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EDITORIAL

Who should be taking the blood pressure?

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ABSTRACT

Given the variability of blood pressure, it is often difficult to make a diagnosis of hypertension or to evaluate the effect of treatment on the basis of single blood pressure readings in the office. To obtain multiple measurements one can either turn to ambulatory blood pressure monitoring or have the patient take his or her own pressure. Both approaches require the availability of reliable, validated devices. Currently, only some instruments which measure blood pressure oscillometrically at the upper arm can be recommended for self-measurements. Studies are in progress to assess the prognostic significance of self-measured blood pressure data.

Throughout the day, considerable variations in blood pressure occur which make it virtually impossible to diagnose hypertension on the basis of one single measurement. Although it is true that one measurement of blood pressure, taken at the office, already correlates reasonably well with cardiovascular morbidity and mortality, substitution of casual pressure by 'usual blood pressure', defined as the average of a series of measurements, improves the relationship considerably.[1] Therefore, all current guidelines emphasise the importance of obtaining multiple readings, taken on separate occasions. The recent recommendations by the Joint National Committee[2] and the European Societies of Hypertension and Cardiology[3] still advocate to first and foremost measure blood pressure in the office or clinic. However, such measurements can easily elicit the white-coat effect which, incidentally, is a poorly reproducible phenomenon.[4] Consequently, treatment may be instituted or intensified on the basis of spuriously elevated blood pressure data. While a set of clinic blood pressure readings may be more or less equivalent to 24-hour ambulatory measurements for assessing usual pressure and cardiovascular risk,[5] the latter technique is much more practical and yields results within one day. Thus, a major advantage of ambulatory blood pressure monitoring (ABPM) lies in its ability to provide an estimate of usual blood pressure without observer bias in patients engaged in normal activities. Indeed, under a variety of conditions ABPM has proven to be superior to conventional blood pressure measurements for the diagnosis of hypertension. In addition, recent evidence suggests that also in treated hypertensives ABPM may predict cardiovascular prognosis over and above office pressure. The development of relatively cheap validated devices which can be easily worn by the patient make ABPM, therefore, an interesting tool to employ in clinical practice as well as in antihypertensive drug trials. Still, it will be difficult to implement ABPM in primary care and the technique will certainly not be available to every hypertensive patient. Accordingly, cheaper and easier solutions are necessary from which every patient can benefit. One such solution may be self-measurement of blood pressure which allows for the collection of multiple readings without being bothered by the white-coat effect.[6-8] In addition, self-measurements may enhance compliance to prescribed drugs[9-11] and reduce the number of clinic visits.[12-14] Over the past decade, self blood pressure monitoring (SBPM) has become very popular among patients themselves.

Before SBPM can be widely advocated, further research is needed to investigate the accuracy of home blood pressure measurements and the devices that are used for this

purpose. This issue of the Journal features two papers by Braam and colleagues which deal with exactly this aspect of SBPM.[15,16] They describe the protocols which have been developed to validate the devices and the most important conclusions that can be drawn from these validations. They focus on the oscillometric technique but it should be emphasised that there are several types of monitors available for SBPM. These include mercury sphygmomanometers, aneroid manometers and electronic devices.[17] However, the banning of mercury will lead to the disappearance of all mercury manometers, at least in Europe, and it no longer makes sense to put much effort in the validation of such equipment. Aneroid manometers are often difficult to handle and have lost popularity as well. Thus electronic devices, which all use the oscillometric technique, seem to be the most relevant ones in the near future.

Oscillometric blood pressure can be measured at the upper arm, wrist and finger. The last-mentioned technique was not discussed by Braam and colleagues, but in the context of SBPM finger oscillometry is not recommended because it is too inaccurate.[17] Although wrist devices are more accurate than finger devices, they still suffer from substantial reading error as pointed out by Braam. Hence, we should still consider these with caution. Nevertheless, the implementation of a position sensor such as in the BP 2000 may overcome the problems related to the position of the wrist and produce more reliable results.[18] So far, however, too few data are available to recommend wrist devices as part of the armature of the hypertensive patient or his doctor. This leaves us with the upper-arm devices which, true enough, are the most reliable of all but which are facing a market heavily polluted by poorly functioning instruments. It is essential, therefore, that both patients and treating physicians have rapid access to the results of validation tests. Moreover, only devices which have outstanding test results should be allowed to be sold. To some extent, one can compare the free availability of monitors for self-measurement with that of over-the-counter medications. For both, we should demand that these are safe and do exactly what patients expect them to do. Yet, there is a striking contrast in our attitude towards medications on the one hand and diagnostic devices on the other.

If SBPM is to become an indispensable tool in the management of hypertensive patients, far more information is needed about the optimal timing and frequency of measurements. Despite the currently proposed recommendations,[17] there is no evidence yet to support this advice. There is a need also to standardise the type of instruments. Generally, automatic devices are preferred above semi-automatic ones and each device should be checked on each patient. Ideally, the instrument should be equipped with a memory so that data can be stored until the clinic visit. The usefulness of telemetry is still under evaluation. A further problem is that home pressures usually represent the level of pressure at the lower end of the waking range, when the patient is relatively relaxed. Thus, they do not necessarily provide a good guide to what happens to the patient's pressure when undergoing the stresses of daily life, such as occur during work. In theory home monitoring could also be used to record the pressure at work, but this has not been fully investigated. Obviously, home monitoring cannot assess the sleeping pressure, which is assuming increasing importance as an independent predictor of cardiovascular risk. This raises the question whether SBPM has any role at all in assessing cardiovascular risk. Several large-scale trials have been designed which address these issues. The Ohasama study has demonstrated that SBPM correlates better with mortality than conventional pressures[19] and in cross-sectional studies SBPM is superior to clinic pressures in predicting target organ damage. Recently, the THOP trial has been completed which examined the question whether treatment based on SBPM compares favorably with office measurements in terms of blood pressure control.[20] The results of that trial are expected shortly. A study of similar design, the HOMERUS trial, is currently being conducted in the Netherlands. This trial started in April 2002 and has just closed enrolment of patients; final results are expected by the end of 2004. We anticipate, therefore, that in a few years time we will have more definitive data to answer the question 'who should be taking the pressure: the patient or the doctor?'

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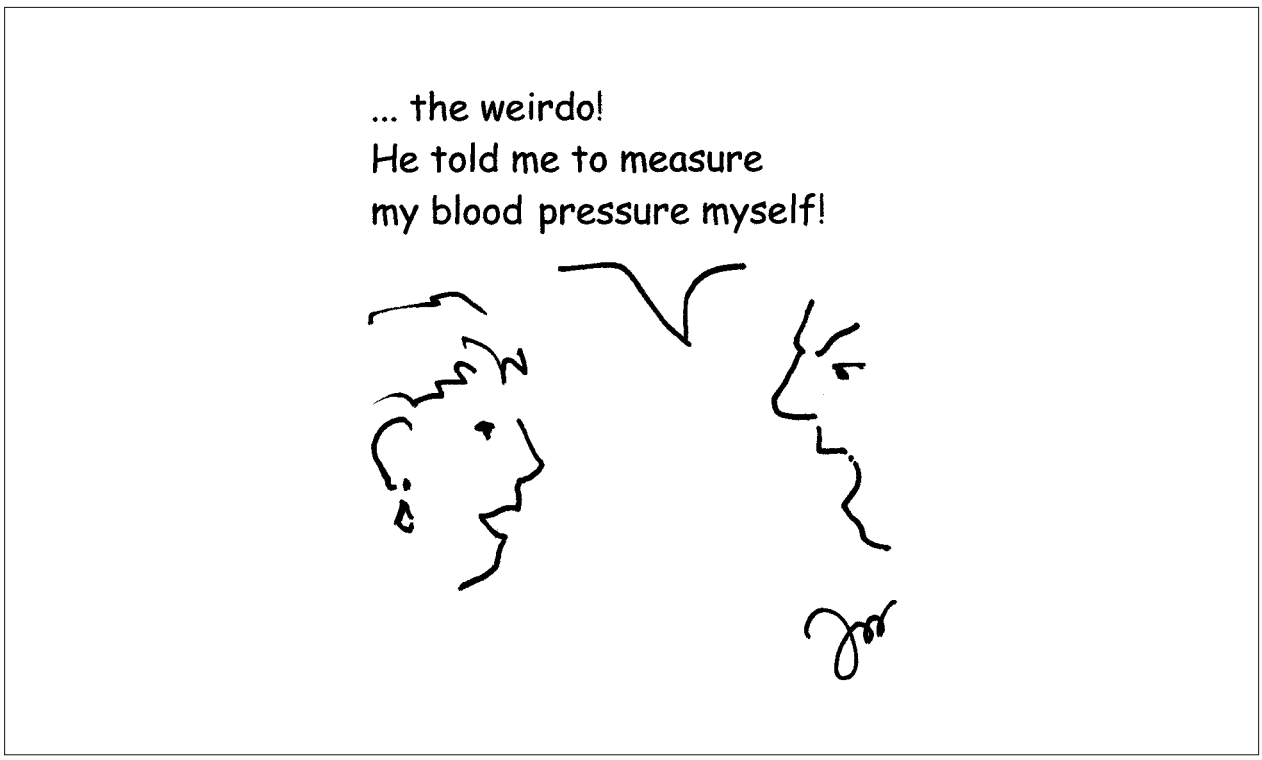

