to the intravenous infusion of $1 \mu\text{g min}^{-1}$ isoprenaline.
- 2 In general, there was good agreement between the SBP/DBP-measurements based on auscultatory Korotkoff-I- and -IV-criteria and the reference method; the average method difference in estimating the isoprenaline responses for SBP_a - SBP_g was: -1.1 , 95% CI: -5.4 to 3.1 mm Hg with a within-subject between-method repeatability coefficient (REP) of 11.6 mm Hg and for DBP_{a-IV} - DBP_g : 3.5 , 95% CI: -0.5 to 6.5 mm Hg, REP: 11.5 mm Hg. The auscultation of Korotkoff-V substantially overestimated the isoprenaline induced reduction of DBP: method difference DBP_{a-V} - DBP_g : -11.3 , 95% CI: -17.8 to -4.7 mm Hg, REP: 31.8 mm Hg.
- 3 Oscillometry yielded good approximations for the SBP response to isoprenaline (average method difference SBP_o - SBP_g : -2.9 , 95% CI: -9.0 to 3.3 mm Hg, REP: 17.6 mm Hg) but was poorly sensitive with regard to the DBP responses: method difference DBP_o - DBP_g : 6.5 , 95% CI: -1.3 to 14.3 mm Hg, REP: 25.7 mm Hg.
- 4 Whilst the finger pulse pressure agreed well with regard to DBP (method difference for the DBP responses to isoprenaline: DBP_f - DBP_g : 1.8 , 95% CI: -5.1 to 8.6 mm Hg, REP: 18.5 mm Hg) it was rather unsatisfactory with regard to SBP (method difference SBP_f - SBP_g : -14.1 , 95% CI: -28.2 to -0.1 mm Hg, REP: 49.9 mm Hg).
- 5 Non-invasive measurements of blood pressure are method specific estimates likely to be subject to method x effect-interaction. In consequence they are not interchangeable.

Keywords non-invasive blood pressure Korotkoff sounds oscillometry finger pulse
Finapres Dinamap isoprenaline bias agreement

Introduction

Blood pressure is one of the most frequently measured and reported variates in experimental clinical pharmacology. In many instances and with healthy subjects in particular, there is little need or justification to use invasive methods. Various non-invasive alternatives are used instead: 1) acoustic methods to detect the changes of the vascular wall motion sounds of the brachial artery on deflation of a proximal

compressing cuff (Riva/Rocci [1]) by stethoscope auscultation (Korotkoff-I, -IV and -V [2–4]) or by graphical analysis of analogue microphone signals [5–8], 2) oscillometric methods (f.i. Dinamap® [9]) and 3) photoplethysmographic measurements of finger pulse blood pressure (f.i. Finapres® [10–12]).

We recently reported the lack of agreement between acoustic methods based on the Korotkoff-IV-

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('sound muffling') and Korotkoff-V-criterion ('sound disappearance') in estimating the inodilatory reductions of diastolic blood pressure in response to food, the β -adrenergic agonists isoprenaline and adrenaline, the PDE-III-inhibitors meribendan and isomazol and celiprolol, a β_1 -adrenoceptor antagonist with β -adrenoceptor agonistic properties (at high doses) [13].

We conducted the present study in order to assess whether and to which extent method specificity also affected the further non-invasive methods routinely used to measure blood pressure in clinical pharmacology studies. The infusion of isoprenaline was used as investigational manoeuvre in order to evaluate the extent of agreement between different methods not only for resting values but for investigational responses as well. In the absence of invasive measurements, the graphical analysis of vascular wall motion sounds ($\approx$ Korotkoff-I and -IV) was used as reference [8].

Methods

Subjects

Eight young male subjects (23 to 31 years of age) judged to be healthy on the basis of extensive medical and laboratory investigations participated. The study was conducted in agreement with the declaration of Helsinki (Hong Kong Amendment), the German Drug Law and the European Guidelines for Good Clinical Practice [14], on the basis of formal protocol that was reviewed and approved by an independent Ethics Committee. The subjects were fully informed about the nature of the study and the medications. They confirmed their consent in writing and in presence of a witness.

Study design

The subjects were studied on one occasion. After 1 h supine rest, isoprenaline was infused at a constant rate of $1 \mu\text{g min}^{-1}$ for 10 min. One hour later this procedure was repeated. During each infusion finger pulse pressure (Finapres®) was measured either along with the acoustic methods or with the oscillometric method which could not be applied simultaneously. The sequences (oscillometric $\rightarrow$ acoustic and acoustic $\rightarrow$ oscillometric) were randomly allocated.

