Methodological aspects of blood pressure measurement and adherence to antihypertensive drug therapy

R.L. Braam

Cover design	Irene Verbaan/Richard Braam
Lay-out	Irene Verbaan, Breukelen
Printed	Gildeprint Drukkerijen B.V., Enschede

Methodological aspects of blood pressure measurement and adherence to antihypertensive drug therapy / Richard Louis Braam
Thesis Nijmegen
ISBN-10: 90-9021474-7
ISBN-13: 978-90-9021474-0

Publication of this thesis was financially supported by the St. Antonius Hospital, CenE Bankiers, Stichting bloedlink, Nederlands Hypertensie Genootschap, J.E. Jurriaanse Stichting and Stichting Carel Nengerman Fonds.
Additional financial support was provided by: Merck Sharp & Dohme B.V., Astellas Pharma B.V., Bayer B.V., Abbott B.V. and Pfizer B.V.

Methodological aspects of blood pressure measurement and adherence to antihypertensive drug therapy

Een wetenschappelijke proeve
op het gebied van de Medische Wetenschappen

Proefschrift
ter verkrijging van de graad van doctor
aan de Radboud Universiteit Nijmegen
op gezag van de Rector Magnificus prof. dr. C.W.P.M. Blom,
volgens besluit van het College van Decanen
in het openbaar te verdedigen op
woensdag 31 januari 2007 om 15.30 uur precies

door

Richard Louis Braam
geboren op 1 oktober 1975
te Haarlem

Promotores:	Prof. dr. Th. Thien Prof. dr. J.W.M. Lenders
Manuscriptcommissie:	Prof. dr. F.W.A. Verheugt Prof. dr. J.F.M. Wetzels Dr. W.J.W. Bos (St. Antonius Ziekenhuis, Nieuwegein)

Financial support by the Netherlands Heart Foundation and Jacques H. de Jong Stichting for publication of this thesis is gratefully acknowledged.

Voor mijn ouders
Voor Frederieke

Table of contents

Chapter 1

Introduction and aim of the thesis

Introduction

Hypertension is an important risk factor for fatal and non-fatal cardiovascular events. After age and gender, blood pressure (BP) level is the most accurate predictor of life expectancy.[1] Worldwide hypertension affects millions of people. Not surprisingly, indirect BP measurement is one of the most frequently performed health care procedures.[1,2] However, it is one of the measurements performed most inaccurately.[3]

Blood pressure measurement techniques

Indirect BP measurement has developed revolutionary over the past two centuries. In the 19th and 20th century a vast amount of different devices was developed.[4] In 1896 the Italian physician Scipione Riva Rocci introduced the use of an occluding arm cuff allowing the measurement of systolic pressure. The Russian surgeon Nicolai Sergeivich Korotkoff discovered the auscultatory method of systolic and diastolic BP measurement in 1905.[4,5] Technological progress in the twentieth century has resulted in the development of the automated oscillometric measurement of BP.[6] When pressure in a cuff was lowered from above systolic to below diastolic BP, oscillations in pressure were observed.[7] The point where oscillations are maximal has been shown to coincide with the mean arterial pressure. Using the automated oscillometric technique, it has become relatively simple to measure BP. Hypertensive patients or other interested individuals can easily measure their BP outside the clinical setting (self-measurement). The market for automated oscillometric devices is rapidly growing and these devices increasingly replace the use of the mercury sphygmomanometer. A variety of automated devices can be acquired through the Internet[8] or bought at several shops.

For clinical BP measurement readings taken by a trained health care provider using a mercury sphygmomanometer and auscultation of Korotkoff sounds, have always been the gold standard. When BP was identified as an important cardiovascular risk factor in early prospective studies, like the Framingham study, it was measured with the mercury sphygmomanometer. However, BP measurements performed at home showed that office measurements may lead to misclassification of large numbers of normotensive individuals as hypertensive (white-coat hypertension).[3,9] More recently, the opposite was also observed, namely a normal BP in the office with a higher BP at home (so called: 'masked hypertension').[3,10] These two clinical situations can be explained by a number of factors: inaccuracy in the BP measurement, doctor related errors like terminal

digit preference, differences in the devices used an the inherent biological variability of BP.[3,11] Concern exists about the accuracy of the oscillometric method. With the oscillometric technique systolic and diastolic BP are not actually measured, but are determined using an algorithm. These algorithms differ among devices and the contents of these algorithms are kept secret by the manufacturers. Thus, whereas mercury sphygmomanometers have been comparable concerning design and hence accuracy, the accuracy of different oscillometric devices can be expected to vary substantially.
Before automated devices can substitute the mercury sphygmomanometer, they should be tested for their accuracy. For this purpose the British Hypertension Society (BHS), the European Society of Hypertension and the Association for the Advancement of Medical Instrumentation (AAMI) have each issued their own validation protocol.[12-16] Because of the importance of BP measurement in hypertension management we investigated the accuracy of several automated oscillometric BP measuring devices.

Drug adherence in hypertension treatment

Despite the availability of effective drugs to treat hypertension, about two third of patients with hypertension in the United States are either untreated or undertreated.[17,18] In almost one out of two patients BP remains too high despite treatment.[18] One of the reasons for this is insufficient drug adherence.
Drug adherence can be expected to decrease over time, because hypertension is largely an asymptomatic condition. Indeed the percentage of patients with hypertension that continued treatment for ten years was shown to be only 39%. Twenty-two percent of patients temporarily discontinued treatment (drug holidays) and 39% of patients discontinued permanently.[19]
The effect of different interventions to increase the level of adherence has been shown to be limited.[20,21] The absence of a gold standard method to measure sufficient drug adherence, is a problem.[22] The judgement of the physician has been shown to be inaccurate and many patients will not admit their non-adherence.[22] Counting the remaining tablets after a treatment period, is frequently used in clinical trials for measuring drug adherence, but is known to be inaccurate. A promising technique known as electronic Medication Event Monitoring System (MEMS), was introduced in 1987. Electronic recording of date and time of each opening of a pill box, can help to monitor drug adherence. Unfortunately, also with this technique patients can mislead the investigator by throwing away medication. Truly objective methods that measure actual drug intake are still not available. Drug intake can be demonstrated by measuring

the amount of a chemical marker which is added to the drug a patient has to take.[22] The ideal marker should have a long half life and has to be safe in the amounts administered. Preferably the marker is biologically inactive and is not metabolised. The anion bromide could be such a marker. The utility of bromide as a method to assess drug adherence and the application of this technique in clinical practice was examined as part of this thesis.

Aim of the thesis

The aim of part I of this thesis was to study the accuracy of different automated oscillometric BP measuring devices as an alternative to the mercury sphygmomanometer. First, the current validation protocols were critically evaluated. Then the accuracy of two different oscillometric BP measuring devices, one measuring at the upper-arm and one at the wrist, was tested. The influence of the BP level on the accuracy of oscillometric BP measuring devices was further investigated. Finally a general overview on oscillometric BP devices is given.The aim of part II of this thesis was to study the use of the chemical marker bromide to measure drug adherence in healthy volunteers and hypertensive patients. The results were compared to other methods available to estimate drug adherence.

References

1. Beevers DG, Beevers M. Blood pressure measurement: worsening chaos. J Hum Hypertens 2000;14:415-416.

2. Grim CM, Grim CE. Manual blood pressure measurement – still the gold standard. Why and how to measure blood pressure the old-fashioned way. In: Weber MA (editor). Hypertension Medicine; Chapter 11. Humana Press Inc., Totowa, New Jersey 2001.

3. Pickering TG, Hall JE, Appel LJ, Falkner BE, Graves J, Hill MN, Jones DW, Kurtz T, Sheps S, Roccella EJ. Recommendations for blood pressure measurements in humans and experimental animals. Part 1: blood pressure measurement in humans. A statement for professionals from the subcomittee of professional and public education of the American Heart Association Council on high blood pressure research. Hypertension 2005;45:142-161

4. O'Brien E, Fitzgerald D. The history of blood pressure measurement. J Hum Hypertens 1994;8:73-84.

5. Postel-Vinay N. A century of arterial hypertension, 1896-1996. John Wiley & Sons Ltd., Chichester, 1996.

6. O'Brien E, Fitzgerald D. Chapter 1: The history of indirect blood pressure measurement. In: Handbook of hypertension, Volume 14: Blood pressure measurement. Editors: O'Brien E, O'Malley K. Elsevier, Amsterdam, 1991:1-54.

7. Mauck GW, Smith CR, Geddes LA, Bourland JD. The meaning of the point of maximum oscillations in cuff pressure in the indirect measurement of blood pressure – part II. J Biomech Eng 1980;102:28-33.

8. Graves JW. A survey of validated automated home blood pressure monitors available for the Internet shopper. Blood Press Monit 2005;10: 103-107.

9. William G, Ogedegbe G, Schwartz JE, Chaplin WF, Goyal T, Clemow L, Davidson KW, Burg M, Lipsky S, Kentor R, Jhalani J, Shimbo D, Pickering TG. Assessment of the white-coat effect. J Hypertens 2006;24(1):67-74.

10. Aksoy I, Deinum J, Lenders JWM, Thien Th. Does masked hypertension exist in healthy volunteers and apparently-well controlled hypertensive patients? Neth J Med 2006;64(3):72-77.

11. Mallion JM. Home blood pressure. In: Mancia G, Chalmers J, Julius S, *et al.* (eds). Manual of Hypertension. Chapter 3.2. Churchill Livingstone London, 2002.

12. O'Brien E, Petrie J, Littler W, de Swiet M, Padfield PL, O'Malley K, *et al.* The British Hypertension Society protocol for the evaluation of automated and semiautomated blood pressure measuring devices with special reference to ambulatory systems. J Hypertens 1990;8:607-619.

13. O'Brien E, Petrie J, Littler WA, de Swiet M, Padfield PL, Altman D, *et al*. The British Hypertension Society protocol for the evaluation of blood pressure measuring devices. J Hypertens 1993;11(suppl 2):S43-S63.

14. Association for the Advancement of Medical Instrumentation. The national standard of electronic or automated sphygmomanometers. Arlington, VA: AAMI;1987.

15. Association for the Advancement of Medical Instrumentation. American national standard. Electronic or automated sphygmomanometers. Arlington, VA:AAMI;1993.

16. O'Brien E, Pickering T, Asmar R, Meyers M, Parati G, Staessen J, Mengden T, Imai Y, Waeber B, Palatini P, Atkins N, Gerin W. Working group on blood pressure monitoring of the European Society of Hypertension International Protocol for validation of blood pressure measuring devices in adults. Blood Press Monit 2002;7:3-17.

17. Wang TJ, Ramachandran SV. Epidemiology of uncontrolled hypertension in the United States. Circulation 2005;112:1651-1662.

18. Hajjar I, Kotchen TA. Trends in prevalence, awareness, treatment, and control of hypertension in the United States, 1988-2000. JAMA 2003;290:199-206.

19. Wijk van BLG, Klungel OH, Heerdink ER, Boer de A. Rate and determinants of 10-year persistence with antihypertensive drugs. J Hypertens 2005;23:2101-2107.

20. Haynes RB, McKibbon KA, Kanani R. Systematic review of randomised trials of interventions to assist patients to follow prescriptions for medications. Lancet 1996;348:383-386.

21. Schroeder K, Fahey T, Ebrahim S. How can we improve adherence to blood pressure-lowering medication in ambulatory care? Systematic review of randomised controlled trials. Arch Intern Med 2004;164:722-732.

22. Urquhart J. Role of patient compliance in clinical pharmacokinetics. A review of recent research. Clin Pharmacokinet 1994;27(3):202-215.

Part I

Methodological aspects of blood pressure measurement

Chapter 2

Validation of oscillometric blood pressure measuring devices

Chapter 2.1

The influence of the method of data analysis on the reported accuracy of automated blood pressure measuring devices

Richard L. Braam
Theo Thien

Department of Internal Medicine
University Medical Centre St. Radboud, Nijmegen, The Netherlands

Journal of Hypertension 2001;19:1765-1767

Abstract

Objective To show that different methods of data analysis affect the grading that blood pressure measuring devices achieve according to the British Hypertension Society (BHS)-protocol.

Methods Based on the somewhat unclear description of the exact method of data analysis in the BHS-protocol four different methods can be discerned. The effect on the grading-results is calculated for these four different options.

Results and Conclusions It is shown that using these four different options the achieved grade can range for diastolic blood pressure from C (option 1) to almost A (option 4) and for systolic blood pressure from D (option 1) to B (option 4). Different researchers may well have used different methods. Option 1 is the method that should be used. Also it is stated that the systematic error and the standard deviation of differences (SDD) are measures that give more insight to describe a device's performance. Calculating the grades after correction for the systematic error shows its influence and that of the SDD on the reported accuracy of a blood pressure measuring device.

Introduction

Different methods of data analysis affect the grading that blood pressure measuring devices achieve according to the British Hypertension Society (BHS) protocol. As a consequence of the somewhat unclear description of the method of analysis in the BHS-protocol, it is to be feared that different investigators have used different methods of analysis in their validation studies with unmistakable effects on the results of these studies. Moreover, the grading system of the BHS-protocol does not differentiate between the influence of the systematic error and the standard deviation of differences of a blood pressure measuring device on its accuracy. We describe a method to distinguish between these two factors.

One of the most frequently used protocols to test the accuracy of automatic blood pressure measuring devices is the BHS-protocol.[1] In phase IV, sequential blood pressure (BP) measurements are carried out in 85 subjects, as shown in Figure 1.

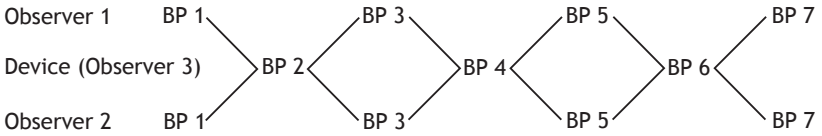

Figure 1. Sequential blood pressure measurements carried out in 85 subjects

Methods

Observers 1 and 2 measure BP simultaneously using a mercury sphygmomanometer (see Figure 1). For the analysis, absolute differences between device- and observer-measurements and, subsequently the percentage of differences ≤ 5, ≤ 10 and ≤ 15 mmHg are calculated. Based on these percentages, a grade is given (Table 1).

The differences between device- and observer-measurements should be calculated as follows: 'To compare one observer and test instrument, first analyse the data on 85 subjects using the pairs BP1 versus BP2, BP3 versus BP4, BP5 versus BP6. Then similarly analyse the pairs BP2 versus BP3, BP4 versus BP5, BP6 versus BP7. The result most favourable for the test device is selected'.[1] This paragraph from the BHS-protocol (1993) caused a great deal of concern, because how the precise analysis should be carried out is not clear. Four possible options will be explained, using a fictitious example (Figure 2).

Table 1. British Hypertension Society grading criteria for sequential measurements

	Absolute difference between standard and test device (mmHg)		
Grade	≤ 5	≤ 10	≤ 15
Cumulative percentages			
A	60	85	95
B	50	75	90
C	40	65	85
D		Worse than C	

To achieve a grade A, all percentages must be ≥ those in Table 1. Idem grade B and C.

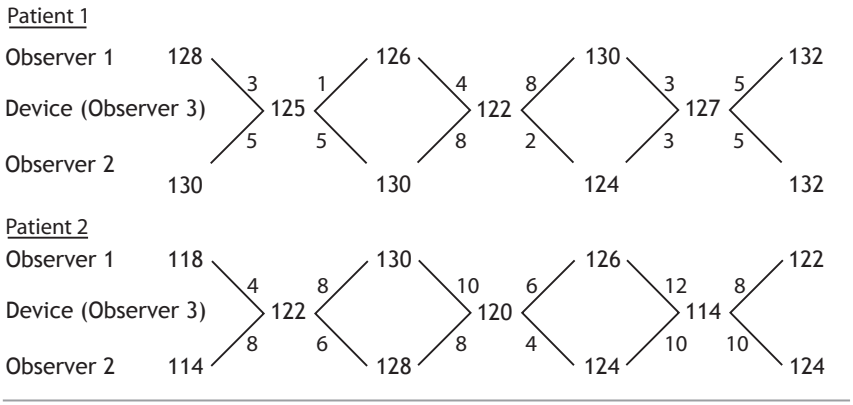

Figure 2. Examples of systolic (diastolic) pressure.

Option 1

For all 85 subjects, the differences BP1-BP2, BP3-BP4, BP5-BP6 are calculated (thus for observer 1: 3, 4, 3 for patient 1 and 4, 10, 12 for patient 2). One grade is therefore calculated for each observer. The same is done using the observer-measurements after each device-measurement, i.e. BP2-BP3, BP4-BP5, BP6-BP7 (example: 1, 8, 5 and 8, 6, 8 for observer 1 and 5, 2, 5 and 6, 4, 10 for observer 2). This leads to a grade for each observer. From the four grades from observers 1 and 2, the best is chosen.

Option 2

The three differences obtained by calculating BP1-BP2, BP3-BP4, BP5-BP6 for one patient (example: 3, 4, 3 for patient 1), are compared to the three calculated by BP2-BP3, BP4-BP5, BP6-BP7 (example: 1, 8, 5 for patient 1). From

these two groups, one is chosen, based on how many times the differences ≤ 5, ≤ 10 and ≤ 15 occur in each group (example: 3, 4, 3 for observer 1 and 5, 2, 5 for observer 2). The same procedure applies to subjects 2-85, resulting in one grade for observer 1 and one for observer 2. Of these two, the best is chosen.

Option 3

The difference between the device-measurement and an observer-measurement taken before the device measurement, is compared with the difference between the same device-measurement and an observer-measurement taken after the device-measurement (BP1-BP2 versus BP2-BP3; BP3-BP4 versus BP4-BP5, BP5-BP6 versus BP6-BP7). For every device-measurement, the smallest of two differences is chosen (example: for observer 1: patient 1: 1, 4, 3 and patient 2: 4, 6, 8). This is done separately for both observers, leading to one grade for each observer. The best of these two is chosen.

Option 4

Differences between each device-measurement and the four surrounding observer measurements are calculated (i.e. BP1-BP2, BP2-BP3, observer 1 and BP1-BP2, BP2-BP3, observer 2). The smallest of these four differences is chosen (example: patient 1: 1, 2, 3; patient 2: 4, 4, 8) resulting in one grade for systolic and one for diastolic pressure.

The grades that can be calculated for an automated blood pressure measuring device tested by us, according to the BHS-protocol using the four different options, are presented in Table 2. The BHS-grading improves going from option 1 to 4. A device with grade A or B for both diastolic and systolic blood pressure can be recommended for clinical use. According to option 1 the device certainly cannot be recommended for clinical use, according to option 4, it can almost. The option used clearly affects the final grading. Option 2 is sometimes unclear about which of the two groups of measurements has to be chosen, for example for observer 1, patient 2 we have to chose between 4, 10, 12 and 8, 6, 8. The first group of three means; once ≤ 5; twice ≤ 10, and 3 times ≤ 15, whereas the second group means 0 times ≤ 5; 3 times ≤ 10; 3 times ≤ 15. Which of the two groups should be chosen? We would have chosen the first group of three.
From O'Brien's group, we learnt that the correct method for analysis is Option 1 (personal communication), but Jones *et al*. (personal communication) used Option 2 for their analysis.[2] Our fear is that investigators use different analyses in their validation studies.

The accuracy of a blood pressure measuring device can be described using two parameters: the mean of differences (i.e. the systematic error) and the standard deviation (SD) of differences (SDD). The latter being the most important, because the systematic error can be corrected. Thus in our opinion, a device with a mean difference of 10±0.1 (SDD, mmHg) is superior to a device with 0.5±5 mmHg. In the BHS-grading the first device would have graded D, whereas the second would have achieved a grade A. Thus, the BHS grades do not give enough information about the blood pressure measuring qualities of a device. Calculating the grades before and after correction for the systematic error can help to distinguish the impact of the mean of differences and the SDD of a device on the final grading. To illustrate this we again calculated the grades for the automated blood pressure measuring device, using Option 1, after first correcting for the systematic error. For diastolic blood pressure, the grading improved from C to B (almost A) and for systolic blood pressure, from D to B (Table 2).

Perhaps an adaptation of the BHS-protocol is required.

Table 2. Grading results for diastolic and systolic blood pressure using different methods of analysis

	Diastolic				Systolic			
	≤ 5	≤ 10	≤ 15	Grade	≤ 5	≤ 10	≤ 15	Grade
Option 1	43	77	94	C	35	68	90	D
Option 2	48	79	95	C	41	71	89	C
Option 3	53	85	97	B	46	75	93	C
Option 4	58	86	97	B	49	77	94	C
Correction	59	88	97	B	51	88	96	B

References

1. O'Brien E, Petrie J, Littler W, de Swiet M, Padfield PL, Altman DG, *et al*. The British Hypertension Society protocol for the evaluation of blood pressure measuring devices. J Hypertens 1993;11(suppl 2):S43-S62.

2. Jones C, Taylor K, Poston L, Shennan A. Validation of the Welch Allyn 'Vital Sign' Oscillometric Blood Pressure Monitor. Abstract. American Society of Hypertension. Chicago, Congress 2000:S121.

Chapter 2.2

Letter to the Editor

The 'International Protocol': more insight or more arithmetic?

Reply by O'Brien and Atkins

Richard L. Braam
Theo Thien

Department of Internal Medicine
University Medical Centre St. Radboud, Nijmegen, The Netherlands

Blood Pressure Monitoring 2002;7:289-291

Dear Sir,

It was with interest that we read the recent article concerning the 'International Protocol', a newly proposed protocol for the validation of automated blood pressure measuring devices.[1] The objective of this new protocol was to simplify the most widely used protocols currently available, namely the British Hypertension Society (BHS) protocol 1993 and the protocol of the Association for the Advancement of Medical Instrumentation (AAMI). This has principally been achieved by eliminating phases 1 to 3 of the BHS-protocol, by decreasing the required number of subjects from 85 to 33 and by relaxing the recruitment of subjects in high and low blood pressure ranges. The 'International Protocol' is two-phased, making it possible to eliminate hopeless devices at an early stage.

Despite these obvious improvements we would like to make some critical remarks. In the 'International Protocol' the A, B, C, D grading system has been replaced by a pass/fail system. This hinders direct comparison between validated devices. In our opinion the best measures to describe a device's performance are the mean of differences and the standard deviation of differences (SDD). However these measures are not advocated by the current protocol. We find this strange not in the least because the minimum required number of differences <5, <10 and <15 mmHg (respectively 65, 80 and 95; Table 2b of the 'International Protocol') are originally based on a normal distribution with a mean error of 0 mmHg and a standard deviation of approximately 5 mmHg.

It is also stated that a large mean difference is usually accompanied with a greater standard deviation of differences; i.e. the standard deviation increases with error.[1] Using the same validation studies that formed the basis for the current changes in protocol we found a correlation coefficient of 0.19 for systolic and -0.09 for diastolic blood pressure between mean error and standard deviation (see Figure 1).[2-15] We therefore claim that it is possible for a device to show a large mean error with a relative small SDD. For such a device, simple correction of blood pressure readings with a constant factor would be appropriate.[16] Applying the new 'International Protocol' would probably classify such a device as unsuitable at the early phase. We therefore recommend studying whether, on the basis of earlier validation reports, it is possible to restore and redefine the AAMI criteria.

To test whether a device can accurately determine blood pressure in individuals a tertiary phase is introduced. In at least 22 out of 33 individuals two out of three differences should be <5 mmHg and a difference >5 mmHg for all

three comparisons is allowed in no more than three subjects. Large blood pressure fluctuations over time in a few individuals could therefore result in the failure of an accurate device to pass. We support the idea of Shirasaki *et al.*, to correct the SDD by subtracting the standard deviation of individual blood pressure variation from the overall standard deviation of differences.[17] This would allow the user to adjust for the influence of intra-subject variability on the calculated accuracy of devices.

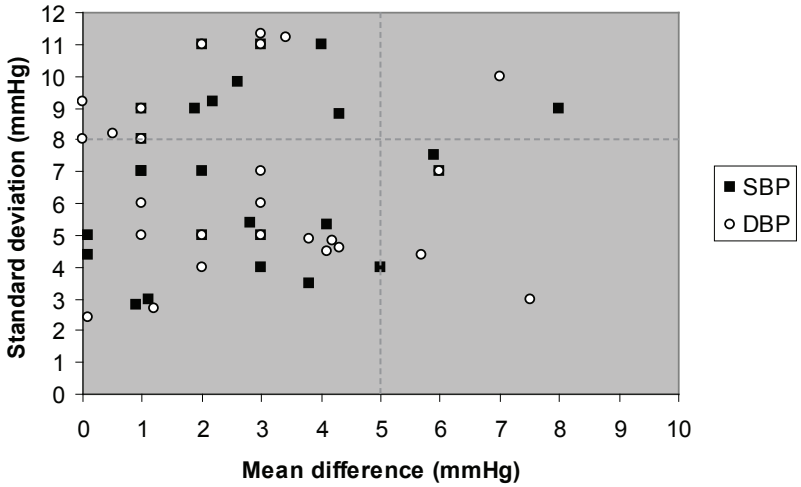

Figure 1. Mean difference versus standard deviation for different blood pressure measuring devices. Data are derived from the validation studies used to adapt the British Hypertension Society protocol.[1,3-16] For some devices more than one combination of mean error and standard deviation is used. For systolic blood pressure (SBP) a correlation coefficient of 0.19 and for diastolic blood pressure (DBP) of -0.09 is found. The vertical and horizontal lines are based on AAMI-criteria.

References

1. O'Brien E, Pickering T, Asmar R, Myers M, Parati G, Staessen J, *et al.* on behalf of the Working Group on Blood Pressure Monitoring of the European Society of Hypertension. Working Group on Blood Pressure Monitoring of the European Society of Hypertension International Protocol for validation of blood pressure measuring devices in adults. Blood Press Monit 2002;7:3–17.

2. O'Brien E, Mee F, Atkins N, O'Malley K. Inaccuracy of the Hawksley random-zero sphygmomanometer. Lancet 1990;336:1465–1468.

3. O'Brien E, Mee F, Atkins N, O'Malley K. Inaccuracy of seven popular sphygmomanometers for home-measurement of blood pressure. J Hypertens 1990; 8:621–634.

4. O'Brien E, O'Ferrall J, Galvin J, Costelloe R, Lydon S, Sheridan J *et al.* Evaluation of the Accutracker II non-invasive ambulatory blood pressure recorder according to the AAMI Standard. J Ambul Monitor 1991;4:27–33.

5. O'Brien E, Mee F, Atkins N, O'Malley K. Evaluation of the SpaceLabs 90202 according to the AAMI standard and BHS criteria. J Hum Hypertens 1991;5:223–226.

6. O'Brien E, Mee F, Atkins N, O'Malley K. Accuracy of the Del Mar Avionics Pressurometer IV determined by the British Hypertension Society Protocol. J Hypertens 1991;9(suppl 5):S1–S7.

7. O'Brien E, Mee F, Atkins N, O'Malley K. Accuracy of the Novacor DIASYS 200 determined by the British Hypertension Society Protocol. J Hypertens 1991; 9(suppl 5):S9–S15.

8. O'Brien E, Mee F, Atkins N, O'Malley K. Accuracy of the SpaceLabs 90207, Novacor DIASYS 200, Del Mar Avionics Pressurometer IV and Takeda TM-2440 ambulatory systems according to the AAMI and BHS criteria. J Hypertens 1991;9(suppl 6): S332–S333.

9. O'Brien E, Mee F, Atkins N, O'Malley K. Short report: accuracy of the SpaceLabs 90207 ambulatory blood pressure measuring system in normotensive pregnant women determined by the British Hypertension Society Protocol. J Hypertens 1993; 11(suppl 5):S869–S873.

10. O'Brien E, Mee F, Atkins N, O'Malley K. Accuracy of the Dinamap portable monitor, Model 8100, determined by the British Hypertension Society protocol. J Hypertens 1993;11:761–763.

11. O'Brien E, Mee F, Atkins N, O'Malley K. Accuracy of the CH-Druck/Pressure ERKA ambulatory blood pressure measuring system determined by the British Hypertension Society protocol. J Hypertens 1993;11(suppl 2):S1–S.

12. O'Brien E, Mee F, Atkins N, O'Malley K. Accuracy of the Profilomat ambulatory blood pressure measuring system determined by the British Hypertension Society protocol. J Hypertens 1993;11(suppl 2):S9–S15.

13. O'Brien E, Mee F, Atkins N, Thomas M. Evaluation of three devices for self-measurement of blood pressure: according to the revised British Hypertension Society Protocol: the Omron HEM-705CP, Philips HP5332 and Nissei DS-175. Blood Press Monit 1996;1:55–61.

14. Mee F, Atkins N, O'Brien E. Evaluation of the Profilomat IIR ambulatory blood pressure system according to the protocols of the British Hypertension Society and the Association for the Advancement of Medical Instrumentation. Blood Press Monit 1998;3:353–361.

15. O'Brien E, Mee F, Atkins N. Evaluation of the Schiller BR-102 ambulatory blood pressure system according to the protocols of the British Hypertension Society and the Association for the Advancement of Medical Instrumentation. Blood Press Monit 1999;4:35–43.

16. Braam RL, Thien T. The influence of the method of data analysis on the reported accuracy of automated blood pressure measuring devices. J Hypertens 2001; 19:1765–1767.

17. Shirasaki O, Tereda H, Niwano K, Nakanishi T, Kanai M, Miyawaki Y, *et al*. The Japan Home-health Apparatus Industrial Association: investigation of home-use electronic sphygmomanometers. Blood Press Monit 2001;6:303–307.

Reply by Eoin O'Brien and Neil Atkins

Doctors Braam and Thien kindly acknowledge that the recently published International Protocol from the Working Group on Blood Pressure Monitoring of the European Society of Hypertension[1] incorporates 'obvious improvements' over the earlier protocols of the British Hypertension Society (BHS)[2] and the Association for the Advancement of Medical Instrumentation (AAMI).[3]

However, they are critical of some aspects of the International Protocol. Their first concern is that replacement of the A–D grading system by a pass/fail system will hinder direct comparison between validated devices. The purpose of this approach was simply an acknowledgement of previous policy whereby devices gaining A and B grades according to the BHS protocol were recommended for clinical use, whereas those with C and D grades were not recommended.[2] Moreover, the tables in the International Protocol give full details of how the results are calculated and provide a more comprehensive means of device comparison than the former grading system.

The use of the mean and standard deviation as the basis for assessing the performance of a device is recommended in the AAMI protocol.[3] However, this approach is founded on the false assumption that device errors are normally distributed around the mean error. If the International Protocol had used a distribution based on a mean error of 0 mmHg and a standard deviation of 5 mmHg, the requirements for <5 mmHg, <10 mmHg and <15 mmHg would have been 67, 94 and 99 measurements respectively. It is not mathematically possible to choose a simple mean and standard deviation that will give a distribution comparable to that in the protocol. If, for example, the AAMI limits of a mean error of 5 mmHg and a standard deviation of 8 mmHg were used, the <5 mmHg, <10 mmHg and <15 mmHg requirements would be 39, 70 and 89 measurements. Even relating the standard deviation to the mean does not help. If, for example, the standard deviation were set so that at most 85% of the measurements would have an error of 10 mmHg, then depending on the mean difference, there would be an expected 5 mmHg limit of between 48 and 53% of the measurements and a restrictive 15 mmHg limit of between 97 and 98%. If values are chosen to ensure that the percentage of accurate measurements at a particular limit are reasonable then the requirements at lower limits will be too liberal whereas those at higher limits will be too restrictive. The use of non-parametric limits in the International Protocol is a valid, simple, and meaningful solution to this problem.

The International Protocol does not state that 'a large mean difference is usually accompanied with a greater standard deviation of differences'; what it does say is that 'standard deviations tend to increase with the error', which is quite different and indeed is supported by the data of Braam and Thien. It would not be appropriate to pass a device with a large mean error with a relatively small SDD as long as a simple constant correction factor was provided, because it would be totally impractical for manufacturers to sell devices and expect users to employ a correction factor. The onus should be on the manufacturer to do this prior to submitting the device for validation. The purpose of Phase 1 in the International Protocol is to detect such devices at an early stage so as not to dissipate resources on proceeding with a validation that is doomed to failure.

