Method specificity of the auscultatory estimates of the inodilatory reduction of diastolic blood pressure based on Korotkoff IV and V criteria

CHRISTIAN DE MEY

Centre for Cardiovascular Pharmacology, Wiesbaden, Germany

- 1 Non-invasive measurements of blood pressure (BP) are method-specific estimates of actual blood pressure. The agreement of the auscultatory Korotkoff V ('disappearance' of sound, kv) and Korotkoff IV ('sound muffling' kiv) cut-off points in measuring diastolic blood pressure (DBP) was evaluated in healthy subjects in the presence of various controlled inodilatory interventions.
- 2 Eating ($n = 8$), 10 min i.v. infusion of $1 \mu\text{g min}^{-1}$ isoprenaline and adrenaline ($n = 12$), p.o. administration of 40 mg of the PDE-III inhibitors isomazole and meribendan ($n = 18$) and p.o. administration of 1200 mg celiprolol ($n = 15$) caused evident chrono-inodilatory responses: average HR increases of 7, 19, 10, 17, 17 and 8 beats min^{-1} , estimated CO increases of 1.6, 4.5, 2.3, 1.9, 2.6 and 1.8 l min^{-1} and average shortening of QS_{2c} of 18, 41, 8, 37, 42 and 9 ms for food, isoprenaline, adrenaline, isomazole, meribendan and celiprolol, respectively.
- 3 In general, there was good agreement between DBP_{kv} and DBP_{kiv} measurements before the administration of the inodilatory treatments (bias $\text{DBP}_{kv}-\text{DBP}_{kiv}$: 1–2 mm Hg) but the extent of inodilatory DBP reduction (–8, –6, –10, –2, –7 and –8 mm Hg according to DBP_{kiv} for food, isoprenaline, adrenaline, isomazole, meribendan and celiprolol, respectively) was substantially overestimated when based on Korotkoff-V rather than -IV (bias $\text{DBP}_{kv}-\text{DBP}_{kiv}$ in estimating the inodilatory effect on DBP: –8, –12, 1, –13, –12 and –7 mm Hg for food, isoprenaline, adrenaline, isomazole, meribendan and celiprolol, respectively).
- 4 This bias on DBP had some impact on calculated mean blood pressure but the bias on TPR was substantially reduced: for the largest inodilatory TPR reduction, caused by isoprenaline, DBP_{kiv} related estimates were on average $-345 \text{ dyn s cm}^{-5}$; the DBP_{kv} derived estimates were only 51, 95% CI: -96 to -7 dyn s cm^{-5} larger; this is explained by the blunting of the DBP error propagation by the inodilatory rise of SBP and CO.
- 5 Measurements of DBP based on Korotkoff-IV and -V criteria should be seen as distinctly different and specific variates of inodilatory cardiovascular behaviour. The former is likely to be more accurate, whilst the latter is of value because of its high sensitivity.

Keywords blood pressure non-invasive bias Korotkoff sounds
food intake isoprenaline meribendan celiprolol inodilators

Introduction

One of the main non-invasive methods to measure blood pressure indirectly is based on the analysis of the changing vascular wall motion sounds on deflation of a proximal occluding cuff [1] as detected by stethoscope auscultation [2–4]. This allows delineation of systolic blood pressure (SBP) as the cuff pressure coinciding with Korotkoff-I sound (first appearance of a clear tapping sound that gradually increases in intensity) and diastolic blood pressure (DBP) as coinciding with either the Korotkoff-IV (sound muffling : DBP_{KIV}) or -V auscultatory criteria (sound disappearance : DBP_{KV}). The latter is widely used as it relies on a less observer-sensitive 'yes/no'-decision and thus can be automated quite easily. The former in contrast, is highly observer-dependent and difficult to automate. Less observer-dependent estimates of Korotkoff-IV DBP can be derived by the graphical analysis of the analogue acoustic signals of the vascular wall motion sounds detected by microphone [5, 6].