General procedures

The subjects were investigated in a recumbent relaxed position. They fasted from the night before up to the end of the investigation. They had abstained from smoking, alcohol and xanthines for at least 24 h.

Measurements

During each infusion cardiovascular function was investigated using ECG, phonocardiogram, carotid pulse curve and conventional impedance cardiography ZCG [15, 16]. Stroke volume (SV, ml) was

estimated from ZCG using Kubicek's equation [17]. During each infusion, heart rate (HR, beats min^{-1}) was averaged from the ECG-signals recorded for at least 15 s. Systolic (SBP, mm Hg) and diastolic blood pressure (DBP, mm Hg) were measured continuously by Finapres® (Ohmeda GmbH, Puchheim, Germany). During one of the infusions systolic (SBP, mm Hg) and diastolic blood pressure (DBP, mm Hg) were measured by stethoscope auscultation of the vascular wall motion sound (Korotkoff-I, -IV and -V) using a mercury sphygmomanometer (Erkameter® 660/304) and by graphical analysis of the analogue signals of vascular wall motion (Korotkoff-IV equivalents, Infraton®, Boucke, Tübingen, Germany). During the other isoprenaline infusion, blood pressure was measured by an automated oscillometric device (Dinamap®, Critikon, Norderstedt, Germany).

Measurements were carried out 10 and 5 min before infusion, after 5 and 10 min infusion, and at 5 and 10 min subsequent to the infusion. Measurements were made by well trained observers; all measurements within the subject were carried by the same observer. General methodological directives (posture, cuff size, bladder size, inflation rate, deflation rate, etc.) were well-standardised. The registrations of the microphone signals at each time lasted as long as the alternative method used concomitantly (i.e. at least 15 beats). Responses to isoprenaline are rapidly changing; the measurements during the infusion in consequence were not pooled or assessed for within-method repeatability.

Variates

- Stethoscope auscultation: SBP_a , DBP_{a-IV} , DBP_{a-V}
- Graphical analysis of vascular sound: SBP_g , DBP_g
- Oscillometric measurement: SBP_o , DBP_o and mean pressure MBP_o
- Finger pulse pressure: SBP_{fd} , DBP_{fd} as displayed by the machine and SBP_{fg} , DBP_{fg} as derived by subsequent graphical analysis of the tracings
- For all methods mean MBP was calculated as $[\text{MBP} = \text{DBP} + 0.43 \times (\text{SBP} - \text{DBP})]$ according to Wezler & Böger [18]: MBP_{a-IV} , MBP_{a-V} , MBP_{oc} , MBP_{fd} and MBP_{fg}

Cardiac output was calculated from heart rate (HR) and SV ($\text{CO} = \text{HR} \times \text{SV} / 1000$; l min^{-1}). Total peripheral resistance (TPR) was calculated from CO and MBP as $\text{TPR} = 79.92 \times (\text{MBP} - \text{mAtP}) / \text{CO}$, in which mAtP represents the mean atrial pressure (≈ 3 mm Hg).

Data analysis

Agreement of the various methods was analysed relative to the graphical analysis of the changing vascular wall motion sounds (as reference) for the pre-infusion baseline readings and for the isoprenaline responses (arithmetic difference of the readings at the end of the infusion from pre-infusion baseline). The various techniques were contrasted separately with the reference. Each time the average difference (= extent of disagreement, 'bias') between the test and reference methods was estimated as the difference between

the mean measurements for test *minus* reference and the corresponding 95% CI. Considering the measurements with different methods to be observational reproductions, the between-method within-subject 'repeatability' coefficient was estimated as $REP = t \cdot s.d.$ in which *s.d.* is standard deviation of the individual differences between the methods and *t* is Student's *t*-value for a 2-sided α : 0.05 and the corresponding degrees of freedom (in view of the small sample size, *t* is larger than 2, which is otherwise often used as approximation [19, 20]). Within this context REP represents the estimated maximum absolute difference reached with 95% confidence between the two methods within the same subject. The limits of agreement between the methods are then defined as average method difference $\pm$ REP [21, 22].

Results

BP-independent observations

Blood pressure independent observations were well reproducible between the two consecutive isoprenaline infusions: there was a -2 beats min^{-1} (95% CI:

-5 to 1) difference with regard to the HR-response of on average 17 beats min^{-1} and an average difference of 0.6 l min^{-1} (95% CI: -0.3 to 1.5) for the CO-response (average response of $+4.3$ l min^{-1}).