De Leeuw, et al. Home blood pressure measurement.

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Home blood pressure measurement with oscillometric upper-arm devices

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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.

 # Th. Thien was not involved in the handling and review process of this paper.

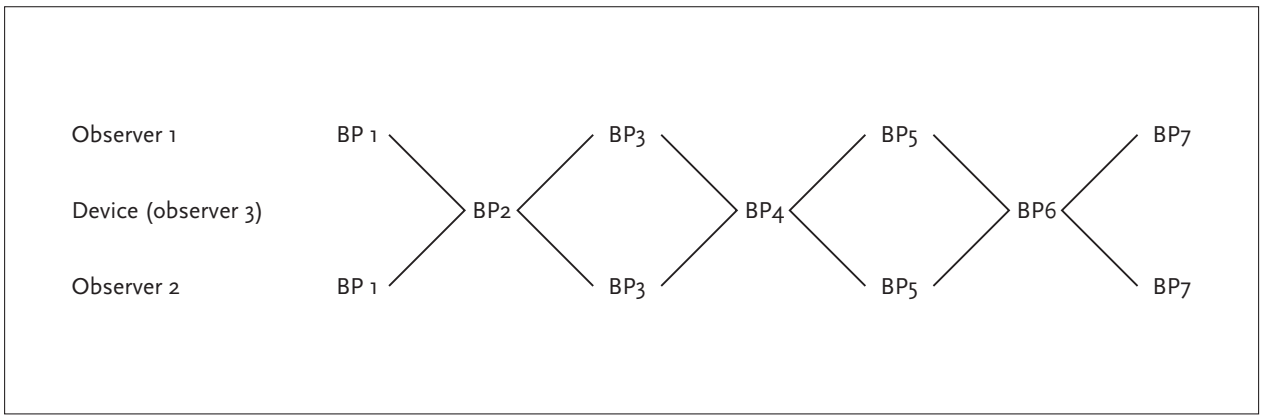

Figure 1
Sequential blood pressure measurements according to the British Hypertension Society protocol 1993 (also used in the International Protocol)

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 equal to or greater than 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[1]

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

[1] *In 85 subjects, 3 readings/subject, n=255.*

In the International Protocol adjustments have been made to simplify the validation procedure of the BHS protocol 1993. 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 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

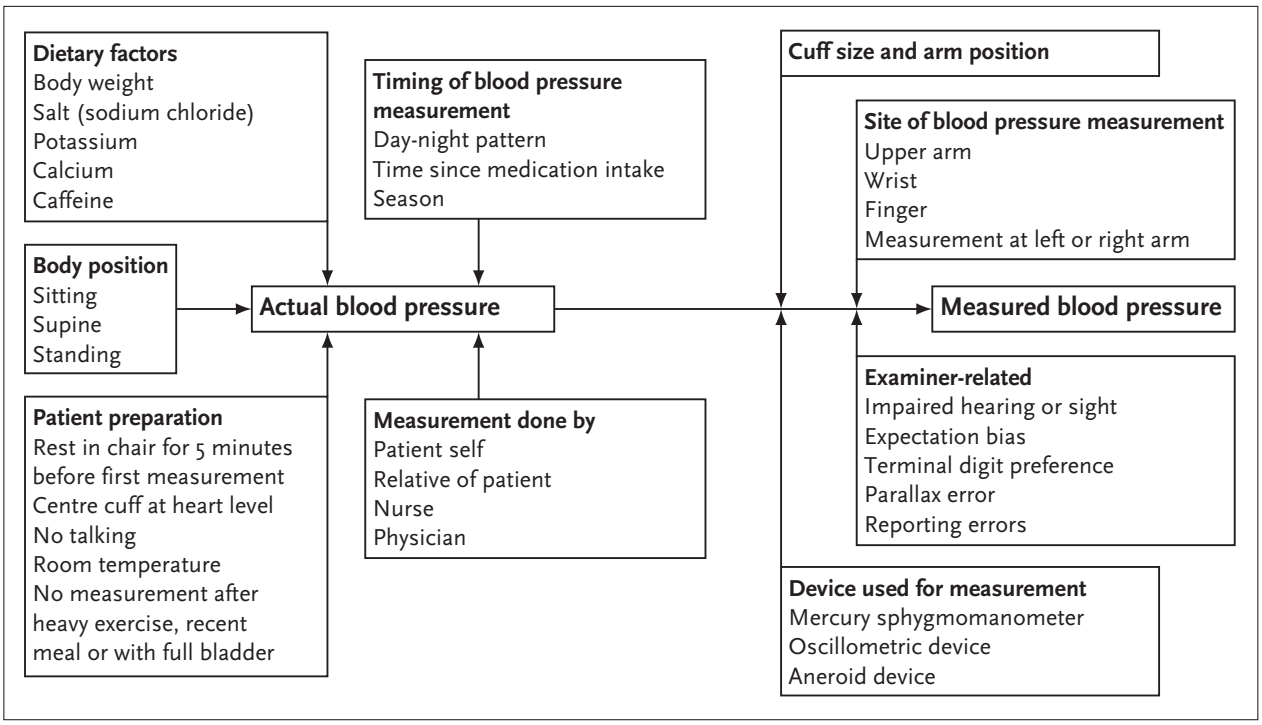

Figure 2

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

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. 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.

(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

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.

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)	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	NA4	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).

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REVIEW

Oscillometric wrist blood pressure measuring devices

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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.

 # Th. Thien was not involved in the handling and review process of this paper.

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 predictive 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

DISADVANTAGES OF 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

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[25]		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, Au = auscultatory sphygmomanometer, device not mentioned, 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.*

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	-1.0 ± 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.

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.

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. 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.

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ABOUT THE COVER

History of intervening space from 1991

Bienette Moraal

This month's artist lives and works in Nijmegen as a pictorial artist. She calls herself a still-life painter. Between 1975 and 1980 she studied in Arnhem. Since 1983 she has been exhibiting her work in several solo exhibitions, such as Gallery K-Dijk in Gendt, and in group exhibitions. Her work has been shown at PRENT '99 and at PRENT 2001 and in Gallery Ursula van Heesch in Kleve, Germany. In 2000 and 2001 she exhibited at HUNTENKUNST in Doetinchem. Premises of her series of work are always visibility and tangibility. Even when she makes graphic art, in particular lithography, she works and observes as a painter. Points of special interest in Bienette's work differ per period. In this three-colour stone print, which is part of a panel of 15 lithographies (10 x 10), the theme 'space between objects' or 'emptiness in still life' is well reflected. A limited edition (12) is available at a price of € 150 (the complete series of 15 prints costs € 2000), at Galerie Unita, Rijksstraatweg 109, 6573 CK Beek-Ubbergen, the Netherlands or by e-mail: galerie-unita@planet.nl.