The last issue of concern relates to the tertiary phase of the International Protocol in which a 'difference of >5 mmHg for all three comparisons is allowed in at most three subjects'. This has been introduced to allow specifically for the 'large blood pressure fluctuations over time in a few individuals'. Based on the evidence of previous validation studies good devices will meet this criterion, and devices that do not are inaccurate by definition. It is accepted that studies based on statistical analyses can have Type I and Type II errors, and that a small percentage of devices (mostly marginal ones) will either incorrectly pass or fail a particular validation study. However, it is hoped that the much simplified International Protocol will result in the same devices being validated in a number of different centres thus reducing greatly the probability of such errors.

Finally, the overall concern that the International Protocol may fail 'accurate' devices that have a 'few' shortcomings, may be countered by the argument that poor devices are being recommended on the basis of the current validation criteria being applied in the AAMI protocol.[3] We are grateful to Braam and Thien for allowing us this opportunity to clarify these important aspects of the International Protocol.

References

1. O'Brien E, Pickering T, Asmar R, Myers M, Parati G, Staessen J, *et al.* on behalf of the Working Group on Blood Pressure Monitoring of the European Society of Hypertension. Working Group on Blood Pressure Monitoring of the European Society of Hypertension International Protocol for validation of blood pressure measuring devices in adults. Blood Press Monit 2002;7:3–17.

2. O'Brien E, Petrie J, Littler WA, de Swiet M, Padfield PL, Altman D, *et al.* The British Hypertension Society Protocol for the evaluation of blood pressure measuring devices. J Hypertens 1993; 11(Suppl 2):S43–S63.

3. American National Standard. Electronic or automated sphygmomanometers. Arlington, VA: Association for the Advancement of Medical Instrumentation;1993.

Chapter 2.3

Accuracy of the Welch Allyn Vital Signs Monitor 52000 automatic blood pressure measuring device according to a modified British Hypertension Society protocol

Richard L. Braam
Carlijn de Maat
Theo Thien

Department of Internal Medicine
University Medical Centre St. Radboud, Nijmegen, The Netherlands

Blood Pressure Monitoring 2002;7:185-189

Abstract

The accuracy of the Welch Allyn Vital Signs Monitor, a compact device for the oscillometric measurement of blood pressure, was determined according to the British Hypertension Society protocol. The monitor achieved a grade C for diastolic and a grade D for systolic blood pressure. The device is suitable for monitoring a patient, for example post-operatively, in the emergency department or during an intervention. The device cannot, however, be recommended for an exact determination of blood pressure when compared with the mercury sphygmomanometer. In an earlier validation report, the Welch Allyn Vital Signs Monitor achieved a grade A for both diastolic and systolic blood pressure. After adjusting for the difference in method of calculating the grades used in the two studies, there remained a considerable difference in grading results, for which no clear reason could be found.

Introduction

The market for automated blood pressure measuring devices is a rapidly growing one, devices for self-measurement being sold in vast quantities. The use of automated blood pressure measuring devices is increasing not only in the home, but also in the clinical setting. Mercury sphygmomanometers are currently still used in some hospitals, but with the inevitable banning in the near future of mercury because of environmental hazards, clinicians will be forced to look for alternatives.[1-3] Aneroid devices have, when calibrated against mercury sphygmomanometers, been shown to perform adequately in the beginning but poorly after a period of clinical use.[1,4] The introduction of aneroid devices will therefore mandate a verifying and stamping procedure at least every year.[5] Automated blood pressure measuring devices could be an alternative, but only if they are accurate enough. They are, however, rather expensive. These devices should be tested for their accuracy before using them in clinical practice or at home and a number of protocols have been drawn up in order to do this. Of these, the protocols of the British Hypertension Society (BHS) and the Association for the Advancement of Medical Instrumentation (AAMI)[6,7] are the most widely used. A great number of devices has so far been tested according to these protocols.[8] Both protocols are quite elaborate so proposals have recently been made for their simplification.[9] We used here the 1993 BHS protocol to determine the accuracy of the Welch Allyn Vital Signs Monitor (VSM).

Methods

The Welch Allyn VSM 52000 series is a compact, portable, light-weight (2.5 kg) device for the oscillometric measurement of blood pressure. It can measure systolic pressures of between 60 and 250 mmHg, diastolic pressures of between 30 and 160 mmHg and heart rates ranging from 40 to 200 beats per min. Blood pressure measurements (up to 99) can be stored and can also be printed out if required. The cuff pressure deflation occurs in steps of 8–10 mmHg. A number of hospitals in the Netherlands currently use this device in clinical practice.

British Hypertension Society protocol

The 1993 BHS protocol[6] consists of five phases: (1) before-use device calibration, (2) in-use assessment, (3) after-use device calibration, (4) static device validation and (5) report of the evaluation. To test the Welch Allyn VSM, we followed these five phases of the protocol, having first made a few adaptations to some of the phases, as explained below.

Before-use device calibration

In this phase, the performance of the device as a manometer is compared with that of a mercury sphygmomanometer. The device is connected to a mercury sphygmomanometer, which is in turn connected to another mercury sphygmomanometer. All three manometers are then connected to a cuff wrapped around a cylinder. Observer 1 reads a mercury sphygmomanometer, and observer 2 reads the device. A third observer calls out 'now' at certain pressures according to a table, and observers 1 and 2 read the pressures indicated by their respective devices. There should be five calls per deflation and six deflations per device. Twenty-eight out of the 30 measurements taken by observers 1 and 2 should differ no more than 3 mmHg. If the device does not pass phase 1, further testing is not performed. Because performing phase 1 in this manner is relatively time-consuming, and because of the possible error that can occur when undertaking this phase in the manner described, we used a somewhat different approach. We used a device named the CuffLink (Dynatech, Carson City, Nevada, USA) to test the performance of the Welch Allyn VSM as a manometer.[10] The CuffLink is linked to the Welch Allyn VSM and a mercury sphygmomanometer and subsequently generates pressures of between 0 and 300 mmHg. The pressure measured by the VSM can then be compared with that measured simultaneously by the mercury sphygmomanometer. At least 30 measurements are made. These two approaches are in essence the same.

In-use assessment

The device is used for 1 month to assess its performance in daily practice. There should be at least 400 inflations per device, and problems encountered during this phase should be recorded.

After-use device calibration

During this phase, the procedure described in phase 1 is repeated to see whether there is any change in accuracy of the device as a manometer as a result of 1 month's use in practice.

Device validation

The observers were first trained using the method described in the BHS protocol.[6] Contrary to the BHS protocol, we used two observers, instead of three, both of whom were blinded to each other and to the device. Sequential same-arm measurements were then carried out in different subjects. The first blood pressure measurement was used to determine which blood pressure

category the subject belonged to. It has been reported that recruiting subjects with extremes of blood pressure blood is difficult[9] so we adapted the required distribution into different blood pressure categories as previously proposed: for diastolic blood pressure, the distribution was one-third with a pressure less than 80 mmHg, one-third with a pressure between 80 and 100 mmHg, and one-third with one over 100 mmHg; for systolic blood pressure, one-third were placed in each of three categories – less than 130 mmHg, between 130 and 160 mmHg and greater than 160 mmHg.[9]

The subjects used in the systolic blood pressure group do not have to be the same subjects who are used for the diastolic blood pressure group. A subject can, for example, have a diastolic blood pressure of 110 mmHg and a systolic blood pressure of 150 mmHg, being allocated to the category with a diastolic blood pressure of 100 mmHg or above, but not to the systolic group of 130–160 mmHg if this has already been filled. Thus, the groups for the two pressures are not necessarily composed of the same subjects, and it may be necessary to perform sequential measurements in more than 85 subjects before enough suitable individuals have been recruited to each blood pressure category.

All the measurements were carried out with the subjects lying supine after at least 5 min rest. The Welch Allyn VSM and the mercury sphygmomanometer were connected to the same bladder and cuff, alternating measurements being made possible by the use of a T-tap, which prevented manual cuff changes having to be made after each reading. The arm circumference of each subject was determined to check whether it was appropriate for the cuff size. The two observers' hearing was checked prior to the measurements.

Analysis was carried out separately for each observer, each device receiving a grade A, B, C or D according to Table 1.

Table 1. Britsh Hypertension Society grading criteria for sequential measurements[6]

Absolute difference between standard and test device (mmHg)[a]			
Grade	≤ 5	≤ 10	≤ 15
Cumulative percentages			
A	60	85	95
B	50	75	90
C	40	65	85
D		Worse than C	

[a]To achieve a particular grade, all the percentages must be equal to or greater than those in the table

To calculate a grade, the percentages of device measurements differing from those of the mercury sphygmomanometer by less than 5, 10 and 15 mmHg were calculated. The final grade was the best grade out of four (two from observer 1 and two from observer 2).[6] The same procedure is followed for both systolic and diastolic blood pressure. It is therefore possible that the best grade for systolic blood pressure is obtained with observer 1, whereas the best grade for diastolic blood pressure is obtained from observer 2. Only devices reaching a grade A or B for both systolic and diastolic blood pressure can be recommended for use in clinical practice. According to the AAMI criteria, the mean difference has to be 5 mmHg or less and the standard deviation of the differences 8 mmHg or less.[7] The discrepancy between the two observers has to be such that 80% of the differences between observer 1 and 2 fall within 5 mmHg and 95% within 10 mmHg.[6]

Another method for visualizing the relation between the differences and the absolute blood pressure values has been developed by Bland and Altman.[11] In this study, we also present Bland–Altman plots.

Results

Phases 1–3

The Welch Allyn VSM passed the before- and after-use device calibrations without any problems. During the in use assessment, the device appeared to be very reliable and easy to use.

Device validation

Two observers were trained by an experienced clinician at our hospital. Sequential measurements were carried out on 123 subjects recruited from the out-patient clinic of the department of internal medicine at our centre. Patients with a cardiac arrhythmia were excluded from the measurements. The 123 subjects were arranged according to the sequence of measurements. Among these subjects, individuals were selected based on their diastolic and systolic (entry) blood pressure until a sufficient number had been recruited to each subgroup. The characteristics of the group of 85 subjects selected for the diastolic and the systolic blood pressure groups are as shown in Table 2.

A total of 118 subjects had to be included in order to reach the right distribution of blood pressure level. The differences between the observers lay well within the acceptable range (Table 3).

The VSM achieved a grade C for diastolic and a grade D for systolic blood pressure measurement (Table 3). Also shown are the results for the different

blood pressure categories. It can be seen that the device becomes less accurate in the higher blood pressure categories (Table 3).

Table 2. The characteristics of the two groups of 85 subjects whose diastolic and systolic blood pressures, respectively, were used for grading. A total of 118 subjects participated (see text)

	Diastolic blood pressure	Systolic blood pressure
Mean age±SD	51±16	48±18
Number of women (%)	52(61)	54(64)
Mean arm circumference±SD (cm)	27.6±3.1	27.4±3.2
Mean height±SD (cm)	170±10	170±9
Mean weight±SD (kg)	78±15	76±14

Table 3. Grading results for the Welch Allyn Vital Signs Monitor

Absolute difference between standard and test device (mmHg)						
		n	≤5 (%)	≤10 (%)	≤15 (%)	Mean±SD (AAMI)[a]
Difference between observers						
DBP	A	255	92	100	100	-0.4±2.8
SBP	A	255	91	99	99	0.5±3.2
Final grade						
DBP	C	255	43	77	94	5.3±6.7
SBP	D	255	35	67	90	7.5±7.1
Accuracy of the Welch Allyn Vital Signs Monitor for different blood pressure levels						
Blood pressure <80/<130 mmHg						
DBP	B	84	52	87	98	2.1±6.5
SBP	C	84	46	77	96	5.9±6.0
Blood pressure 80-100/130-160 mmHg						
DBP	C	87	45	77	95	6.6±5.5
SBP	D	87	28	64	93	7.8±6.1
Blood pressure >100/>160 mmHg						
DBP	D	84	31	67	89	7.3±7.0
SBD	D	84	31	60	80	10.5±13.5
	Method of Jones *et al.* [12,13]					
DBP	C	255	48	79	95	
SBP	C	255	40	75	93	

[a]Criteria for passing Association for the Advancement of Medical Instrumentation grading: mean difference <5 mmHg and standard deviation <8 mmHg (for both systolic (SBP) diastolic (DBP) blood pressure).[7]

Figures 1 and 2 show the results for diastolic and systolic blood pressure as Bland–Altman plots. For diastolic blood pressure, there was a significant correlation of $r=0.44$ ($P<0.0001$). There was no significant correlation for systolic blood pressure.

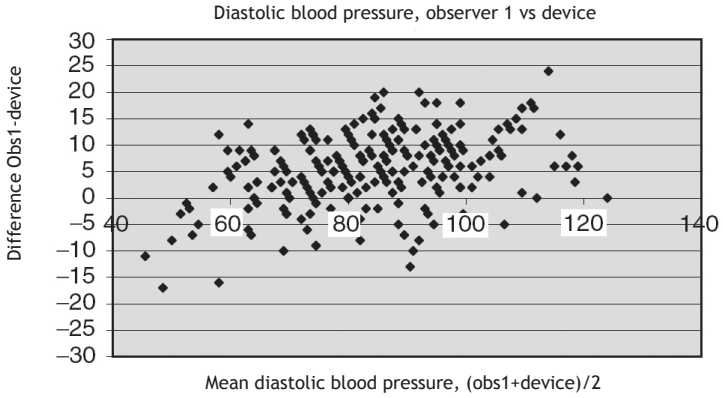

Figure 1. Bland–Altman plot for diastolic blood pressure showing absolute blood pressure versus difference between blood pressure measured by observer and device: *n*=255, *r*=0.44 (P<0.0001). Obs, observer. For further details see text.

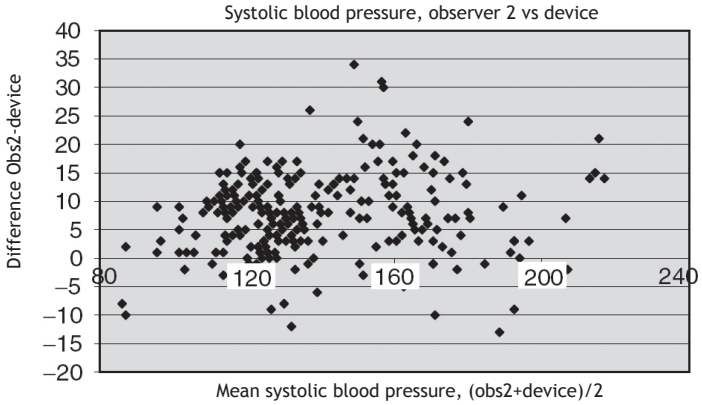

Figure 2. Bland–Altman plot for systolic blood pressure showing absolute blood pressure versus difference between blood pressure measured by observer and device: *n*=255, *r*= not significant. Obs, observer. For further details see text.

Discussion

The Welch Allyn VSM appeared to be a reliable easy-to-use device. Jones *et al*. have also tested the Welch Allyn VSM, reporting a grade A for both systolic and diastolic blood pressure. Moreover, they found that this grading was not affected when the data were divided into low-, medium- and high-pressure categories, except for medium diastolic blood pressure (range 80–100 mmHg), for which the grading became a B.[12]

The conclusion reached by Jones *et al*. was therefore that 'the monitor achieved the highest possible grade A, for both systolic and diastolic blood pressure and very few devices achieved such accuracy, which uniquely remained consistent over all blood pressure ranges'.[12]

So how can this difference in results be explained? The method of data analysis influences the reported accuracy of automated blood pressure measuring devices[13], and Jones *et al*. used a somewhat different method of calculating the grades from that used in the BHS protocol.[5,13] Sequential measurements are carried out as indicated in Figure 3. Using an example (Figure 3), we will explain the difference in the method employed in the BHS-protocol and that used by Jones *et al*. These authors calculated the grades by comparing for patient 1 the three differences calculated from BP1 – BP2, BP3 – BP4 and BP5 – BP6 (3, 4 and 3 in the example) with the three values BP2 – BP3, BP4 – BP5, BP6 – BP7 (1, 8 and 5 in our example). From these two sets of figures, one is chosen based on how many times the differences <5, <10 and <15 mmHg occur in each group (in this example, 3, 4 and 3 being chosen). The same is done for subjects 2 – 85, resulting in one grade for observer 1 and one for observer 2, the best of which is chosen.

According to the BHS protocol, the following calculation should be performed. For all 85 subjects, the differences BP1 – BP2, BP3 – BP4 and BP5 – BP6 are calculated (giving, in our example, 3, 4 and 3 for observer 1, and 5, 8 and 3 for observer 2). Thus, one grade is calculated for each observer. The same is done using the observer measurements after each device measurement, i.e. BP2 – BP3, BP4 – BP5 and BP6 – BP7 (in the example, 1, 8 and 5 for observer 1, and 5, 2 and 5 for observer 2). This also leads to a grade being given to each observer. From the two grades for observer 1 and the two grades for observer 2, the best is chosen. If we had used Jones *et al*.'s method, the grading results would have been slightly better, as shown in Table 3, but we would still have been unable to reach a grade A for diastolic and systolic blood pressure in our study.

We can find no explanation for the remaining difference in grading results: both investigations used sequential measurements as described in the BHS protocol, the inter-observer differences lay well within acceptable limits and were comparable in the two studies, and both studies employed well-trained observers to make the measurements. There have, to our knowledge, not been any validation studies involving conventional oscillometric devices using the BHS protocol that have compared the accuracy of the same device when used by different groups. Different investigators can apparently come up with

different grading results for the same device, making the results of validation reports of individual research groups more difficult to interpret.

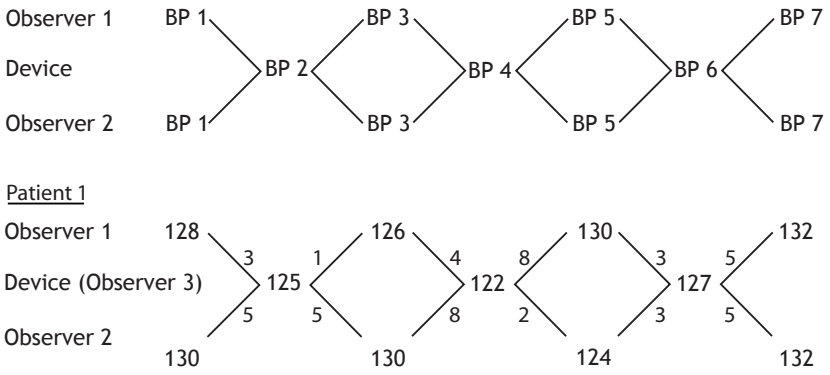

Figure 3. Sequential measurements used in the 1993 British Hypertension Society protocol, with an example for systolic pressure

Based on our results, the Welch Allyn VSM cannot be regarded as a good substitute for the mercury sphygmomanometer. On the other hand, because of the relatively small standard deviation of the differences, the device is certainly suitable for monitoring a patient, for example post-operatively, during a stay in the emergency department or during an intervention. Because of its ability to detect blood pressure fluctuations over time in the same patient, the device is equipped to perform adequately the task its name suggests, that of monitoring the 'vital signs'. For the diagnosis, treatment and control of hypertensive patients, a more accurate automatic blood pressure measuring device is, however, needed.

References

1. O'Brien E. Will the millimetre of mercury be replaced by the kilopascal? J Hypertens 1998;16:259–261.

2. O'Brien E. Will the mercury manometer soon be obsolete? J Hum Hypertens 1995;9:933–934.

3. O'Brien E. Replacing the mercury sphygmomanometer. Requires clinicians to demand better automated devices. BMJ 2000;320:815–816.

4. Jones CR, Khanna M, Rushbrook J, Poston L, Shennan AH. Are aneroid devices suitable replacements for mercury sphygmomanometers? (abstract). J Hum Hypertens 2001;15:843.

5. Canzanello VJ, Jensen PL, Schwartz GL. Are aneroid sphygmomanometers accurate in hospital and clinic settings? Arch Intern Med 2001;161:729–731.

6. O'Brien E, Petrie J, Littler W, de Swiet M, Padfield PL, Altman DG, *et al*. The British Hypertension Society protocol for the evaluation of blood pressure measuring devices. J Hypertens 1993; 11(suppl 2):S43–S62.

7. Association for the Advancement of Medical Instrumentation. American national standard for electronic or automated sphygmomanometers. Arlington, VA: AAMI;1987.

8. O'Brien E. State of the market in 2001 for blood pressure measuring devices. Blood Press Monit 2001;6:171–176.

9. O'Brien E. Proposals for simplifying the validation protocols of the BHS and the AAMI. Blood Press Monit 2000;5:43–45.

10. Amoore JN. Assessment of oscillometric non-invasive blood pressure monitors using the Dynatech Nevada CuffLink analyser. J Med Eng Technol 1993;17(1):25–31.

11. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet 1986;1:307–310.

12. Jones CR, Taylor K, Poston L, Shennan AH. Validation of the Welch Allyn 'Vital Signs' oscillometric blood pressure monitor. J Hum Hypertens 2001;15:191–195.

13. Braam RL, Thien Th. The method of data-analysis influences the reported accuracy of blood pressure measuring devices. J Hypertens 2001;19:1765–1766.

Chapter 2.4

Accuracy of the Omron RX-M, an automated blood pressure measuring device, measuring blood pressure at the wrist, according to a modified British Hypertension Society protocol

Richard L. Braam
Bünyamin Aslan
Theo Thien

Department of Internal Medicine
University Medical Centre St. Radboud, Nijmegen, The Netherlands

Blood Pressure Monitoring 2004;9:25-30

Abstract

Objective To determine the accuracy of the Omron RX-M, a device measuring blood pressure oscillometrically at the wrist.

Methods In 89 subjects (mean age 55 ± 14 years) blood pressure measurements at the wrist with the Omron RX-M were compared to sequential blood pressure measurements with a mercury sphygmomanometer at the (same) upper-arm and to simultaneous measurements with the Omron HEM-705 CP at the opposite arm.
Measurements were analyzed according to the British Hypertension Society (BHS) - protocol 1993, to the protocol of the Association for the Advancement of Medical Instrumentation (AAMI) and (retrospectively) to the new 'International Protocol'.

Results Mean differences (± SD) between the measurements with the mercury sphygmomanometer and the Omron RX-M were – 7.5 ± 8.4 mmHg for diastolic blood pressure (DBP) and – 2.5 ± 12.2 mmHg for systolic blood pressure (SBP), thus not fulfilling the AAMI-criteria (≤5 ± 8). According to the BHS-criteria a grade D was achieved for both DBP and SBP. Compared to the Omron HEM 705 CP results were – 6.3 ± 7.1 for DBP (grade D) and – 4.1 ± 12.7 for SBP (grade D). The Omron RX-M also failed to pass the new 'International Protocol' in phase 1.

Conclusion Although easy to use, based on this study the Omron RX-M can not be recommended to determine blood pressure accurately.

Introduction

The market for automated blood pressure-measuring devices is a rapidly growing one. Over 11 million devices were sold worldwide in 2000.[1] Self-measurement (home measurement) of blood pressure is becoming increasingly popular. Self-measurement could help to increase compliance to medical therapy and avoids the 'white-coat' effect. Ohkubo *et al*.[2] showed that home blood pressure measurement was a stronger predictor of cardiovascular mortality than office blood pressure. However in order to interpret measurements correctly new reference values have to be defined.[3] Also measurements should be reliable and the devices should be easy to operate.[1]

A great number of blood pressure measuring devices for self-measurement of upper arm blood pressure so far have been validated.[4] However there have been only a few reports concerning the accuracy of devices measuring blood pressure at the wrist. These devices have the advantage of easy applicability and small volume, making it possible to measure blood pressure in a variety of circumstances. A number of protocols have been drawn up to test the accuracy of blood pressure measuring devices. Of these protocols two have been extensively used, the British Hypertension Society (BHS) and the protocol of the Association for the Advancement of Medical Instrumentation (AAMI).[5,6] Only recently a newly developed protocol, named the 'International Protocol' has been added on behalf of the Working Group on Blood Pressure Monitoring of the European Society of Hypertension.[7] In the present study we have still used the BHS-protocol (1993) as a directive to determine the accuracy of the Omron RX-M wrist blood pressure measuring device.

Methods

The Omron RX-M is a compact, light-weight (150 g) device, designed for measuring blood pressure oscillometrically at the wrist. It can measure blood pressures between 40–280 mmHg and heart rates between 40–200 beats/min. Up to 14 measurements can be stored. Wrist circumference should be between 13.5–19.5 cm.

BHS-protocol (1993)[5]

The former BHS-protocol 1993 consists of five phases: (1) before-use device calibration; (2) in-use assessment; (3) after-use device calibration; (4) static device validation and (5) report of evaluation.

To test the Omron RX-M the most important phase of this protocol, phase 4, was followed, after having made some adaptations that will be explained

below. In accordance with the new 'International Protocol' phases 1 to 3 have not been performed. These phases were mainly introduced to secure uniform manufacturer's standards for production of devices.

Device validation

First a human observer trained by the method described in the BHS-protocol.[5] Contrary to the BHS-protocol we used one human observer instead of two performing sequential blood pressure measurements on the same arm as the test-device. The Omron HEM-705 CP was used as a second 'observer'. Simultaneous measurements on the opposite arm were performed using this device. The Omron HEM-705 CP has been shown to be a reliable and accurate blood pressure measuring device, achieving a grade 'A' and 'B' for diastolic and systolic blood pressure respectively in a previous validation report.[4,8] It also passed the AAMI criteria.[8]

Sequential same-arm measurements are carried out in different subjects. A total of 85 subjects for diastolic and systolic blood pressure are required. The first blood pressure measurement is used to determine which blood pressure category the subject belongs to. It has been mentioned before that recruiting subjects with blood pressures at the extremes of high and low blood pressure range is difficult.[9] Therefore we adapted the required distribution into different blood pressure categories as previously proposed: for diastolic blood pressure the distribution has to be 1/3 <80 mmHg, 1/3 between 80–100 mmHg, and 1/3 >100 mmHg and for systolic blood pressure, 1/3 <130 mmHg, 1/3 between 130–160 mmHg and 1/3 >160 mmHg.[8] These blood pressure ranges have now also been introduced in the 'International Protocol'.[7]

The subjects used in the systolic blood pressure group are not necessarily the same subjects used in the diastolic blood pressure group. For example a subject can have a diastolic blood pressure of 110 mmHg and a systolic blood pressure of 150 mmHg and therefore can be used in the category with a diastolic blood pressure >100 mmHg, but the category with a systolic blood pressure between 130–160 mmHg has already been filled. Thus the total group of subjects for diastolic and systolic blood pressures are not necessarily composed of the same subjects and it can be necessary to perform measurements in more than 85 subjects before enough suitable subjects have been recruited for each blood pressure category.

All measurements were carried out with the subjects supine after at least 5 min rest. Measurements with the Omron RX-M were done with the wrist at heart level. Sequential measurements were carried out according to the scheme

described in the BHS-protocol.[5,10] Also simultaneous measurements with the Omron RX-M (wrist) and the Omron HEM-705 CP (opposite arm) were performed. Differences in blood pressure between left and right arm have been shown to be small.[11] However in order to compensate for a possible systematic left/right difference in blood pressure for all subjects, the position of the wrist device at the left or right side was determined by chance.

The wrist circumference of each subject was determined to check whether it was appropriate for the cuff-size. Only subjects with a wrist circumference between 13.5–19.5 cm were selected. Six of 95 subjects were excluded because the wrist circumference was too large. Upper-arm circumference had to be between 22–32 cm. Analysis was carried out separately for observer I and 'II' (i.e., the Omron HEM-705 CP). Each device receives a grade A, B, C or D according to Table 1. To calculate a grade the percentages of device measurements differing from the mercury sphygmomanometer by 5, 10 and 15 mmHg or less were calculated. The same procedure is followed for systolic and diastolic blood pressure. For the simultaneous measurements of the Omron RX-M and Omron HEM-705 CP the more stringent grading criteria of the BHS-protocol 1990 were used.[12] Only devices reaching a grade A or B for both systolic and diastolic blood pressure can be recommended for use in clinical practice. According to the AAMI criteria the mean difference has to be 5 mmHg or less and the standard deviation of differences has to be 8 mmHg or less.[6] A method to visualize the dependency of the differences from the absolute blood pressure values is developed by Bland and Altman.[13] In this study we also present Bland–Altman plots.

Table 1. Britsh Hypertension Society grading criteria for simultaneous (upper part) and for sequential measurements (lower part) from the protocols 1990 and 1993[5,12]

	Absolute difference between standard and test device (mmHg)*		
Grade	≤ 5	≤ 10	≤15
Cumulative percentages			
1990			
A	80	90	95
B	65	85	95
C	45	75	90
D		Worse than C	
1993			
A	60	85	95
B	50	75	90
C	40	65	85
D		Worse than C	

*To achieve a certain grade all percentages must be equal to or greater than those in the table.

Results

The human observer was trained by an experienced clinician at our hospital. Mean difference (±SD) between observer and expert measurements in 18 subjects (three measurements per subject) were – 0.2 (±2.2) mmHg for diastolic and 0.1 (±3.6) mmHg for systolic blood pressure. Subsequently, measurements were carried out in 89 subjects mainly recruited from the outpatient clinic of the department of internal medicine. The characteristics of the 89 subjects are shown in Table 2. The distribution of the subjects over the predefined blood pressure levels is also shown in Table 2.

Table 2. The characteristics of the group of 89 subjects whose diastolic and systolic blood pressure were used for grading and distribution over predefined blood pressure levels (see text).

Mean age ± SD				55±13.7		
Number of women (%)				49 (55)		
Mean wrist circumference ± SD in cms				17±1.3		
Mean upper arm circumference ± SD in cms				29±2.8		
	Diastolic blood pressure (mmHg)			Systolic blood pressure (mmHg)		
	<80	80-100	>100	<130	130-160	>160
Wanted	29	29	28	28	29	28
Achieved	23	47	19	11	34	44

As can be seen the predefined number of subjects with a systolic blood pressure below 130 mmHg was not reached. Based on the comparison between observer measurements and device measurements the Omron RX-M achieved a grade 'D' for diastolic and 'D' for systolic blood pressure. Results are shown in Table 3 and Figure 1. Grading results were unaffected by blood pressure level and by patient's age. Based on the (sequential) measurements with the Omron HEM-705 CP and the mercury sphygmomanometer at opposite arms, difference of blood pressure between left and right arm were shown to be small. With the mercury sphygmomanometer on the right arm, mean blood pressure difference was +2 mmHg and – 2 mmHg for systolic and diastolic blood pressure, respectively and with the mercury sphygmomanometer on the left arm +1 mmHg and – 1 mmHg. Differences between measurements with the mercury sphygmomanometer and the Omron HEM-705 CP are shown in Table 3 and Figure 2. In comparison with the Omron HEM-705 CP the test device achieved a grade 'D' for diastolic and 'D' for systolic blood pressure (see Table 3 and Figure 3).

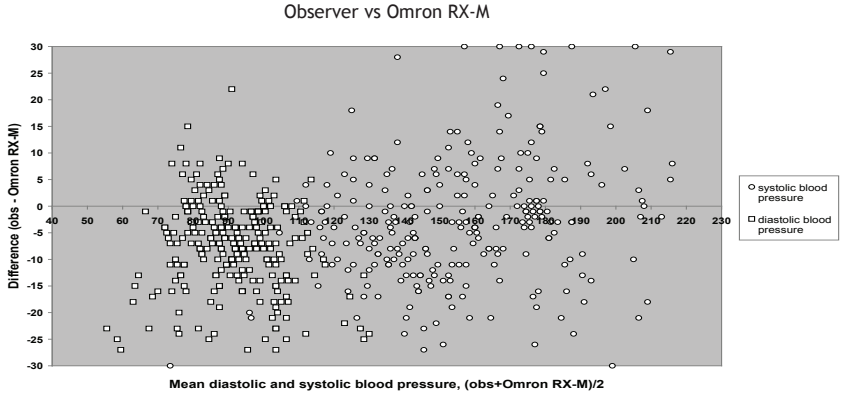

Figure 1. Bland-Altman plot for diastolic and systolic blood pressure showing absolute blood pressure versus difference between blood pressure measured by observer and wrist device (sequential measurements, same arm). Obs, observer; Vs, versus.

We retrospectively followed the method of the recently published 'International Protocol'. The device would have been rejected in phase 1 of the protocol (see Table 3). Blood pressure measurements in 21 people would have been enough to reject the device in phase 1.