In spite of the relatively good agreement between DBP_{KIV} and DBP_{KV} estimates at rest [7, 8], concern has been expressed about their disagreement in estimating DBP changes in hyperkinetic cardiovascular states in particular [9–11]. This might be of special relevance in the evaluation of BP changes induced by inodilatory interventions, i.e. cardiovascular effects that comprise as well a vasodilatory action as a direct chronotropic and inotropic enhancement of systolic pump performance. We analysed DBP_{KIV} and DBP_{KV} simultaneously during detailed investigations of the inodilatory responses to food intake, i.v. infusion of isoprenaline and adrenaline, p.o. administration of the PDE-III inhibitors isomazole and meribendan and high doses of celiprolol in healthy man in order to address this issue.

Methods

Subjects

The data relate to four separate studies in which young male subjects (25 to 35 years of age) judged to be healthy on the basis of extensive medical and laboratory investigations participated: $n = 8$ (postprandial effects), $n = 12$ (isoprenaline and adrenaline), $n = 18$ (isomazole and meribendan) and $n = 15$ (celiprolol). The studies were conducted in agreement with the declaration of Helsinki (Hong Kong Amendment), the German Drug Law and the European Guidelines for Good Clinical Practice [12], on the basis of formal protocols that were reviewed and approved by an independent Ethics Committee. The subjects were fully informed about the nature of the studies and the medications. They confirmed their consent in writing and in presence of a witness.

Study designs

Each study was conducted in a period balanced multiple-way within-subject cross-over design with randomly allocated treatment sequences to evaluate the impact of an (assumed) inodilatory intervention relative to an appropriate control. In these studies, BP was measured by stethoscope auscultation of Korotkoff-I and -V sounds and Korotkoff-IV equivalents derived by graphical analysis of the analogue signals of vascular wall motion sound.

General procedures

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

Investigational treatments

Postprandial effects After 60 min rest for baseline equilibration, the subjects ($n = 8$) sat upright in bed for 15 min, either reading (control treatment PF) or eating a standard meal (PE: 1 boiled egg, 2 bread rolls, 3 teaspoons margarine, 40 g ham, 40 g cheese and 230 ml orange juice; *circa* 3100 kJ representing approximately 19% protein, 39% fat, and 42% carbohydrates, 1.2 g sodium, 0.76 g potassium and 0.45 g calcium) as used in our previous studies [5, 13]. Subsequently, the subjects resumed the supine position for a further 4 h.

Isoprenaline and adrenaline After 60 min rest for baseline equilibration, the subjects ($n = 12$) received either placebo or different doses of a β -adrenoceptor antagonist. Three hours later, isoprenaline in saline (Isuprel®, Boehringer Ingelheim, Germany) was infused intravenously at a dose of $1 \mu\text{g min}^{-1}$ for 10 min. One hour later a 10 min i.v. infusion of $1 \mu\text{g min}^{-1}$ adrenaline was administered as well. The data reported here relate to the catecholamine infusions subsequent to placebo.

PDE-III inhibitors After 60 min rest for baseline equilibration, the subjects ($n = 18$) received either placebo or 40 mg isomazole or 40 mg meribendan p.o. (Merck, Darmstadt, Germany). Subsequently, the subjects were investigated in the recumbent resting and fasting state for a further 6 h.

Celiprolol After 120 min rest for baseline equilibration, the subjects ($n = 15$) received either placebo or 1200 mg celiprolol (Seloken®, Upjohn GmbH, Germany). Subsequently, the subjects were investigated in the recumbent resting and fasting state for a further 4 h.