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ORIGINAL ARTICLE

Cardiac and metabolic effects in patients who present with a multinodular goitre

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ABSTRACT

Twenty-six consecutive patients who presented with clinically euthyroid multinodular goitre were studied for an overnight fasting serum lipid profile and 24h Holter monitoring. Mean serum TSH was 0.6 ± 0.4 *vs* 2.4 ± 1.3 mU/l (p<0.0001) and mean TT3 2.4 ± 0.4 *vs* 2.0 ± 0.5 nmol/l (p=0.009) in patients *vs* controls (n=15) while mean FT4 was not different from controls. Total serum HDL, LDL cholesterol and triglycerides were lower in patients but creatinine, ferritin and SHBG levels did not differ between patients and controls. The 24-hour ambulatory continuous ECG recordings did not demonstrate significant differences in mean, minimal and maximal heart rate between the study and the control group. Nocturnal heart rate, measured between 23.00 and 06.00 hours, also showed no differences between the two groups. Atrial fibrillation was absent in both the study and the control group. Premature atrial and ventricular complexes occurred equally frequently in both groups. Comparison of patients with a serum TSH below 0.4 mU/l (n=11) and patients with a TSH above 0.4 mU/l revealed no differences.

In conclusion, in consecutive patients who present with multinodular goitre, effects were found on the lipid profile, but not on the heart. It is argued that in this type of patients, cardiac effects depend on the degree of subclinical hyperthyroidism.

INTRODUCTION

Sporadic nontoxic goitre is one of the most common thyroid disorders, with a prevalence of 5 to 10% in the general population.[1,2] It is defined as a benign enlargement of the thyroid, with normal thyroid function in subjects not living in an endemic area.[1] Its aetiology is multifactorial.[3] The natural course of multinodular goitre is characterised by a gradually increasing size with concomitant rising plasma thyroid hormone levels and lowering thyroid-stimulating hormone (TSH) levels.[4,5] Ultimately a multinodular goitre can cause overt hyperthyroidism often complicated by cardiac rhythm disturbances, in particular atrial fibrillation.[6] Recently, in a population-based study, cardiovascular mortality was found to be increased in elderly people with a low serum TSH.[7] In the last decade, publications focused on the cardiac effects in patients with a low TSH. One study published findings of an increased heart rate, an increased left ventricular mass and impaired diastolic function in patients on T4 suppressive therapy ('subclinical thyrotoxicosis').[8] These findings, however, were not confirmed by others.[9] Very recently abnormalities in heart rate and function, similar to the patients with subclinical thyrotoxicosis due to T4 treatment, were also found in patients with 'endogenous' subclinical hyperthyroidism i.e. caused by a multinodular goitre or an autonomously functioning thyroid nodule.[10] In the patients of that study mean values of both T4 and T3 were in the upper normal range, suggesting an advanced state of subclinical hyperthyroidism compared with patients with subclinical hyperthyroidism in whom only mean serum T3 is increased. In that study only patients were included with a low or suppressed TSH level.[10] However, in most multinodular goitre patients plasma TSH levels often vary between the minimal detection limit of the assay and the lower normal limit, while plasma T3 and T4 levels are

still within the normal range. The clinical significance of these different TSH levels is not known. The aim of this study was, therefore, to study heart rate, the incidence of cardiac arrhythmias and metabolic effects in consecutive patients who presented with clinically euthyroid multinodular goitre.

SUBJECTS AND METHODS

All consecutive patients who presented with clinically euthyroid multinodular goitre at the medical clinics of our hospital between June 1997 and October 1999 were eligible. Those patients taking medication influencing cardiac or thyroid function, lipid metabolism and/or with a history of cardiac diseases, hypertension or diabetes mellitus were excluded. Most complaints were of a compressive nature or patients wanted to have information about the nature of the disease. There were no spontaneous complaints of cardiac palpitations. All patients were clinically euthyroid and had thyroid hormone levels within the normal range. A group of 15 healthy females matched for age served as controls. In all participants an overnight fasting serum lipid profile and 24h Holter monitoring were performed.

Assays

Serum TSH was determined using a chemiluminometric (sandwich) immunoassay, normal range from 0.4 to 4.2 mU/l (interassay variation 4.5-10%). Serum FT4 and TT3 were determined using a competitive immunoassay, normal ranges 10.0 to 22.0 pmol/l (interassay variation 4-6.5%) and 1.25 to 2.80 nmol/l (interassay variation 4.5-7%), respectively. Serum lipids were measured using an enzymatic colorimetric assay. Plasma creatinine was measured by a kinetic assay according to Jaffe, and ferritin and sex hormone binding globulin (SHBG) by an immunoluminescent assay.

Electrocardiography

A standard 12-lead electrocardiogram (ECG) was performed at the time of inclusion. All ECGs were screened for frequency, rhythm, conduction and depolarisation abnormalities and for evidence of left ventricular mass hypertrophy. A 24-hour ambulatory continuous recording was performed in each subject at the time of inclusion for measurement of heart rate and to detect any rhythm disturbances.

Statistical analysis

Student's test was used for comparison of results between patients and controls. Results are given as the mean ± standard deviation (SD). All p values are based on two-tailed analysis.

RESULTS

Fifty-eight patients were evaluated. Thirty-two patients were excluded for single or multiple reasons: cardiac history (n=10), hypertension (n=8), medication (n=6), diabetes mellitus (n=4), toxic goitre (n=6), other reasons (n=7). Twenty-four females and two males were in the patient group and 15 healthy females served as controls (*table 1*). The patients were divided in two subgroups, with a serum TSH above or below 0.4 mU/l. Mean serum TSH

Table 1
Characteristics of the multinodular goitre patients (mean ± SD)

	PATIENTS TSH >0.4 MU/L	PATIENTS TSH <0.4 MU/L	ALL PATIENTS	CONTROLS	P VALUE
Number	15	11	26	15	
Females	14	10	22	15	
Mean age (years)	53 ± 10	55 ± 11	54 ± 10	59 ± 10	NS
TSH (mU/l)	0.2 ± 0.2	0.9 ± 0.2	0.6 ± 0.4	2.4 ± 1.3	0.0001
FT4 (pmol/l)	13.4 ± 1.3	14.8 ± 3.0	14.0 ± 2.2	13.7 ± 2.1	NS
TT3 (nmol/l)	2.4 ± 0.4	2.4 ± 0.3	2.4 ± 0.4	2.0 ± 0.5	0.009
Creatinine (µmol/l)	58 ± 10	61 ± 9	61 ± 9	64 ± 9	NS
Ferritin (µg/l)	52 ± 40	85 ± 45	72 ± 52	116 ± 93	NS
Total cholesterol (mmol/l)	5.3 ± 1.0	5.4 ± 1.0	5.4 ± 1.0	6.2 ± 1.1	0.02
HDL cholesterol (mmol/l)	1.4 ± 0.2	1.3 ± 0.2	1.4 ± 0.3	1.6 ± 0.4	0.02
LDL cholesterol (mmol/l)	3.7 ± 0.9	3.6 ± 0.7	3.7 ± 0.8	4.4 ± 1.1	0.04
Triglycerides (mmol/l)	0.9 ± 0.4	0.8 ± 0.6	0.8 ± 0.5	1.3 ± 0.4	0.009
Sex hormone-binding globulin (nmol/l)	62.1 ± 32.4	54.1 ± 30.1	61.1 ± 37.7	52.9 ± 28.6	NS

P values: statistic tests between all patients and controls. TT3 = total trijodothyronine, TSH = thyroid-stimulating hormone.

and TT3 levels were lower and higher in both patient groups compared with the control group, respectively. Mean serum FT4 levels were not different. Mean total, HDL and LDL cholesterol and triglyceride levels were lower in both patient groups. Mean creatinine, ferritin and SHBG levels did not differ between patients and controls (*table 1*).

The 24-hour ambulatory continuous ECG recordings did not demonstrate differences in mean, minimal and maximal heart rate between both patient groups and the control group. Nocturnal heart rate, measured between 23.00 and 06.00 hours also showed no differences between the groups. Atrial fibrillation was absent in both the patients and the controls. Premature atrial and ventricular complexes were observed, but occurred equally frequently in patients and controls (*table 2*). Thyroid hormone levels and 24 hour or nocturnal heart rate were not significantly correlated in patients and controls.