Table 3. Grading results for the Omron RX-M

Absolute difference between standard and test device (mmHg)						
	Grade	*n*	<5	<10	<15	Mean±SD (AAMI)*
Observer versus Omron RX-M						
DBP	D	267	37%	67%	83%	-7.5±8.4
SBP	D	267	37%	65%	81%	-2.5±12.2
Observer versus Omron HEM 705 CP						
DBP	A	267	60%	85%	96%	-1.3±7.6
SBP	C	267	42%	71%	88%	1.6±10.9
Omron HEM 705 CP vs Omron RX-M						
DBP	D	267	42%	72%	88%	-6.3±7.1
SBP	D	267	29%	50%	78%	-4.1±12.7
Observer versus Omron RX-M using International Protocol[7]						
Phase 1						Pass/Fail
DBP		45	16	31	37	F
SBP		45	17	29	38	F
Phase 2.1						
DBP		99	35	59	79	F
SBP		99	32	61	78	F
Phase 2.2			At least 2/3	0/3<5		
DBP		99	13	14		F
SBP		99	14	12		F

*Criteria for passing AAMI: mean difference <5 mmHg and standard deviation <8 mmHg (for both systolic and diastolic blood pressure).

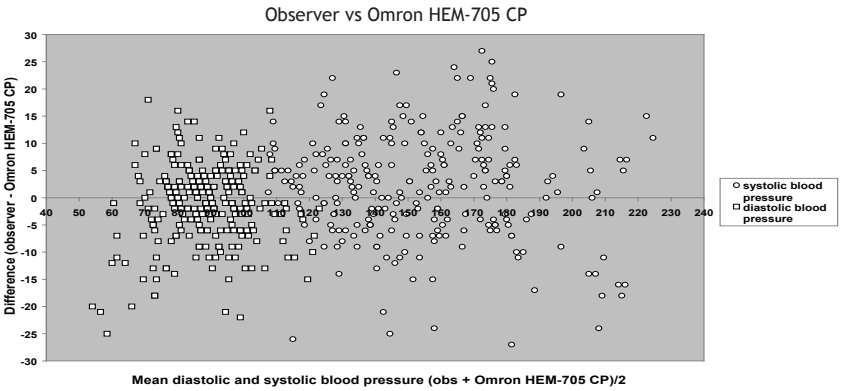

Figure 2. Bland-Altman plot for diastolic and systolic blood pressure showing absolute blood pressure versus difference between blood pressure measured by observer and Omron HEM-705 CP (sequential measurements, opposite arm). Obs, observer; Vs, versus.

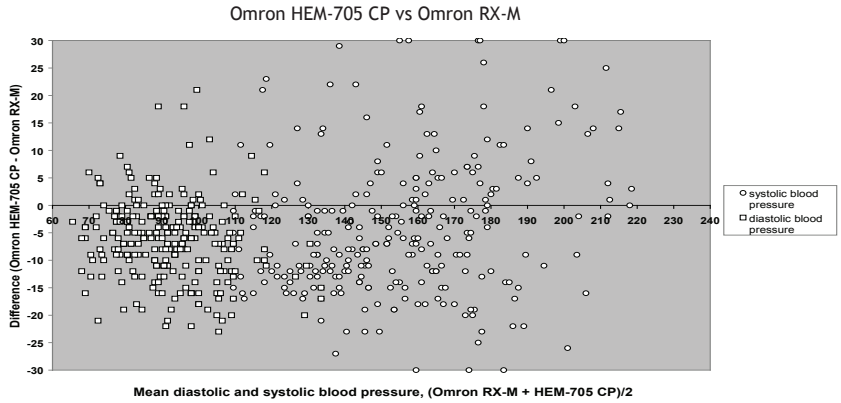

Figure 3. Bland-Altman plot for diastolic and systolic blood pressure showing absolute blood pressure versus difference between blood pressure measured by Omron HEM-705 CP and Omron RX-M (simultaneous measurements, opposite arms). Vs, versus.

Discussion

The Omron RX-M proved to be an easy to use device. Less than 4% of measurements were erroneous. The Omron RX-M achieved a grade 'D' for systolic and diastolic blood pressure. These results were highly reproducible when using the Omron HEM-705 CP as a reference. This validation report is the first to use an independent oscillometric blood pressure measuring device as a reference standard. The Omron HEM-705 CP has previously been shown to be a reliable and accurate blood pressure measuring device, validated according to the BHS-protocol and AAMI.[4,8]

A number of wrist blood pressure measuring devices have been tested.[4] But most of the devices have shown poor results. The Omron RX [HEM-608] achieved a grade 'B' for diastolic and systolic blood pressure in a previous validation report, but failed to achieve the AAMI criteria due to the large standard deviation of differences (nine for diastolic and systolic blood pressure).[14] The differences in grading results between the previous study and ours may in part be explained by a difference in method of data analysis as has been shown previously for the validation of the Welch Allyn Vital Signs Monitor.[9,15]

One more fundamental question is whether blood pressures measured at the radial artery and brachial artery are suitable for comparison. O'Rourke *et al*.[16], have shown that systolic blood pressure increases and diastolic blood pressure decreases (and hence pulse pressure increases) moving more distal from the ascending aorta.

Therefore a moderate difference between blood pressure measured at the upper arm and wrist can be expected. However mean blood pressure will be the same at these two sites and most oscillometric devices use algorithms to extrapolate systolic and diastolic blood pressure from this mean value.

In this study only one human observer was used instead of two. This leads to the potential danger that errors in blood pressure measurement by the human observer may greatly influence grading results. However the observer was well trained and with the Omron HEM-705 CP as a second independent 'observer' the same grading results were obtained. As can be seen in Table 2 the desired distribution of subjects over the blood pressure categories was not reached: especially the category of systolic blood pressure <130 mmHg could not be filled.

Using the 'International Protocol' we would have rejected the Omron RX-M in an early phase. The new protocol therefore seems to offer us the advantage of eliminating inaccurate devices at an early stage, thereby saving money, resources and time.

We conclude that based on our results the Omron RX-M is not able to determine blood pressures accurately. A more accurate wrist blood pressure measuring device has to be awaited.

References

1. Shirasaki O, Tereda H, Niwano K, Nakanishi T, Kanai M, Miyawaki Y, *et al*. The Japan Home-health Apparatus Industrial Association: investigation of home-use electronic sphygmomanometers. Blood Press Monit 2001; 6:303–307.

2. Ohkubo T, Imai Y, Tsuji I, Nagai K, Kato J, Kikuchi N. Home blood pressure measurement has a stronger predictive power for mortality than does screening blood pressure: a population-based observation in Ohasama, Japan. J Hypertens 1998;16:971–975.

3. Gaudemeris R de, Nguyen PC, Mallion JM. Home blood pressure: variability, comparison with office readings and proposal for reference values. J Hypertens 1994;12:831–838.

4. O'Brien E. State of the market for devices for blood pressure measurement. Blood Press Monit 2001;6:281–286.

5. O'Brien E, Petrie J, Littler W, de Swiet M, Padfield PL, Altman DG, *et al*. The British Hypertension Society protocol for the evaluation of blood pressure measuring devices. J Hypertens 1993;11(Suppl 2):S43–S62.

6. Association for the Advancement of Medical Instrumentation. American national standard for electronic or automated sphygmomanometers. Arlington VA: Association for the Advancement of Medical Instrumentation; 1987.

7. O'Brien, Pickering T, Asmar R, Myers M, Parati G, Staessen J, *et al.*, on behalf of the Working Group on Blood Pressure Monitoring of the European Society of Hypertension. Working Group on Blood Pressure Monitoring of the European Society of Hypertension International Protocol for validation of blood pressure measuring devices in adults. Blood Press Monit 2002; 7:3–17.

8. O'Brien E, Mee F, Atkins N, Thomas M. Evaluation of three devices for self-measurement of blood pressure according to the revised British Hypertension Society Protocol: the Omron HEM-705CP, Philips HP5332, and Nissei DS-175. Blood Press Monit 1996;1:55–61.

9. O'Brien E. Proposals for simplifying the validation protocols of the BHS and the AAMI. Blood Press Monit 2000;5:43–45.

10. Braam RL, Thien T. The influence of the method of data analysis on the reported accuracy of automated blood pressure measuring devices. J Hypertens 2001;19:1765–1767.

11. Lane D, Beevers M, Baines N, Bourne J, John A, Malins S, *et al*. Inter-arm difference in blood pressure: when are they clinically significant? J Hypertens 2002;20:1089–1095.

12. O'Brien E, Petrie J, Littler W, de Swiet M, Padfield PL, O'Malley K, *et al*. The British Hypertension Society protocol for the evaluation of automated and semi-automated blood pressure measuring devices with special reference to ambulatory systems. J Hypertens 1990;8:607–619.

13. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet 1986;1:307–310.

14. Shennan AH, Rushbrook J, Power J, Wright J, Poston L. An accurate oscillometric wrist blood pressure monitor: validation of the Omron RX (HEM-608). J Hum Hypertens 1998;12:794 (abstract).

15. Braam RL, Maat C de, Thien T. Accuracy of the Welch Allyn Vital Signs Monitor 52000 automatic blood pressure measuring device according to a modified British Society Hypertension protocol. Blood Press Monit 2002; 7:185–189.

16. O'Rourke MF, Kelly RP, Avolio AP. Chapter 2: What is the pulse? In: The arterial pulse. Philadelphia: Lea and Febiger;1992.

Chapter 2.5

Is the accuracy of blood pressure measuring devices underestimated at increasing blood pressure levels?

Richard L. Braam
Theo Thien

Department of Internal Medicine
University Medical Centre St. Radboud, Nijmegen, The Netherlands

Blood Pressure Monitoring 2005;10:283-289.

Background In validation studies reporting on the accuracy of blood pressure measuring devices (ambulatory and non-ambulatory systems), it is frequently stated that the accuracy of blood pressure devices seems to decrease at increasing blood pressure levels. This has been shown for several ambulatory devices in the past. Whether more recently validated devices are less accurate at increasing blood pressure levels is unknown, however.

Objectives We therefore retrospectively searched the literature for studies performed between 1993 and 2003, reporting on the accuracy of blood pressure measuring devices over different blood pressure levels. When needed, additional information from the authors was requested.

Methods In total, 30 studies were selected. Of these, the studies reporting on the accuracy of 13 different ambulatory and nine different non-ambulatory devices were useful. For both ambulatory and non-ambulatory devices, accuracy appeared to decrease at increasing blood pressure levels. This was particularly shown for systolic blood pressure.

Results We speculate whether this finding is due to the oscillometric method of blood pressure measurement. Another explanation may exist, however. Blood pressure variability increases with higher blood pressure. Further, the British Hypertension Society protocol 1993 uses sequential measurements. This may be the reason that, owing to the increased blood pressure variability, the accuracy of most devices tends to decrease at higher blood pressure levels. Consequently, the accuracy of blood pressure measuring devices may be underestimated at higher blood pressure levels.

Conclusion Currently used automated blood pressure measurement devices seem to be less accurate at increasing blood pressure levels. It is important to be aware of this phenomenon when treating hypertensive patients. The reported decrease in accuracy, however, may well be explained by the increasing blood pressure variability at increasing blood pressure and the use of sequential measurements. If this is the case, then the accuracy of these devices is perhaps underestimated.

Introduction

Hypertension is one of the major risk factors for the development of cardiovascular disease. Therefore, accurate detection of patients with hypertension is very important. Increasingly, blood pressure (BP) measurements are done with devices measuring BP oscillometrically. It is frequently stated in validation studies that automated devices become less accurate at increasing BP levels.[1] This has been shown to be correct for six ambulatory devices validated in the past.[2] Whether the same is still true for more recently validated ambulatory and non-ambulatory systems remains to be seen. We therefore analysed data obtained from validation studies performed between 1993 and 2003 regarding the accuracy of BP measuring devices at different BP levels. These devices were tested according to the British Hypertension Society (BHS) protocols or the protocol of the Association for the Advancement of Medical Instrumentation (AAMI).[3,4]

Methods

Using Pubmed (www.ncbi.nih.gov/entrez/query.fcgi) validation studies were selected on the basis of the following criteria: 1) studies had to have been performed between 1993 and 2003. 2) Validation was performed according to the BHS protocols or AAMI criteria. Use of a slightly modified BHS protocol (instead of the original) with, for example, two instead of three observers, was accepted. 3) Studies had to report the accuracy of the devices according to different BP levels. If not available, the authors were asked to give this information. 4) Devices had to measure BP auscultatorily (e.g. auscultatory mode for ambulatory BP measuring devices) or oscillometrically. 5) Studies that tested the accuracy of the BP measuring device during exercise, in pregnant women or in children were excluded. Devices listed in a recent review article were used as a directive for selection.[5] Studies were divided according to the BP measurement system tested: ambulatory or non-ambulatory.

Results

On the basis of the criteria mentioned, 12 studies reporting on ambulatory BP measuring devices and 18 studies reporting on the accuracy of non-ambulatory devices could be selected.[1,2,6-15,16-34] Of these, the studies reporting on the accuracy of 13 different ambulatory and nine different non-ambulatory devices were useful (Tables 1 and 2). We approached a number of authors for additional data. Unfortunately, there was only minimal response on the requests for

information. Only Altunkan *et al.*[13] could provide us with additional data. The minimal response was probably owing to the lack of time for most authors or because of the longer time period that had evolved since their original study. As shown in Tables 1 and 2, only a limited number of studies reported the mean difference and standard deviation of differences for the different BP levels. Therefore, the percentages of differences ≤ 5 mmHg across the different BP levels were used as a measure of accuracy: the percentages are plotted for the different devices in Figure 1 and 2. As with other biological parameters, one can expect the difference between actual and measured BP (i.e. the absolute BP difference) to increase with BP level.

Table 1. Accuracy of nine blood pressure measuring devices according to blood pressure level: non-ambulatory oscilometric devices for self-measurement or clinical use

Device	BP level		BHS grade		Percentage difference ≤ 5 mmHg		AAMI (mean±SDD) (mmHg)	
	DBP	SBP	DBP	SBP	DBP	SBP	DBP	SBP
Omron HEM-705 CP[1]	<80	<130	A	C	69	49	1±7	-2±6
	80-100	130-160	A	A	88	60	-1±4	-2±6
	>100	>160	B	C	64	47	-2±7	-3±8
Welch-Allyn VSM[27]	<80	<130	A	A	81	82	n.g.	n.g.
	80-100	130-160	B	A	56	73	n.g.	n.g.
	>100	>160	A	A	78	70	n.g.	n.g.
A&D UA-767[26]	<80	<130	B	A	78	88	0±5	1±4
	80-100	130-160	A	B	81	74	0±5	-1±5
	>100	>160	B	C	82	70	-1±6	-3±8
Microlife BP 3BTO-A[24]	<80	<130	A	A	77	80	n.g.	n.g.
	80-100	130-160	A	A	70	61	n.g.	n.g.
	>100	>160	B	C	56	50	n.g.	n.g.
Omron-MIT[25]	<80	<130	A	A	69	70	n.g.	n.g.
	80-100	130-160	A	B	73	54	n.g.	n.g.
	>100	>160	B	B	67	58	n.g.	n.g.
Welch-Allyn VSM[34]	<80	<130	B	C	52	46	-2±7	-6±6
	80-100	130-160	C	D	45	28	-7±6	-8±6
	>100	>160	D	C	31	31	-7±7	-11±14
Philips HP 5332[1]	<80	<130	A	C	69	51	-2±5	-5±5
	80-100	130-160	A	B	72	50	-4±5	-4±6
	>100	>160	A	D	67	32	-4±5	-9±9
Nissei DS-175[1]	<80	<130	B	B	73	59	0±9	-4±6
	80-100	130-160	A	D	69	24	-4±7	-9±6
	>100	>160	A	D	67	24	-4±6	-12±11
Dinamap 8100[a)] [23]	<80	<130	D	B	42	65	n.g.	n.g.
	80-100	130-160	D	B	52	70	n.g.	n.g.
	>100	>160	D	C	39	62	n.g.	n.g.

BP, blood pressure; BHS, Britsh Hypertension Society; SDD, standard deviation of differences; DBP, diastolic blood pressure; SBP, systolic blood pressure; n.g., not given. [a)]Tested according to the BHS protocol of 1990.

The relative difference, however, will be less dependent on the actual BP level. Perhaps using percentages instead of absolute values is preferable. We therefore calculated both the relative and absolute differences for the different BP levels using data from two devices we recently tested: the Welch Allyn Vital Signs Monitor, an oscillometric upper arm device and the Omron RX-M, an oscillometric device measuring BP at the wrist [34,35]

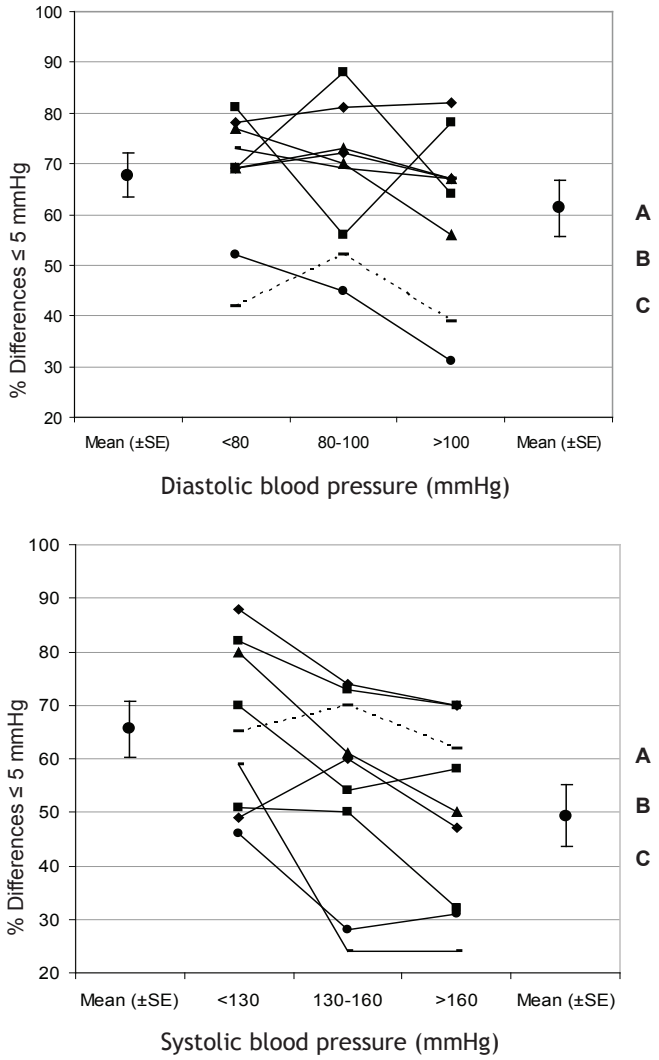

Figure 1. Number (percentages) of differences ≤ 5 mmHg for non-ambulatory blood pressure measuring devices for different diastolic and systolic blood pressure levels. The device that was tested according to the BHS protocol of 1990 is shown using a broken line. The thresholds shown on the right of the figure concern the BHS protocol of 1993. BHS, British Hypertension Society.

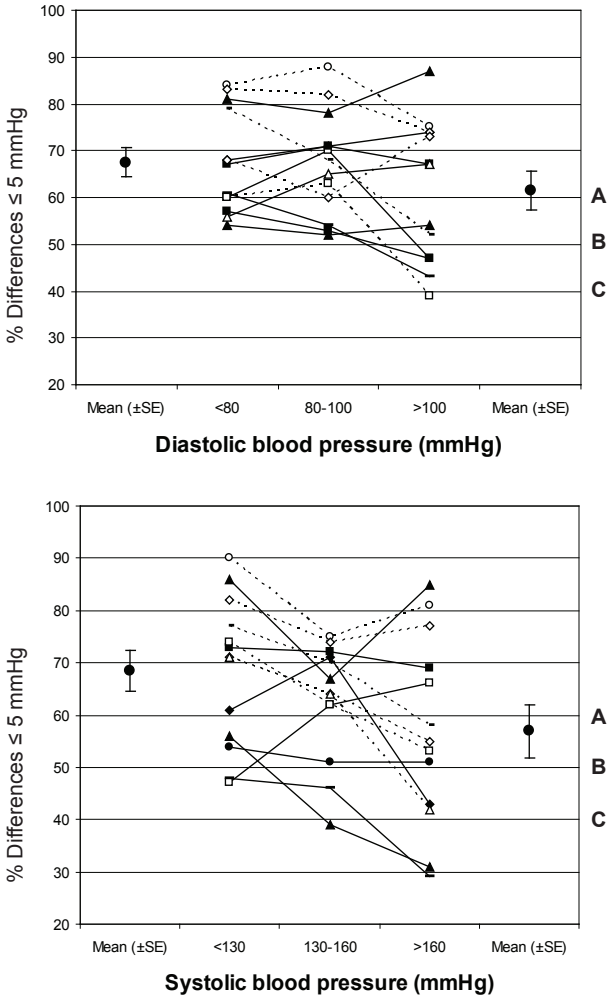

Figure 2. Idem as in Figure 1, for ambulatory blood pressure measuring devices. Open symbols designate auscultatory and closed symbols designate oscillometric blood pressure measuring devices. Devices that were tested according to the BHS protocol of 1990 are shown using broken lines. The thresholds shown on the right of the figure concern the BHS protocol of 1993.
BHS, British Hypertension Society.

Results are shown in Figures 3 and 4, for diastolic and systolic BP. As can be seen for the Welch Allyn Vital Signs Monitor, the absolute difference increases, while the relative difference remains the same for increasing BP levels. The same results are found for the Omron RX-M, although for diastolic BP the absolute difference appears to be more constant for different BP levels.

Table 2. Accuracy of 14 blood pressure measuring devices according to blood pressure level: ambulatory blood pressure monitoring devices

Device	BP level		BHS grade		Percentage difference ≤ 5 mmHg		(mean±SDD)	
	DBP	SBP	DBP	SBP	DBP	SBP	DBP	SBP
Tensioday[8]	<80	<130	A	A	81	86	0±5	1±4
	80-100	130-160	A	A	78	67	2±6	2±7
	>100	>160	A	A	87	85	1±4	1±6
Meditech ABPM-04[7]	<80	<130	B	B	54	54	n.g.	n.g.
	80-100	130-160	B	B	52	51	n.g.	n.g.
	>100	>160	B	B	54	51	n.g.	n.g.
SpaceLabs 90217[6]	<80	<130	A	A	67	73	n.g.	n.g.
	80-100	130-160	A	A	71	72	n.g.	n.g.
	>100	>160	B	A	67	69	n.g.	n.g.
SpaceLabs 90207[2]	<80	<130	B	B	79	77	n.g.	n.g.
	80-100	130-160	B	B	68	70	n.g.	n.g.
	>100	>160	B	B	52	58	n.g.	n.g.
Nissei DS-250[a)13]	<80	<130	n.g.	n.g.	n.g.	n.g.	-3±4	0±7
	80-100	130-160	n.g.	n.g.	n.g.	n.g.	-1±7	-5±10
	>100	>160	n.g.	n.g.	n.g.	n.g.	-1±9	-1±9
Mobil O Graph[12]	<80	<130	A	A	68	61	n.g.	n.g.
(version 12)	80-100	130-160	A	A	71	71	n.g.	n.g.
	>100	>160	A	C	74	43	n.g.	n.g.
Schiller BR-102 (Au)[10]	<80	<130	A	C	60	47	-3±4	-5±5
	80-100	130-160	B	B	70	62	-3±3	-2±4
	>100	>160	C	A	47	66	-4±6	-2±4
Schiller BR-102(Oscill)[12]	<80	<130	A	C	61	48	-3±4	-3±5
	80-100	130-160	B	C	54	46	-4±4	-5±7
	>100	>160	C	D	43	29	-5±6	-9±8
CH-Druck (Au)[2]	<80	<130	A	A	84	90	n.g.	n.g.
	80-100	130-160	A	B	88	75	n.g.	n.g.
	>100	>160	C	B	75	81	n.g.	n.g.
Profilomat (Au)[2]	<80	<130	A	A	83	82	n.g.	n.g.
	80-100	130-160	A	B	82	74	n.g.	n.g.
	>100	>160	D	C	74	77	n.g.	n.g.
Novacor DIASYS 200R (Au)[2]	<80	<130	C	C	68	71	n.g.	n.g.
	80-100	130-160	C	C	60	64	n.g.	n.g.
	>100	>160	B	C	73	55	n.g.	n.g.
Pressurometer IV (Au)[2]	<80	<130	D	B	60	74	n.g.	n.g.
	80-100	130-160	D	C	63	62	n.g.	n.g.
	>100	>160	D	D	39	53	n.g.	n.g.
Takeda TM-2420 (Au)[2]	<80	<130	D	B	56	71	n.g.	n.g.
	80-100	130-160	D	C	65	64	n.g.	n.g.
	>100	>160	D	D	67	42	n.g.	n.g.
Profilomat II[11]	<80	<130	B	B	57	56	-1±7	-1±6
	80-100	130-160	B	D	53	39	1±7	2±9
	>100	>160	C	D	47	31	2±9	4±11

BP, blood pressure; BHS, British Hypertension Society; SDD, standard deviation of differences; DBP, diastolic blood pressure; SBP, systolic blood pressure; ABPM, ambulatory blood pressure monitoring; n.g., not given; Au, auscultatory; Oscill, oscillometrically.

[a)]Validated according to the International Protocol. Additional data were provided by Altunkan *et al.*[13] Results for this device are not shown in Figure 2 because relevant data were missing. Devices from Ref.2 were tested according to the BHS protocol of 1990.

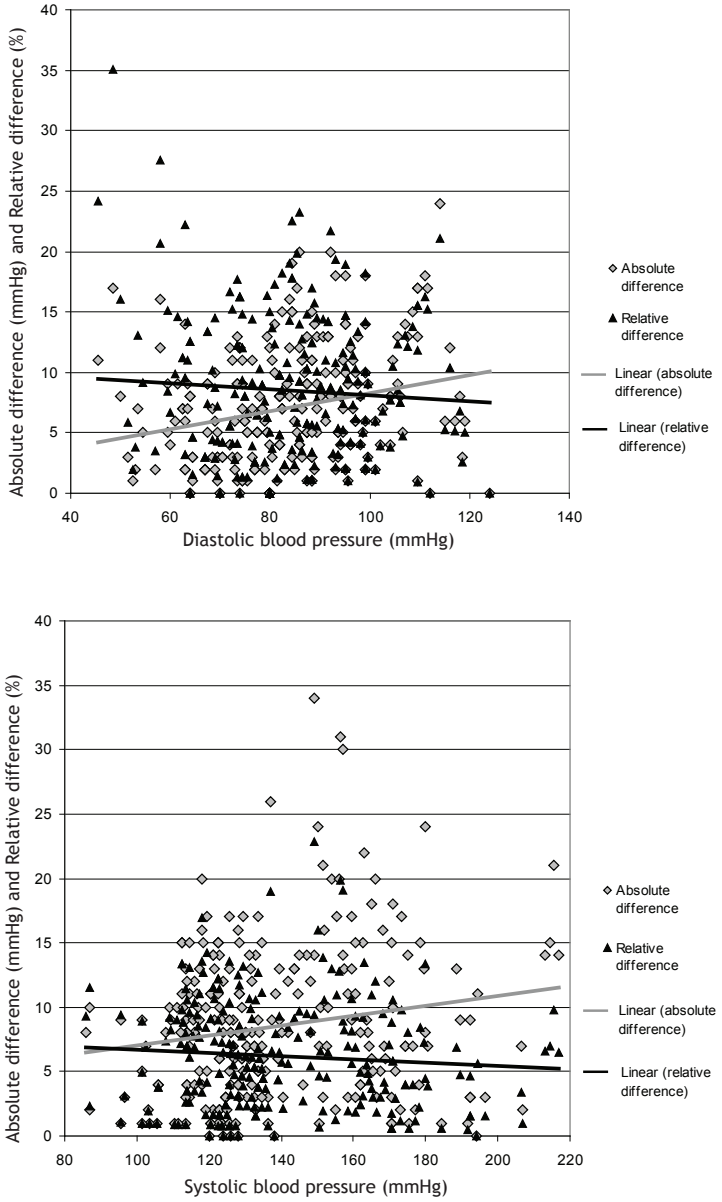

Figure 3. Absolute and relative differences between measurements by the Welch Allyn Vital Signs Monitor and standard mercury sphygmomanometer for diastolic (upper panel) and systolic (lower panel) blood pressure

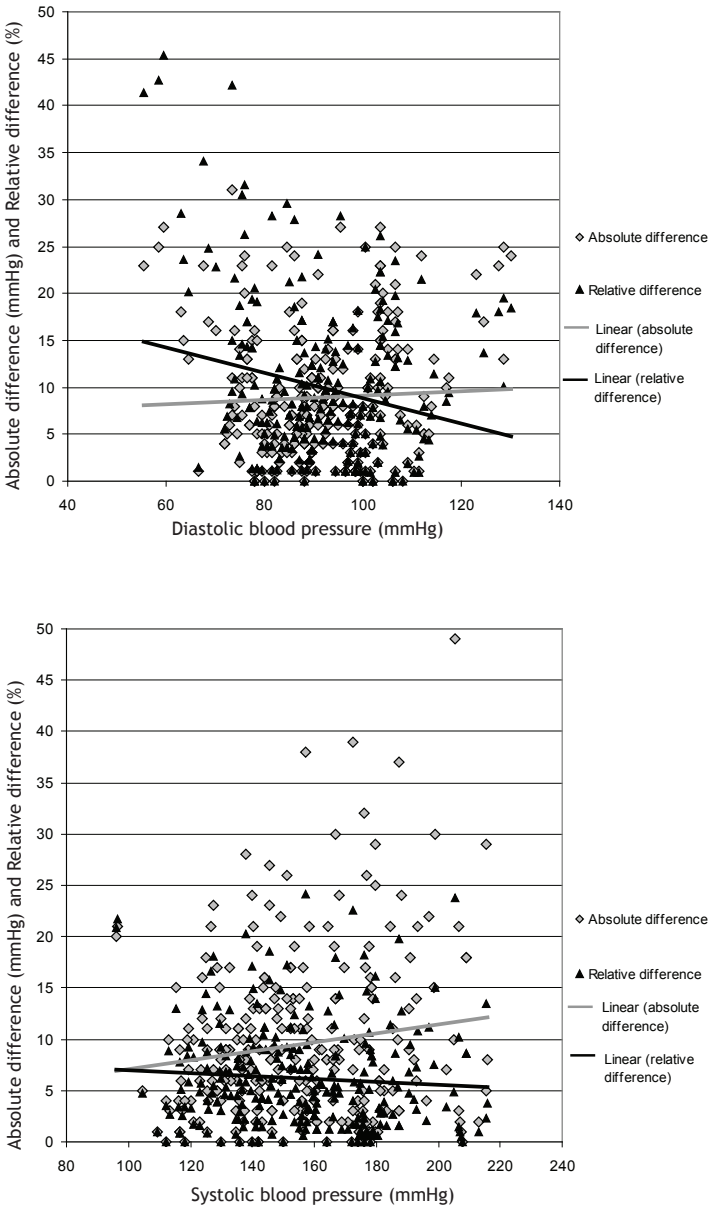

Figure 4. Idem as in Figure 3, for the Omron RX-M

Discussion

On the basis of the results of the studies available for this report, it could be concluded that the accuracy for most of the devices decreases at increasing BP levels. This would especially be the case for systolic BP in nonambulatory devices. We believe, however, that this conclusion would be incorrect. It is our opinion that BP measuring devices seem to become less accurate at increasing BP levels because of a combination of two factors: the sequential measurements used during validation studies and the increasing BP variability at increasing BP levels.