Agreement between the acoustic methods of BP-measurement

There was good agreement between auscultatory SBP_a and DBP_{a-IV} and graphical SBP_g and DBP_g , respectively, with regard to the resting baseline measurements: SBP_a - SBP_g : 0.6 , 95% CI: -4.1 to 5.4 mmHg, REP: 12.7 mm Hg and DBP_{a-IV} - DBP_g : 2.0 , 95% CI: -2.2 to 6.2 mm Hg, REP: 12.1 mm Hg). There was also good agreement between these methods in estimating the isoprenaline induced BP-changes (see Table 1 and Figure 1).

For the resting values, there was a small method difference between DBP_{a-IV} according to the Korotkoff-IV- and DBP_{a-V} according to the Korotkoff-V-criterion: average DBP_{a-V} - DBP_{a-IV} : -5.5 , 95% CI: -8.0 to -3.0 mm Hg, REP: 14.6 mm Hg and DBP_{a-V} - DBP_g : -3.5 , 95% CI: -8.8 to 1.8 mm Hg, REP: 12.8 mm Hg. But there was a substantial method difference between DBP_{a-V} and both DBP_{a-IV} and DBP_g

Table 1 Agreement of the various methods in estimating the average responses (Δ) of systolic (SBP), diastolic (DBP) and mean blood pressure (MBP) and calculated total peripheral resistance (TPR) to a 10 min i.v. infusion of $1 \mu\text{g min}^{-1}$ isoprenaline ($n = 8$). The graphical analysis of the analogue microphone signals of the vascular wall motion sound was taken as reference (SBP_g , DBP_g , MBP_g and TPR_g). The comparisons assess blood pressure measurements by stethoscope auscultation (SBP_a based on Korotkoff-I, DBP_{a-IV} , MBP_{a-IV} and TPR_{a-IV} based on Korotkoff-IV and DBP_{a-V} , MBP_{a-V} and TPR_{a-V} based on Korotkoff-V), oscillometry (SBP_o , DBP_o , MBP_o and TPR_o) and finger pulse pressure (from the automated display: SBP_{fd} , DBP_{fd} , MBP_{fd} and TPR_{fd} and from a graphical analysis of the tracings: SBP_{fg} , DBP_{fg} , MBP_{fg} and TPR_{fg}). For each method and variate, the mean responses to isoprenaline (Δ), the average method differences (plus 95% CI), the between-method within-subject repeatability coefficient (REP) and limits of agreement (LLA: lower limit, ULA: upper limit) for the paired method comparisons are detailed.

Method 1 method	ΔI	Method 2 method	$\Delta 2$	Mean method difference $\Delta 2 - \Delta 1$	95% CI	REP	Agreement LLA	ULA
SBP: systolic blood pressure (mm Hg)								
SBP_g	21.0	SBP_a	19.9	-1.1	-5.4 to 3.1	11.6	-12.7	0.4
SBP_g	21.0	SBP_o	18.1	-2.9	-9.0 to 3.3	17.6	-20.5	14.7
SBP_g	21.0	SBP_{fg}	10.0	-11.0	-21.3 to -0.7	37.7	-48.7	26.7
SBP_g	21.0	SBP_{fd}	6.9	-14.1	-28.2 to -0.1	49.9	-64.1	35.8
DBP: diastolic blood pressure (mm Hg)								
DBP_{a-IV}	-8.0	DBP_{a-V}	-22.8	-14.8	-23.6 to -5.9	42.0	-56.8	27.3
DBP_{a-IV}	-11.5	DBP_{a-IV}	-8.0	3.5	0.5 to 6.5	11.5	-8.0	5.0
DBP_g	-11.5	DBP_{a-V}	-22.8	-11.3	-17.8 to -4.7	31.8	-43.1	20.6
DBP_g	-11.5	DBP_o	-5.0	6.5	-1.3 to 14.3	25.7	-19.2	32.2
DBP_g	-11.5	DBP_{fg}	-9.8	1.8	-5.1 to 8.6	18.5	-16.8	20.3
DBP_g	-11.5	DBP_{fd}	-8.4	3.1	-4.0 to 10.3	20.4	-17.2	23.5
MBP: mean blood pressure (mm Hg)								
MBP_g	2.5	MBP_{a-IV}	4.0	1.5	-0.8 to 3.8	7.0	-5.5	8.5
MBP_g	2.5	MBP_{a-V}	-4.4	-6.9	-11.6 to -2.2	20.5	-27.4	13.6
MBP_g	2.5	MBP_o	-3.0	-5.5	-10.1 to -0.9	17.7	-23.2	12.3
MBP_g	2.5	MBP_{fg}	-1.3	-3.8	-10.6 to 3.1	20.3	-24.0	16.5
MBP_g	2.5	MBP_{fd}	-1.8	-4.3	-13.9 to 5.3	27.3	-31.6	23.0
TPR: estimated total peripheral resistance (dyn s cm^{-5})								
TPR_g	-260	TPR_{a-IV}	-258	2	-25 to 28	70	-68	71
TPR_g	-260	TPR_{a-V}	-307	-47	-92 to -1	164	-211	117
TPR_g	-260	TPR_o	-300	-40	-124 to 44	242	-282	202
TPR_g	-260	TPR_{fg}	-306	-46	-108 to 16	197	-243	151
TPR_g	-260	TPR_{fd}	-312	-52	-144 to 40	272	-325	220