DISCUSSION

Reports on effects of 'endogenous' subclinical hyperthyroidism on heart and lipids are limited. A recent study showed cardiac abnormalities in patients who were on TSH suppressive T4 therapy but with thyroid hormone levels within the normal range. These abnormalities were reflected by a higher mean daytime and nocturnal heart rate, a higher prevalence of atrial or ventricular arrhythmias, an increased cardiac mass and diastolic dysfunction.[8] These findings could not be confirmed by another group of investigators in a comparable patient group.[9] Interestingly, however, in another study in T4-suppressed patients, an increased left ventricular mass and reduced exercise tolerance was found. If, in these patients, T4 dose was lowered to the minimal amount to keep TSH at 0.1 mU/l, echocardiographic and ergometric parameters normalised.[11] Recently, cardiac abnormalities, this time in patients with subclinical hyperthyroidism due to a multinodular goitre, were published by Biondi *et al.*[10] The authors found an increased basal heart rate and also an abnormal systolic and diastolic function. In the present study we were unable to find cardiac effects. The two studies differ, however, in several aspects. Firstly, our study is a consecutive study whereas Biondi *et al.* presented results of a study of patients selected from a larger number of outpatients with a low TSH. Secondly, the patients in Biondi's study were probably more thyrotoxic than our patients as reflected by the fact that both mean TT3 and FT4 levels were in the upper normal range[10] whereas in our patients only mean TT3 was higher. Thirdly, the patients in Biondi's study – as in most other studies (*table 3*) – were significantly younger than our patients. These differences could very well explain that their patients showed cardiac effects whereas ours did not. Interestingly, in a consecutive study of 102 consecutive multinodular goitre patients performed in the Amsterdam area several years ago, TT3 was also higher but FT4 was not different compared with 50 healthy adults.[4] These data confirm again that in the natural course of multinodular goitre TT3 levels start to rise first, before FT4 levels rise, with a concomitant decrease in plasma TSH levels. Also of interest is the finding in our study that TT3 was in the upper normal range in all patients studied, both in patients with a TSH level below as well as above 0.4 mU/l.

Contrary to the findings in our patients with respect to the heart, there was evidence of an effect on plasma lipids in that serum levels were significantly lower than in controls. However, other metabolic parameters such as SHBG, ferritin or creatinine, known to be affected by thyroid hormone, were not different. Similar changes in circulating lipids have been found in another study in subjects with subclinical hyperthyroidism.[12] In that study, FT4 was also higher compared with controls, but still within normal

Table 2
Heart rate and incidence of arrhythmias in multinodular goitre patients

	PATIENTS TSH >0.4 MU/L	PATIENTS TSH <0.4 MU/L	ALL PATIENTS	CONTROLS	P VALUE
Number	15	11	26	15	
Mean heart rate (bpm)	81 ± 8	81 ± 8	81 ± 8	80 ± 9	NS
Minimal heart rate (bpm)	53 ± 7	54 ± 8	53 ± 7	52 ± 6	NS
Maximal heart rate (bpm)	141 ± 14	151 ± 24	145 ± 19	138 ± 23	NS
Mean nocturnal heart rate	69 ± 9	70 ± 9	70 ± 9	67 ± 6	NS
Minimal nocturnal heart rate	55 ± 7	54 ± 8	54 ± 7	53 ± 6	NS
Maximal nocturnal heart rate	107 ± 13	114 ± 23	110 ± 18	105 ± 11	NS
Premature ventricular complexes >100	3	0	3	3	NS
Premature atrial complexes >100	4	3	7	4	NS

Statistical analysis between all patients and controls. TSH = thyroid-stimulating hormone.

Table 3
Comparison of cardiac and metabolic effects in subclinical thyrotoxicosis due to T4 suppressive therapy and subclinical hyperthyroidism due to multinodular goitre

AUTHOR	YEAR	N	MEAN AGE	FT4*	TT3*	HEART RATE	PREMATURE BEATS	LV MASS	SHBG	LIPIDS
Subclinical thyrotoxicosis in subjects on T4 suppressive therapy										
Bell[15]	1983	7	28	↑	=	↑	nd	nd	nd	nd
Biondi[8]	1993	20	39	↑	=	↑	↑	↑	↑	nd
Ching[16]	1996	11	45	↑	=	=	nd	↑	nd	nd
Shapiro[9]	1997	17	45	↑	=	=	=	↑	nd	nd
Subclinical hyperthyroidism in patients with multinodular goitre										
Biondi[10]	2000	23	43	↑	↑	↑	=	↑	nd	nd
Faber[17]	2001	6	64	↑	↑	↑	nd	nd	nd	nd
Berghout	2003	11	55	=	↑	=	=	nd	=	↓

*LV = left ventricular, SHBG = sex hormone-binding globulin, nd = not done. * Levels within the normal range, ↑ elevated as compared with controls, ↓ decreased as compared with controls, = not different as compared with controls.*

limits.[12] In a study of 44 patients with clinically euthyroid goitre plasma levels of bone gla protein and SHBG were found to be higher compared with controls in those patients who had a lowered TSH.[13] A study of 27 consecutive multinodular goitre patients reported elevated levels of serum osteocalcin, which correlated with FT4 levels.[14] TSH was lower and FT4 was higher, but still within the normal range.[14]

From an analysis of all available studies of patients with subclinical hyperthyroidism caused by a multinodular goitre or with thyrotoxicosis caused by T4 suppressive therapy it is apparent that cardiac effects are seen in both groups but not in all studies (*table 3*).[8-10,15-17] It remains debatable whether endogenous subclinical hyperthyroidism in patients with a goitre and subclinical thyrotoxicosis due to exogenous T4 therapy are two different entities. In both situations plasma TSH levels are low or suppressed. In endogenous subclinical hyperthyroidism first TT3 and later both TT3 and FT4 are elevated – within the normal range – while in subclinical thyrotoxicosis due to T4 suppressive treatment only FT4 is elevated.[8] In both situations TSH is suppressed because the pituitary can respond independently to changes in plasma levels of T4 that enter the thyrotroph and is locally converted to T3, and to changes in plasma T3 that is directly taken up by the pituitary.[18] It is also evident that one cannot conclude from these studies whether the human heart is more sensitive to plasma T3 or T4 levels, in contrast to the liver that appears to be sensitive mainly to the plasma T3 concentration. The situation in the human heart is largely unknown. In neonatal rats cardiac uptake was mostly for T3 but not T4.[19] The conversion of T4 into T3 in human cardiac myocytes has thus far only indirectly been demonstrated by the finding of the expression of mRNA of type II deiodinase.[20]

In summary, in consecutive patients with euthyroid multinodular goitre metabolic effects are found. The expression of these effects depends upon the degree of increased thyroid function as occurring in the natural course of 'nontoxic' goitre.

NOTE

Part of the data in this article were presented at the 26th Annual Meeting of the European Thyroid Association in Milan, Italy from 28 August to 1 September 1999.

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ORIGINAL ARTICLE

F-18-fluorodeoxyglucose positron emission tomography in diagnosis and follow-up of patients with different types of vasculitis

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ABSTRACT

Background: F-18-fluorodeoxyglucose (FDG) accumulates in inflammatory cells due to an increased metabolic rate. Therefore, FDG positron emission tomography (PET) represents a promising imaging technique in patients with vasculitis. The aim of this study was to assess the value of FDG PET in the diagnosis of different types of vasculitis.

Methods: The results of FDG PET performed because of suspected vasculitis or fever of unknown origin with results indicating vasculitis were reviewed. These results were compared with the final diagnosis, based on the American College of Rheumatology 1990 criteria.

Results: FDG PET was ordered because of suspected vasculitis in 20 patients, because of fever of unknown origin in two patients, and for follow-up of vasculitis in five patients. Fourteen patients were diagnosed with vasculitis (giant cell arteritis n=5, polymyalgia rheumatica n=2, polyarteritis nodosa n=3, Takayasu n=1, Churge-Strauss n=1, Wegener's granulomatosis n=1, vasculitis skin n=1), two patients were diagnosed with fibromuscular dysplasia and one patient had media necrosis of the aorta. In five patients no diagnosis could be reached. FDG PET results were considered to be true-positive in ten patients, true-negative in 14 patients and false-negative in three patients resulting in a positive predictive value of 100% and a negative predictive value of 82%.