BP has been shown to be more variable at increasing BP levels. Mancia *et al*.[36] showed that absolute short-term variability in BP was greater for hypertensive patients than for normotensive individuals. This was shown for systolic, diastolic, as well as mean arterial BP. For systolic BP, short-term variability increased from 9.5 mmHg (for normotensive individuals) to 12.2 mmHg (for severe hypertensive patients). For diastolic BP, short-term BP variability increased from 6.1 mmHg (for normotensive individuals) to 9.0 mmHg (for severe hypertensive patients). The percentual BP variabilities, however, were similar. BP variability has been linked to target organ damage in hypertension and has been shown to be an independent predictor for cardiovascular mortality in a general population.[37,38]

In the BHS protocol of 1993, sequential measurements are used for the validation of BP measuring devices. The absolute difference between test device and 'the gold standard' (mercury sphygmomanometer) is calculated independent of BP level.[3] The influence of the sequential measurements on the results of the validation of automated BP measuring devices was investigated by Atkins *et al*.[39] They performed sequential BP measurements using the same mercury sphygmomanometer. The percentage of differences within 5 mmHg was only 69% (for systolic BP), when comparing a BP measurement using the mercury sphygmomanometer with the mean of the measurement before and after the index measurement using the same device. The only explanation could be that BP fluctuated during the sequential measurements.

Owing to the increasing variability of BP at increasing BP levels, analysis using the absolute BP differences in sequential measurements will underestimate the accuracy of BP measuring devices at these levels. Noticeably, all devices in the first study showing decreasing accuracy at increasing BP levels were tested using sequential measurements.[2] Analyses of the data both from the literature and from our own studies with the Welch Allyn Vital Signs Monitor and the Omron RX-M indeed shows that the absolute difference seems to be dependent on the BP level, whereas the relative difference seems to be more or less independent of the BP level.

Another explanation for the current findings is that the oscillometric method itself may be responsible. The exact way in which the systolic and diastolic BPs are determined using oscillometry is held secret by the different device manufacturers. It may well be that the observed inaccuracy is due to the algorithm used to calculate the systolic and diastolic BP values.

Decreasing accuracy of BP measuring devices at increasing BP levels is a very troublesome phenomenon, as hypertension is the indication for their use. The consequence may be that patients with hypertension can erroneously be classified as non-hypertensive and treatment withheld. Furthermore, in treated hypertensive patients the necessary adaptation of treatment will not take place, while BP is judged adequately regulated. Alternatively, it is possible that a device gives readings that are too high. Non-hypertensive individuals could, therefore, erroneously be classified as hypertensive.

Owing to the limited studies available for this report, selection bias could have been introduced. The studies used, however, are well performed and the results are consistent, especially with regard to systolic BP. It is within the BP range of 80–100 mmHg for diastolic BP and 130–160 mmHg for systolic BP that the threshold for the diagnosis of hypertension is encompassed. The effect of the BP level on the accuracy of BP measuring devices within this important BP range cannot be estimated on the basis of the information currently available.

Validation studies should continue to report the accuracy of devices at different BP levels, although not explicitly stated in the new 'International Protocol'.[40] Besides the frequently shown Bland–Altman plots, we would like to report separately the accuracy at the different BP levels as shown in Tables 1 and 2. With the new 'International Protocol', however, the sample size of each BP category being 11 is quite small.

In conclusion, we would like to state that BP measuring devices seem to become less accurate at increasing BP levels. Owing to sequential measurements used during validation and to the increasing variability of BP at increasing BP levels, the decreasing accuracy of BP measuring devices, however, may have been overestimated.

Nonetheless, this is a very troublesome phenomenon as accuracy at increasing BP levels is most important for diagnosis and follow-up of hypertensive patients. Perhaps the accuracy of a device at different BP levels could become an independent criterion for recommending in favour of or against its use in clinical practice. It is our opinion that validation reports should not only address the absolute but also the relative accuracy at different BP levels.

References

1. O'Brien E, Mee F, Atkins N, Thomas M. Evaluation of three devices for self-measurement according to the revised British Hypertension Society Protocol: the Omron HEM-705CP, Philips HP5332, and Nissei DS-175. Blood Press Monit 1996;1:55–61.

2. O'Brien E, Atkins N, Mee F, O'Malley K. Comparative accuracy of six ambulatory devices according to blood pressure levels. J Hypertens 1993; 11:673–675.

3. O'Brien E, Petrie J, Littler W, de Swiet M, Padfield PL, Altman DG, *et al*. The British Hypertension Society protocol for the evaluation of blood pressure measuring devices. J Hypertens 1993;11(Suppl 2):S43–S62.

4. White WB, Berson AS, Robbins C, Jamieson MJ, Prisant LM, Roccella E, Sheps SG. National Standard for measurement of resting and ambulatory blood pressures with automated sphygmomanometers. Hypertension 1993; 21:504–509.

5. O'Brien E, Waeber B, Parati G, Staessen J, Myers MG; on behalf of the European Society of Hypertension Working Group on Blood Pressure Monitoring. Blood pressure measuring devices: recommendations of the European Society of Hypertension. BMJ 2001;322:531–536.

6. Baumgart P, Kamp J. Accuracy of the SpaceLabs Medical 90217 ambulatory blood pressure monitor. Blood Press Monit 1998;3:303–307.

7. Barna I, Keszei A, Dunai A. Evaluation of Meditech ABPM-04 ambulatory blood pressure measuring device according to the British Hypertension Society protocol. Blood Press Monit 1998;3:363–368.

8. Németh Z, Móczár K, Deák G. Evaluation of the Tensioday ambulatory blood pressure monitor according to the protocols of the British Hypertension Society and the Association for the Advancement of Medical Instrumentation. Blood Press Monit 2002;7:191–197.

9. Germano G, Muscolo M, Angotti S, Bravo S, Codispoti P, Frederico L, Damiani S. Evaluation of a new ambulatory blood pressure device. Am J Hypertens 1998;11:1486–1491.

10. O'Brien E, Mee F, Atkins N. Evaluation of the Schiller BR-102 ambulatory blood pressure system according to the protocols of the British Hypertension Society and the Association for the Advancement of Medical Instrumentation. Blood Press Monit 1999;4:35–43.

11. Mee F, Atkins N, O'Brien E. Evaluation of the Profilomat II^{R} ambulatory blood pressure system according to the protocols of the British Hypertension Society and the Association for the Advancement of Medical Instrumentation. Blood Press Monit 1998;3:353–361.

12. Jones CR, Taylor K, Chowienczyk P, Poston L, Shennan AH. A validation of the Mobil O Graph (version 12) ambulatory blood pressure monitor. Blood Press Monit 2000;5:233–238.

13. Altunkan S, Iliman N, Altunkan E. Validation of the Nissei DS-250 ambulatory blood pressure monitoring device according to the international protcol. J Hypertens 2003;21(Suppl 4):S22.

14. Kuwajima I, Nishinaga M, Kanamaru A. The accuracy and clinical performance of a new compact ambulatory blood pressure monitoring device, the ES-H531. Am J Hypertens 1998;11:1328–1333.

15. Keavney B, Bird R, Caiazza A, Casadei B, Conway J. Measurement of blood pressure using the auscultatory and oscillometric methods in the same cuff deflation: validation and field trial of the A&D TM2421 monitor. J Hum Hypertens 2000;14:573–579.

16. Livi R, Teghini L, Cagnoni S, Scarpelli PT. Simultaneous and sequential same-arm measurements in the validation studies of automated blood pressure measuring devices. Am J Hypertens 1996;9:1228–1231.

17. Gosse P, Laforge A, Ansoborlo P, Jullien V, Lemetayer P, Clementy J. Clinical evaluation of the Diasys Integra blood pressure recorder. J Hypertens 1997; 15(Suppl 4):S18.

18. Mattu GS, Perry TL Jr, Wright JM. Comparison of the oscillometric blood pressure monitor (BPM-100Beta) with the auscultatory mercury sphygmomanometer. Blood Press Monit 2001;6:153–159.

19. Wright JM, Mattu GS, Perry TL Jr, Gelfer ME, Strange KD, Zorn A, Chen Y. Validation of a new algorithm for the BPM-100 electronic oscillometric office blood pressure monitor. Blood Press Monit 2001;6:161–165.

20. Mano GMP, Souza VF, Pierin AMG, Lima JC, Ignes EC, Ortega KC, Mion D Jr. Assessment of the DIXTAL DX-2710 automated oscillometric device for blood pressure measurement with the validation protocols of the British Hypertension Society (BHS) and the Association for the Advancement of Medical Instrumentation (AAMI). Arq Bras Cardiol 2002;79:606–610.

21. Bortolotto LA, Henry O, Hanon O, Sikias P, Mourad JJ, Girerd X. Validation of two devices for self-measurement of blood pressure by elderly patients according to the revised British Hypertension Society protocol: the Omron HEM-722C and HEM-735C. Blood Press Monit 1999;4:21–25.

22. Anwar YA, Giacco S, McCabe EJ, Tendler BE,White WB. Evaluation of the efficacy of the Omron HEM-737 Intellisense device for use on adults according to the recommendations of the Association for the Advancement of Medical Instrumentation. Blood Press Monit 1998;3:261–265.

23. O'Brien E, Mee F, Atkins N, O'Malley K. Short report: accuracy of the Dinamap portable monitor, model 8100 determined by the British Hypertension Society protocol. J Hypertens 1993;11:761–763.

24. Cuckson AC, Reinders A, Shabeeh H, Shennan AH. Validation of the Microlife BP 3BTO-A oscillometric blood pressure monitoring device according to a modified British Hypertension Society protocol. Blood Press Monit 2002;7:319–324.

25. Golara M, Jones C, Randhawa M, Shennan AH. Inflationary oscillometric blood pressure monitoring: validation of the Omron-MIT. Blood Press Monit 2002;7:325–328.

26. Rogoza AN, Pavlova TS, Sergeeva MV. Validation of A&D UA-767 device for the self-measurement of blood pressure. Blood Press Monit 2000;5:227–231.

27. Jones CR, Taylor K, Poston L, Shennan AH. Validation of the Welch Allyn 'Vital Signs' oscillometric blood pressure monitor. J Hum Hypertens 2001; 15:191–195.

28. Artigao LM, Llavador JJ, Sanchis C, Abril JL, Torres C, Rubio M, *et al*. Evaluation of three devices for self-measurement of blood pressure according to the British Hypertension Society Protocol: the Omron M1 MX2 Y M4. Am J Hypertens 1998;11:60A.

29. Bobrie G, Battaglia Ch. Assessment of Tensionic Mod EPS 112, semiautomatic device of blood pressure measurement (manufactured by Spengler – France). J Hypertens 1999;17(Suppl 3):S22.

Chapter 3

Which device should be chosen?

Chapter 3.1

Home blood pressure measurement with oscillometric upper-arm devices

Richard L. Braam
Theo Thien

Department of Internal Medicine
University Medical Centre St. Radboud, Nijmegen, The Netherlands

The Netherlands Journal of Medicine 2003;61:307-312

Abstract

The market for automated blood pressure measuring devices is growing rapidly. Many patients want to buy a device for blood pressure measurement at home and ask their physician for advice about which one to choose. In this article an overview is given of the different devices available for blood pressure measurement and possible pitfalls in the interpretation of measurements taken at home are pointed out. A second article will specifically address those devices that are used to take blood pressure measurements at the wrist.

Introduction

The market for automated blood pressure measuring devices is growing rapidly. Home blood pressure measurement (HBPM) is becoming more and more popular. Many of the devices designed for HBPM have now been validated according to different protocols. Most (78%) of the 11 million devices for HBPM sold in 2000 were produced by Japanese manufacturers.[1] Of the sold devices, 64% are upper-arm devices and 35% are wrist devices.[1] HBPM has been shown to have a stronger predictive power for mortality than screening blood pressure (BP).[2] Many patients with hypertension ask their general practitioners and specialists which device they should buy. The purpose of this article is to help physicians to better advise patients in choosing between different devices for HBPM. Moreover, it will help the physician to interpret the readings taken at home better and to pin-point possible pitfalls such as (reverse) white-coat hypertension or white-coat effect.These and many other factors should be taken into account when medication changes are made based on home readings.

Overview of validation protocols currently in use

A number of validation protocols for BP measuring devices have been published in the past years. The most widely used are the British Hypertension Society (BHS) protocol 1990, which was revised in 1993, and the protocol of the Association for the Advancement of Medical Instrumentation (AAMI) published in 1987 and revised in 1992.[3-6] Recently an effort has been made to develop a universal protocol in the form of an 'International Protocol'.[7] In Germany the Deutsches Institut für Normierung (DIN) developed a protocol and in Australia another protocol has been drafted.[8,9] Of these protocols, the BHS protocol 1993, the International Protocol and the AAMI 1992 protocol will be discussed briefly. In the BHS protocol 1993 a mercury sphygmomanometer is used as reference standard. In the main part of the protocol, BP measurements are done in 85 subjects. In each subject seven BP measurements are performed alternately with the device being tested (read by one observer) and by two other observers with the mercury sphygmomanometer (Figure 1). After calculating the differences between the standard and the test device a grade for both systolic (SBP) and diastolic (DBP) blood pressure can be calculated using Table 1. Only devices with a grade A or B for both SBP and DBP are recommended for clinical use. In the International Protocol adjustments have been made to simplify the validation procedure of the BHS protocol 1993.

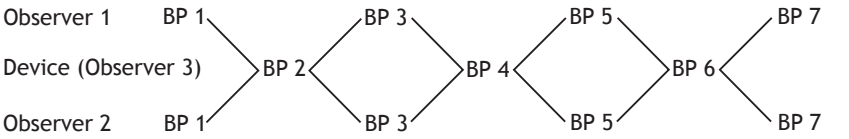

Figure 1. Sequential blood pressure measurements according to the British Hypertension Society protocol 1993 (also used in the International Protocol)

This was done by using the data from 19 validation studies performed according to the BHS protocol. A two-phased approach is used. During phase 1 sequential BP measurements are carried out in 15 subjects (according to the scheme shown in Figure 1). Requirements shown in Table 1 must be met in order to proceed to phase 2. This approach will help to eliminate very inaccurate devices in an early phase. When the device tested enters phase 2, measurements are done in an additional 18 subjects. Differences between test device and mercury sphygmomanometer have to be within the requirements shown in Table 1 in order to pass. So a pass/fail system has replaced the A,B,C and D grading system of the BHS protocol 1993. Analysis is done separately for systolic and diastolic BP. Only a few devices have been tested according to this new protocol so far. In the AAMI protocol mean differences and standard deviation of differences (SDD) are calculated. BP measurements are done in 85 subjects with three sets of comparative BP measurements for each subject. Measurements are taken by two trained observers. Simultaneous measurements are preferred, but sequential measurements are also allowed. To pass the AAMI protocol the absolute mean difference has to be ≤ 5 mmHg and SDD ≤ 8 mmHg (Table 1) for both systolic and diastolic BP. Comparisons with intra-arterial measurements are also allowed: ten measurements should be done simultaneously in a minimum of 15 subjects. The upper limits of acceptance (mean and SDD) are the same as for noninvasive measurements.[6]

Instructions for home measurement and factors influencing blood pressure

To obtain reliable results patients and/or their relatives should be instructed on how to perform home measurements. Many factors influence the BP that is measured at a given moment and in a given situation.[10,11] There are factors that influence the actual BP level and factors that are related to the method of BP measurement itself.

These are shown in Figure 2. Patients should be aware of a number of these factors when measuring BPs at home. Each measurement should be done only

Table 1. Grading criteria for sequential measurements according to the British Hypertension Society (BHS), the International Protocol and the Association for the Advancement of Medical Instrumentation (AAMI). All calculations should be done separately for systolic and diastolic blood pressure[4,6,7]

BHS Protocol (1993)

	Absolute difference between standard and test device (mmHg)*		
Grade	≤ 5 mmHg	≤ 10 mmHg	≤ 15 mmHg
Cumulative percentages			
A	60	85	95
B	50	75	90
C	40	65	85
D		Worse than C	

*To achieve a certain grade, all percentages must be ≥ those in the table, n=255

International Protocol (2002)

Phase 1: Measurements[1]	<5 mmHg	<10 mmHg	<15 mmHg
At least one of	25	35	40
Phase 2.1: Measurements[2]	<5 mmHg	<10 mmHg	<15 mmHg
All of	60	75	90
Two of	65	80	95
Phase 2.2: Measurements[3]	2/3 <5 mmHg	0/3 within 5 mmHg	
Two of	22		
All of		3	

[1] After measurements in 15 subjects (45 comparisons) at least 25 comparisons should lie within 5 mmHg or at least 35 within 10 mmHg or at least 40 within 15 mmHg to proceed to phase 2. [2] After measurements in all 33 subjects 60, 75 and 90 comparisons should lie within 5, 10 and 15 mmHg, respectively. Also, 65 comparisons should lie within 5 mmHg and 80 within 10 mmHg or 65 within 5 mmHg and 95 within 10 mmHg or 80 within 10 mmHg and 95 within 15 mmHg. [3] To complete phase 2.2 in 22 of the 33 subjects at least two out of three comparisons should lie within 5 mmHg and at most 3 of the 33 subjects can have all three comparisons over 5 mmHg apart.

AAMI[4]

Mean difference	Absolute value ≤ 5 mmHg and standard deviation of differences ≤ 8 mmHg

[4] In 85 subjects, 3 readings/subject, n=255

after proper preparation, i.e. patients should begin measurements only after at least five minutes of rest.[12] Measurements should preferably be done while sitting in a comfortable chair. Care should be taken to position the centre of the cuff at heart level. The cuff size should be appropriate for the size of the arm and placed with the centre over the brachial artery. During measurements there should be no talking. A device properly validated and found accurate

enough for home measurement should be used. It could be argued that BP measurements should only be done by those who are equipped to do so, i.e. healthcare professionals. However one should keep in mind the following citation: '*Indirect BP measurement is one of the most frequently performed healthcare procedures. Because BP measurement is a simple procedure, it is taken for granted that all graduates from medical training programmes have the ability to record accurate, precise and reliable BP readings. However, research since the 1960s has shown this assumption to be false. Most health professionals do not measure BP in a manner known to be accurate and reliable. If you doubt this statement, watch as BPs are taken in your own clinical setting to determine whether the guidelines are followed, and then examine recorded readings for signs of observer bias.*'[10] So, adequate training and education in BP measurement are pivotal and more important than the person who performs the measurements. Self-measurement of BP is feasible for the majority of hypertensive patients.[13] Proper instruction with, for example, a short teaching session at the outpatient clinic should preferably be given to all patients performing home measurements.

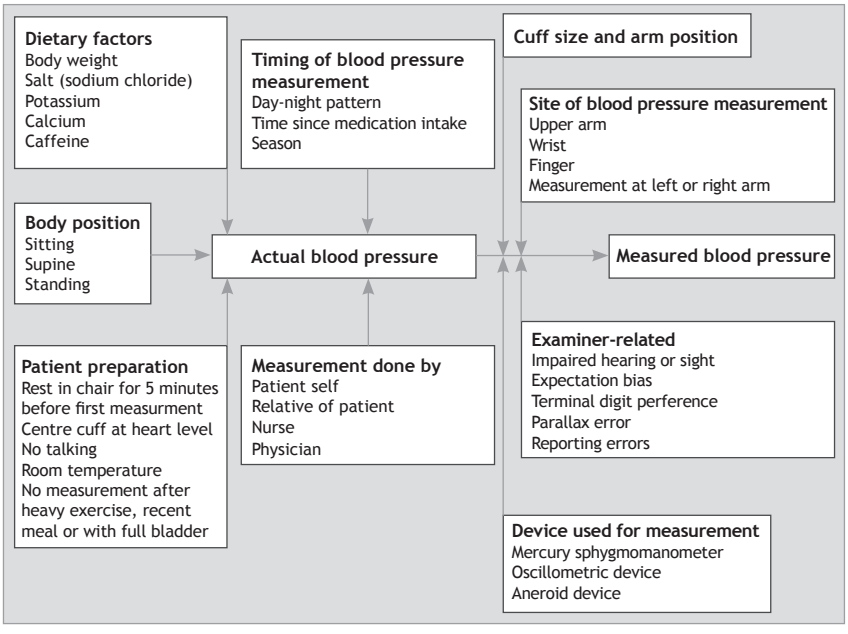

Figure 2. Factors influencing the actual blood pressure level and factors accounting for the difference between actual blood pressure and measured blood pressure level

After thorough instruction, mercury and aneroid sphygmomanometers could also be used for self-measurement. However aneroid devices have been shown to become inaccurate over time.[14] Patients should be instructed to report all measurements. No values should be discarded. Memory-equipped devices could help to check the values reported by patients.[15] To obtain reliable results a sufficient number of measurements should be done. Three successive measurements two times a day (before meals, between 06.00 and 08.00 and between 18.00 and 20.00) for at least three to four days are recommended.[16]
BP measured at home will not automatically give the same results as BP measured at the office. About 10 to 15% of hypertensive patients will have isolated office hypertension (widely known as 'white-coat hypertension'), in which persistent office hypertension is accompanied by home BP values below 130/85 mmHg.[17] Indeed many factors influence the BP measured in the two situations. As with ambulatory blood pressure measurement (ABPM), one would expect to measure lower BPs at home as compared with in the office. However the opposite is also commonly seen.[18] Wing *et al*. showed that in a group of 713 older hypertensives, 21 to 41% of patients had higher daytime systolic or diastolic ambulatory BPs than office readings. This was confirmed by research at our own institution (Aksoy, unpublished data). BP measurement is not easy and the interpretation of the values measured is not at all easy, indeed it is rather complex. The development of automated BP measuring devices for use in the office and at home has actually made interpretation even more difficult, because different devices are commonly used in these different settings. To help interpret the BP values obtained during self-measurement, thresholds for normality of self-measured BP have been proposed as shown in Table 2.[19] These values are mainly based on cross-sectional studies and not yet related to cardiovascular prognosis.

Table 2. Proposed thresholds for automated measurements of blood pressure[19]

	Blood Pressure (mmHg)	95th Percentiles[1]	Normotension[2]	Hypertension[3]
Ambulatory	24 hour	132/82	≤130/80	>135/85
	Daytime	138/87	≤135/85	>140/90
	Night-time	123/74	≤120/70	>125/75
Self-recorded	Morning	136/85	≤135/85	>140/90
	Evening	139/86	≤135/85	>140/90
	Morning and evening	137/85	≤135/85	>140/90

[1] Mean values for the 95th percentiles for normotensive subjects in large-scale studies.
[2] Obtained by rounding off downwards to the next blood pressure ending in 0 or 5 mmHg.
[3] Obtained by rounding off upwards to the next blood pressure ending in 0 or 5 mmHg.

(Dis)advantages of home measurement

Different devices can be used for HBPM: the mercury sphygmomanometer, aneroid devices and oscillometrically measuring devices. The last category of devices has won the 'contest' for HBPM, because of their ability to perform measurements automatically. HBPM has several advantages. It can provide us with more measurements than office readings. It can help to diagnose isolated office hypertension, to quantify the 'white-coat effect' and it may help to improve compliance to therapy, improving BP control. Terminal digit preference and expectation bias is no longer a problem. Measurements are independent of the hearing of the observer. The costs of self-measurement are lower than for ABPM.[20] However, in contrast to ABPM, no BP values can be obtained at night and the prognostic value of self-measurement needs further investigation.[21] The device used for self-measurement has to be validated and accurate. Thresholds for normal levels are still under investigation. Mengden *et al*. showed that there was a substantial error in the reporting of the BP values obtained during self-measurement by hypertensive patients during two weeks.[15] Some patients omitted high BP readings. This bias may be reduced by using memory-equipped BP devices.[15] Another disadvantage is that it is not possible to control the circumstances in which measurements are taken. Also there is no information about proper cuff position during measurements.

Automated devices validated for home use

A substantial number of devices for self-measurement have been validated according to the British Hypertension Society protocol, the International Protocol or the protocol of the Association for the Advancement of Medical Instrumentation. Most of these devices measure BP oscillometrically. The development of the oscillometric technique goes back to the late 19th century. It is based on the assumption that the maximal oscillation in the cuff air pressure observed during deflation corresponds to the mean arterial pressure. Systolic and diastolic BP values are then computed through a specific algorithm.[22] These algorithms are kept secret, differ per device and can be changed easily.

Table 3 shows the devices that have been validated for self-measurement at the upper arm.[22] A device can be either recommended (i.e. fulfilling the AAMI criteria for both systolic and diastolic BPs and achieving a BHS grade B or A for both systolic and diastolic blood pressures) or not recommended (i.e. failing the AAMI criteria and achieving a BHS grade C or D for either systolic or diastolic pressure). A device achieves a 'questionable recommendation' when there is

uncertainty about the strength of evidence (e.g. protocol violation, results presented only in abstract form etc).[23]

Table 3. Automated blood pressure measuring devices for self-measurement at the upper arm that have been validated using the protocols of the British Hypertension Society (BHS), the International Protocol or the protocol of the Association for the Advancement of Medical Instrumentation (AAMI) – devices measure blood pressure oscillometrically unless otherwise stated (adapted with permission)[23]

	Protocol			
Device	**AAMI**	**BHS[1]**	**Year**	**Recommendation**
Omron HEM-400C	Failed	Failed[2]	1990	Not recommended
Philips HP5308 (Au)[3]	Failed	Failed[2]	1990	Not recommended
Philips HP5306/B	Failed	Failed[2]	1990	Not recommended
Healthcheck CX-5 060020	Failed	Failed[2]	1990	Not recommended
Nissei analogue monitor (Au)[3]	Failed	Failed[2]	1990	Not recommended
Systema Dr MI-150	Failed	Failed[2]	1990	Not recommended
Fortec Dr MI-100	Failed	Failed[2]	1990	Not recommended
Philips HP5332	Failed	C/A	1996	Not recommended
Nissei DS-175	Failed	D/A	1996	Not recommended
Omron HEM-705CP	Passed	B/A	1996	Recommended
Omron HEM-706	Passed	B/C	1994	Not recommended
Omron HEM-403C	Failed	C/C	1995	Not recommended
Omron HEM-703CP	Passed	NA[4]	1994	Questionable
Omron M4	Passed	A/A	1998	Questionable
Omron MX2	Passed	A/A	1998	Questionable
Omron HEM-722C	Passed	A/A	1997	Questionable
Omron HEM-722C	Passed	A/A	1999	Recommended
Omron HEM-735C	Passed	B/A	1999	Recommended
Omron HEM-713C	Passed	B/B	1996	Recommended
Omron HEM-737 Intellisense	Passed	B/B	1998	Recommended
Visomat OZ2	Passed	C/B	1998	Not recommended

[1] According to the BHS protocol separate judgements are given to systolic and diastolic blood pressures, e.g. A/A both very good, C/A insufficient for systolic, but good for diastolic blood pressure. [2] In the first seven devices grading criteria had not yet been established. [3]Au= auscultatory. [4]NA = not applied.

Most devices become more inaccurate at higher BP levels. This has been shown for ambulatory blood pressure measuring devices, but in general applies for most automated BP measuring devices.[24] This is in part attributable to the design of the BHS protocol: independent of the BP level the absolute difference is used to calculate the grades.

Conclusion

As can be seen in Table 3, many devices have been tested so far. However, only a few have achieved at least a grade B for both systolic and diastolic BP according to the BHS protocol or have passed the International Protocol. Based on the results shown in this Table one of the Omron devices graded B/B or better could be advised for HBPM. The field of BP measurement is developing rapidly. Recently the Omron-MIT has been validated: this device measures oscillations during inflation instead of deflation.[25] Wrist devices are also becoming more and more popular and will be addressed in a separate article.
O' Brien *et al*. periodically publish an update on validated devices in the British Medical Journal.[23] Devices that have passed the BHS protocol can also be found on the website of the British Hypertension Society: http://www.hyp.ac.uk (blood pressure monitors).

References

1. Shirasaki O, Terada H, Niwano K, *et al*. The Japan Home-health Apparatus Industrial Association: investigation of home-use electronic sphygmomanometers. Blood Press Monit 2001;6:303-307.

2. Ohkubo T, Imai Y, Tsuji I, *et al*. Home blood pressure measurement has a stronger predictive power for mortality than does screening blood pressure measurement: a population-based observation in Ohasama, Japan. J Hypertens 1998;16:971-975.

3. O'Brien E, Petrie J, Littler W, *et al*. The British Hypertension Society protocol for the evaluation of automated and semi-automated blood pressure measuring devices with special reference to ambulatory systems. J Hypertens 1990;8:607-619.

4. O'Brien E, Petrie J, Littler W, *et al*. The British Hypertension Society protocol for the evaluation of blood pressure measuring devices. J Hypertens 1993;11(suppl 2):S43-562.

5. Association for the Advancement of Medical Instrumentation. American National Standard for Electronic or Automated Sphygmomanometers. Arlington VA: Association for the Advancement of Medical Instrumentation, 1987.

6. White WB, Berson AS, Robbins C, *et al*. National Standard for Measurement of Resting and Ambulatory Blood Pressures with Automated Sphygmomanometers. Hypertension 1993;21:504-509.

7. O'Brien E, Pickering T, Asmar R, *et al*, on behalf of the Working Group on Blood Pressure Monitoring of the European Society of Hypertension. Working Group on Blood Pressure Monitoring of the European Society of Hypertension International Protocol for validation of blood pressure measuring devices in adults. Blood Press Monit 2002;7:3-17.

8. Non-invasive sphygmomanometers: Clinical investigation. E DIN 58130. Berlin Germany: DIN Deutsches Institut für Normierung, 1995.

9. Sphygmomanometers. Australian Standard. AS 3655-1989. North Sydney, NSW, Australia: Standards Australia, 1989.

10. Grim CM, Grim CE. Manual blood pressure measurement – still the gold standard. Why and how to measure blood pressure the old-fashioned way. In: Weber MA (ed). Hypertension Medicine. Chapter 11. Totowa, New Jersey: Humana Press Inc., 2001.

11. Kaplan NM. Measurement of Blood Pressure. In: Kaplan NM (ed). Clinical Hypertension. Chapter 2. Philadelphia: Lippincott Williams & Wilkins, 2002.

12. Bakx JC, Netea RT, Hoogen HJM van den, *et al*. The influence of a rest period on blood pressure measurement. Huisarts Wetenschap 1999;42:53-56.

13. Denolle T, Waeber B, Kjeldsen S, Parati G, Wilson M, Asmar R. Self-measurement of blood pressure in clinical trials and therapeutic applications. Blood Press Monit 2000;5:145-149.

14. Jones CR, Khanna M, Rushbrook J, Poston L, Shennan AH. Are aneroid devices suitable replacements for mercury sphygmomanometers? J Hum Hypertens 2000;14:843.

15. Mengden T, Medina RMH, Beltran B, Alvarez E, Kraft K, Vetter H. Reliability of reporting self-measured blood pressure values by hypertensive patients. Am J Hypertens 1998;11:1413-1417.

16. Mallion J-M. Home blood pressure. In: Mancia G, Chalmers J, Julius S, *et al*. (eds). Manual of Hypertension. Chapter 3.2. London: Churchill Livingstone, 2002.

17. Mancia G, Parati G. Isolated office hypertension. In: Mancia G, Chalmers J, Julius S, *et al*. (eds). Manual of Hypertension. Chapter 9.5. London: Churchill Livingstone, 2002.

18. Wing LM, Brown MA, Beilin LJ, Ryan P, Reid CM. 'Reverse white-coat hypertension' in older hypertensives. J Hypertens 2002;20(4):639-644.

19. Staessen JA, Thijs L, and the participants of the First International Consensus Conference on Blood Pressure Self-Measurement. Development of diagnostic thresholds for automated self-measurement of blood pressure in adults. Blood Press Monit 2000;5:101-109.

20. Herpin D, Pickering T, Stergiou G, Leeuw de P, Germano G. Consensus Conference on Self-blood pressure measurement. Clinical applications and diagnosis. Blood Press Monit 2000;5:131-135.

21. Imai Y, Poncelet P, Buyzere M de, Padfield PL, Montfrans GA van. Prognostic significance of self-measurements of blood pressure. Blood Press Monit 2000;5:137-143.

22. Parati G, Mancia G. Ambulatory blood pressure monitoring. In: Mancia G, Chalmers J, Julius S, *et al*. (eds). Manual of Hypertension. Chapter 3.3. London: Churchill Livingstone, 2002.

23. O'Brien E, Waeber B, Parati G, Staessen J, Meyers MG, on behalf of the European Society of Hypertension Working Group on Blood Pressure Monitoring. Blood pressure measuring devices: recommendations of the European Society of Hypertension. BMJ 2001;322:531-536.

24. O'Brien E, Atkins N, Mee F, O'Malley K. Comparative accuracy of six ambulatory devices according to blood pressure levels. J Hypertens 1993;11:673-675.