Figure 1 Time course of the mean ($n = 8$, $\pm$ s.e. mean) BP and TPR values based on the graphical analysis of the analogue microphone signals of vascular wall motion sound ($\bullet$), stethoscope auscultation according to Korotkoff-I and -IV criteria ($\circ$) and Korotkoff-V criterion ($\square$) before, during and after a 10 min i.v. infusion (time 0:00 to 0:10) of $1 \mu\text{g min}^{-1}$ isoprenaline.

in estimating the isoprenaline induced reduction of DBP (which was estimated to be substantially larger when the Korotkoff-V-criterion was used).

Agreement between the oscillometric method and the acoustic reference method

There was good agreement between SBP_o and SBP_g with regard to the resting baseline measurements ($\text{SBP}_o - \text{SBP}_g$: 1.0, 95% CI: -3.6 to 5.6 mm Hg, REP: 12.3 mm Hg) and the estimates of the isoprenaline responses (see Table 1 and Figure 2); for the diastolic values however, the between-method repeatability for the baseline readings was weak ($\text{DBP}_o - \text{DBP}_g$: -6.3 , 95% CI: -15.5 to 3.0 mm Hg, REP: 28.6 mm Hg) and the oscillometric technique estimated smaller inodilatory reductions of DBP (see Table 1) with a generally poor repeatability between the two methods as well (REP: 25.7 mm Hg).

Agreement between the finger pulse pressure and the acoustic reference method

There was good average agreement between DBP_{fg} (data derived by graphical analysis of the Finapres®-tracings) and DBP_g with regard to the resting baseline measurements ($\text{DBP}_{fg} - \text{DBP}_g$: -0.8 , 95% CI: -11.5 to 10.0 mm Hg) but the between-method repeatability

was relatively poor (REP: 28.6 mm Hg); this technique was nevertheless quite suitable to estimate isoprenaline induced reduction of diastolic blood pressure (average method difference $\text{DBP}_{fg} - \text{DBP}_g$: 1.8, 95% CI: -5.1 to 8.6 mm Hg, REP: 18.5 mm Hg, see Table 1 and Figure 3). It was quite unreliable though in estimating SBP at rest (average method difference $\text{SBP}_{fg} - \text{SBP}_g$: 18.3, 95% CI: 7.0 to 29.5 mm Hg, REP: 52.4 mm Hg) and clearly underestimated the isoprenaline induced rise of SBP: $\text{SBP}_{fg} - \text{SBP}_g$: -10.0 , 95% CI: -21.3 to -0.7 mm Hg, REP: 37.7 mm Hg). The outcome of the comparison was about similar when the automated displays of the device were taken rather than the more tedious graphical analysis of the tracings.

Error propagation

The isoprenaline induced rise of CO and SBP seem to blunt the error propagation in the calculation of TPR (see Figure 4); in consequence methods with substantial disagreement in estimating the isoprenaline induced reduction of DBP still have a rather good agreement in estimating the reduction of TPR (f.i. $\text{TPR}_{a-v} - \text{TPR}_g$: -15.8 , 95% CI: -54.0 to 22.3 dyn s cm^{-5} , REP: 107.8 dyn s cm^{-5} which is hardly different from $\text{TPR}_{a-IV} - \text{TPR}_g$: 17.7, 95% CI: -21.8 to 57.2 dyn s cm^{-5} , REP: 112.5 dyn s cm^{-5}).

Figure 2 Time course of the mean ($n = 8$, $\pm$ s.e. mean) BP and TPR values based on the graphical analysis of the analogue microphone signals of vascular wall motion sound (●) and oscillometry (▽) before, during and after a 10 min i.v. infusion (time 0:00 to 0:10) of $1 \mu\text{g min}^{-1}$ isoprenaline. For the mean blood pressure, the calculated MBP is shown as well (△).