Conclusions: FDG PET appears to be a promising new imaging technique in diagnosing and determining the extent of various forms of vasculitis. Furthermore, FDG PET may become a useful tool for evaluating the effect of treatment of vasculitis.

INTRODUCTION

Early and accurate diagnosis and assessment of the extent of vasculitis is important for adequate therapeutic measures and improvement of prognosis. Diagnosing vasculitis is often difficult due to the absence of specific symptoms and signs, the limited specificity of the available biochemical tests and the limited sensitivity of detecting the frequently subtle vessel abnormalities with conventional imaging techniques. The various kinds of vasculitis are classified based on the type of inflammation, the predominant size of the involved arteries, and the extent and location of the inflammation. The American College of Rheumatology 1990 criteria for the classification of vasculitis (ACR criteria)[1-11] are considered to be the gold standard. Although these criteria were established for research, they are often used for clinical diagnosis of vasculitis. In a study of 198 patients suspected of vasculitis, however, the ACR criteria functioned poorly in the clinical diagnosis of specific types of vasculitis.[12] In clinical practice, diagnosing vasculitis and evaluating the extent and location of the disease is difficult or even impossible in many cases. In those types of vasculitis in which it is difficult to obtain histological proof, imaging techniques are used for diagnosis. Vasculitis of the medium-sized and large blood vessels can

[#] J.W.M. van der Meer was not involved in the handling and review process of this paper.

be detected by several radiological techniques including classic angiography, computerised tomography (CT), magnetic resonance imaging (MRI) and ultrasonography. Since these techniques only show anatomical changes of the vessel lumen, inflammation of the vessel wall cannot be detected in an early phase due to the lack of substantial anatomical changes at this time. Also, it is difficult if not impossible to distinguish active inflammatory lesions from residual anatomical changes due to previous inflammation.

Scintigraphic imaging is a noninvasive method allowing delineation of both localisation and number of foci in all parts of the body, based on functional changes of tissues. F-18-fluorodeoxyglucose (FDG) positron emission tomography (PET) has become an established imaging tool in oncology and is now entering the field of infectious and inflammatory diseases.[13] FDG accumulates in organ tissues with a high rate of glycolysis,[14] which does not exclusively occur in neoplastic cells. Lesions with a high concentration of activated inflammatory cells also show increased uptake of FDG.[15,16] Furthermore, from almost all other sites of the body, including the blood compartment, it is cleared very rapidly. FDG PET could thus be a promising new imaging technique for evaluation of metabolic activity in the vessel wall in both diagnosis and follow-up of patients with vasculitis. FDG accumulation on PET scanning has been reported in patients with giant cell arteritis and polymyalgia rheumatica,[17-20] Takayasu's arteritis,[20-24] periaortitis due to Wegener's granulomatosis,[25] aortitis,[20,26] unspecified large vessel vasculitis[27,28] and infectious vasculitis.[29] To further assess the role of FDG PET imaging in diagnosis and follow-up of patients with different types of vasculitis, we evaluated the results of FDG PET scans, performed either because of suspected vasculitis or fever of unknown origin with results suggesting the presence of vasculitis.

MATERIALS AND METHODS

Patients

The results of all FDG PET scans ordered in the University Medical Centre of Nijmegen from January 1999 to April 2003 because of suspected vasculitis or fever of unknown origin with results suggesting the presence of vasculitis were reviewed. Fever of unknown origin was defined according to the revised Petersdorf criteria: a febrile illness of >3 weeks duration, a temperature of >38.3°C on several occasions, and no diagnosis after one week of evaluation in hospital or after three visits to the outpatient department.[30] The patients were evaluated with other imaging modalities and laboratory tests, as was considered clinically appropriate. Patients were included if the diagnostic process had been completed at the time of data analysis in April 2003. The patients with fever of unknown origin are also included in a retrospective study investigating the diagnostic contribution of FDG PET in patients with fever of unknown origin that will be published elsewhere.[31]

FDG PET

A dedicated, full-ring PET scanner (ECAT-EXACT, Siemens/CTI, Knoxville, Tenn., USA) was used for data acquisition. Prior to FDG injection patients had fasted for at least six hours. Intake of sugar-free liquids was permitted. Immediately prior to the procedure, the patients were hydrated with 500 ml of water. One hour after intravenous injection of 200 to 220 MBq FDG (Mallinckrodt Medical, Petten, the Netherlands) and 10 to 15 mg furosemide, emission images or emission and transmission images of the area between the proximal femora and the base of the skull were acquired (10 minutes per bed position). When only an emission study was recorded, the images were not corrected for attenuation and were reconstructed using filtered back protection (Butterworth filter with a cut-off frequency of 0.4 Nyquist). When emission and transmission studies were recorded, the images were corrected for attenuation and were reconstructed using the ordered subsets-expectation maximisation (OSEM) algorithm. Reconstructed images were displayed in coronal, transverse and sagittal planes.

Interpretation

FDG PET scans were interpreted by two staff members of the department of nuclear medicine blinded for other diagnostic test results and the final diagnosis. FDG PET scans were rated as normal or abnormal. Results were judged to be abnormal if focal accumulation of the tracer was detected outside of the areas of physiological uptake. Normally no visible FDG uptake is present in blood vessel walls. Disagreements were resolved by consensus.

Clinical assessment of test results and diagnosis

Results were considered to be true-positive when abnormal vascular FDG uptake was present in patients with a clinical diagnosis of vasculitis. Abnormal results were categorised as false-positive when the abnormality was not related to the illness or when no final diagnosis could be reached. A normal FDG PET scan was considered to be true-negative when no cause was identified for the symptoms despite an extensive diagnostic work-up. In cases of suspected vasculitis, the diagnostic work-up had to be complete according to the ACR criteria. A normal FDG PET scan was considered false-negative when vasculitis was diagnosed except for vasculitis limited to the brain because of known low sensitivity of FDG PET due to high physiological FDG uptake in the brain, or vasculitis limited to the legs, because the legs are not routinely imaged if not specially mentioned on the FDG PET request. A final diagnosis of

vasculitis was based on the ACR criteria. When this was not possible, a probable diagnosis was made based on clinical follow-up and conventional radiological studies. No criteria defining an exacerbation or recurrence of a known vasculitis syndrome are available. To define a probable exacerbation or recurrence, the clinical diagnosis based on a combination of recurrence of symptoms resembling the symptoms at the time of the first episode with vasculitis, an elevated erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) and other biochemical tests were used. The final or probable clinical diagnosis served as a standard of reference and was used for the comparisons with the FDG PET results.

RESULTS

From January 1999 to April 2003, 25 patients were referred for a total of 30 FDG PET scans because of suspected vasculitis or fever of unknown origin with FDG PET results indicating vasculitis. Three patients had to be excluded because of insufficient data in follow-up, so the results of 27 FDG PET scans in 22 patients were evaluated. Of these patients, two were male and 20 were female with a median age of 60 years (range 17 to 81 years). Nine patients had at least one period of hospitalisation with a median duration of 14 days (range 8 to 62 days). Thirteen patients only visited the outpatient department.

The clinical diagnoses of the patients are shown in *table 1*. Fourteen patients (64%) were diagnosed with vasculitis based on the ACR criteria. Fibromuscular dysplasia was diagnosed in two patients: one patient was diagnosed with fibromuscular dysplasia of the right renal artery and the hepatic artery based on typical changes on angiography, which is the gold standard for diagnosing this disease. In the other patient a probable diagnosis of fibromuscular dysplasia of the carotid arteries was reached based on typical changes on magnetic resonance angiography (MRA). One patient suspected of vasculitis of the thoracic aorta because of a progressively dilating ascending aorta and a variable elevation of CRP was eventually diagnosed with media necrosis of the ascending aorta after replacement of the affected part with an aortic graft. No signs of vasculitis or infection were found and the definite cause of the media necrosis remained unresolved. The media necrosis was possibly caused by previous aortitis in this patient with a combined immunodeficiency. In five patients suspected of vasculitis, no cause could be established for their symptoms after a median follow-up of seven months (range 1 to 17 months): one patient had persisting symptoms without treatment and died of cerebral haemorrhage 17 months after FDG PET (no autopsy was performed), two patients had persisting symptoms while treated with nonsteroidal anti-inflammatory drugs for one and six months, respectively, in one patient symptoms completely disappeared after prednisone treatment and in one patient severity of symptoms decreased and ESR normalised spontaneously.