25. Golara M, Jones C, Randhawa M, Shennan AH. Inflationary oscillometric blood pressure monitoring: validation of the OMRON-MIT. Blood Press Monit 2002;7:325-328.

Chapter 3.2

Oscillometric wrist blood pressure measuring devices

Richard L. Braam
Bünyamin Aslan
Theo Thien

Department of Internal Medicine
University Medical Centre St. Radboud, Nijmegen, The Netherlands

The Netherlands Journal of Medicine 2003;61:313-317

Abstract

Devices measuring blood pressure oscillometrically at the wrist are becoming more and more popular. These devices are small, easy to handle and can measure blood pressure without the need to undress. However, few of the wrist devices have been validated properly, i.e. according to internationally accepted protocols. In this article current literature on wrist blood pressure measuring devices is presented. The importance of positioning the wrist at heart level for accurate measurements is stressed.

Introduction

The first devices constructed to measure blood pressure in humans were devices measuring blood pressure at the wrist.[1] Early experiments in this field in the 19th century eventually led to the development of the conventional blood pressure measuring technique at the upper-arm by Scipione Riva Rocci.[2] However, the art of feeling the pulse has an even longer history, going back to Chinese medicine. Nowadays, oscillometric blood pressure (BP) measuring devices for home blood pressure measurement (HBPM) are becoming increasingly popular. When asked, patients choose HBPM as the preferred method for measuring BP over ambulatory blood pressure measurement (ABPM) or measurements by the nurse or physician.[3] Moreover HBPM has been shown to have a stronger predictive power for mortality than screening BP measurement.[4] Over 11 million devices for HBPM were sold world-wide in 2000.[5] Most of these devices measure blood pressure at the upper-arm. However the proportion of the sold devices that measure BP at the wrist is increasing.[5] Devices measuring BP at the finger have shown to be inaccurate.[6] Many patients ask their physician for advise on which device to buy. Using the available literature on wrist BP measuring devices this overview will hopefully help physicians to advise their patients better in their choice for a particular BP measuring wrist device.

Factors determining blood pressure level at the wrist

Many factors determine the BP measured at a given moment. In general there should be an adequate resting period before starting the measurements. Differences in the order of 5 to 10 mmHg can result from differences in arm position.[7] The influence of arm position on the measured blood pressure level is due to the influence of the hydrostatic pressure: raising the arm (or wrist) 1 cm lowers the blood pressure by 0.7 mmHg and vice versa.[8] The cuff should be held at heart level, i.e. at the level of the right atrium. This generally means midway between the jugular notch and the xiphoid process.[7] Because of its more distal position accurate positioning of the cuff at heart level is of even more importance for BP measurement at the wrist. The importance of the arm position on measured BP level has led to the development of a positioning system by Braun®.[9] A wrist BP device equipped with an inclination sensor helps to manoeuvre the patient's wrist to the same position for every measurement. This ensures that subsequent measurements are comparable.

The measured BP level is further influenced by flexion and extension of the wrist.[10] BP measured with the wrist in palmar flexion is significantly higher than that measured in palmar extension. BP measured in palmar dorsiflexion is significantly lower than that in palmar extension (for both diastolic and systolic BP). Besides these positional aspects, the BP itself is different at the wrist compared with the arm. Moving more distally from the ascending aorta to the radial artery, systolic BP increases and diastolic BP decreases, hence pulse pressure increases.[11] Most wrist BP measuring devices are validated relative to upper arm BP measurements. So differences in BP between these two measurement sites can be expected from the outset. However, mean arterial pressure differs only slightly.[12]

Instruction for self-measurement and (dis)advantages of wrist devices

Proper instruction is pivotal to be able to obtain reliable results. Patients should be instructed on how to operate the device and to adequately register all measurements taken. A short course should preferably be given at the outpatient clinic. Unless the device has been equipped with a positioning system, proper positioning of the cuff at heart level should be stressed. HBPM can have several advantages. These are shown in Table 1. HBPM can help to establish the diagnosis of hypertension, to find cases of white-coat hypertension, assess the efficacy of antihypertensive therapy, evaluate the effect of dose adjustments, detect unexpected BP derangements, reduce costs and to increase compliance.[1,13] However BP levels during sleep are not obtained as they are in ABPM, reference values have not been firmly established and misreporting of the measured BPs can occur. The cut-off values for hypertension are lower for the BP measured at home than at the office.[4,14-16] This should be taken into account when interpreting BP measurement taken at home. BPs measured at home can be lower than at the office as part of white-coat hypertension. However the opposite (BP at home higher than at the office) can also occur. This phenomenon has been described as the so-called reverse white-coat hypertension or masked hypertension, which is actually a misnomer and self-measurement related hypertension would be a better term.[17] These phenomena make interpretation of BP levels acquired through self-measurements more difficult. Using wrist devices can have additional advantages: measurements at the wrist can be more comfortable, because these small, light-weight devices are easy to use, patients do not need to undress for measurements and measurements can be done in various circumstances.[1] However, most wrist devices have not been properly validated or have been found inaccurate.

Table 1. (Dis)advantages of home blood pressure measurement with automated devices in general and wrist devices in specific

GENERAL ADVANTAGES
May help to diagnose hypertension
May help to detect white-coat hypertension/white-coat effect
Stronger preditive power for mortality than screening blood pressure
Patient's compliance may increase
Efficacy of antihypertensive medication and effect of dose adjustments can be better monitored
Earlier detection of derangement of blood pressure
ADVANTAGES OF WRIST DEVICES
Devices are light-weight
Easy applicability, greater comfort, no need to undress
Costs in general lower than ABPM/upper-arm devices
GENERAL DISADVANTAGES
No blood pressure measurements during the night
Reference values for hypertension not firmly established
Misreporting of measured blood pressure values possible
VALIDATION REPORTS ON WRIST DEVICES
Most devices not properly validated or not meeting BHS/AAMI criteria
Blood pressure level at the wrist is influenced by many factors (angle between hand and fore-arm, hydrostatic pressure)

Validation reports on wrist devices

Validation studies on wrist blood pressure measuring devices are scarce. The British Hypertension Society (BHS) protocol 1993 and the protocol of the Association for the Advancement of Medical Instrumentation (AAMI) are the most widely used protocols for validating BP measuring devices.[18,19] For a short review of these protocols we would like to refer to our article on upper-arm devices. In a recent review by O'Brien only three wrist devices were shown to be tested by the British Hypertension Society (BHS) and/or Association for the Advancement of Medical Instrumentation (AAMI) criteria.[20] Only one device passed the requirements of these protocols. For this review, we selected well-performed studies using the following criteria: a minimum number of 40 patients had to be included and an internationally accepted protocol (BHS or AAMI) had to be used as a guideline to evaluate the test device. The studies

that fulfilled these criteria are presented in Table 2. Table 3 shows the rest of available validation reports on wrist BP measuring devices.
Comparison between different validation reports testing the same device is quite difficult because validation is not always carried out in the same way. Moreover it is often difficult to determine which type of device has actually been tested, because the type and serial number of the device is not always stated exactly. In general, in comparison with oscillometric measuring devices at the arm, wrist devices seem to be less accurate.

Table 2. Validation reports on wrist devices, including at least 40 patients and using BHS- or AAMI-protocols as a guideline[10,21-28]

Device		N	Standard	Mean difference (±SD) (device-standard) SBP	DBP	AAMI	BHS
BP 2000[21]		86	M	0.1±7.1	1.9±7.0	P/P	
Boso-Mediwatch[22]*	Nt	20	M	3.9(0.1;7.6)	7.0(4.7;9.2)		
	Ht	20	M	-5.8(-11.6;-0.3)	-5.5(1.4;6.3)		
Klock[23]		255	M	16±25	6±17	F/F	
Matsushita Denko EW[10]		92	M	2.3±10.2	5.6±8.6		D/B
NAiS EW 28[24]	S	125	An	-1.1±5.0	-1.7±3.0		
	C	40	An	-1.9±2.9	-1.2±2.8		
Nissei WS-310		87	M	-4.6±8.3	-2.8±4.8	F/P	B/A
Omron HEM 601[10]		173	M	2.1±9.7	-1.2±7.3		C/B
Omron RX (HEM 608)[26]		85	M	0.3±9.0	2.6±9.0	F/F	B/B
Omron RX[25]		87	M	-4.9±8.8	-4.2±6.4	F/P	B/A
Omron RX-M[27]		89	M	2.5±12.2	7.5±8.4	F/F	D/D
Omron R3[28]		85	M	-5.7±6.2	-6.8±6.8	F/F	D/D
Omron R3[22]*	Nt	20	M	3.2(0.6;5.8)	4.2(1.6;6.7)		
	Ht	20	M	-5.8(-8.8;-2.8)	-5.5(-9.3;1.6)		

M = mercury sphygmomanometer, An = aneroid sphygmomanometer, Nt = normotensives, Ht = hypertensives, S = surgery, C = community, SBP = systolic blood pressure, DBP = diastolic blood pressure, P = passed; F = failed. * 95% confidence interval instead of SD.

Conclusion

The market for automated BP measuring devices is growing rapidly. Particularly the sales of wrist devices are increasing. They have the advantage of a small volume and easy applicability. However, the development of these devices should be watched with caution. First we should recommend our patients to use only devices that have been properly validated. At present too few wrist devices have been validated according the protocols of AAMI and/or BHS, so no particular device can be recommended.

Secondly the readings with these devices should be interpreted with caution and compared with measurements with an ABPM and BP measurements at the office. Interpretation is further hindered by the lack of firmly established cut-off values for normotension and hypertension at the wrist.

Table 3. Various validation reports of wrist devices, not fulfilling the criteria stated in table 2[9,27,29-34]

Device	N	Mean difference (±SD) SBP	DBP	AAMI	Standard
Intra-arterial measurements as standard					
NAiS Matsushita BP Watch[29]	27	1.5±10.2	4.1±7.3	F/P	
NAiS BP Watch[30]	100	4.3±14.1	6.0±8.9	F/F	
Omron HEM-601[31]	25	-4.0±18.0	3.0±9.0	F/F	
Omron R3[32]	100	-1±13.0	1.0±9.0	F/F	
Oscillometric arm device as standard					
NAiS BP Watch[30]	100	3.4±13.3	3.8±9.5	F/F	Hestia OZ80
Omron HEM-601[33]	26	-0.04±10.0	2.8±8.0	F/P	Visomat Hestia OZ40
Omron RX-M[27]	89	4.1±12.7	6.3±7.1	F/F	Omron HEM 705 CP
BOSO medistar[34]	21	2±7	3±6	P/P	BOSO medicus
Ambulatory blood pressure monitor as standard					
BP 2000[9]	43	-1.5±13.7	5.2±7.9(P+)		A&D TM-2430
		-0.5±15.0	6.0±8.9(P-)		
Omron HEM-601[31]	50	n.g.	n.g.		SpaceLabs 90207

SBP = systolic blood pressure, DBP = diastolic blood pressure, P = passed, F = failed, n.g. = not given.

Thirdly, to be able to compare different wrist devices more easily, accurate description of type and serial number of the device tested is needed. Accurate and reproducible positioning of the wrist at heart level is crucial for BP measurement. However, we think that with recent innovative developments as the position sensor by Braun and developments yet to come, wrist BP measuring devices will gain a prominent place in BP measurement and BP control. Instead of attributing to the diagnosis of hypertension, wrist devices could be of help in giving follow-up data. That is, provided that sequential measurements are done in the same manner, wrist devices could help to give information about (changes in) blood pressure level over time.

References

1. Parati G, Asmar R, Stergiou GS. Self blood pressure monitoring at home by wrist devices: a reliable approach? J Hypertens 2002;20:573-578.

2. Riva-Rocci S. Un nuovo sphygmomanometro. Gazz Med Torino 1896;50:982-1017.

3. Little P, Barnett J, Barnsley L, Marjoram J, Fitzgerald-Barron A, Mant D. Comparison of agreement between different measures of blood pressure in primary care and daytime ambulatory blood pressure. BMJ 2002;325:254.

4. Ohkubo T, Imai Y, Tsuji I, *et al*. Home blood pressure measurement has a stronger predictive power for mortality than does screening blood pressure measurement: a population-based observation in Ohasama, Japan. J Hypertens 1998;16:971-975.

5. Shirasaki O, Terada H, Niwano K, *et al*. The Japan Home-Health Apparatus Industrial Association: investigation of home-use electronic sphygmomanometers. Blood Press Monit 2001;6:303-307.

6. Veerman DP, Lenders JWM, Thien T, Montfrans GA van. LAM 100/Marshall F-88: accuracy and precision of a new device for discontinuous finger blood pressure measurement. J Hum Hypertens 1993;7:113-115.

7. Netea RT, Lenders JWM, Smits P, Thien T. Arm position is important for blood pressure measurement. J Hum Hypertens 1999;13:105-109.

8. Netea RT, Bijlstra P, Lenders JWM, Smits P, Thien T. Influence of the arm position on intra-arterial blood pressure measurement. J Hum Hypertens 1998;12:157-160.

9. Uen S, Weisser B, Wieneke P, Vetter H, Mengden T. Evaluation of the performance of a wrist blood pressure measuring device with a position sensor compared to ambulatory 24-hour blood pressure measurements. Am J Hypertens 2002;15:787-792.

10. Kikuya M, Chonan K, Imai Y, Goto E, Masao I, on behalf of the Research Group. Accuracy and reliability of wrist-cuff devices for self-measurement of blood pressure. J Hypertens 2002;20:629-638.

11. O'Rourke MF, Kelly RP, Avolio AP. What is the pulse? Chapter 2. In: The arterial pulse. Pennsylvania: Lea & Febiger, 1992.

12. Bernards JA, Bouman LN. Bloedstroom. Chapter 13. In: Bernards JA, Bouman LN (eds). Fysiologie van de mens. 6th edition. Houten/Zaventum: Bohn, Stafleu, van Loghum, 1994.

13. Verdecchia P. Reference values for ambulatory blood pressure and self-measured blood pressure based on prospective outcome data. Blood Press Monit 2001;6: 323-327.

14. Kwaliteitsinstituut voor de Gezondheidszorg CBO. Herziene richtlijn Hoge Bloeddruk. Alphen aan den Rijn: Van Zuiden Communcations B.V., 2000.

15. O'Brien, Coats A, Owens P, *et al*. Use and interpretation of ambulatory blood pressure monitoring: recommendations of the British Hypertension Society. BMJ 2000;320:1128-1134.

16. Gaudemeris R de, Phong Chau N, Mallion J-M, for the Groupe de la Mesure, French Society of Hypertension. Home blood pressure: variability, comparison with office readings and proposal for reference values. J Hypertens 1994;12:831-838.

17. Wing LMH, Brown M, Beilin L, *et al*. Reverse white-coat hypertension in older hypertensives. J Hypertens 2002;20:639-644.

18. O'Brien E, Petrie J, Littler W, *et al*. The British Hypertension Society protocol for the evaluation of blood pressure measuring devices. J Hypertens 1993;11(suppl 2):S43-S62.

19. White WB, Berson AS, Robbins C, *et al*. National Standard for Measurement of Resting and Ambulatory Blood Pressures with Automated Sphygmomanometers. Hypertension 1993;21:504-509.

20. O'Brien E. State of the market for devices for blood pressure measurement. Blood Press Monit 2001;6:281-286.

21. Wessig K, Hollinger S, Schmalzhaf I, Lenz T. Clinical evaluation of the efficacy of the Braun PrecisionSensor oscillometric wrist blood pressure monitor for use on adults versus auscultation as defined by ANSI/AAMI SP10-1992. Blood Press Monit 2000;5:239-245.

22. Rogers P, Burke V, Stroud P, Puddey IB. Comparison of oscillometric blood pressure measurements at the wrist with an upper-arm auscultatory mercury sphygmomanometer. Clin Exp Pharmacol Physiol 1999;26:477-481.

23. Zweiker R, Schumacher M, Fruhwald FM, Watzinger N, Klein W. Comparison of wrist blood pressure measurement with conventional sphygmomanometry at a cardiology outpatient clinic. J Hypertens 2000;18: 1013-1018.

24. Lusignan S de, Thiru K, Meredith K, Majeed A, Johnson P. Measuring blood pressure at the wrist: more comfortable for patients and more convenient for doctors? Public Health 2000;114:165-168.

25. Altunkan S, Yildiz S, Azer S. Wrist blood pressure-measuring devices: a comparative study of accuracy with a standard auscultatory method using a mercury manometer. Blood Press Monit 2002;7:281-284.

26. Shennan AH, Rushbrook J, Power J, Wright J, Poston L. An accurate oscillometric wrist blood pressure monitor: validation of the Omron [Rx HEM-608]. J Hum Hypertens 1998;12:794.

27. Braam RL, Aslan B, Thien Th. Accuracy of the Omron RX-M, an automated blood pressure measuring device, measuring blood pressure at the wrist, according to a modified British Hypertension Society Protocol. Blood Press Monit 2004;9:25-30.

28. Dieterle T, Battegay E, Bucheli B, Martina B. Accuracy and 'range of uncertainty' of oscillometric blood pressure monitors around the upper arm and the wrist. Blood Press Monit 1998;3:339-346.

29. Weber F, Erbel R, Schäfers R, Philipp Th. Wrist measurement of blood pressure: some critical remarks to oscillometry. Kidney Blood Press Res 1999;22:161-165.

30. Saul F, Klaus D, Aristidou Y, Wiemeyer A, Lösse B. Non-invasive oscillometric wrist and upper arm blood pressure measurements compared with invasive values. Z Kardiol 1996;85(suppl 3):127-129.

31. Eckert S, Gleichmann S, Gleichmann U. Blood pressure self-measurement in upper arm and in wrist for treatment control of arterial hypertension compared to ABPM. Z Kardiol 1996;85(suppl 3):109-111.

32. Watson S, Wenzel R, Matteo C di, Meier B, Lüscher TF. Accuracy of a new wrist cuff oscillometric blood pressure device. Comparisons with intra-arterial and mercury manometer measurements. Am J Hypertens 1998;11:1469-1474.

33. Widmer Ch, Bachmann LM, Koch J, Vetter W. Blood pressure measurements from the upper arm or the wrist: is there a difference? Praxis 2000;89:389-396.

34. Heise T, Magnusson K, Gröbel B, *et al*. A cross-over evaluation of different methods and devices to measure blood pressure in type 1 diabetic patients with nephropathy. Blood Press Monit 2000;5:175-180.

Part II

Adherence to antihypertensive drug therapy

Chapter 4

Drug adherence in hypertension treatment

Chapter 4.1

Insufficient response to antihypertensive drug therapy: consider non-adherence

Richard L. Braam
Jacques W.M. Lenders
Theo Thien

Department of Internal Medicine
University Medical Centre St. Radboud, Nijmegen, The Netherlands

Stan H.M. van Uum

Endocrinology and Metabolism, Department of Medicine and
Lawson Health Research Institute,
University of Western Ontario, London, Ontario, Canada

Nederlands Tijdschrift voor Geneeskunde (accepted in adapted form)

Abstract

Drug adherence should be an important issue in everyday clinical practice. In asymptomatic conditions like hypertension adherence can be expected to be low and to decrease over time. We present five hypertensive patients in whom drug adherence was shown to be an important reason for inadequate blood pressure control. Different causes and risk factors of non-adherence as well as methods to estimate the level of drug adherence are discussed. A number of practical advices to increase drug adherence are given. Increased awareness of decreased adherence is the first important step to improve blood pressure control.

Introduction

Many patients have to take a great number of drugs during the day for varying medical conditions and for prolonged time periods. An increasing number of (asymptomatic) 'patients' are treated with drugs because of the presence of risk factors like hypertension and hypercholesterolemia (primary prevention). In order for primary prevention to be successful adequate drug adherence is crucial, as was recently stated by the World Health Organization (WHO).[1]
Haynes *et al*. defined drug adherence (compliance) as: 'the extent to which a person's behaviour (in terms of taking medications, following diets, or executing lifestyle changes) coincides with medical or health advice'.[2] This definition is still valid today. The term 'compliance' was first changed to 'adherence' and later to 'concordance'[1,3] in order to stress the importance of autonomy of the patient. The physician offers the patient several treatment options and together they choose a specific treatment plan.[1,3] In this article the term 'adherence' will be used.
The mean level of drug adherence is about 50% in chronic conditions. In one out of three patients drug adherence is good, in one out of three it is moderate and in one out of three it is insufficient.[4] For the lifelong treatment of asymptomatic conditions or risk factors like hypertension, the success of treatment depends largely on the level of drug adherence.

The next cases show the influence of adherence on the treatment results reached, in which case one has to think about insufficient drug adherence and which advices can be given to improve adherence.

CASE 1. A 62-year-old single man was admitted to the department of general internal medicine because of fever and general weakness. He was known with hypertension, an inferior wall myocardial infarction and cerebrovascular accident. On the age of 61 patient underwent a percutaneous coronary intervention. In the foregoing years the patient had participated in various cardiovascular clinical trials. At admission he indicated to take the following drugs: bisoprolol, amlodipine, isosorbide dinitrate, acetylsalicylic acid, levomepromazine, oxazepam, medication because of participation in a randomised clinical trial and amoxicillin for several days. The systolic blood pressure (BP) at admission was 170 mmHg and the diastolic BP was 110 mmHg. The patient brought with him all the drugs he said to be using in several bags

(Figure 1). The bags contained a large number of predominantly unopened medication boxes. He was asked why he made the effort to fill every prescription at his pharmacy and subsequently did not take the drugs. He answered that after every visit to his physician, he had the intention to take the drugs as prescribed ('at every visit the physican looked at him so faithfully'), however after reading the instruction leaflet he decided not to take them.

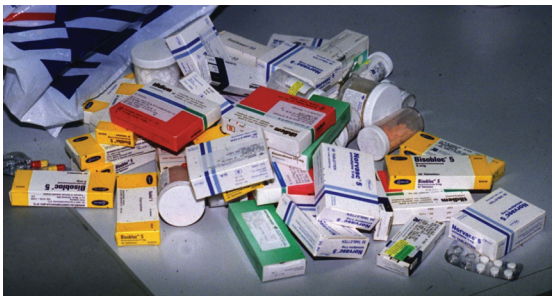

Figure 1. Bag filled with partially unopened medication boxes of patient 1.

CASE 2. A 43-year-old man was referred to our clinic by a cardiologist because of therapy resistant hypertension. Despite treatment with five antihypertensive drugs systolic BP was still too high with levels between 180 to 210 mmHg and with levels of diastolic BP between 100 to 120 mmHg. There were signs of organ damage (electrocardiographic as well as echocardiographic left ventricular hypertrophy and an increased urinary albumin excretion rate of 82 µg/min, normal < 20). Because further investigations showed no signs of secondary hypertension, insufficient adherence to the antihypertensive drugs was suspected. All the more because resting pulse rate was over 80 beats/min, while using the beta-adrenoceptor blocker atenolol 100 mg once daily. A therapeutic blood level of this drug could not be demonstrated (< 0.04 mg/l, therapeutic level: 0.2-0.6 mg/l).

He was admitted to our hospital for a short period. Drug intake was checked during the hospital stay. The BP was lowered to 150 mmHg systolic and 95 mmHg diastolic, while using four different drugs: atenolol 50 mg twice daily, hydrochlorothiazide 50 mg twice daily, nifedipine retard 40 mg twice daily and enalapril 10 mg twice daily. After a leave for the weekend the BP level had increased again to 180/142 mmHg and pulse rate increased from 65 to 90 beats/min. Again the drug level of atenolol was subtherapeutic (< 0.04 mg/l). Patient was followed up for a prolonged time period at the outpatient clinic.

BP remained high, despite treatment with a great number of antihypertensive drugs. Several times blood levels of atenolol were determined (Figure 2), most of them where subtherapeutic. On several occasions the issue of insufficient drug adherence was discussed without any success.

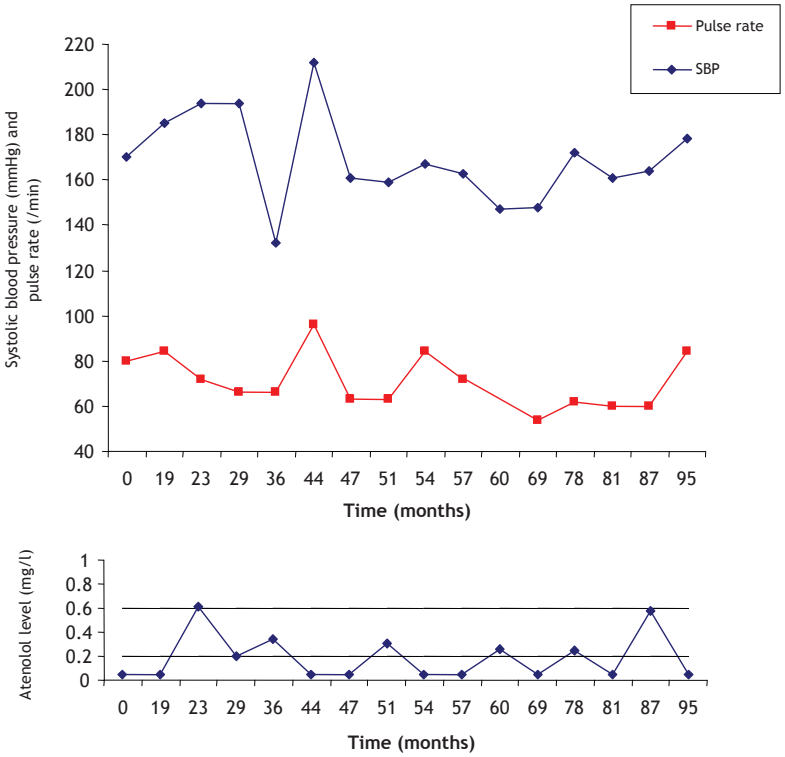

Figure 2. Variable intake of atenolol of patient 2, reflected by fluctuating levels of atenolol. The fluctuating blood pressures and pulse rates were probably due to the varying intake of atenolol: for example sometimes several days a week and sometimes only once a week. The therapeutic range of atenolol levels is indicated by horizontal lines. SBP, systolic blood pressure.

CASE 3. A 48-year-old woman, was referred by an internist from a general hospital because of therapy resistant hypertension. Systolic BP was 240 mmHg and diastolic BP 140 mmHg during treatment with three antihypertensive drugs. There was also severe overweight of 99,7 kgs with a height of 169 cms. No signs of secondary hypertension were present. The BP did not change despite increasing the number of antihypertensive drugs to six. The number of drugs was subsequently reduced, without any change in BP.

Patient was admitted to our hospital for further investigations. Drug intake was monitored during her hospital stay. During treatment with two antihypertensive drugs, a beta-adrenoceptor blocker and a diuretic, BP was lowered from 205/135 mmHg to 120-140 mmHg systolic and 70-85 mmHg diastolic. BP could be regulated well afterwards for a prolonged time period with systolic BPs of 120 to 130 mmHg and diastolic BPs of 85-90 mmHg.

CASE 4. A 35-year-old man was referred to our hospital because of therapy resistant hypertension. During treatment with three antihypertensive drugs his systolic BP was 160 mmHg and his diastolic BP 112 mmHg. Secondary hypertension was suspected, but additional investigations did not reveal any abnormalities. During treatment with an angiotensin converting enzyme (ACE) – inhibitor and a diuretic BP was lowered to a level of 130/86 mmHg. Further treatment and follow-up were done by his general practitioner.
Five years later patient was again referred because of difficult to treat hypertension. During treatment with three antihypertensive drugs (atenolol had been added by the general practitioner) BP was 220/140 mmHg. Despite treatment with atenolol resting pulse rate was high (between 80 to 95 beats/min). A subtherapeutic atenolol level was measured. Insufficient adherence was suspected. During later visits at the outpatient clinic BP was much lower: 135/95 mmHg and pulse rate was 58 beats/min. He told mistakenly to have used paracetamol (acetaminophen) instead of atenolol.

CASE 5. A 53-year-old woman was seen because of high BPs despite treatment with several antihypertensive drugs. She was known with an appendectomy, cholecystectomy, an abdominal extirpation of the uterus and an arthrodesis of the left knee after several orthopaedic operations. At the outpatient clinic BP was 206/112 mmHg and pulse rate 80 beats per min. Physical examination showed no abnormalities, except obesity (body weight 92 kgs, height 161 cms). There were no signs of secondary hypertension. Laboratory investigation showed a potassium level of 4.8 mmol/l despite treatment with chlorthalidone. Gradually the number of antihypertensive drugs was increased. Finally she used a beta-adrenoceptor blocker, a diuretic and a vasodilating drug. Because there was no decrease of the BP patient was admitted to our hospital.
During treatment with chlorthalidone 50 mg once daily systolic BP was lowered after several days to 120 – 130 mmHg and diastolic BP to 75 – 80 mmHg. With chlorthalidone alone BP was lower than during treatment with three antihypertensive at the office. Moreover a clear decrease in the potassium

level was observed and an accompanying decrease in body weight (Figure 3). Chlorthalidone was not detectable in the blood at admission, but it was after several days of treatment (0.21 mg/l).

Insufficient drug adherence was suspected. Several times the importance of adequate adherence was discussed with our patient, however this did not improve the situation. At the outpatient clinic again much higher BPs were measured.

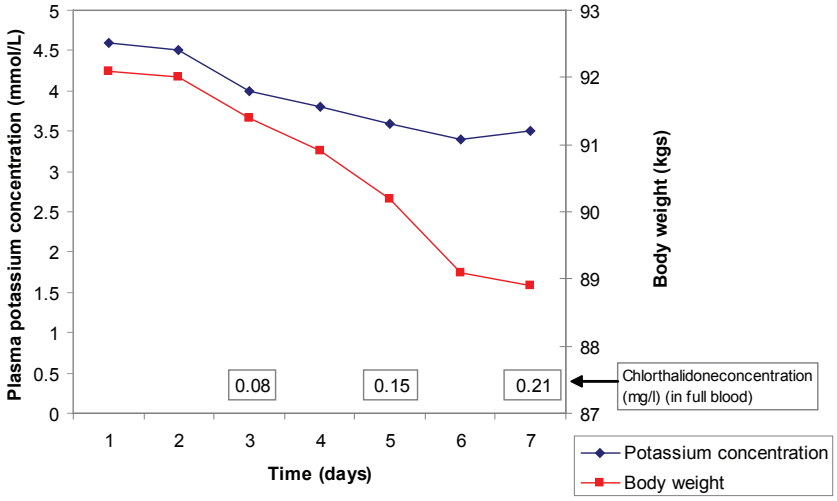

Figure 3. Effect of treatment with thiazide diuretic chlorthalidone (patient 5); decrease of potassium concentration and body weight.

Discussion

Adherence should always be an important issue, but particularly with more or less chronic conditions that are not accompanied by symptoms.[5] In the United States two out of three patients with known hypertension are either untreated or undertreated.[6] One of the most important reason for this is insufficient adherence.[6]

Adherence is not an all or nothing phenomenon. The level of adherence can vary. In general the level of adherence that is required for treatment to be effective, is unknown. Besides the type of condition this will depend on half-life, dosage prescribed and the number of doses per day of the drug and further on possible interactions with other drugs.[7] For the treatment of hypertension it

is assumed that minimally 80% of drugs prescribed in adequate amounts should be taken, to achieve a stable BP control.[2,5] For patients infected with human immunodeficiency virus (HIV) adherence with antiretroviral therapy should be at least 95%.[5]

It is often difficult to recognize insufficient adherence. It should be considered when BP is not lowered despite adequate antihypertensive therapy. One can ask the patient about its drug adherence. If the patient admits to be non-adherent (like case 1), improvement of adherence is often possible, because the subject of inadequate adherence has become debatable. Several direct and indirect methods exist to estimate the level of adherence (Table 1).[4,5,7] Unfortunately, the majority of these methods are not useful, because they are either too unpractical, too labour-intensive or too costly.