Cardiovascular investigations

Cardiovascular performance was investigated using ECG, phonocardiogram, carotid pulse curve and con-

ventional impedance cardiography ZCG [14, 15]. Stroke volume (SV, ml) was estimated from ZCG using Kubicek's equation [16]. Cardiac output was calculated from heart rate (HR) and SV ($CO = HR \times SV/1000$; $l \text{ min}^{-1}$). Systolic (SBP, mm Hg) and diastolic blood pressure (DBP, mmHg) were measured by stethoscope auscultation of the vascular wall motion sound (Korotkoff-I and -V) using a mercury sphygmomanometer (Erkameter® 660/304) and by graphical analysis [5, 13] of the analogue signals of vascular wall motion (Korotkoff-IV equivalents, Infraton®, Boucke, Tübingen, Germany). Measurements were made by well trained observers; all measurements within the subject were carried out by the same observer. General methodological directives (posture, cuff size, bladder size, inflation rate, deflation rate, etc.) were standardised within- and between all studies. Total peripheral resistance (TPR) was calculated from CO and the mean pressure ($MBP = DBP + 0.43 \times (SBP - DBP)$ according to Wezler & Böger [17]) as $TPR = 79.92 \times (MBP - mAtP)/CO$, in which mAtP represents the mean atrial pressure ($\approx 3 \text{ mm Hg}$).

Data analysis

For the postprandial changes, meribendan, isomazole and celiprolol, the differences between the inodilatory test treatment and its control ('effects') were evaluated for the values before the administration of the investigational treatments ('baseline values') and for the maximum of the arithmetic changes subsequent to the application of the treatments ('inodilatory responses'). For the adrenergic agonists only the inodilatory responses were assessed as the values

before the infusions served as control for the subsequent responses. The *bias* (= extent of disagreement) between the estimates of these effects according to the auscultatory kiv and kv criteria was estimated as the difference between the mean effects according to the different criteria and the corresponding 95% CI.

Results

Agreement of baseline readings of DBP

There was little difference between the active treatments and their controls with regard to the baseline values prior to the administration of the inodilatory interventions. There was excellent agreement between the two methods in estimating these small differences (Table 1).

Non-agreement of the estimates of the inodilatory DBP reduction

Relative to the control treatment (for food, isomazole, meribendan and celiprolol) or the pre-infusion resting values (for isoprenaline and adrenaline) each of the inodilatory interventions caused a qualitatively similar inodilatory response: a rise in heart rate (HR), systolic blood pressure (SBP) and cardiac output (CO) with a shortening of the electromechanical systole (QS_{2c}), a reduction of DBP and TPR (Table 2, Figure 1).

On the basis of the kiv criterion, the DBP-reduction ranged from -6 (isoprenaline) to -10 mm Hg

Table 1 Mean values of diastolic blood pressure (DBP, mm Hg) and estimated total peripheral resistance (TPR, dyn s cm^{-5}) before (baseline) and after (responses) the inodilatory intervention. For the baseline values, the mean for the control treatment (based on kiv measurements), the average treatment difference ('effect' = active *minus* control treatment for kiv measurements) and the average method bias (effect according to kv *minus* effect according to kiv) plus 95% CI on the effect estimates are detailed. For the inodilatory responses (i.e. arithmetic changes subsequent to the inodilatory intervention relative to pre-intervention baseline), the average effect estimates (= responses for the active *minus* responses for control treatment) and the average method bias (see above) plus 95% CI on the estimates of these effects are listed. *Note:* for the infusion of the adrenergic agonists (adrenaline and isoprenaline) there was no control other than the baseline readings before the infusion. For the other interventions a suitable control was investigated in within-subject cross-over fashion