Table 1
Clinical diagnosis in 22 patients suspected of vasculitis or with fever of unknown origin and FDG PET results indicating vasculitis

CATEGORY	NO. OF CASES
Vasculitis	14
Giant cell arteritis	5
Polymyalgia rheumatica	2
Polyarteritis nodosa	3
Takayasu	1
Churge-Strauss	1
Wegener's granulomatosis	1
Vasculitis skin (unspecified)	1
Fibromuscular dysplasia	2
Media necrosis aorta (of unknown origin)	1
No diagnosis	5

The median duration of symptoms before FDG PET was performed was five weeks (range 2 weeks to 41 months). In three patients (14%) the symptoms had persisted for more than six months before FDG PET was ordered. The first FDG PET scan was requested because of suspected vasculitis in 20 patients and because of fever of unknown origin in the remaining two patients. *Table 2* shows the classification of the FDG PET results. Ten of the total number of 22 'first' FDG PET scans were abnormal (45%) and all these abnormal FDG PET results were found in patients with active vasculitis and were thus considered to be true-positive. Examples are shown in *figures 1* and *2*. In two patients with active temporal arteritis and in one patient with vasculitis limited to the skin who had not been treated with corticosteroids, the results of FDG PET were classified as false-negative. Normal FDG PET results were categorised as true-negative in five patients in whom no diagnosis could be reached, in two patients with fibromuscular dysplasia, and in the patient with media necrosis. One patient with a history of Takayasu's arteritis, which had been inactive for almost four years, was suspected of recurrence of active vasculitis because of painful shoulders and a slightly elevated ESR. Symptoms spontaneously disappeared, ESR normalised and no diagnosis of recurrence of active vasculitis was made, so the normal FDG PET results were also considered to be true-negatives in this case.

In three patients with polyarteritis nodosa, one patient with temporal arteritis and one patient with Wegener's

Table 2
Classification of the results of 27 FDG PET scans in patients suspected of vasculitis or with fever of unknown origin with FDG PET results indicating vasculitis

CATEGORY	TRUE-POSITIVE	TRUE-NEGATIVE	FALSE-NEGATIVE	FALSE-POSITIVE
Vasculitis (diagnosis)	10	1	3	0
Vasculitis (follow-up)	0	5	0	0
Fibromuscular dysplasia	0	2	0	0
Media necrosis aorta	0	1	0	0
No diagnosis	0	5	0	0
Total	*10*	*14*	*3*	*0*

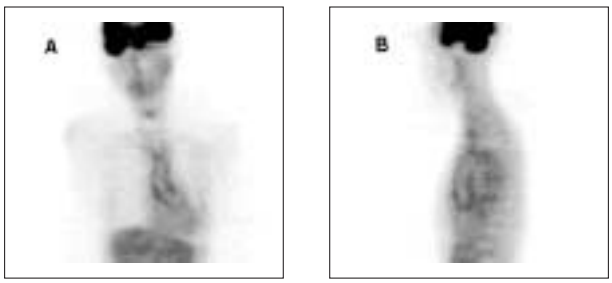

Figure 1
PET scan of an 80-year-old woman with temporal arteritis

This woman was diagnosed with temporal arteritis in 1999, based on the ACR criteria including typical changes on temporal artery biopsy. She responded well to high-dose prednisone, which was slowly tapered to 5 mg. She remained well until January 2002 when she presented with headaches, painful shoulders and weight loss (8 kg). Physical examination had not changed and revealed absence of pulsation of the temporal arteries, but was otherwise normal. ESR was slightly elevated to 22 mm/h (normal <12 mm/h). She did not respond to prednisone 20 mg daily. Since recurrence of giant cell arteritis was suspected, FDG PET was performed to evaluate whether her symptoms were caused by active vasculitis. PET demonstrated increased FDG uptake especially in the ascending aorta indicating active aortitis (A = coronal projection, B = sagittal projection). She was diagnosed with reactivation of giant cell arteritis and her symptoms disappeared again after high-dose prednisone treatment.

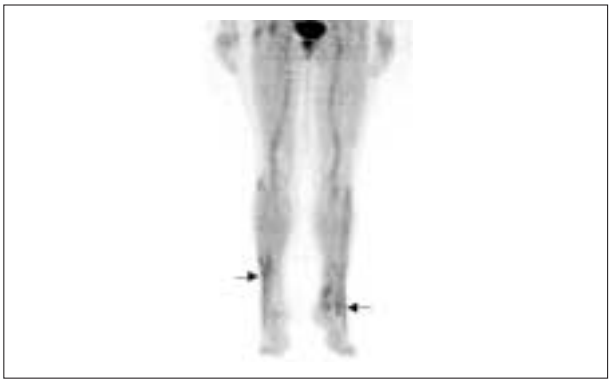

Figure 2
PET scan of a 60-year-old woman with myalgia of the lower legs, skin ulcerations on both legs, livedo reticularis and mild polyneuropathy

A skin biopsy of this previously healthy woman showed fibrosing panniculitis and necrotising vasculitis of medium-sized arteries. Polyarteritis nodosa was diagnosed according to the ACR criteria. FDG PET was performed to determine the extent of the vasculitis. Increased FDG uptake was found in both femoral arteries and several superficial lesions on the lower legs (arrows); the latter were probably caused by the skin ulcerations. No vascular FDG uptake was noticed elsewhere (not shown). She was treated with high-dose prednisone and her symptoms disappeared.

granulomatosis, a second FDG PET scan was performed to evaluate the effect of treatment with a median time between the first and second FDG PET scans of 11 weeks (range 4 to 25 weeks). FDG PET results were normal in these five patients who all had a good clinical and biochemical response to therapy (*table 2*). After the second FDG PET scan proved to be normal, the corticosteroid dose was tapered in all five patients without relapse of symptoms thus far. The results of these FDG PET scans were considered to be true-negative. The sensitivity of all 27 FDG PET scans in these 22 patients was 77%, specificity was 100%, positive predictive value was 100% and negative predictive value was 82%.

DISCUSSION

In this study we retrospectively evaluated the utility of FDG PET in diagnosis and follow-up of vasculitis. The results demonstrate that vascular FDG uptake is increased in different types of active vasculitis. To our knowledge, increased FDG uptake on PET scanning has not been reported before in patients with polyarteritis nodosa or Churge-Strauss syndrome. In addition, a remarkable decrease in FDG uptake corresponded well with improvement of symptoms and laboratory results in five patients, suggesting that vascular FDG uptake is only seen in active vasculitis and not in noninflammatory

vascular disease such as fibromuscular dysplasia or in inactive disease. Although inflammation of the arterial wall is most prominent in vasculitis, inflammation also contributes to atherogenesis. In an atherosclerotic rabbit model, increased FDG accumulation was shown in the affected arteries.[32] FDG uptake in the femoral and iliac arteries was increased in 133 patients with at least one risk factor for atherosclerosis when compared with 23 controls.[33] In our experience FDG uptake in vasculitis is much higher than in atherosclerosis, so a distinction between these two diagnoses may very well be possible.