Table 1. Methods to estimate and to improve the level of adherence to antihypertensive drug therapy (adapted from[4,5,7])

Method/criterion	Advantage	Disadvantage
Questionnaires, self reports	Simple, inexpensive	Unreliable
Pill count	Simple	Unreliable
Patient interview	Simple	Unreliable
Impression of the physician	Simple	Unreliable
Check whether prescriptions have been filled at the pharmacy	Objective	Filling prescription does not guarantee drug intake; patient can visit more than one pharmacy
Degree of BP lowering	Simple	Besides adherence other factors determine the degree of BP lowering
Measure physiological marker, side effect (for example pulse rate while using beta-adrenoceptor blockers, decrease in body weight and decrease in potassium concentration while using diuretics)	Simple	Absence of reaction/side effect does not guarantee insufficient adherence
Electronic monitoring	Accurate, results easy to interpret	Relatively costly; opening of the pill box thus not guarantee drug intake
Measure drug, metabolite or marker in blood or urine	Objective	Unpractical, labour intensive, cumbersome, expensive

Actually there is no good standard to measure the level of adherence objectively. Certain side-effects of drugs can sometimes be indicative of adherence, for example the occurrence of ankle oedema while using calcium antagonists. Ankle oedema occurs in 14.6% of women and 5.6% of men using amlodipine.[11] After starting thiazide diuretics one can expect the potassium level and body weight to decrease and urea and uric acid levels to increase. Of course the absence of side effects does not exclude insufficient adherence.

With electronic monitoring a pill box equipped with a built-in chip is used. The date and time of opening of each pill box can be registered. The level of adherence can be estimated quite reliably using this method. If a patient deliberately would like to circumvent this method, then he or she would conscientiously have to open the pill-box every day for months and subsequently not take the drug. Burnier *et al*. used electronic monitoring to improve adherence in a group of patients with therapy resistant hypertension.[8] Patients were informed that during two months adherence would be measured using electronic monitoring. For more than 50% of patients insufficient adherence was shown to be the reason for inadequate BP control.

Another method is to measure the concentration of a drug or its metabolite or marker in blood or urine of the patient. Although this method is objective, the concentration of only a limited number of antihypertensive drugs can be measured. The validity of this method depends on pharmacokinetic properties of the drug measured, like the elimination half-life. In the treatment of hypertension optimal long-term adherence is essential. Determining the concentration of an antihypertensive drug or marker with a short half-life will be less informative. Moreover adherence tends to increase in the period of a planned appointment to the doctor's office.[9] This phenomenon is called "white-coat compliance".[10] During the days preceding the visit to the doctor adherence is likely to increase. Therefore concentrations in plasma or urine of markers or drugs, measured during office visits are possibly not representative of long-term drug adherence, particularly when elimination half-life is short. However a repetitively not measurable or subtherapeutic drug level (cases 2 and 4) does indicate that adherence is insufficient. Sometimes instead of the concentration of a drug, the effect of an antihypertensive drug on a particular enzyme system can be measured. For example ACE-activity can be measured to determine the level of adherence when using ACE-inhibitors. This method can not be used for captopril, because *in vitro* it easily dissociates from ACE.

Several determinants are important for the occurrence of insufficient drug

adherence. The influence of gender, race and socio-economic state of the patient is not entirely clear.[5] The presence of a depression seems to be an important risk factor.[13] (Alleged) side effects or the fear of side effects are often mentioned as a reason for non-adherence (case 1).[10] Side-effects differ from one drug to the other and from patient to patient. Adherence is higher with ACE-inhibitors and angiotensin-II receptor antagonists, compared to diuretics and beta-adrenoceptor blockers. The first two categories of antihypertensive drugs have less side-effects.[14] The level of adherence is also influenced by the organization of the outpatient clinic. Long waiting times will have a negative influence on the level of adherence.[2]

Which measures can help to improve adherence to antihypertensive drug therapy? First of all the schedule of drug intake should be as simple as possible (Table 2). A more complex schedule will decrease drug adherence. The adherence decreases proportionally to the number of daily doses prescribed.[5,15]
A good patient–physician relationship will improve drug adherence. Clear communication between patient and physician is very important. 40-80% of the information provided by a healthcare professional is immediately forgotten. The majority of patients is not deliberately non-adherent. Sometimes simple mistakes are the reason for non-adherence (case 4). In minimally 30% of patients forgetfulness is mentioned as the reason for non-adherence.[5,16] Also holidays, a disease or start of new drugs by another physician can initiate non-adherence. The patient should be given enough time to incorporate the proposed drug schedule into his daily life activities. Admission to a hospital can sometimes improve adherence for longer periods. During the hospital stay it can be shown that BP is lowered with the drugs already prescribed at the outpatient clinic this can help to improve adherence. One should be aware that BP can drop too much when the same drug schedule is followed as in the outpatient setting. However, sometimes hospital admission fails to improve adherence.
Patients indicating that they have difficulties to adhere are often accessible for improvement. Accurate and extensive information and a motivating attitude of the physician can help to improve adherence. Self BP measurements with validated devices[17] and contact using e-mail about the results of self-measurements can help to increase adherence, without much extra effort. A dedicated nurse can also improve long term results.[18,19] It is often helpful to discuss the occurrence of side-effects and possible fears for side-effects with patients.

Table 2. Methods to improve the level of adherence to antihypertensive drug therapy (adapted from 4,5,17-19)

- Simplifying the medication regimen
- Use of memory aids: patient diary, medication box, watch equipped with alarm
- Provide adequate information on hypertension
- Motivating attitude of physician; invest in good physician-patient relationship
- Use help of other health care providers (nurses, pharmacists)
- Discuss the occurrence of side-effects and possible fear for side-effects

Conclusion

An open discussion with patients about their drug taking behaviour with adequate instruction about the importance of good adherence should be an important part of every patient-physician contact. This is especially important for those patients that are asymptomatic and use drugs for primary prevention. The level of adherence is difficult to estimate. There are only few methods to measure it objectively. Insufficient adherence should be suspected whenever the desired BP goal is not reached.

References

1. Sabaté E. Adherence to long-term therapies. Evidence for action. World Health Organization 2003.

2. Haynes RB, Taylor DW, Sackett DL, editors. Compliance in Health Care. The Johns Hopkins University Press, Baltimore and London,1979.

3. Marinker M. Personal paper: Writing prescriptions is easy. BMJ 1997;314:747-748.

4. Wright EC. Non-compliance – or how many aunts has Matilda? Lancet 1993;342:909-913.

5. Osterberg L, Blaschke T. Adherence to medication. N Engl J Med 2005;353:487-497.

6. Wang TJ, Ramachandran SV. Epidemiology of uncontrolled hypertension in the United States. Circulation 2005;112:1651-1662.

7. Urquhart J. Role of patient compliance in clinical pharmacokinetics. A review of recent research. Clin Pharmacokinet 1994;27:202-215.

8. Burnier M, Santschi V, Favrat B, Brunner H. Monitoring compliance in resistant hypertension: an important step in patient management. J Hypertens 2003;21(suppl 2):S37-S42.

9. Cramer JA, Scheyer RD, Mattson RH. Compliance declines between clinic visits. Arch Intern Med 1990;150:1509-1510.

10. Feinstein AR. On white-coat effects and the electronic monitoring of compliance. Arch Intern Med 1990;150:1377-1378.

11. Kaplan NM. Treatment of hypertension: drug therapy. In: Kaplan NM. Clinical Hypertension. 8th Edition. Baltimore: Lippincott, Williams & Wilkins;2002, Chapter 7:237-338.

12. Kalmthout PM van, Vree TB, Thien Th. Therapietrouw en kaliumgehalte in het plasma bij patiënten behandeld met chloorthalidon. Ned Tijdschr Geneeskd 1983;127:192-195.

13. Wang PS, Bohn RL, Knight E, Glynn RJ, Mogun H, Avorn J. Noncompliance with Antihypertensive Medications. The impact of depressive symptoms and psychosocial factors. J Gen Intern Med 2002;17:504-511.

14. Mancia G, Seravalle G, Grassi G. Tolerability and treatment compliance with angiotensin II receptor antagonists. Am J Hypertens 2003;16:1066-1073.

15. Eisen SA, Miller DK, Woodward RS, Spitznagel E, Przybeck TR. The effect of prescribed daily dose frequency on patient medication compliance. Arch Intern Med 1990;150:1881-1884.

16. Düsing R, Weisser B, Mengden T, Vetter H. Changes in antihypertensive therapy-the role of adverse effects and compliance. Blood Pressure 1998;7:313-315.

17. Marquez-Contreras E, Martell-Claros N, Gil-Guillen V, de la Figuera-Von Wichmann M, Casado-Martinez JJ, Martin-de Pablos JL, Figueras M, Galera J, Serra A ; Compliance Group of the Spanish Society of Hypertension (SEE). Efficacy of a home blood pressure monitoring programme on the therapeutic compliance in hypertension: the EAPACUM-HTA study. J Hypertens 2006;24:169-175.

18. Allen H. Promoting compliance with antihypertensive medication. Br J Nurs 1998;7(20):1252-1258.

19. Rudd P, Miller NH, Kaufman J, Kraemer HC, Bandura A, Greenwald G, Debusk RF. Nurse management for hypertension. A systems approach. Am J Hypertens 2004;17:921-927.

Chapter 4.2

Bromide as a marker to measure adherence to drug therapy

Richard L. Braam
Theo Thien

Department of Internal Medicine,
University Medical Centre St. Radboud, Nijmegen, The Netherlands

Stan H.M. van Uum

Endocrinology and Metabolism, Department of Medicine and
Lawson Health Research Institute,
University of Western Ontario, London, Ontario, Canada

Frans G.M. Russel

Department of Pharmacology and Toxicology,
University Medical Centre St. Radboud, Nijmegen, The Netherlands

Dorine W. Swinkels

Department of Clinical Chemistry,
University Medical Centre St. Radboud, Nijmegen, The Netherlands

European Journal of Clinical Pharmacology 2006;62:285-290

Abstract

Objective Several methods have been described to measure adherence to prescribed drug therapy. However, most of these have been shown to be inaccurate. Bromide is an anion that is readily absorbed in the gut and has an elimination half-life of about 12 days. In the present study, we investigated the pharmacokinetic properties of bromide with the objective to use it as a measure of drug adherence.

Methods Three groups of each 8 healthy volunteers took 15, 24 or 30 mg potassium bromide, respectively, daily for 20 weeks. Serum concentrations of bromide were measured every two weeks. Results: There was a linear relationship between the daily dosage taken and the mean increase of bromide concentration. In every group considerable inter-individual variability was seen. Correction for body weight resulted in an improved correlation between daily bromide dose and increase in concentration ($r=0.78$, $p<0.01$).

Conclusions Unfortunately, the inter-individual variability in clearance of bromide was considerable. This limits the use of bromide to primarily measuring adherence in individual patients during long term follow-up. Bromide appears to be a potentially useful marker to be added to drugs for assessment of individual adherence to long term drug therapy. This needs to be investigated in various patients, particularly for patients with relatively asymptomatic diseases (e.g. hypertension).

Introduction

Adherence to prescribed drug therapy is very important both in clinical practice and in studies on effects of drugs. About one-third or more of patients adhere poorly with prescribed regimens.[1,2] Adherence to a prescribed drug regimen has been found to decrease over time, and also declines between clinic visits.[3] Non-adherence appears to occur irrespective of the type of disease or its prognosis.[2] Adherence is a very difficult subject to study.[4] The subjective assessment of adherence by either patients or doctors is notoriously unreliable. Pill counting is often used, but does not accurately reflect actual intake of pills and correct timing of intake. It often overestimates drug intake.[2,5] Electronic registration using recording devices for monitoring medication intake (MEMS) is excellent in monitoring times of opening the pill bottle, but does not measure actual intake of the drug. Several markers have been added to the study drug to assess adherence, these include bromide, digoxin, phenobarbitone and isoniazid or its metabolites, acetylisoniazid and isonicotinic acid.[6-9] As adherence is particularly an issue with chronic therapy, an ideal marker should have a half-life over 3–4 days. Isoniazid and its metabolites could well be measured in urine, but their half-life is short (1 and 4 h, respectively), so these markers can only assess adherence over a short period of time. Digoxin has a longer half-life of about 60 h.[7] Phenobarbitone has the disadvantage of causing mild sedation in higher doses.[8] Bromide is readily absorbed throughout the gut, almost exclusively distributed in the extracellular space and innocuous if used in small doses.[10] Its half-life is long, about 12 days.[10] Because of these characteristics bromide may be a suitable marker of drug adherence, in particular in chronic diseases. Therefore, in the present study the (pharmacokinetic) properties of potassium bromide were further investigated.

Methods

The study was approved by the Hospital Ethics Committee, and all participants gave written informed consent before inclusion. In total, 24 healthy volunteers participated in the study. At baseline, weight, height and creatinine clearance (using 24-h urine collection) were measured. The participants were randomised in a double-blind fashion to three groups taking either 15, 24 or 30 mg of potassium bromide capsules once daily for 20 weeks. The maximum potassium bromide dose of 30 mg daily was chosen to allow for a detectable increase of the serum bromide concentration, while staying well below the serum levels associated with symptoms. Given the long half life of bromide it was

assumed that a daily potassium bromide dose of 15 mg would be equivalent to a situation of 50% adherence compared to a daily potassium bromide dose of 30 mg (provided that there was 100% adherence during the study). A daily dose of 24 mg of potassium bromide would then represent 80% adherence. Full adherence to once daily intake was therefore critical and monitored closely. The volunteers were continuously encouraged to be fully compliant. Blood samples for measurement of serum bromide concentration were taken twice at baseline, once every two weeks during the 20 weeks of potassium bromide intake, and 4 and 8 weeks after discontinuation. Adherence was monitored by capsule counting at each control visit and by Medication Event Monitoring System (MEMS)-devices throughout the study. These devices are pill-boxes that electronically record the date and time of each opening of the box.[11]

Whole blood samples were centrifuged after collection and the sera were stored at −20°C until analysis. Bromide concentrations were determined using high-performance liquid chromatography (HPLC) and pre-analysis ultrafiltration as described previously.[12] In short, 1 ml of serum was pipetted in the reservoir of a Centrifree Micropartition Device (Amicon) and centrifuged at 2,000 g for 60 min at 18°C. Subsequently, 10 µl of the clear ultrafiltrate was injected into the chromatographic system. This system consisted of an anion-exchange column (Whatman Partisil SAX 10 µm particles), an isocratic phospate-buffered mobile phase and ultraviolet detection at 195 nm. Plots of peak area versus concentration of the potassium bromide standards were used to calculate the amount of bromide in the samples. The standard curve was linear up to 3.0 mmol/l (240 mg bromide/l). The between run coefficient of variation was 17% for a 0.04 mmol/l (3 mg/l) sample and 12% for a 0.10 mmol/l (8 mg/l) sample. The detection limit of the method was 0.01 mmol/l (0.8 mg/l).

Pharmacokinetic analysis

Bromide concentration-time data were analysed by noncompartmental methods, after correction for baseline values. The bromide half-life ($t_{½}$) was determined by log-linear regression from the slope (ß) of the elimination curve after stopping intake, by the equation ln 2/ß. The steady-state concentration was obtained from the mean of the bromide concentrations measured over the period V7 to V9 (weeks 14 to 18). The apparent oral clearance (CL/F) was determined by dividing the dosing rate (dose/day) by the concentration at steady-state, and the apparent volume of distribution (V/F) by dividing Cl/F by ß (where F represents the oral bioavailability).

Based on the assumption that all participants did indeed take the prescribed dose every day the average concentrations in the 24 mg daily and 15 mg daily group were used to determine bromide concentrations associated with 80% (24/30) and 50% (15/30) adherence, respectively. All analyses were done with and without correction for body weight to assess if variations of body weight would affect bromide concentrations.

Results

Twenty-four healthy volunteers participated in the study. Their baseline characteristics are shown in Table 1. There were no significant differences between the three groups. Table 2 shows the adherence to daily capsule intake as assessed by capsule counting and electronic registration. At each 2-weekly visit to the clinic, the number of tablets taken from the container was registered. This number can be compared to the number of container openings registered during the same period. The level of adherence was very high, over 99%, in this highly motivated group of subjects. All participants completed the study, no side effects of bromide were noted.

The mean bromide concentrations during potassium bromide intake for each dosage group are shown in Figure 1.

Table 1. Baseline characteristics of participants taking 15, 24 or 30 mg potassium bromide per day

Group	15 mg/day	24 mg/day	30 mg/day
n	8	8	8
Age (years)	39±13	40±16	41±12
Weight (kg)	79±12	71±17	76±19
Height (cm)	174±10	172±13	169±8
Gender (male:female)	3:5	3:5	1:7
Creatinine clearance (ml/min/1.73m^2)[a]	92±16	89±16	90±13

All data are presented as mean±SD, unless stated otherwise.
[a]Calculated using 24-h urine collection

Table 2. Adherence as assessed by capsule counting and electronic monitoring

Group	Days (total)	Capsule counting	Trackcap (MEMS)
15 mg/day	1,109	1,109	1,108
24 mg/day	1,124	1,110	1,110
30 mg/day	1,091	1,090	1,079
All three groups	3,324	3,309	3,297

At 2-weekly intervals the number of capsules taken (measured using capsule counting and the electronic registration of container openings) was compared to the expected number, i.e. the number of days that had passed since the start of bromide intake. The total number of days varies slightly between the different groups because some subjects stopped taking tablets a few days earlier because of holidays

At baseline, there were no differences in serum bromide concentrations between the three groups. During potassium bromide intake the bromide concentrations varied between groups. Six to ten weeks after the start of bromide the concentrations stabilised, suggesting a steady-state situation.
Pharmacokinetic data on bromide for each dose group are presented in Table 3. There were no statistically significant differences in elimination half-life, apparent oral clearance and the apparent volume of distribution of bromide between the three groups. The steady-state concentration was significantly higher in both the 24 mg and 30 mg group when compared to the 15 mg group, and there was borderline significance between the 30 mg and 24 mg group (p=0.07). However, inter-individual variability in the apparent oral clearance was considerable within each of the three groups.

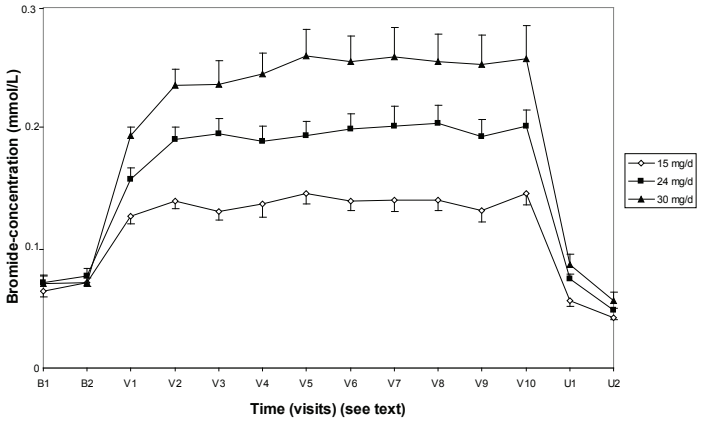

Figure 1. Bromide-concentrations in subjects taking 15, 24 or 30 mg potassium bromide daily (n=8 for each group). B1 and B2; baseline measurements. V1-V10; 2-weekly visits during bromide intake. Visit 1 (V1) is the first bromide measurement 2 weeks after starting with bromide intake. U1 and U2: bromide concentration measurement, 4 and 8 weeks, respectively, after stopping intake. Data are presented as mean±SE.

The mean increase of bromide concentrations was calculated by subtracting the mean of the two baseline results from the mean of the concentrations at visits 7, 8 and 9. Figure 2 shows the mean increase of bromide-concentrations at visits 7 to 9 (weeks 14 to 18) for the 24 subjects according to the bromide content of the capsules taken. The increases (mean±SD) in bromide concentrations were 0.070±0.024, 0.125±0.039 and 0.185±0.068 mmol/l in the 15 mg, 24 mg and 30 mg per day groups, respectively. The mean increase in the bromide concentration of the 15 mg group was significantly lower than in both other groups ($p<0.01$).

The difference in the mean increase of the concentrations of the 24 and 30 mg dose groups approached statistical significance (p=0.054) (Figure 2). For the increase in bromide concentrations, there was a considerable overlap between the three groups and there was considerable variation within each group. This makes it difficult to choose cut-off levels that adequately distinguish between the dosage groups. We hypothesised that body weight could be a confounding factor and corrected the results for body weight.

Table 3. Steady-state pharmacokinetic parameters of bromide

Group	15 mg/day	24 mg/day	30 mg/day
Baseline concentration (mmol/l)	0.07±0.004	0.07±0.02	0.07±0.02
Bromide $t_{½}$ (days)	11.0±2.0	10.4±1.6	11.0±1.8
Steady-state concentration (mmol/l)	0.14±0.03	0.20±0.04[a]	0.26±0.07[a,b]
Cl/F (l/day)	2.0±0.7	1.7±0.5	1.6±0.7
V/F (l)	31±9	25±7	24±11

Data are presented as mean±SD. Differences between groups are not significant unless stated otherwise. [a]p<0.01 versus 15 mg bromide/day. [b]p=0.07 versus 24 mg bromide/day. $t_{½}$ elimination half-life; Cl/F, apparent oral clearance; V/F, apparent volume of distribution; F, oral bioavailability

Figure 3 shows the increase of bromide concentration related to the dosage taken per kilogram (kg) body weight. There is a linear relationship between increase of bromide concentration and bromide dosage per kg body weight (Pearson coefficient of correlation 0.78, p<0.01). When 30 mg of potassium bromide per day is added to a drug that is prescribed for a long time, the drug adherence can be calculated from the increase in bromide concentration and the body weight, using the following formula that is derived from Figure 3:

Adherence % = 7.33x {Increase in Br concentration (mmol/l) + 0.0188}x Body weight (kg)

Discussion

In the present study, we show that potassium bromide has pharmacokinetic characteristics that may make it a reliable and stable marker of adherence to prescribed drug therapy. The mean steady state concentration for each group of eight subjects directly depended on the amount of potassium bromide taken (Figure 1). The results of Figure 2 indicate that, although the bromide levels were clearly different between the dosage groups, there is still considerable overlap between groups due to inter-individual variability. Due to the variability in clearance between individuals, the use of bromide as a marker for adherence

is far less useful for patient groups than for individuals. Measuring bromide levels to assess adherence could therefore primarily be used for longitudinal observation in individual patients. This could be particularly helpful when there is a decrease of a therapeutic effect without changes in prescribed medication.

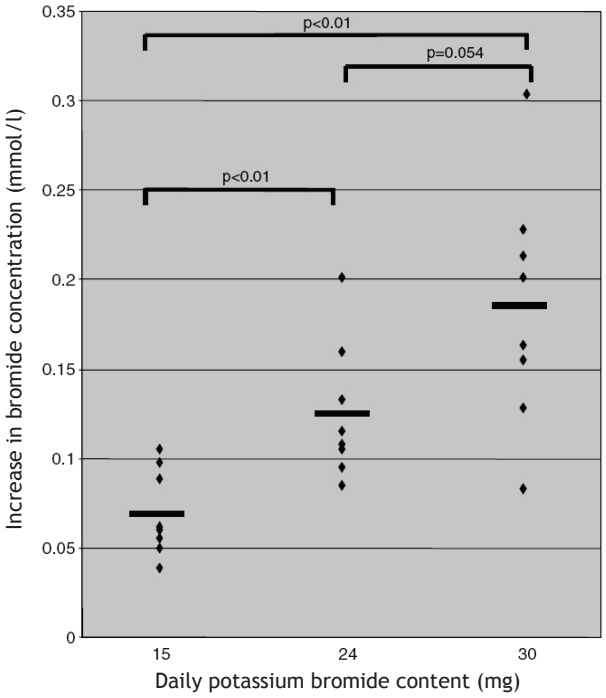

Figure 2. Mean increase in serum bromide concentrations in the 8 subjects of each group as measured at visit 7 to 9 (14 to 18 weeks)

Adjustment of levels for body weight improved the correlation between dose and serum bromide, and thus allows for a better assessment of adherence (Figure 3). Based on the formula that we developed, it is possible to calculate thresholds for the increase in bromide concentration associated with good (i.e. 80% or more) adherence in patients of different body weights.

We preferred to investigate the use of a marker with a long half-life. Our purpose is to help identify nonadherence in patients with chronic conditions. Especially, we would like to identify patients who take their medicines but

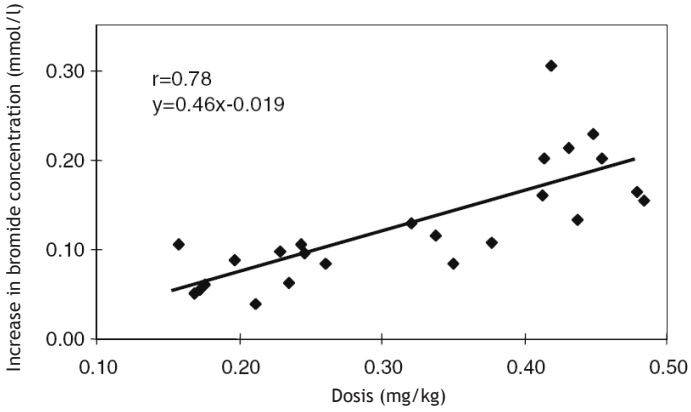

Figure 3. Relationship between the bromide dosage taken per kg body weight and the increase in bromide concentration (calculated as the mean of the increases at visits 7 to 9 (weeks 14 to 18))

are also regularly non-adherent. This group of patients would probably best be accessible for improvement in adherence. We are less interested in short term changes in adherence for which markers with a shorter half-life would be more suitable. This can be compared to the situation in patients with diabetes mellitus, in whom Hba1c is used as a marker for long-term glycaemic regulation. In patients with normal recent glucose levels, but a high Hba1c, insufficient adherence over a longer term needs to be considered.

Using markers with a long half-life may provide an accurate assessment of adherence over a longer period. On the other hand, the disadvantage of using such a marker is that non-adherence in the week before the blood sample was taken may not be detected. However, 'drug-holidays' generally occur between clinic visits, while adherence increases when an appointment date is approaching (referred to as the so called 'white-coat adherence'). In this situation, use of a marker with a short half-life may in fact overestimate long-term adherence.[3]

One area where long-term adherence is important is treatment of hypertension, where non-adherence is highly prevalent. Use of bromide may help raise consciousness of the importance of adherence, and help both the physician and the patient to address adherence issues.

Bromide appears to be well tolerated, and its half-life of about 11 days makes

it a useful marker for long term adherence. A limitation of our study could be that we did not actually test the effect of skipping daily doses. Instead, we studied the effect of 80% and 50% decrease in dose of the daily taken potassium bromide capsule. However, given the long half-life of bromide, it is not likely that this would have affected the results. Using a marker like bromide clearly also has some other disadvantages. Adherence to only one drug at a time can be tested and short term changes in adherence will not be detected. Also, no information is obtained concerning the pattern of adherence, so it is unknown if the patient is taking the tablets at the prescribed regular intervals or at a more random pattern. We suggest that adherence can best be assessed by a combination of bromide as a marker and the use of electronic registration (MEMS pill boxes). In addition, this monitoring of the adherence requires blood sampling, probably at least once every 6 weeks during drug intake.

Pharmacokinetic aspects of bromide

The oral bioavailability of bromide is about 95% and the elimination half-life 12 days.[13] Bromide is not bound to plasma protein or sequestered in cells; it occupies the same volume of distribution as chloride and competes with that ion for excretion by the kidney.[10] Because bromide is excreted by the kidney, serum bromide concentrations will be expected to be higher in patients with renal insufficiency. However, for the amounts of potassium bromide given in the current study, toxic concentrations are not expected to occur even in renal insufficiency, although caution in these patients is of course warranted. Normal values for bromide in relation to the severity of renal insufficiency are not available. In patients with chloride depletion the clearance of bromide is markedly reduced. Until further studies have determined the specific effects of impaired renal function and the effect of diuretics on bromide clearance and steady state levels, the currently proposed formula for assessment of adherence based on bromide concentrations should not be used in these patients.

The safety of bromide as a marker

Bromide was discovered in 1826 by Balard and since then has been used in various preparations as sedative and anticonvulsant.[10] Before the discovery of phenobarbitone as an anti-epileptic drug in 1912, potassium bromide was the only known effective agent to treat epilepsy.[14] Table salt is the major source of dietary bromide.[10] Van Gelderen *et al*.[15] proposed a no-effect level (NOEL) of 4 mg sodium bromide/kg body weight (equivalent to 4.6 mg potassium bromide/

kg). Sangster *et al*.[16] also showed that administration of different dosages of bromide up to 9 mg/kg/day for a period of 12 weeks was safe. The mean intake of potassium bromide in our group of 24 healthy volunteers was 0.32 mg/kg (±0.11; range 0.16–0.48), which is well below the NOEL. Baseline blood concentrations of bromide are 3–4 mg/l (0.0375–0.05 mmol/l).[17] The highest concentration of bromide that we measured (34 mg/l; 0.43 mmol/l) was well below the levels that are associated with complaints (500–1,000 mg/l; 6.3–12.5 mmol/l) or toxicity (>2,000 mg/l; 25 mmol/l).

Safety of potassium

The usual daily intake of potassium is 40–120 mmol (1 mmol/kg/day).[18] The amount of potassium administered daily amounts to 0.25 mmol when taking 30 mg of potassium bromide. This amount is therefore negligible compared to the usual daily amount of potassium taken.

Conclusion

Assessment of adherence should be a daily topic in every patient–doctor consultation. Efforts should be made to increase awareness of the consequences of non-adherence (both clinically and economically). The results of this study suggest that low-dose bromide, despite its limitations, may be used to improve reliable assessment of adherence. Further studies need to assess its use in clinical trials and practice.

Acknowledgements
We would like to thank Henk Baadenhuijsen and Bea Peek for their technical support.
This study was supported by an unrestricted grant from Knoll B.V. (now part of Abbott).

References

1. Urquhart J. Patient non-compliance with drug regimens: measurement, clinical correlates, economic impact. Eur Heart J 1996;17[suppl A]:8–15.

2. Urquhart J. Role of patient compliance in clinical pharmacokinetics. A review of recent research. Clin Pharmacokinet 1994;27:202–215.

3. Cramer JA, Scheyer RD, Mattson RH. Compliance declines between clinic visits. Arch Intern Med 1990;150:1509–1510.

4. Osterberg L, Blaschke T. Adherence to medication. N Engl J Med 2005;353:487–497.

5. Pullar T, Kumar S, Tindall H, Feely M. Time to stop counting the tablets? Clin Pharmacol Ther 1989;46:163–168.

6. Roth HP, Caron HS, Bartholomew P. Measuring intake of a prescribed medication, a bottle count and a tracer technique compared. Clin Pharmacol Ther 1970;11:228–237.

7. Mäenpää H, Javela K, Pikkarainen J, Mälkönen M, Heinonen OP, Manninen V. Minimal doses of digoxin: A new marker for compliance to medication. Eur Heart J 1987;8[suppl I]:31–37.

8. Feely M, Cooke J, Price D, Singleton S, Mehta A, Bradford L, Carlvert R. Low-dose phenobarbitone as an indicator of compliance with drug therapy. Br J Clin Pharmacol 1987;24:77–83.

9. Ellard GA, Jenner PJ, Downs PA. An evaluation of the potential use of isoniazid, acetylisoniazid and isonicotinic acid for monitoring the self-administration of drugs. Br J Clin Pharmacol 1980;10:369–381.

10. Ritschel WA, Vachharajani NN. Review of electrolyte pharmacokinetics. Meth Find Exp Clin Pharmacol 1992;14:241–254.

11. Burnier M, Santschi V, Favrat B, Brunner HR. Monitoring compliance in resistant hypertension: an important step in patient management. J Hypertens 2003;21[suppl 2]:S37–S42.

12. Miller ME, Cappon CJ. Anion-exchange chromatographic determination of bromide in serum. Clin Chem 1984;30:781–783.

13. Vaiseman N, Koren G, Pencharz P. Pharmacokinetics of oral and intravenous bromide in normal volunteers. J Toxicol Clin Toxicol 1986;24:403–413.

14. Pearce JMS. Bromide, the first effective antiepileptic agent. J Neurol Neuro surg Psychiatry 2002;72:412.

15. Van Gelderen CE, Savelkoul TJ, Blom JL, van Dokkum W, Kroes R. The no-effect level of sodium bromide in healthy volunteers. Hum Exp Toxicol 1993;2:9–14.

16. Sangster B, Blom JL, Sekhuis VM, Loeber JG, Rauws AG, Koedam JC, Krajnc EI, van Logten MJ. The influence of sodium bromide in man: a study in human volunteers with special emphasis on the endocrine and the central nervous system. Food Chem Toxicol 1983;21:409–419.