DBP (mm Hg)	Control	Baseline values		Inodilatory responses	
		Effect (kiv) active— control	Method bias on the effect estimates: effect (kiv)—effect (kv) Mean 95% CI	Effect (kiv) active— control	Method bias on the effect estimates: effect (kiv)—effect (kv) Mean 95% CI
Isoprenaline	67.2		1.2 -1.7 to 4.0	-6.2	-12.2 -21.2 to -3.1
Adrenaline	68.3		-0.4 -5.6 to 4.8	-9.6	0.8 -4.9 to 6.4
Celiprolol	80.4	-0.6	-0.7 -5.8 to 4.3	-8.3	-6.9 -12.4 to -1.5
Isomazole	63.8	0.6	0.2 -3.7 to 4.1	-2.3	-12.9 -20.1 to -5.7
Meribendan	63.8	0.6	0.1 -2.9 to 3.0	-6.6	-12.4 -18.9 to -5.9
Food	70.5	1.7	-0.8 -2.3 to 0.7	-7.5	-7.6 -11.8 to -3.4
TPR (dyn s cm^{-5})					
Isoprenaline	958		4 -24 to 32	-345	-51 -96 to -7
Adrenaline	979		-12 -72 to 48	-278	4 -56 to 64
Celiprolol	1066	42	-12 -49 to 25	-245	-22 -54 to 10
Isomazole	844	-62	-8 -44 to 27	-129	-42 -94 to 10
Meribendan	844	-11	-3 -28 to 22	-195	-42 -86 to 2
Food	1312	-50	-13 -58 to 31	-278	-44 -79 to -9

Table 2 Mean (plus s.d.) inodilatory changes of heart rate (HR, beats min^{-1}), systolic blood pressure (SBP, mm Hg), impedance cardiographic cardiac output (CO, l min^{-1}) and HR-corrected electromechanical systole (QS_{2c} , ms) in response to the inodilatory interventions.

	HR (beats min^{-1})	SBP (mm Hg)	CO (l min^{-1})	QS_{2c} (ms)
Isoprenaline	19.3 (7.2)	18.0 (9.0)	4.5 (1.7)	-40.6 (11.3)
Adrenaline	9.9 (5.4)	2.0 (5.0)	2.3 (1.2)	-8.1 (7.5)
Celiprolol	7.8 (5.0)	1.7 (7.2)	1.8 (0.9)	-9.4 (11.8)
Isomazole	16.6 (10.6)	6.6 (11.9)	1.9 (1.7)	-36.9 (10.2)
Meribendan	17.3 (10.6)	12.4 (9.3)	2.6 (1.6)	-42.3 (19.9)
Food	6.5 (5.9)	8.0 (3.6)	1.6 (0.8)	-18.2 (9.6)

Figure 1 Time course of mean heart rate (HR, beats min^{-1}), systolic (SBP, mm Hg), diastolic (DBP, mm Hg), mean blood pressure (MBP, mm Hg), impedance cardiographic estimates of cardiac output (CO, l min^{-1}) and calculated total peripheral resistance (TPR, dyn s cm^{-5}) subsequent to the administration of a single p.o. dose of 1200 mg celiprolol relative to placebo. Measurements (DBP) and calculations (MBP and TPR) based on auscultatory Korotkoff-IV end points (placebo: $\square$ celiprolol: $\blacksquare$) are contrasted with those of auscultatory Korotkoff-V end points (placebo: $\circ$ celiprolol: $\bullet$).

(adrenaline). With the exception of adrenaline, all inodilatory reductions of DBP were estimated to be substantially larger when the kv criterion was considered: the bias ranged from a further drop of 7 (for celiprolol) to 12 mm Hg (for isoprenaline, isomazole and meribendan) on top of the effect according to kiv (Table 1).

Agreement of the estimates of TPR

In spite of the bias on the estimates of DBP, there was only a slight disagreement between the estimates of TPR derived from DBP_{kiv} and DBP_{kv} . This reflects that the propagation of the DBP error was blunted by the rise of SBP (thus reducing the bias on MBP) and the rise of CO (thus reducing the bias on TPR).

Discussion

Indirect non-invasive 'measurements' of blood pressure are *estimates* of actual blood pressure derived from detectable physiological phenomena (for instance changing vascular wall motion sound on deflation of a proximal initially occluding cuff) 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-related effects and method*intervention interaction [18]: the interventional changes might be overestimated or underestimated in a method-specific way.