Besides several case reports and a case series in patients with giant cell arteritis or polymyalgia rheumatica,[17,19,20] Takayasu's arteritis,[20-24] periaortitis due to Wegener's granulomatosis,[25] aortitis of the thoracic aorta[20,26] and large vessel vasculitis,[27,28] only two prospective studies exploring the diagnostic value of FDG PET imaging in vasculitis have been published. Blockmans *et al.*[18] found a sensitivity of FDG uptake in the large thoracic arteries for the diagnosis of temporal arteritis or polymyalgia rheumatica of 56%, a specificity of 98%, a positive predictive value of 93% and a negative predictive value of 80% in 25 patients with biopsy-proven temporal arteritis or polymyalgia rheumatica. The extent of the vasculitis to a much larger part of the arterial system than is usually suspected in giant cell arteritis was remarkable. It was also suggested that the results of this study support the hypothesis that polymyalgia rheumatica is caused by the same kind of vasculitis,[18] therefore these patients were included in the present study. Meller *et al.*[20] compared FDG PET with MRI in 15 patients with aortitis due to giant cell aortitis (n=14) or Takayasu's arteritis (n=1) at the time of diagnosis and during follow-up (n=7). It was concluded that FDG PET is a valuable technique in both diagnosis and follow-up of patients with aortitis, because it identified more vascular regions involved in the inflammatory process than did magnetic resonance imaging.[20] Sensitivity of FDG uptake in vasculitis in the study by Blockmans *et al.* seems to be lower when compared with the results of the present study (56 versus 77%). However, we found false-negative results in two out of seven patients diagnosed with temporal arteritis or polymyalgia rheumatica suggesting that sensitivity of FDG PET may be lower in these patients than in patients with other types of vasculitis. Due to high uptake in the brain, the small diameter of the vessel, and the relatively high background of the skin, direct evaluation of the temporal arteries is not possible on whole body PET imaging. This could explain the difficulty of detecting giant cell arteritis by FDG PET, especially in cases where vasculitis is really limited to the temporal arteries.

Conventional scintigraphic techniques have also been used occasionally in patients with vasculitis. In a prospective study of 19 patients with biopsy-proven temporal arteritis, gallium-67-citrate scintigraphy (Ga-67) had a 94% specificity and a 90% positive predictive value with normalisation of Ga-67 uptake after six months of steroid therapy.[34] In one study radio-labelled leucocyte scintigraphy seemed to be superior to conventional angiography and CT for detecting and monitoring vasculitic involvement of the respiratory tract.[35] In Takayasu's arteritis, however, indium-111-leucocyte scintigraphy had a low sensitivity for active disease.[36] Compared with conventional nuclear medicine techniques, advantages of FDG PET in diagnosing inflammation are early imaging (one hour), resulting in early reporting,[37] tomographic information with higher spatial resolution, resulting in more anatomic information, and high inter-observer agreement.[38]

Recently, imaging techniques for demonstrating anatomic blood vessel changes in vasculitis, such as CT angiography, MRI and colour duplex ultrasonography, have greatly improved. This improvement and the invasive nature of classic angiography makes one inclined to perform these imaging techniques instead of angiography in diagnosis and follow-up of patients with vasculitis. CT angiography is able to detect luminal and vessel wall changes in patients with Takayasu's arteritis with high accuracy.[39,40] Vascular wall thickening is also an important finding on MRI in the acute phase of Takayasu's arteritis, subsiding after appropriate therapy.[41,42] Mural oedema is a characteristic pattern of active and progressive Takayasu's arteritis, which is absent in the chronically active state.[43] In patients with giant cell arteritis, MRA is potentially useful for follow-up the effect of treatment.[44,45] Duplex ultrasonography is able to demonstrate luminal changes, aneurysms and a hypoechoic halo, most probably caused by vessel wall oedema, in patients with temporal arteritis and Takayasu's arteritis.[46-48] In a study of 86 patients with biopsy-proven temporal arteritis, it was concluded that colour duplex ultrasonography made only a modest contribution to diagnosing temporal arteritis.[49] In another study, duplex ultrasonography was found to be a noninvasive, relatively inexpensive, and efficient method, suitable for repeated follow-up in patients with Takayasu's arteritis.[40] However, ultrasonography is limited in the extent to which it can detect all diseased vessels, especially the pulmonary arteries, aorta and visceral vessels. Positive aspects of FDG PET imaging compared with CT, MRI and ultrasonography are whole-body screening, high contrast resolution, absence of disturbance by metallic implants (MRI) and absence of contrast-related side effects (CT). Also, FDG PET shows functional changes caused by activation of inflammatory cells and does not depend on anatomical changes in contrast to CT, MRI and ultrasonography. Disadvantages of FDG PET are the higher cost, still limited availability and more limited anatomic information due to lower spatial resolution as compared with CT and MRI.

In conclusion, FDG PET appears to be a valuable new imaging technique in diagnosing and determining the extent of various forms of vasculitis. Furthermore, FDG PET may become a useful tool for evaluating the effect of treatment of vasculitis that cannot reliably be visualised by conventional techniques. However, for a validation of FDG PET in patients with suspected vasculitis and for determination of its exact position in the follow-up of response to treatment, prospective studies in a larger number of patients are warranted.

NOTE

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Hypertension in neurofibromatosis

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CASE REPORT

A 52-year-old woman presented with severe hypertension. Repeated measurements at the outpatient clinic and after admission to hospital revealed blood pressures between 194-230/112-136 mmHg. The patient was known with familiar congenital neurofibromatosis, diagnosed at the age of 18 years. Indeed, besides the multiple café-au-lait spots numerous neurofibromas were observed (see *figure 1*), such as a large one within the mouth.

WHAT IS YOUR DIFFERENTIAL DIAGNOSIS?

See page 340 for the answer to this photo quiz.

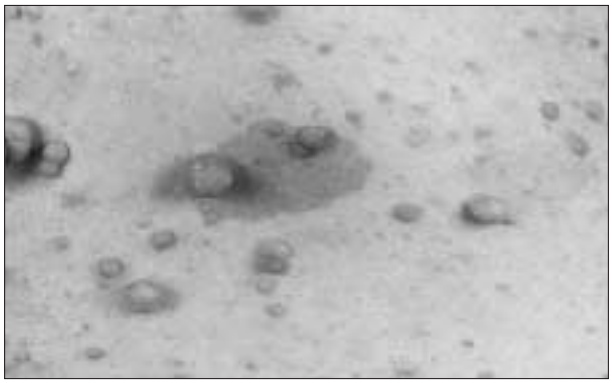

Figure 1

A colour version of this photo quiz can be found on our website www.njmonline.nl.

[#] **Th. Thien was not involved in the handling and review process of this paper.**

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CASE REPORT

Unexpected survival from severe metformin-associated lactic acidosis

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ABSTRACT

Lactic acidosis is a recognised complication of the anti-hyperglycaemic biguanide agent metformin, especially in patients with renal failure. We report a case of severe lactic acidosis and hypothermia due to metformin treatment and renal impairment. The favourable outcome despite extremely unfavourable clinical signs and symptoms for survival after admission and initial treatment was unexpected. Specific aspects of the clinical course are addressed.

INTRODUCTION

Oral hypoglycaemic medications are often used in hyperglycaemic patients. Metformin, the only available biguanide compound in the Netherlands, is frequently used in type 2 diabetes mellitus patients. Phenformin, another biguanide, was withdrawn in several countries because of its association with lactic acidosis and related mortality.[1]

Although lactic acidosis is reported less frequently with metformin than phenformin, it can be considered a serious and life-threatening adverse event.[2] In the present case we report the unexpected survival of an extreme case of metformin-associated lactic acidosis (MALA).

CASE REPORT

A 72-year-old woman was admitted to the hospital because of severe dyspnoea. Her medical history revealed diabetes mellitus for 15 years with diabetic nephropathy for five years (albuminuria 264 mg/l, Cockroft estimated creatinine clearance 28 ml/min), adequately treated hypertension for the last four years and cerebrovascular accidents (TIA, minor stroke) three years ago without major lasting sequelae.

On admission she was unable to give additional information due to her clinical condition. Family members confirmed the existence of rapidly progressive dyspnoea. She had been anorectic for three days and had not drunk at all. Furthermore, during the three days before admission, she had developed a cough with purulent sputum and severe diarrhoea. A general practitioner prescribed doxycycline. Other medication consisted of enalapril 20 mg tid, metformin 850 mg tid, glibenclamide 5 mg tid, dipyridamole 75 mg qid and aspirin 30 mg. Family members confirmed that patient had not been taking all her medications.