Figure 3 Time course of the mean ($n = 8$, $\pm$ s.e. mean) BP and TPR values based on the graphical analysis of the analogue microphone signals of vascular wall motion sound (●) and finger pulse pressure (□: automated digital display and ◇: graphical analysis of the tracings) during and after a 10 min i.v. infusion (time 0:00 to 0:10) of $1 \mu\text{g min}^{-1}$ isoprenaline.

Figure 4 Time course (time in min) of the mean ($n = 8$, $\pm$ s.e. mean) arithmetic changes of DBP and TPR from pre-infusion baseline (= 'responses') during and after a 10 min i.v. infusion (time 0:00 to 0:10) of $1 \mu\text{g min}^{-1}$ isoprenaline. The values are shown for the graphical analysis of the analogue microphone signals of vascular wall motion sound (●), auscultation by stethoscope according to Korotkoff-I and -IV (○) and Korotkoff-V (□), oscillometry (▽) and finger pulse pressure (◇: analysis of tracings).

Discussion

Indirect non-invasive 'measurements' of blood pressure are *estimates* of actual blood pressure derived from detectable physiological phenomena that are mainly but not exclusively related to blood pressure. Indirect blood pressure estimates therefore should be considered as method-dependent and -specific. Different methods might yield different estimates of interventional blood pressure *changes*, i.e. the estimates of these changes might be subject to method*effect interaction [23]. This implies—as shown also here—that method-specific estimates of BP might agree reasonably well at rest but could disagree substantially when estimating interventional BP-changes.

We recently reported the disagreement between auscultatory estimates of isoprenaline induced changes of DBP based on the Korotkoff-IV- ('sound muffling', $\text{DBP}_{\text{a-IV}}$) and Korotkoff-V-criteria ('sound disappearance', $\text{DBP}_{\text{a-V}}$): the former being more accurate, whilst the latter is more sensitive (as it substantially overestimates the effect as is confirmed here) [13]. The acoustic methods, in order to be accurate, are tedious as they either require careful auscultation of Korotkoff-IV ($\text{DBP}_{\text{a-IV}}$) or graphical analysis of the analogue microphone signals of vascular wall motion (DBP_{g}). We therefore assessed two further methods than can be automated (and thus are also less observer-dependent): oscillometry (Dinamap®) and the photoplethysmographic measurement of finger pulse blood pressure (Finapres®). In the absence of invasive measurements, we again took the graphical analysis of the microphone signals as reference, as this method was shown to correlate well with invasive measurements [8] and is less subject to observer-effects. It needs to be stressed that the lack of invasive measurements as control makes it impossible to judge the relative validity (capacity to truly measure what is intended or claimed to be measured) of the methods.

The oscillometric estimates of SBP agreed well with the reference both in terms of the measurements at rest as for the responses to isoprenaline. For DBP however, the agreement was poor and DBP_{o} yielded smaller isoprenaline induced reductions of DBP. The oscillometric method in consequence is not very sensitive (but is also less affected by environmental interference such as postprandial effects). The method might nevertheless be useful when rather large changes are to be detected, and confidence rather than power is of primary concern.

The finger pulse pressure in contrast agreed well with the reference in terms of DBP but was quite unsatisfactory with regard to SBP. This is not surprising if one considers this signal as a 'reversed' digital plethysmographic pulse: it equals the pressure required to counterbalance the digital vascular pulsations and therefore not only relates to the systemic blood pressure but also to the peripheral conditions that modulate this reflection wave. The signal in consequence is likely to be biased by pressure independent changes of the pulse reflection. The finger pulse pressure technique, which has the major advantage of allowing continuous measurement, hence is mainly useful for quantitative monitoring of DBP and qualitative monitoring of SBP but it did not appear suitable for accurate investigations of pharmacodynamic effects that involve the peripheral circulation as well.

The present study thus confirmed that auscultatory estimates of DBP based on the Korotkoff-V criterion yield highly biased estimates of isoprenaline induced reductions of diastolic blood pressure, which they grossly overestimate, so that estimates based on the Korotkoff-IV criterion should be used instead; it is furthermore concluded that the finger pulse pressure offers a practical alternative to auscultation of DBP but is unsatisfactory with regard to SBP; for the latter, oscillometry proved to be more reliable, whereas it was low in sensitivity with regard to DBP, which it tended to underestimate. These findings again emphasise that indirect blood pressure measurements

are method-specific estimates of blood pressure that should not be combined across methods and that agreement between different methods for obser-

vations at rest does not preclude substantial disagreement in estimating interventional blood pressure changes.

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