17. Toseland PA. Bromide in blood. Lancet 1991;338:386.

18. Singer GG, Brenner BM. Chapter 49: fluid and electrolyte disturbances. In: Fauci A, Braunwald E, Isselbacher KJ, Wilson JD, Martin JB, Kasper DL, Hauser SL, Longo DL (eds) Harrison's principles of internal medicine, 14th ed. McGraw Hill, New York 1998:265–277.

Chapter 4.3

Bromide as marker for drug adherence in hypertensive patients

Richard L. Braam
Jacques W.M. Lenders
Theo Thien

Department of Internal Medicine,
University Medical Centre St. Radboud, Nijmegen, The Netherlands

Stan H.M. van Uum

Endocrinology and Metabolism, Department of Medicine and
Lawson Health Research Institute,
University of Western Ontario, London, Ontario, Canada

Submitted

Abstract

Introduction Adherence to prescribed antihypertensive medication is essential for adequate long term control of blood pressure (BP) in hypertensive patients. We performed a study to compare different methods of measuring adherence and to investigate the relation between adherence and effect of treatment with trandolapril 2 mg/verapamil SR 180 mg on BP in patients inadequately controlled with one antihypertensive drug.

Methods Patients were included if BP was insufficiently controlled (diastolic blood pressure (DBP) > 95 mmHg and/or systolic blood pressure (SBP) > 160 mmHg) on monotherapy. At the start of the study antihypertensive medication was stopped. After a placebo period of 4 weeks, treatment with trandolapril 2 mg/verapamil SR 180 mg was started. The effect on BP was determined throughout the study period using a mercury sphygmomanometer and ambulatory blood pressure monitoring (ABPM, SpaceLabs 90207). Adherence was measured using three methods: capsule counting, electronic registration of pill-box openings (Medication Event Monitoring System, MEMS) and by measuring serum bromide concentrations. Potassium bromide (30 mg) had been added to each capsule of trandolapril 2 mg/verapamil SR 180 mg. Changes in bromide levels were compared to the previously measured change in serum bromide in volunteers taking 24 mg bromide daily (simulating 80% adherence).

Results Thirty patients participated in the study, 14 men and 16 women. Treatment with trandolapril 2 mg/verapamil SR 180 mg for 20 weeks lowered office BP by 9.6/7.5 (± 11.4/6.4) mmHg. ABPM also showed a significant decrease in SBP and DBP after 8 and 16 weeks of treatment.
Adherence as assessed by capsule counting, MEMS and measurement of bromide concentration was good for the majority of patients. The serum bromide concentrations indicated good adherence in 93% of patients at weeks 12 and 20. Adherence was highest when assessed by capsule counting. Results for electronic monitoring and adherence based on bromide measurements were comparable.

Conclusion Measuring serum bromide levels may be suitable for assessment of adherence to drug therapy. However measuring bromide is a rather time-, cost- and work-consuming method for determining adherence.

Introduction

Hypertension is one of the most important risk-factors for cardiovascular morbidity and mortality. In general, high blood pressure (BP) responds well to drug treatment. However, it is often challenging for patients to take antihypertensive drugs for many years, especially if drug intake is associated with side effects while the increased BP itself is asymptomatic.

Adherence to a medication regimen, defined as the extent to which patients take prescribed medications,[1] is a major factor determining the success of hypertension treatment. In chronic conditions, including hypertension, adherence to prescribed drug regimen is often low. Adherence rates are higher in clinical trials for chronic conditions, but even in these trials adherence rates of 43 to 78 percent have been reported.[1] Adherence is difficult to measure and although several methods have been described and tested,[1] objective methods to measure drug-adherence are needed. We have previously documented that potassium bromide has pharmacokinetic properties that may make it an useful marker to estimate drug intake.[2]

Aim of the present study was to examine whether bromide addition to an antihypertensive drug with measurement of serum bromide is a better measure of therapy adherence than electronic monitoring of drug intake.

Patients and methods

Hypertensive patients were recruited via advertising in local newspapers and were included after written informed consent. Patients were included if they had a diastolic blood pressure (DBP) ≥95 mmHg and/or a systolic blood pressure (SBP) ≥160 mmHg despite at least four weeks of antihypertensive monotherapy. Patients were informed that the purpose of the study was to see if BP could be adequately lowered with a combination of two antihypertensive drugs. They were not informed that the study was actually designed to assess adherence to drug therapy, as this would possibly affect study outcome. The study was approved by the Hospital Ethics Committee.

Antihypertensive medication was stopped at the start of the study. Patients received a placebo for four weeks and then treatment with the combination of the angiotensin converting enzyme inhibitor trandolapril 2 mg and the calcium antagonist verapamil SR 180 mg once daily was started and continued for 20 weeks. This combination was given in one capsule and to each capsule 30 mg potassium bromide was added. Office blood pressure (OBP) was measured every two weeks during the placebo period and at weeks 2, 4, 8, 12, 16 and 20 of the

treatment period. Ambulatory blood pressure monitoring (ABPM) was carried out three times: two weeks after starting placebo and 8 and 16 weeks after start of active drugs.

OBP was measured using a mercury sphygmomanometer after patients had been resting in sitting position for 10 minutes, with the back supported and the arm on the desk. The average of three BP readings was calculated. ABPM was carried out using a SpaceLabs 90207. Measurements were performed every 20 minutes during the day and every 30 minutes during night time. Trough (T) BP was calculated as the mean SBP and DBP within a window of one hour before and half an hour after drug intake at the end of ABPM. Within each 1 hour time frame during the nine hours after study drug intake, the mean SBP and DBP were calculated. The lowest SBP and DBP of all 1 hour time frames were determined and were defined as the peak BP (PBP), i.e. the BP level at the time of largest drop in BP.

Adherence with prescribed drug regimen was measured using three methods: capsule counting, an electronic "track cap" system (Medication Event Monitoring System, MEMS), and measuring serum bromide concentration. Adherence based on capsule counting was measured by dividing the number of capsules taken (calculated as dispensed minus returned number of capsules) by the expected number of capsules taken, defined as the number of days within the period, first day (container handed over) included, last day (container taken in) excluded. A container with 40 placebo capsules was handed out at the start of the study and taken in at week 4 of the placebo period. A container with 100 capsules of trandolapril 2 mg/ verapamil SR 180 mg was handed out at the end of the placebo period and taken in at week 12 of the treatment period. A second container with 70 capsules was handed out at week 12 and taken in at the end (week 20) of the treatment period. Adherence was defined as "good", when the drug intake was ≥80% based on capsule counting.

The second method for measuring adherence was electronic monitoring. Using a special container the number, time and date of each opening of the container was registered. As one capsule should be taken every day it was expected that the container was opened once daily. Adherence was calculated as the number of times the container was opened divided by the number of days the capsules should have been taken. It was defined as "good" when adherence was ≥80% based on electronic monitoring.

The third method for assessment of adherence was measuring serum bromide concentrations. All drug capsules (but not the placebo capsules) had been supplemented with 30 mg of potassium bromide. Blood samples for bromide

levels were taken at clinic visits throughout the study period: every two weeks during the placebo period and at weeks 2, 4, 8, 12, 16 and 20 of the treatment period. Recently we studied the pharmacokinetic properties of bromide in a group of 24 healthy volunteers using different amounts of potassium bromide.[2]
The mean increase in bromide level in the eight volunteers taking 24 mg potassium bromide daily was used as cut-off level for 80% adherence: values above this concentration were considered indicative of good adherence, whereas values below this level were considered as poor adherence.

A prespecified secondary outcome was the number of patients in whom the office BP normalised and/or responded to treatment with the antihypertensive drug combination. Normalisation of DBP was defined as a decrease of DBP to a level equal to or lower than 90 mmHg. Patients were identified as a 'responder' when BP normalised or when the decrease in DBP was at least 10% of baseline BP (placebo period).
Normalisation of SBP was defined as a decrease of SBP to a level equal to or lower than 140 mmHg. Patients were identified as a 'responder' when BP normalised or the decrease in SBP was at least 10% of baseline BP (placebo period).
For ABPM, normalisation of DBP was defined as a decrease of daytime DBP to a level equal to or lower than 85 mmHg and for SBP as a decrease of daytime SBP to a level equal to or lower than 135 mmHg. Patients were identified as a 'responder' if BP normalised or if the decrease in DBP, respectively SBP was at least 10% of baseline BP (placebo period). Daytime was defined as the period between 10.00 hours a.m. and 8.00 hours p.m.

Statistical analysis

Results were analysed using Student’s t-test. Differences with a p-value <0.05 (two-sided) were considered statistically significant. Correlations were calculated by using the Pearson’s coefficient of correlation. Results are presented as mean ± SD, unless indicated otherwise.

Results

Thirty patients, 14 men and 16 women, participated in the study. Baseline characteristics are shown in Table 1. One patient discontinued the drug in week 2 of the treatment period because of a maculo-papular skin reaction. Another patient discontinued treatment at week 16 because of dramatic personal events not related to the study or drug-intake. No serious adverse effects were reported.

Table 1. Baseline characteristics of patients (mean ± SD are given).

	Mean	(± SD)
age (yrs)	53	(±10)
height (cm)	171	(±7)
body-weight (kg)	82	(±13)
BMI (kg/m^2)	27.9	(±4.6)
heart rate (bpm)	76	(±12)
blood pressure (mmHg)	Office SBP	Office DBP
- at start of placebo period	151 (±13)	101 (±4)
- at week 2 of placebo period	159 (±15)	105 (±5)
- at week 4 of placebo period	158 (±15)	105 (±5)

SBP, systolic blood pressure; DBP, diastolic blood pressure; bpm, beats per minute.

The results for measuring adherence by the three methods are shown in Table 2. Based on capsule counting almost all patients showed good adherence (intake ≥80% of expected) over the whole 20 week treatment period. One patient returned the container two weeks after the last visit and was considered to be non-adherent. According to electronic monitoring adherence was “good” (at least 80% of expected openings of the drug container) for all patients except for 2 patients during the second treatment period (between 12 weeks and 20 weeks of treatment). Two other patients were considered to be non-adherent because recordings were missing after the last visit.

The bromide concentration increased from 0.06±0.01 mmol/l at baseline to 0.26±0.06 mmol/l (mean of bromide concentrations at weeks 12, 16 and 20 of treatment period). The change in bromide concentration for the individual patients during the treatment period is shown in Figure 1. The mean of the change in bromide concentration of the hypertensive patients after 12, 16 and 20 weeks of treatment was 0.21 ± 0.01 mmol/l (standard error, SE).

In a previous study we demonstrated that the increase in serum bromide levels in a defined dose of potassium bromide of for example 30 mg, negatively correlates with body weight.[2]

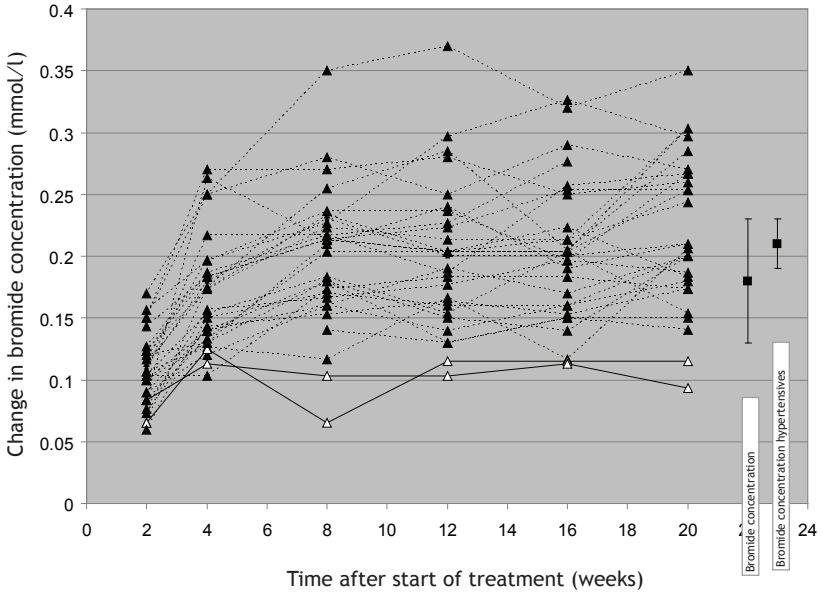

Figure 1. Changes in serum bromide concentration in 30 patients treated with trandolapril/ verapamil. The broken lines indicate patients with good adherence. The two patients with poor adherence are shown (solid lines, open triangles). On the right side of the figure the mean change in bromide concentration (± 2SE) are shown for the volunteers (n=8)[2] and hypertensive patients (n=29), both using 30 mg potassium bromide.

This was confirmed in the current study, the coefficient of correlation between body weight and change in bromide concentration was –0.53 (Figure 2). As shown in Figure 2 there was a linear relationship between the dose of potassium bromide administered per kilogram body weight and the mean increase in bromide concentration (for weeks 12, 16 and 20).

For comparison with the other two methods for assessment of adherence, we used the increase in bromide levels measured at weeks 12 and 20 of treatment (Table 2). Adherence based on the measurement of serum bromide was 'good' for 93% of participants at both time points. The two patients that were categorized as 'poor' adherent appeared to have a high body-weight: 91 kgs and 98 kgs, respectively. The patients that were identified as non-adherent by electronic monitoring and those identified by measuring serum bromide levels were not the same patients. For one patient with poor adherence based on serum bromide measurement, adherence was 82% during the second treatment period (weeks 12 to 20) based on electronic monitoring. But for the other patient the adherence rate was 102% at the second treatment period based on electronic monitoring. For all four patients that were found to be non-adherent

based on electronic monitoring (two patients were classified as non-adherent because containers were missing at the last visit) adherence was good based on serum bromide measurements.

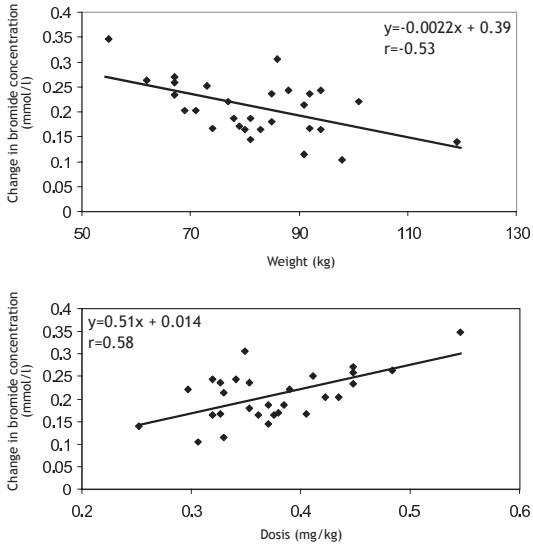

Figure 2. Relationship between body weight and increase in bromide concentration (r=-0.53). The association between the mean increase in bromide concentration (weeks 12, 16 and 20) and the dose of potassium bromide per kilogram body weight is shown in the lower part of the figure.

Blood pressure response following treatment with trandolapril/verapamil.

The results of office BP measurements are shown in Figure 3. Treatment with trandolapril 2 mg/ verapamil SR 180 mg for 20 weeks decreased OBP by 9.6/7.5 (±11.4/6.4) mmHg (both p-values <0.05).

Results of ABPM are shown in Table 3. During the study period ABPM measurements were technically insufficient in three patients. Compared to baseline (visit 2), there was a significant decrease in systolic and diastolic BP, for mean, trough and peak BPs during treatment (Table 3).

Table 4 shows the number of 'normalisers' and 'responders' to treatment with trandolapril/verapamil. Using office measurements 29% of patients responded after 20 weeks of treatment with trandolapril/verapamil for DBP and 39% of patients for SBP. Results for patients that fulfilled criteria of 'normalisers' or 'responders' for both SBP and DBP are also shown in Table 4.

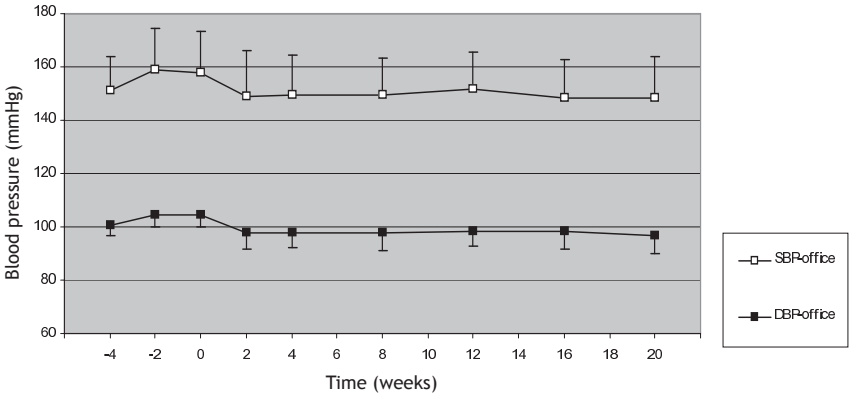

Figure 3. The course of the office blood pressure during the study period (mean ± SD).

Discussion

In the present study, adherence with antihypertensive therapy was evaluated using three different methods: capsule counting, electronic monitoring and measuring serum concentrations of bromide, that had been added as a marker to the active drug. In general, adherence with drug therapy was good according to all methods. Several methods have been developed for assessment of adherence.[1] All methods have advantages and limitations. Capsule counting is known to be less reliable as a method of measuring adherence, because its results can easily be influenced by the patient who can discard capsules.[4] However it is one of the most simple methods to measure adherence.[4] More recently electronic monitoring has been introduced, in which a special container is able to record time and date of each container opening.[1,5,6] Electronic monitoring is an accurate method of measuring adherence. A patient would consistently have to open and close the pill container without taking medication to circumvent this method. However, both capsule counting and electronic monitoring do not document the actual intake of chronically used drugs. To overcome this particular disadvantage, markers have been added to the drugs and the marker concentrations have been used to measure adherence. In the past low doses of digoxine, phenobarbitone, phenobarbital and bromide have been used.[7-10] This study confirms that bromide is potentially suitable as a marker for adherence as has previously been shown, because of its long half life (about 12 days) and because it is not associated with side-effects in the small dosages used.[2] The mean of the change in bromide concentration of the hypertensive patients in the

current study was comparable to the mean increase in bromide concentration observed in the eight volunteers taking 30 mg potassium bromide (0.21 ± 0.01 mmol/l versus 0.18 ± 0.02 mmol/l, Figure 1).[2]

Although measurement of bromide added to the antihypertensive drug confirms actual drug intake, there are also disadvantages. Multiple blood samplings are necessary and the method is quite time-, cost- and work-consuming. Another disadvantage is that it can only monitor intake of one drug or a fixed combination of drugs in one capsule. The inter-individual variation in the serum bromide levels is quite large (Figure 1).

Measuring serum bromide levels seems therefore to be most useful as a method to follow-up adherence in an individual patient. Its main application probably would be as a research tool in situations in which actual drug ingestion over longer time periods has to be confirmed.

In this small study all three methods of measuring adherence appeared to give similar results. Not surprisingly capsule counting was associated with the highest level of adherence. By using electronic monitoring and measuring serum bromide levels non-adherent patients could be identified. However these were not the same patients for the two methods. The non-adherent patients identified by measuring serum-bromide levels had a high body weight. As was previously shown the increase in bromide level correlated negatively with body weight (Figure 2).[2]

Table 2. Assessment of adherence by three different methods.

Method	n	Number adherent at 12 weeks of treatment period (%)	n	Number adherent at 20 weeks of treatment period (%)
Capsule counting[1)] 'Good' adherence	29	29 (100)	28	27 (96)
Electronic monitoring[2)] 'Good' adherence	29	29 (100)	28	24 (86)
Serum bromide level 'Good' adherence	29	27 (93)	28	26 (93)

n, number of patients. For all methods: one patient withdrawn at week two of treatment period, one patient at week 16. [1)] One patient returned container two weeks after last visit, this patient was considered to be non-adherent. [2)] For two patients track cap recording was missing at last visit (week 20). These patients were considered to be non-adherent. Also two patients were found to have an adherence rate less than 80%.

Table 3. Results of Ambulatory Blood Pressure Measurements

Week	Number	SBP (mmHg) Mean (±SD)	DBP (mmHg) Mean (±SD)
2 of placebo period	25	146.2 (±13.9)	92.7 (±8.4)
8 of treatment period	25	135.4 (±12.8)[a)]	85.0 (±7.7)[a)]
16 of treatment period	25	135.8 (±11.6)[a)]	85.5 (±8.0)[a)]
		Trough BP	
2 of placebo period	25	145.4 (±19.5)	92.7 (±13.7)
8 of treatment period	25	133.8 (±16.3)[a)]	84.2 (±11.2)[a)]
16 of treatment period	25	134.2 (±12.9)[a)]	86.4 (±11.7)[a)]
		Peak BP	
2 of placebo period	25	138.5 (±13.8)	86.8 (±9.4)
8 of treatment period	25	125.1 (±16.8)[a)]	76.1 (±11.3)[a)]
16 of treatment period	25	125.7 (±13.3)[a)]	78.1 (±10.8)[a)]
		Trough/Peak ratio*)	
2 of placebo period	25	1.049	1.069
8 of treatment period	25	1.077	1.117
16 of treatment period	25	1.076	1.120

SBP, systolic blood pressure; DBP, diastolic blood pressure. *) T/P ratio was calculated by dividing trough value by peak value. [a)] $p<0.05$ versus week 2 of placebo period. Two patients were withdrawn during the study period and therefore excluded from the analysis. An additional three patients were excluded because of inadequate ambulatory blood pressure measurements for peak and trough blood pressures.

Several factors may have contributed to the very high adherence in this patient group. First, patients were selected via advertising in local media. This probably resulted in self-selection of a highly motivated group of hypertensive patients. This is also demonstrated by the fact that adherence did not decrease substantially over the 20-week study period in contrast to the results of other studies.[3] As overall adherence was very high for all thirty patients, it can be expected that correlating the level of drug adherence to the efficacy of drug therapy (the decrease in BP) is less informative. Actually there was no correlation between the change in mean arterial pressure from visit 3 (start of treatment period) to visit 9 (week 20 of the treatment period) and the change in serum bromide concentration.

Second, although the patients were not aware that assessment of adherence was the most primary objective of this study, they were aware of participation in a clinical trial, and the rate of adherence with drug therapy is usually higher in clinical trials. Third, combination therapy of two drugs was given in the simplest form (one pill, once daily), and it is known that adherence to drug therapy is inversely proportional to frequency of dose.[11] Fourth, the frequency of clinic visits (every 2-4 weeks) was much higher than in usual clinical care,

and studies have demonstrated that patients usually improve their medication taking behaviour in the five days before and after a clinic visit (also referred to as white-coat adherence).[12]

Table 4. Number and percentage of normalisers and responders for office blood pressure (see text for definitions) and daytime ambulatory blood pressure measurements (see text for definitions) during treatment period. Results are shown for systolic and diastolic blood pressure (SBP, DBP) separately and together (both). Office measurements for one patient were missing at week 4, two patients were withdrawn during the study period.

Office BP				Normalisers				Responders					
week	n	SBP	%	DBP	%	both	%	SBP	%	DBP	%	both	%
2	29	10	34	3	10	3	10	13	45	6	21	5	17
4	28	7	25	2	7	0	0	10	36	7	25	3	11
8	29	7	24	4	14	2	7	10	34	5	17	4	14
12	29	7	24	1	3	1	3	9	31	4	14	3	10
16	28	8	29	2	7	1	4	11	39	6	21	3	11
20	28	7	25	4	14	2	7	11	39	8	29	5	18

ABPM				Normalisers				Responders					
week	n	SBP	%	DBP	%	both	%	SBP	%	DBP	%	both	%
8	28	10	36	9	32	6	21	17	61	15	54	12	43
16	28	9	32	8	29	6	21	13	46	15	54	11	39

Finally, implicit in the study design was handing out the medication at the clinic visit by the physician, which removed the need for a special visit to a pharmacist as a potential barrier for good adherence.
As overall adherence was very high for all thirty patients, it can be expected that correlating the level of drug adherence to the efficacy of drug therapy (the decrease in BP) is less informative. Actually there was no correlation between the change in mean arterial pressure from visit 3 (start of treatment period) to visit 9 (week 20 of the treatment period) and the change in serum bromide concentration.

Measuring adherence with several methods is difficult to do in clinical practice. For general clinical practice measuring bromide is too time-, cost- and work-consuming. Electronic monitoring is a reliable and less complex method of measuring adherence. However, in clinical trials adequate assessment of adherence is critical for proper evaluation of study outcomes. Therefore in research studies, the combination of several methods may be helpful in avoiding the disadvantages inherent to each individual method.

In conclusion, all three methods indicated good overall adherence with prescribed drug therapy. The results of assessment of adherence were fairly similar for the three methods in most patients. In this study bromide was not better than electronic monitoring for measuring adherence. Bromide can have a place when definite ingestion of the drug has to be known. The long half life of bromide makes it a potentially suitable marker for drug adherence in patients with asymptomatic conditions like hypertension. However because measuring bromide is relatively time-, work- and cost-consuming it is probably best used as a research tool. Electronic monitoring is a better candidate for application in everyday clinical practice.

Acknowledgements
We thank Wim Lemmens, statistical analyst.

References

1. Osterberg L, Blaschke T. Adherence to Medication. N Engl J Med 2005;353:487-497.

2. Braam RL, van Uum SH, Russel FG, Swinkels DW, Thien T. Bromide as a marker to measure adherence to drug therapy. Eur J Clin Pharmacol 2006;62:285-290.

3. Stephenson BJ, Rowe BH, Haynes RB, Macharia WM, Leon G. Is this patient taking the treatment as prescribed? JAMA 1993;269:2779-2781.

4. Urquhart J. Role of patient compliance in clinical pharmacokinetics. A review of recent research. Clin Pharmacokinet 1994;27:202-215.

5. Burnier M, Santschi V, Favrat B, Brunner HR. Monitoring compliance in resistant hypertension: an important step in patient management. J Hypertens 2003;21(suppl 2):S37-S42.

6. Baulmann J, Düsing R, Vetter H, Mengden Th. Therapy resistant hypertension – significance of electronic compliance monitoring. Dtsch Med Wochenschr 2002;127:2379-2382.

7. Roth HP, Caron HS, Bartholomew P. Measuring intake of a prescribed medication, a bottle count and a tracer technique compared. Clin Pharmacol Ther 1970;11:228-237.

8. Pullar T, Kumar S, Tindall H, Feely M. Time to stop counting the tablets? Clin Pharmacol Ther 1989;46:163-168.

9. Mäenpää H, Javela K, Pikkarainen J, Mälkönen M, Heinonen OP, Manninen V. Minimal doses of digoxin: A new marker for compliance to medication. Eur Heart J 1987;8(suppl):31-37.

10. Feely M, Cooke J, Price D, Singleton S, Mehta A, Bradford L, Carlvert R. Low-dose phenobarbitone as an indicator of compliance with drug therapy. Br J Clin Pharmacol 1987;24:77-83.

11. Claxton AJ, Cramer J, Pierce C. A systematic review of the association between dose regimens and medication compliance. Clin Ther 2001;23:1296-1310.

12. Cramer JA, Scheyer RD, Mattson RH. Compliance declines between clinic visits. Arch Intern Med 1990;150:1509-1510.

Chapter 5

General discussion and summary

PART I:
METHODOLOGICAL ASPECTS OF BLOOD PRESSURE MEASUREMENT

The diagnosis of hypertension depends on accurate blood pressure (BP) measurement. The consequence of inaccurate measurements could be unnecessary treatment of individuals incorrectly diagnosed as hypertensive, accompanied by possible adverse effects of drug treatment. Conversely inadequate BP measurement may increase cardiovascular risk in hypertensive patients who remain untreated.
The mercury sphygmomanometer is still the gold standard for BP measurement,[1] but has to be replaced by other BP measuring devices due to the environmental hazard associated with mercury. Devices based on the oscillometric principle are good candidates to replace the mercury sphygmomanometer. They determine systolic and diastolic BP intrinsically different from mercury sphygmomanometry. The oscillometric technique uses algorithms (which are sometimes changed) to calculate systolic and diastolic BP, which are not made public by the manufacturer.

Validation of BP measuring devices

Before using a BP measuring device in clinical practice one has to be sure that its accuracy is adequate. For this purpose a number of validation protocols has been developed.[2-4] In **chapters 2.1** and **2.3** of this thesis it is shown that despite the existence of a detailed protocol, two groups of investigators have interpreted the same guidelines of the protocol in a different manner, resulting in different validation results for the same device. Therefore, one always has to consider whether validation has been performed correctly.

In the recent International Protocol for the validation of BP measuring devices, nine sequential same-arm measurements are recorded, using the test-instrument and a mercury sphygmomanometer.[2] These sequential measurements have their drawbacks. BP is known to be variable, which may lead to different readings when a patient's BP is measured sequentially even in a short period of time.[2,3,5] Therefore we questioned whether there would be a better method to determine the accuracy of a BP measuring device. It would be best to measure BP simultaneously with the device to be tested and the reference device at one arm. For oscillometric devices this is often impossible. Most oscillometric devices deflate stepwise, making simultaneous measurements

with the mercury sphygmomanometer inaccurate.[6] Some devices do not inflate the cuff sufficiently to be able to hear the first Korotkoff sound for determining systolic BP. In addition cuff pressure is frequently released too rapidly after the device has detected the diastolic BP, so that phase 5 of the Korotkoff sounds cannot be heard accurately.[6] Many devices produce disturbing sounds which make accurate auscultatory measurements even more difficult. Simultaneous measurements at both arms can be considered as an alternative. Unfortunately, Atkins *et al*. showed that inter-arm difference can vary substantially in the same patient.[6] This makes this approach not suitable.

Intra-arterial measurements, simulators or an accurate oscillometric device can be considered to replace the mercury sphygmomanometer as gold standard during validation studies. Intra-arterial measurements have been advocated by the Association for the Advancement of Medical Instrumentation (AAMI).[4] However, simultaneous same-arm measurements are not possible when intra-arterial measurements are used as the reference. Using both arms has the same disadvantages as encountered with the mercury sphygmomanometer as the gold standard. The second option is more promising. A simulator is a device which simulates different BPs by reproducing oscillometric waveforms. They have the advantage of being objective because there is no observer bias. A disadvantage may be that the oscillometric pulses generated by the device may differ from physiologically occurring pulses.[7] This approach was recently used to test the accuracy of two devices.[8] The results were different from those previously obtained in clinical validation studies. Nevertheless the use of simulators is worth further investigation.

Another oscillometric device was used as a reference in our study described in **chapter 2.4**. Before considering such a device as a reference, it has to be validated and proven to be accurate. In our study grading results were the same irrespective whether the mercury sphygmomanometer or the oscillometric device were used as a reference. The advantage of this method is that only two observers are needed instead of the three observers needed according to the International Protocol.[2] Because the measurements with the reference device are automated, observer bias is avoided. This method deserves further exploration.

The oscillometric technique and its accuracy at higher blood pressure levels

Automated oscillometric devices were originally developed to measure the mean arterial pressure, for instance during surgery. Oscillometry can be used to determine the mean arterial pressure accurately, because this pressure corresponds to the point of maximal oscillations.[10-11] When Geddes *et al*. defined thresholds for cuff pressure oscillations which would indicate the corresponding systolic and diastolic BP[12], they found considerable variability for these thresholds between individuals. As stated before with the oscillometric technique systolic and diastolic BP are not actually measured but calculated based on an algorithm. Each manufacturer uses its own algorithm and depending on the algorithms used some devices may be more accurate than others. Nevertheless, irrespective which algorithm is used, the oscillometric technique itself will always have its limitations in determining systolic and diastolic BP.
Another issue of concern is the influence of higher BP levels on the accuracy of oscillometric BP measuring devices. In **chapter 2.5** the accuracy of the oscillometric devices was shown to decrease at increasing BP levels, but this could well be an apparent decrease instead of a real decrease. The increased BP variability in hypertension as shown by Mancia *et al.*, can also be a factor explaining the decreasing accuracy at higher BP levels.[13] During the validation process several BP measurements are made during a time period, in which the patient's BP will fluctuate. These fluctuations are higher at higher BP levels. It can therefore be expected that the accuracy of BP measuring devices is underestimated at higher BP levels, when sequential measurements are used during validation. Simulators might be a solution to test the influence of higher BPs on a device's accuracy.
It is important to report the accuracy of a device at different BP levels as mean ± standard deviation. The this was not explicitly stated in the new International Protocol.[2] Contrary to the use of Bland Altman plots, this gives the opportunity to compare devices more easily. In **chapters 2.3** and **2.4** the accuracy at different BP levels was reported for the Welch Allyn Vital Signs Monitor and the Omron RX-M.