This relates to the interventional changes of the blood pressure independent determinants of the indirect estimates of blood pressure. This implies that method-specific BP estimates might agree reasonably well at rest (as was the case between DBP_{kV} and DBP_{kIV} in the present evaluation) but could disagree substantially when estimating interventional BP changes.

These issues were exemplified here by the haemodynamic changes induced by inodilatory manoeuvres, i.e. increases in systolic forward pump performance associated with systemic peripheral vasodilatation. The overall inodilatory profile of eating [13], isoprenaline [19, 20], PDE-III inhibition [21, 22] and high doses of celiprolol [23] observed here, confirms previous findings with similar methods in similar populations. In the presence of such inodilatory changes, DBP_{kV} and DBP_{kIV} estimates were found to disagree substantially, the former estimating far larger DBP reductions and less efficient BP-homeostasis (on the basis of MBP) than the latter.

Previous reports indicated that DBP_{kIV} estimates agreed reasonably well with invasively measured BP responses to isoprenaline whereas DBP_{kV} overestimated them [6]. The bias thus primarily affects DBP_{kV} (rather than DBP_{kIV}), indicating a protracted audibility of vascular wall (motion) sound in the presence of inodilatory haemodynamic changes, which is not primarily due to BP itself. This agrees with the observation that the extent of disagreement increases when the associated inodilatory changes (rise of HR and CO and decrease of QS_{2c}) are more pronounced. Surprisingly, there was no evident bias

between the method-specific estimates of the inodilatory DBP responses to adrenaline. This might relate to its vasoactive α -adrenergic component (which becomes evident by a relative vasoconstriction if this dose of adrenaline is infused subsequent to a pre-treatment with a non-selective β -adrenoceptor antagonist [24].

We therefore conclude that a) indirect blood pressure measurements are method-specific estimates of blood pressure that should not be combined across methods, b) agreement between different methods for observations at rest does not preclude substantial disagreement in estimating interventional blood pressure changes, c) auscultatory estimates of DBP based on the Korotkoff-V criterion (disappearance of vascular wall motion sound) yield highly biased estimates of inodilatory reductions of diastolic blood pressure, which they grossly overestimate, so that d) estimates based on the Korotkoff-IV criterion ('muffling' of vascular wall motion sound) should be used instead. It is furthermore concluded that the bias on DBP has little impact on MBP and hardly any on TPR, as the associated inodilatory (cardiac) changes blunt the propagation of the DBP error in their calculation. As the Korotkoff-V measurements are useful as highly sensitive (albeit) non-specific indices of inodilatory cardiovascular changes; there is value in evaluating both Korotkoff-V and Korotkoff-IV DBP provided their different meaning is understood and highlighted.

The author wishes to thank Dr K. Erb, Dr V. Schroeter, Dr R. Butzer and Dr K. Breithaupt-Grögler for their continuous help and assistance.