Which BP measuring device should be chosen in clinical practice?

Aneroid devices are introduced in many hospitals and in primary care as a substitute for the mercury sphygmomanometer. These devices have been shown to become inaccurate in time[14-16] and should therefore only be used when a proper maintenance protocol is followed.[16]

The only alternative is an automated oscillometric device. As we stated before only devices that have been shown to be accurate according to a well performed validation study, should be considered. The current European directive on medical devices states that a medical device has to be safe. The specific section about devices with a measuring function states *'Devices with a measuring function must be designed and manufactured in such a way as to provide sufficient accuracy and stability within appropriate limits of accuracy and taking account of the intended purpose of the device. The limits of accuracy must be indicated by the manufacturer'*.[17] Although both BP measuring devices that we have tested obtained a CE mark, they did not achieve grade A or B, which is needed for clinical recommendation (**chapters 2.3 and 2.4**). The European directive is not specific enough as it leaves the manufacturer free to decide which level of accuracy is sufficient. Therefore the directive should be changed in such a manner, that manufacturers are forced to have their devices tested independently according to an internationally accepted validation protocol before receiving a CE mark. The results of this independent validation should be documented in the user's manual of the device. Every change of a device, like for example update of software, should be clearly indicated by the manufacturer by a change in model number.

Advantages of oscillometric devices

Despite the previously mentioned concerns the use of automated oscillometric devices has several advantages. They can measure BP automatically at programmed time periods and results can be stored. Other advantages are that observer bias, systematic errors and terminal digit preference are no longer an issue with the use of oscillometric devices.[18-20] Because these devices are easy in use, patients can measure their BP at home. This can provide the physician with more measurements than the office readings alone, resulting in a better interpretation of BP during the day and also help to diagnose white-coat hypertension and masked hypertension.[22] Preferably devices equipped with a memory should be used, because Mengden *et al*. showed that patients omitted BP readings from their logbook.[22] Self-measurement of BP can help to improve adherence to drug therapy in hypertensive patients, as they can follow the effect of therapy on their BP.

How to interpret self-measured BP levels?

Because the automated oscillometric devices are easily available general practitioners and other physicians are more and more confronted with patients who self-measure their BP. Before interpreting the results it is important to ask which device has been used and to check if this device has been found accurate in properly performed validation studies, because the number of validated devices is quite small compared to the large number of devices commercially available.[18,23,24] In **chapters 3.1** and **3.2** an overview is given for devices measuring BP at the upper-arm and at the wrist. Also at http://www.dableducational.com an up-to-date list of validated devices can be found. Moreover, one should consider if the device is equipped with a memory to store the results, or that these need to be written down with the possibility of omitting results. The physician should check whether the patient has sufficient knowledge about the procedure of BP measurement. Dietary factors, body position, patient preparation, timing of BP measurement, cuff size, arm position and site of measurement, all influence BP level independent of the kind of device.[18] It is important that several measurements are performed after an adequate period of rest with the patient seated in a comfortable chair in a quiet room.[19,20] Self-measurement should therefore only be performed after careful instruction. According to the recent recommendations by the Working Group on BP monitoring of the European Society of Hypertension, BPs should be measured twice in the morning and twice in the evening for one week. For long-term observation this should be repeated every three months.[25]

The physician must also be aware that thresholds for diagnosis of hypertension are not the same for self-measured BP compared to BP measured at the office,but are equal to the thresholds for mean daytime ambulatory blood pressure monitoring: 135/85 mmHg.[25]

PART II:
ADHERENCE TO ANTIHYPERTENSIVE DRUG THERAPY

Patients are treated lifelong to reduce the increased cardiovascular risk associated with hypertension. Because most patients with hypertension are asymptomatic, drug adherence is not optimal in many patients and frequently decreases over time. Hippocrates already warned physicians to be aware of patient non-adherence.[26] In **chapter 4.1** examples are shown of the influence of drug adherence on hypertension treatment. Wetzels *et al*. showed in their recent review that the relationship between drug adherence and BP control may be less robust than previously thought.[27] Nevertheless good adherence is essential to achieve adequate BP control in general adherence to drug therapy has been shown to be associated with lower mortality.[28]

Objective measurement of drug adherence

Unfortunately, drug adherence is difficult to measure objectively. 'Medication Event Monitoring System' (MEMS) devices can be used to follow a patient's drug taking behaviour over a prolonged period of time.[29] These are pill-boxes which electronically record the date and time of each opening of the box. A disadvantage of the MEMS devices is that the registration of each opening does not ensure actual drug intake. Therefore, the use of a marker added to an antihypertensive drug could be an useful alternative.

In **chapters 4.2** and **4.3** the use of the anion bromide as such a marker is described. In the past bromide had already been used as a marker for drug adherence in patients taking an antacid.[30] We investigated the pharmacokinetic properties of bromide as a marker in a group of healthy volunteers. The half life of bromide was shown to be sufficiently long to follow drug adherence for a longer time period. Subsequently we showed the usefulness of bromide as a marker for drug adherence in a group of 30 hypertensive patients. Adherence was also measured using MEMS devices and by counting tablets. The overall agreement of drug adherence based on bromide levels with MEMS data was good. Disadvantages of this method are that for the determination of the bromide level a venapuncture is needed and that the assay is rather time- and cost-consuming. Moreover, drugs to which potassium bromide has been added are not commercially available. Therefore, the use of bromide as a measure of drug adherence is limited to the research setting. However, for the individual patient in which drug non-adherence is suspected and MEMS fails to prove non-adherence, it might be a useful technique.

Improving drug adherence

Only few interventions are effective in increasing adherence to antihypertensive drugs.[31] A simple method is to reduce the number of daily doses. Other options are motivational strategies, reminders, patient education and special dosing devices. To further investigate different strategies to increase drug adherence, there is a need for objective methods like the one described by us.
Noticeably, hypertensive patients who self-measure their BP at home, were shown to be more drug adherent.[32] Self-measurement with accurate BP measuring devices can therefore be an useful strategy to motivate hypertensive patients to be adherent and to improve BP control in these patients.

PRACTICAL IMPLICATIONS AND DIRECTIONS FOR FURTHER RESEARCH

Irrespective whether BP measurements are performed at home, in primary care or in hospital, only validated devices should be used. For self-measurement, devices equipped with a memory are preferred. The current situation that allows unvalidated devices on the market is unacceptable. The Dutch government should use its regulatory role to ensure that each device has been tested according to an internationally accepted validation protocol. Comparable to the situation for drugs, for each device a registration report should be introduced, permitting control of the validation process and the calculations performed during validation. The accuracy of a device should be given for different BP levels and when changes in software are made the serial number of a device should be changed.
Physicians should inform their patients about the possibility to measure their BP at home. They should stress that only few devices are recommendable. Moreover the BP measurement technique should be explained properly.
Physicians have limited methods to measure adherence reliably. Therefore, for example for those patients whose BP appears difficult to treat, the use of MEMS devices should be made more accessible. Bromide seems to be useful for follow-up of adherence in selected patients. Further research should focus on the development of a more easy-to-use marker, which can be used on a larger scale in daily practice.

References

1. Pickering TG, Hall JE, Appel LJ, Falkner BE, Graves J, Hill MN, Jones DW, Kurtz T, Sheps S, Roccella EJ. Recommendations for blood pressure measurements in humans and experimental animals. Part 1: blood pressure measurement in humans. A statement for professionals from the subcommittee of professional and public education of the American Heart Association Council on high blood pressure research. Hypertension 2005;45:142-161.

2. O'Brien E, Pickering T, Asmar R, Myers M, Parati G, Staessen J, Mengden T, Imai Y, Waeber B, Palatini P, Atkins N, Gerin W, on behalf of the Working Group on Blood Pressure Monitoring of the European Society of Hypertension. Working group on blood pressure monitoring of the European Society of Hypertension International Protocol for validation of blood pressure measuring devices in adults. Blood Press Monitoring 2002;7:3-17.

3. O'Brien E, Petrie J, Littler W, Swiet de M, Padfield PL, Altman DG, Bland M, Coats A, Atkins A. The British Hypertension Society protocol for the evaluation of blood pressure measuring devices. J Hypertens 1993;11(suppl 2):S43-S62.

4. White WW, Berson AS, Robbins C, Jamieson MJ, Prisant M, Roccella E, Sheps SG. National standard for measurement of resting and ambulatory blood pressures with automated sphygmomanometers. Hypertension 1993;21:504-509.

5. Schwan A, Jonsson D. Short-term variation in blood pressure determines the accuracy of simultaneous and sequential recordings in the validation of blood pressure measuring devices. J Hum Hypertens 1993;7:315-319.

6. Atkins N, Mee F, O'Malley K, O'Brien E. The relative accuracy of simultaneous same arm, simultaneous opposite arm and sequential same arm measurements in the validation of automated blood pressure measuring devices. J Hum Hypertens 1990;4:647-649.

7. Amoore JN, Scott DHT. Can simulators evaluate systematic differences between oscillometric non-invasive blood pressure monitors? Blood Press Monit 2000;5:81-89.

8. Amoore JN, Vacher E, Murray IC, Mieke S, King ST, Smith FE, Murray A. Can a simulator that regenerates physiological waveforms evaluate oscillometric non-invasive blood pressure devices? Blood Press Monit 2006;11:63-67.

9. Ramsey M III. Noninvasive automatic determination of mean arterial pressure. Med & Biol Eng & Comput 1979;17:11-18.

10. Ramsey M III. Blood pressure monitoring: automated oscillometric devices. J Clin Monit 1991;7:56-67.

11. Mauck GW, Smith CR, Geddes LA, Bourland JD. The meaning of the point of maximum oscillations in cuff pressure in the indirect measurement of blood pressure – part II. J Biomed Eng 1980;102:28-33.

12. Geddes LA, Voelz M, Combs C, Reiner D, Babbs CF. Characterization of the oscillometric method for measuring indirect blood pressure. Ann Biomed Eng 1982;10:271-280.

13. Mancia G, Ferrari A, Gregorini L, Parati G, Pomidossi G, Bertinieri G, *et al*. Blood pressure and heart rate variabilities in normotensive and hypertensive human beings. Circ Res 1983;53:96-104.

14. Coleman AJ, Steel SD, Ashworth M, Vowler SL, Shennan A. Accuracy of the pressure scale of sphygmomanometers in clinical use within primary care. Blood Press Monit 2005;10:181-188.

15. O'Brien E. Special blood pressure measuring devices. Chapter 3.4. In: Manual of Hypertension. Edited by Mancia G, Chalmers J, Julius S, Saruta T, Weber MA, Ferrari AU, Wilkinson IB. Churchill Livingstone, London, 2002.

16. Canzanello VJ, Jensen PL, Schwartz GL. Are aneroid sphygmomanometers accurate in hospital and clinical settings? Arch Intern Med 2001;161:729-731.

17. European Council Directive 93/42/EEC concerning medical devices, June 1993.

18. Braam RL, Thien Th. Home blood pressure measurement with oscillometric upper-arm devices. Neth J Med 2003;61:307-312.

19. Guidelines Committee. 2003 European Society of Hypertension – European Society of Cardiology guidelines for the management of arterial hypertension. J Hypertens 2003;21:1011-53.

20. Ploin D, Baguet JP, Pierre H, Gaudemeris de R, Mallion JM. Clinical evaluation of a self blood pressure monitor according to the First International Consensus Conference on Self Blood Pressure Measurement. Blood Press Monitor 2002;7: 335-341.

21. Parati G. Clinical relevance of masked hypertension. Am J Hypertens 2006;19: 887-888

22. Mengden T, Medina RMH, Beltran B, Alvarez E, Kraft K, Vetter H. Reliability of reporting self-measured blood pressure values by hypertensive patients. Am J Hypertens 1998;11:1413-1417.

23. Graves JW. A survey of validated automated home blood pressure monitors available for the Internet shopper. Blood Press Monit 2005;10:103-107.

24. Braam RL, Aslan B, Thien Th. Oscillometric wrist blood pressure measuring devices. Neth J Med 2003;61:313-317.

25. O'Brien E, Asmar R, Beilin L, Imai Y, Mancia G, Mengden T, Myers M, Padfield P, Palatini P, Parati G, Pickering T, Redon J, Staessen J, Stergiou G, Verdecchia P on behalf of the European Society of Hypertension Working Group on Blood Pressure Monitoring. Practice Guidelines of the European Society of Hypertension for clinic, ambulatory and self blood pressure measurement. J Hypertens 2005;23:697-701.

26. Osterberg L, Blaschke T. Adherence to medication. N Engl J Med 2005;353:487-497.

27. Wetzels GEC, Nelemans P, Schouten JS, Prins MH. Facts and fiction of poor compliance as a cause of inadequate blood pressure control: a systematic review. J Hypertens 2004;22:1849-1855.

28. Simpson SH, Eurich DT, Majumdar SR, Padwal RS, Tsuyuki RT, Varney J, Johnson JA. A meta-analysis of the association between adherence to drug therapy and mortality. BMJ 2006;333(7557):15.

29. Urquhart J. Role of patient compliance in clinical pharmacokinetics. A review of recent research. Clin Pharmacokinet 1994;27:202-215.

30. Roth HP, Caron HS, His BP. Measuring intake of a prescribed medication. A bottle count and a tracer technique compared. Clin Pharmacol Ther 1970;11:228-237.

31. Schroeder K, Fahey T, Ebrahim S. How can we improve adherence to blood pressure-lowering medication in ambulatory care? Arch Intern Med 2004;164: 722-732.

32. Ashida T, Sugiyama T, Okuno S, Ebihara A, Fujii J. Relationship between home blood pressure measurement and medication compliance and name recognition of antihypertensive drugs. Hypertens Res 2000;23:21-24.

Chapter 6

Samenvatting
Dankwoord
Curriculum vitae
List of publications

Samenvatting

Samenvatting

Hypertensie of hoge bloeddruk is een veel voorkomende en belangrijke risicofactor voor het optreden van hart- en vaatziekten. Voor het vaststellen van hypertensie en vervolgen van patiënten met hypertensie zijn nauwkeurige bloeddrukmetingen van groot belang. De traditionele manier van bloeddrukmeting, die gebruikt maakt van een kwikmanometer en stethoscoop, moest verlaten worden enerzijds vanwege milieuaspecten en anderzijds omdat de kunst van een 'state-of-the-art' bloeddrukmeting steeds minder beheerst wordt en er steeds betere automatisch metende apparaten ter beschikking zijn gekomen. Verreweg de meeste van deze automatische apparaten meten de bloeddruk volgens het oscillometrische principe. Hierbij worden trillingen in de bloeddrukmanchet, die geregistreerd worden tijdens verlagen van de druk, gebruikt om de bloeddruk te bepalen. Feitelijk wordt bij deze methode de gemiddelde bloeddruk gemeten en met behulp van een rekenmodel de boven- en onderdruk berekend. In dit proefschrift wordt nader ingegaan op de nauwkeurigheid van een aantal van deze apparaten die werken volgens dit principe.
Bij vrijwel asymptomatische aandoeningen, zoals hypertensie, is therapietrouw vaak een probleem. Bij uitblijven van effect van de voorgeschreven bloeddrukverlagende medicatie dient onvoldoende therapietrouw dan ook te worden overwogen. Het ontbreekt de arts op dit moment aan objectieve methoden om de therapietrouw te meten. In het tweede deel van dit proefschrift wordt ingegaan op verschillende methoden die gebruikt kunnen worden om de mate van therapietrouw bij de behandeling van hypertensie te meten. Hierbij wordt met name ingegaan op het gebruik van bromide als marker voor de therapietrouw.

Er bestaan verschillende protocollen voor het testen van de nauwkeurigheid (validatie) van bloeddrukmeters. Ieder protocol heeft voor- en nadelen. Het protocol van de British Hypertension Society (BHS) uit 1993 en het protocol van de Association for the Advancement of Medical Instrumentation (AAMI) uit 1992 worden het meest gebruikt. In hoofdstuk 2 worden een aantal aspecten van bovengenoemde protocollen nader toegelicht en bekritiseerd. De uit te voeren analyse blijkt niet eenduidig omschreven te zijn in het BHS-protocol. Dit kan leiden tot verschillen in de gerapporteerde nauwkeurigheid voor dezelfde oscillometrische bloeddrukmeters (hoofdstuk 2.1). In 2002 werd het International Protocol (IP) gepubliceerd met als doel de validatie te vereenvoudigen. In hoofdstuk 2.2 worden de voor- en nadelen van het

IP belicht. Het IP maakt in tegenstelling tot het BHS-protocol geen gebruik van een graderingsysteem (van uitstekend (A) tot zeer slecht (D)) om de nauwkeurigheid van een bloeddrukmeter aan te geven. Het graderingsysteem is in het IP vervangen door een slagen/falen systeem. In hoofdstuk 2.2 wordt toegelicht dat dit de vergelijking tussen gevalideerde apparaten bemoeilijkt en dat ook gegevens als het gemiddelde bloeddrukverschil en de standaard deviatie van de gemeten verschillen tussen testapparaat en kwikmanometer vermeld zouden moeten worden.
De Welch Allyn Vital Signs Monitor 52000, een apparaat dat de bloeddruk oscillometrisch meet aan de bovenarm, blijkt in de studie beschreven in hoofdstuk 2.3 de bloeddruk onnauwkeurig te meten met een graad C voor diastolische bloeddruk en een graad D voor systolische bloeddruk. Deze bloeddrukmeter werd echter ook getest door de onderzoeksgroep van Jones *et al*.[1] Zij concludeerden dat de bloeddrukmeter wel nauwkeurig was met een graad A voor zowel diastolische als systolische bloeddruk. Redenen voor de gevonden verschillen worden nader toegelicht in hoofdstuk 2.3. Naast de Welch Allyn Vital Signs Monitor werd een tweede bloeddrukmeter door ons getest. De resultaten staan beschreven in hoofdstuk 2.4. Het blijkt dat ook de Omron RX-M, een apparaat dat de bloeddruk oscillometrisch meet aan de pols, een onnauwkeurig apparaat is.
In de literatuur wordt steevast vermeld dat de nauwkeurigheid van oscillometrische bloeddrukmeters afneemt bij hogere bloeddrukwaarden. Of dit inderdaad het geval is werd nader onderzocht in het onderzoek beschreven in hoofdstuk 2.5. De nauwkeurigheid van de bloeddrukmeters blijkt inderdaad voor de meeste apparaten af te nemen bij hogere bloeddrukken. In hoofdstuk 2.5 wordt nader ingegaan op de vraag of dit mogelijk een schijnbare afname betreft.

Dankzij de ontwikkeling van automatische bloeddrukmeters is het gemakkelijker geworden voor patiënten om zelf in de thuissituatie de bloeddruk te meten. Bloeddrukmeters zijn tegenwoordig zeer gemakkelijk aan te schaffen, bijvoorbeeld via het Internet. In de hoofdstukken 3.1 en 3.2 wordt nader ingegaan op aspecten die bij thuisbloeddrukmetingen van belang zijn. Daarnaast worden adviezen gegeven over welke apparaten het beste door de patiënt kunnen worden gebruikt. Hoofdstuk 3.1 betreft apparaten die de bloeddruk meten aan de bovenarm en hoofdstuk 3.2 betreft apparaten die de bloeddruk meten aan de pols.

Verschillende aspecten van onvoldoende therapietrouw die bij de behandeling van hypertensie een rol spelen worden nader toegelicht in hoofdstuk 4.1. Aan de hand van een aantal casus wordt benadrukt dat bij elke patiënt waarbij de bloeddruk onvoldoende reageert op de gestarte antihypertensieve medicatie moet worden overwogen of de patiënt wel voldoende therapietrouw is. Helaas ontbreekt tot nu toe een betrouwbare methode om de mate van therapietrouw te meten. Bij elektronische monitoring met behulp van zogenaamde Medication Event Monitoring System (MEMS) potjes wordt de datum en het tijdstip van elke opening van het medicatiepotje geregistreerd en op de PC uitgelezen. De registratie hiervan garandeert echter niet dat de tabletten daadwerkelijk zijn ingenomen. Indien een marker wordt toegevoegd aan een geneesmiddel en deze marker vervolgens wordt bepaald in het bloed van de patient, bestaat er wel controle op de inname. In hoofdstuk 4.2 worden de resultaten beschreven van onderzoek naar het gebruik van bromide als marker voor de mate van therapietrouw bij 24 gezonde vrijwilligers. De farmacokinetische eigenschappen van bromide worden nader toegelicht. De halfwaardetijd van bromide blijkt ongeveer 11 dagen te zijn waardoor het geschikt is als marker voor de mate van therapietrouw over een langere periode. De klinische toepassing van bromide als marker werd onderzocht in een groep van 30 patiënten met hypertensie (hoofdstuk 4.3). Dertig milligram kaliumbromide werd toegevoegd aan een combinatiepreparaat, bestaande uit een angiotensine converterend enzym remmer en een calciumantagonist. De mate van therapietrouw gemeten met behulp van bromide kwam goed overeen met die gemeten met MEMS potjes. De therapietrouw van de geïncludeerde patiënten was in deze studie echter zeer hoog. Hierdoor kon de relatie tussen de mate van therapietrouw en de reactie op de antihypertensieve medicatie niet worden nagegaan.

Het meten van de therapietrouw met behulp van bromide heeft een aantal nadelen. Geneesmiddelen waaraan kaliumbromide is toegevoegd zijn niet commercieel voorhanden. Voor de bepaling van bromide is een bloedafname nodig. Verder is de bepaling vrij arbeidsintensief, tijdrovend en kostbaar. Desalniettemin kan de methode worden toegepast voor het objectief meten en vervolgen van de mate van therapietrouw in bepaalde probleemgevallen.

Referentie

1. Jones CR, Taylor K, Poston L, Shennan AH. Validation of the Welch Allyn 'Vital Signs' oscillometric blood pressure monitor. J Hum Hypertens 2001;15:191-195.

Dankwoord

Dankwoord

Hierbij wil ik iedereen die direct of indirect een bijdrage heeft geleverd aan de totstandkoming van dit proefschrift hartelijk danken.

In het bijzonder wil ik noemen:

Prof. dr. Th. Thien, mijn promotor van het eerste uur. Beste Theo, zonder jou zou dit proefschrift er niet geweest zijn. Jouw enthousiasme, gedrevenheid, eerlijkheid en openheid hebben mij vanaf het begin gegrepen. Dat een iets langer dan drie maanden durende wetenschappelijke stage uiteindelijk zou uitgroeien tot een promotie had ik nooit durven denken. Je wist me door de jaren heen overal te vinden (Zevenaar, Nijmegen, Nieuwegein, Amersfoort) en bleef altijd optimistisch. Je bent een wetenschapper pur sang. Ik heb veel van je geleerd en vind het een eer één van je laatste promovendi te zijn nu je met emeritaat bent gegaan.

Prof. dr. J.W.M. Lenders. Beste Jacques, als promoter ben je in de tweede helft van dit proefschrift een belangrijke rol gaan spelen. Artikelen waar Theo en ik soms al enige tijd mee aan het stoeien waren, werden door jouw zienswijze verder verbeterd. Ik dank je voor de energie en tijd die je hebt willen steken in dit proefschrift.

Alle leden van de manuscript commissie, prof. dr. F.W.A. Verheugt, prof. dr. J.F.M. Wetzels en dr. W.J.W. Bos, wil ik hartelijk danken voor het kritisch doorlezen van het manuscript.

Dr. S.H.M. van Uum. Beste Stan, hartelijk dank voor je substantiële en onmisbare aandeel in dit proefschrift. Het kan haast geen toeval zijn dat jij nu werkzaam bent als internist in Canada in de buurt van dezelfde universiteit waar een groot deel van het onderzoek naar therapietrouw heeft plaatsgevonden.

Dr. D.W. Swinkels en prof. dr. F.G.M. Russel. Beste Dorine en Frans, hartelijk dank voor jullie bijdrage aan het artikel over de bromide bepalingen bij vrijwilligers.

Carlijn de Maat wil ik hartelijk danken voor het helpen uitvoeren van talloze bloeddrukmetingen en het rekruteren van vrijwilligers bij het testen van de Welch Allyn Vital Signs Monitor.

Bünyamin Aslan wil ik danken voor zijn werk bij het testen van de Omron RX-M.

Wim Lemmens, hartelijk dank voor het 'tot leven' brengen van de database met gegevens uit de Tarka studie.

Alle patiënten en vrijwilligers die geheel belangeloos deelnamen aan het onderzoek beschreven in dit proefschrift, hartelijk dank!

Alle leden en oud-leden van de maatschap cardiologie van het St. Antonius Ziekenhuis te Nieuwegein wil ik bedanken voor hun interesse naar de vorderingen van de promotie en de tot nu toe genoten opleiding.

Alle (oud-)collega's van het Canisius-Wilhelmina Ziekenhuis, het Meander Medisch Centrum en het St. Antonius Ziekenhuis wil ik bedanken voor hun gezelligheid, in het bijzonder Hendrik-Jan Dieker uit Nijmegen. Beste Hendrik-Jan, bedankt voor je vriendschap, ontstaan tijdens onze eerste maanden in het CWZ. Succes met de laatste loodjes van jouw promotie.

Menno Dijkhuizen. Beste Menno, jij wist altijd feilloos mijn herhaaldelijk weigerende computer te reanimeren. Hartelijk dank!

Irene Verbaan. Beste Irene, inmiddels is dit alweer je derde boekje. Met je relaxte houding maak je de vaak stressvolle laatste stappen naar de promotie tot een feest.

Maarten Rookmaaker en Marieke Yo. Beste Maarten en Marieke, binnenkort familie Rookmaaker-Yo. Ik wil jullie hartelijk danken voor jullie vriendschap. Maarten, met je lichte(?) vorm van manie wist je me altijd in de goede richting te leiden op momenten dat ik dat blijkbaar even nodig had.

John en Anjo Tabbers. Dat ik de eerste woorden van dit dankwoord typ achter de computer in jullie mooie huis en dito tuin in Waalre zegt genoeg. Hartelijk dank voor jullie steun en liefde.

René en Anne Driessen. Ik geniet altijd erg van onze dineetjes, afwisselend in Oss en Nieuwegein. Hartelijk dank voor jullie gezelligheid.

Annemieke en Evelien. Mijn twee lieve zussen en bovendien paranimfen. Dat jullie ook geneeskunde zijn gaan studeren zal wel een genetische 'tik' zijn geweest. Gelukkig hebben we tot nu toe elk een ander orgaan kunnen kiezen…

Mijn ouders, lieve pappa en mamma. Bedankt voor jullie steun en stimulatie. Dit proefschrift is niet voor niets aan jullie opgedragen.

En tenslotte lieve Frederieke. Met jou aan mijn zijde vliegt de tijd. Bedankt voor je geduld als er weer eens aan het proefschrift moest worden gewerkt, je onvoorwaardelijke steun en liefde.

Curriculum vitae

Curriculum vitae

De auteur van dit proefschrift werd geboren op 1 oktober 1975 te Haarlem. Na het volgen van het VWO van 1988 tot 1994 aan het Liemers College te Zevenaar, begon hij in 1994 met de studie geneeskunde aan de Katholieke Universiteit te Nijmegen. Het artsexamen werd behaald in 2000. Aan het einde van zijn co-schappen werd tijdens een wetenschappelijke stage bij Prof. dr. Th. Thien de grondslag gelegd voor dit proefschrift. Na enkele maanden als poortarts te hebben gewerkt in het Streekziekenhuis te Zevenaar, was hij vanaf december 2000 werkzaam als AGNIO cardiologie in het Canisius-Wilhelmina Ziekenhuis (opleider Dr. T. Hooghoudt) en vanaf eind 2001 in het St. Antonius Ziekenhuis te Nieuwegein. In oktober 2002 begon hij met de opleiding tot cardioloog (opleider dr. W. Jaarsma) en startte in het Meander Medisch Centrum te Amersfoort met de vooropleiding Interne Geneeskunde (opleider dr. A. van de Wiel). Vanaf oktober 2004 is hij wederom werkzaam in het St. Antonius Ziekenhuis voor het vervolg van de cardiologie opleiding. Deze zal in 2008 worden afgerond.

List of publications

Braam RL, Seinen H, Blom VM, Reenalda PE, Niekel RAM. Braken na het eerste trimester van de zwangerschap: een alarmsymptoom. (Klinische lessen). Ned Tijdschr Geneeskd 1998;142:753-757.

Thien Th, Braam RL, Russel FGM. Fatale anafylactische reactie na inname acetazolamide (Diamox) wegens glaucoom. (Ingezonden). Ned Tijdschr Geneeskd 2000;144:2173-2174.

Braam RL, Jacobs EMG, Richter C. Meningokokkenziekte. Ned Tijdschr Geneeskd, studenten-editie 2001;4:17-19.

Braam RL, Thien Th. The influence of the method of data analysis on the reported accuracy of automated blood pressure measuring devices. J Hypertens 2001;19: 1765-1767.

Braam RL, Braam JIM, Winter JB. Oesofagusruptuur met aorta-oesofageale fistel door ingestie van medicatieverpakking. (Ingezonden). Ned Tijdschr Geneeskd 2001;145: 2399-2400.

Braam RL, Pieters GFFM, Thien Th. Hypertensie: eens primair, niet altijd primair. (Klinische lessen). Ned Tijdschr Geneeskd 2002;146:449-454.

Braam RL, Braam JIM. Een patiënt met cutane anthrax in België. (Ingezonden). Ned Tijdschr Geneeskd 2002;146:538-539.

Braam RL, Maat de C, Thien Th. Accuracy of the Welch Allyn Vital Signs Monitor 52000 automatic blood pressure measuring device according to a modified British Hypertertension Society Protocol. Blood Press Monitor 2002;7:185-189.

Braam RL, Thien Th. The “International Protocol”: more insight or more arithmetic? Blood Press Monit 2002;7:289-291.

Braam RL, Deegens J, Jessen H, Oude Ophuis AJM, Meursing BTJ. Ventricular fibrillation after administration of succinylcholine. Neth Heart J 2003;11:519-522.

Braam RL, Thien Th. Home blood pressure measurement with oscillometric upper-arm devices. Neth J Med 2003;61:307-312.

Braam RL, Aslan B, Thien Th. Oscillometric wrist blood pressure measuring devices. The Netherlands Journal of Medicine 2003;61(10):313-17.

Braam RL, Rabelink AJ, Gaillard CAJM. Onderliggende pathologie bij hartfalen, 'Failure of the circulation versus failure of the heart'. In: Veldhuizen van DJ, Voors AA: Leerboek Hartfalen 2003;43-64. Mediselect bv, Leusden.

Braam RL, Aslan B, Thien Th. Accuracy of the Omron RX-M, an automated blood pressure measuring device, measuring blood pressure at the wrist, according to a modified British Hypertension Society Protocol. Blood Press Monitor 2004;9:25-30.

Braam RL, Gaillard CAJM. Underlying pathology in heart failure: 'Failure of the circulation versus failure of the heart'. Neth Heart J 2004;12:303-307.

Braam RL, Gaillard CAJM, Ike B, Hagen EC. A case of multiple aortic thrombi. Neth J Med;2004;62:304.

Braam RL, Gaillard CAJM. Hypertensie en hartfalen. De rol van angiotensine II receptorantagonisten. Clinical Practice. January 2005.

Braam RL, Hertzberger DP, Meursing BTJ, Oude Ophuis AJM. Be smart, don't kick the heart. Neth Heart J 2005;7/8:280-282.

Braam RL, Thien Th. Is the accuracy of blood pressure measuring devices underestimated at increasing blood pressure levels? Blood Press Monitor 2005;10: 283-289.

Braam RL, Uum SHM van, Russel FGM, Swinkels DW, Thien Th. Bromide as a marker to measure adherence to drug therapy. Eur J Clin Pharmacol 2006;62:285-290.

Braam RL, Uum SHM van, Lenders JWM, Thien Th. Geen reactie op antihypertensieve therapie: denk aan therapieontrouw. Accepted for publication in Ned Tijdschr Geneeskd.

Braam RL, Uum SHM van, Lenders JWM, Thien Th. Bromide as marker for drug adherence in hypertensive patients. Submitted.