References

- 1 Riva-Rocci S. Un nuovo sfigmomanometro. *GAZ Med Italiana Torino* 1896; **47**: 981–996.
- 2 Geddes LA, Hoff HE, Badger AS. Introduction of the auscultatory method of measuring blood pressure – including a translation of Korotkoff's original paper. *Cardiovasc Res Cent Bullet* 1966; **5**: 57–74.
- 3 Ettinger W. Auskultatorische Methode der Blutdruckbestimmung und ihr praktischer Wert. *Wien klin Wochenschr* 1907; **20**: 992–926.
- 4 Laher M, O'Brien E. In search of Korotkoff. *Br med J* 1982; **285**: 1796–1798.
- 5 de Mey C, Hansen-Schmidt S, Enterling D. Postprandial haemodynamic changes : a source of bias in cardiovascular research affected by its own methodological bias. *Cardiovasc Res* 1988; **22**: 703–707.
- 6 Dietz U, Belz GG. Low frequency arterial wall movements for indirect blood pressure measurement in man. *Arzneim Forsch/Drug Res* 1991; **41**: 557–562.
- 7 Lichtenstein MJ, Rose G, Shipley M. Distribution and determinants of the difference between diastolic phase 4 and phase 5 blood pressure. *J Hypertension* 1986; **4**: 361–363.
- 8 Folsom AR, Prineas RJ, Jacobs DR, Luepker RV, Gillum RF. Measured differences between fourth and fifth phase diastolic blood pressures in 4885 adults: implications for blood pressure surveys. *Int J Epidemiol* 1984; **13**: 436–441.
- 9 Kaijser L. The indirect method of recording blood pressure during exercise—can the diastolic pressure be measured? *Clin Physiol* 1987; **7**: 175–179.
- 10 Gould BA, Hornung RS, Altman DG, Cashman PM, Raftery EB. Indirect measurement of blood pressure during exercise testing can be misleading. *Br Heart J* 1985; **53**: 611–615.
- 11 Burton AC. Editorial : The criterion for diastolic pressure—revolution and counterrevolution. *Circulation* 1967; **36**: 805–809.
- 12 Good Clinical Practice for Trials on Medicinal Products in the European Community. Note for Guidance II/3976/88-EN, 04.05.1990.
- 13 de Mey C, Hansen-Schmidt S, Enterling D. Food intake as a source of methodological bias in cardiovascular clinical pharmacology. *Pharmaceut Med* 1987; **2**: 251–257.
- 14 de Mey C, Enterling D. Disagreement between standard transthoracic impedance cardiography and the automated transthoracic electrical bioimpedance method in estimating cardiovascular performance in healthy man. *Br J clin Pharmacol* 1993; **35**: 349–355.
- 15 de Mey C, Belz GG, Nixdorf U, Butzer R, Schroeter V, Meyer J, Erbel R. Relative sensitivity of four methods in assessing systolic cardiovascular effects of isoprenaline in healthy volunteers. *Clin Pharmacol Ther* 1992; **52**: 609–619.
- 16 Kubicek WG, Karnegis JN, Patterson RP, Witsoe DA,

- Mattson RH. Development and evaluation of an impedance cardiac output system. *Aerosp Med* 1966; **37**: 1208–1212.
- 17 Wezler K, Böger A. Die Dynamik des arteriellen Systems. *Ergebn Physiol* 1939; **41**: 291–606.
- 18 de Mey C, Matthews J, Butzer R, Schroeter V, Belz GG. Agreement and reproducibility of the estimates of cardiovascular function by impedance cardiography and M-mode echocardiography in healthy subjects. *Br J clin Pharmacol* 1992; **34**: 88–92.
- 19 de Mey C, Enterling D. Noninvasive estimates of the inodilatory effects of isoprenaline and their inhibition by transdermally delivered mepindolol in healthy man. *J cardiovasc Pharmacol* 1992; **20**: 358–366.
- 20 de Mey C, Belz GG, Nixdorf U, Butzer R, Schroeter V, Meyer J, Erbel R. Relative sensitivity of four methods in assessing systolic cardiovascular effects of isoprenaline in healthy volunteers. *Clin Pharmacol Ther* 1992; **52**: 609–619.
- 21 de Mey C, Enterling D, Hanft G. Noninvasive monitoring of systematic and exceptional effects of an investigational PDE III phosphodiesterase inhibitor in normal man. *Am J Noninvasiv Cardiol* 1991; **5**: 115–120.
- 22 Belz GG, Meinicke T, Schäfer-Korting M. The relationship between pharmacokinetics and pharmacodynamics of enoximone in healthy man. *Eur J clin Pharmacol* 1988; **35**: 631–635.
- 23 de Mey C, Breithaupt K, Palm D, Fuhr U, Belz GG. Effects of pretreatment with the selective β_1 -adrenoceptor antagonist bisoprolol on the cardiovascular actions and β -adrenoceptor subtype specific occupancies subsequent to the administration of celiprolol in healthy man. *Eur J clin Pharmacol* 1993; **44**: 341–348.
- 24 Personal observation.

(Received 17 January 1994,
accepted 20 December 1994)