On physical examination the patient appeared to be severely ill. The skin was cool and clammy and capillary refill was slow. Respiratory rate was 40/min. Heart rate was 82 beats/min and arterial blood pressure 120/70 mmHg, rapidly deteriorating to 85/25 mmHg within one hour, despite fluid resuscitation. Core body temperature was 33.8°C and dropped to 32.6°C. EMV score was 3. Pupillary reactions were slow. Physical examination was otherwise unremarkable.

An arterial blood sample showed: pH 6.67 (7.35 to 7.45), pCO_2 1.7 (4.5 to 6.0 kPa), pO_2 29.9 (9.5 to 13.0 kPa), HCO_3 1.4 (22 to 26 mmol/l), BE -27 (-2 to +2), and O_2 saturation 97 (92 to 99%). Venous lactate was 12.6 mmol/l (0.5 to 2.2). Other laboratory results were: CRP 37 (<5 mg/ml), Hb 6.8 (7.5 to 10 mmol/l), leucocytes 14.3 (4 to 11/nl), sodium 144 (135 to 145 mmol/l), potassium

5.9 (3.5 to 5.0 mmol/l), creatinine 986 (50 to 90 μmol/l), urea 33.3 (3 to 7 mmol/l), glucose 15.1 (4.0 to 10.0 mmol/l) and CK 56 (0 to 170 U/l). Liver enzymes were within normal ranges. Metformin levels were not measured.
A chest X-ray showed no abnormalities. An electrocardiogram revealed sinus rhythm and left bundle branch block. An abdominal ultrasound excluded post-renal obstruction and showed no evidence of intra-abdominal pathology.
To exclude a septic aetiology, cultures were taken from blood, tracheal aspirate and catheter urine, and empirical treatment with cefotaxime and gentamicin was started. All cultures remained negative.
The patient was admitted to the Intensive Care Unit. Admission was immediately followed by cardiac arrest; cardiopulmonary resuscitation was successful. Circulatory shock resulted and vasopressors and inotropes were started and increased to maximal levels at dopamine 25.3 $\mu g/kg^{-1}/min^{-1}$, dobutamine 8.4 $\mu g/kg^{-1}/min^{-1}$, noradrenaline 1.05 $\mu g/kg^{-1}/min^{-1}$, and adrenaline 0.04 $\mu g/kg^{-1}/min^{-1}$. Suspected vasopressin deficiency was treated with terlipressin 1 mg bolus iv.
For (supra)ventricular tachycardia, amiodarone was continuously infused restoring sinus rhythm. Hypothermia was treated with external rewarming and resuscitation with nine litres of fluids in the first 24 hours. Corticosteroid, thiamine and insulin suppletion were commenced. Acidosis was corrected by artificial hyperventilation by means of mechanical ventilation and continuous sodium bicarbonate infusion of 1200 ml 8.4% over 12 hours. As a result serum sodium levels rose to 178 mmol/l and chloride to 109 mmol/l. Arterial lactate levels increased to 33.8 mmol/l.
Physical examination after 16 hours showed an EMV score of 3 and absent pupillary reactions. After 24 hours an APACHE II score of 39 was calculated.
Optimal neurological prognostic estimation was complicated if not impossible due to severe hypernatraemia and catecholamine infusion. Therefore, a decision to continue full treatment was made. Anuria persisted and continuous veno-venous bicarbonate-buffered haemofiltration (CVVH, 48 litres replacement fluid) was started. Serum bicarbonate, pH and sodium levels were within normal ranges 24 hours after initiation of CVVH. Within 48 hours all neurological functions returned to normal. Circulatory shock resolved. The patient was transferred to the Department of Internal Medicine and Nephrology after 11 days. After one month renal failure still existed and intermittent haemodialysis was continued.

DISCUSSION

Susceptibility to MALA is not completely understood. Previous data have suggested that metformin is not associated with an increased risk of lactic acidosis compared with other antihyperglycaemic treatments in patients in which metformin contraindications have been respected. Nevertheless, in patients with possible risk factors, which may potentiate the lactacidaemic effect of metformin, MALA has been described before (*table 1*).[2,3]

Table 1
Practical recommendations to minimise risk of MALA[2]

AVOID USE OF METFORMIN
Serum creatinine >135 μg/l (men), 110 μg/l (women) or creatinine clearance <50 ml/min
Septicaemia
Acute myocardial infarction/congestive cardiac failure/shock
Abnormal liver function tests suggestive of impaired liver function
Alcohol abuse
Metabolic acidosis
Surgery
Pregnancy
LIMIT/REVIEW USE OF METFORMIN
Chronic stable cardiac failure
Vitamin B12 deficiency
Intravascular radio-contrast studies
Elderly patients (>80 years)

In the USA the reported rate of confirmed biguanide-associated type B lactic acidosis is three cases per 100,000 patient-years.[2] Because many diabetes mellitus patients are treated with metformin, a large group is at risk of developing MALA.
In our case other causes of lactic acidosis, such as sepsis, thiamine deficiency, acute liver failure or hypoxaemia, were excluded. The patient continued high-dose metformin treatment up to admission. Therefore, it seems highly likely that the observed clinical picture is due to MALA, although metformin levels were not measured. On the other hand, accumulation of metformin does not correlate with lactate concentrations or mortality and metformin levels would therefore probably be of limited value.[4]
Profound severe metabolic acidosis in the absence of hypoxaemia should raise the suspicion of type B, potentially reversible lactic acidosis.[5] The severe renal failure probably contributed to the severe metabolic acidosis. Renal insufficiency should be considered the most likely predisposing factor in the development of this case of severe MALA. In fact, the high-dose metformin (2550 mg a day) should have been withdrawn earlier based on the impaired renal function. Contraindications are often neglected in clinical practice. In a study among patients on metformin

therapy who were admitted to hospital, 27% had specific contraindications for its use. Of these contraindications renal insufficiency was most frequently observed.[6]
Attributable factors for severe renal failure identified in our patient were the diabetic nephropathy combined with reduced fluid intake and water loss due to a probable upper respiratory tract infection and severe diarrhoea causing prerenal failure further aggravated by the use of an angiotensin-converting enzyme inhibitor.
Furthermore, in hypothermic patients major fluid losses have been observed.
The relation of MALA and hypothermia is unclear but another case with similar comorbidity and aetiology has been described in the literature.[7]
ACE inhibitor therapy affects glomerular autoregulation by intrarenal efferent vasodilation with a consequent fall in filtration pressure. In case of reduced renal perfusion due to dehydration, marked reductions in glomerular filtration rate may be observed. In such cases the withdrawal of ACE inhibitor treatment is warranted.[8]
In elderly patients, especially those with vascular disease, dehydration and drug-related causes of renal failure are more often associated with mortality and prolonged renal replacement therapy.[9]
The survival of our patient is remarkable because severe MALA is associated with poor outcome. In a study of 330 patients with biguanide-associated lactic acidosis, only eight had a normal plasma creatinine at the time of diagnosis. The mean blood lactate was 16.9 mmol/l and the mortality about 50%.[10] In cases of MALA with a pH <6.9 with raised urea and a lactate >18 mmol/l prognosis is extremely poor.[11] In 126 MALA patients, all nine patients with an APACHE II score above 30 died within 24 hours.[12] The APACHE II score in our patient was 39.
In our case, neurological signs and symptoms were predictive of poor outcome. Initial neurological evaluation was complicated by hypothermia and later by severe hypernatraemia due to infusion of sodium bicarbonate. During hypothermia, inotropes and catecholamine infusion and severe hypernatraemia, pupil size and reactions to light are difficult to interpret.[13] Hypothermia may have prevented further neurological deterioration after the initial cardiopulmonary resuscitation. Mild hypothermia (12 to 24 h of 32 to 34°C) in comatose patients has been shown beneficial for the neurological outcome even in patients with obvious noncoronary causes for cardiac arrest.[14]
Initially, the treatment strategy was focused on the optimisation of fluid status to correct for hypovolaemia and prerenal failure as well as the reduction of acidosis. However, the supply of sodium bicarbonate had to be stopped because the concentrations of plasma sodium became severely elevated as has previously been described in the literature.[15] After the initiation of CVVH sodium, the bicarbonate levels and pH rapidly normalised.
Therefore, in our opinion as well as others,[16] the early institution of bicarbonate-buffered CVVH is warranted in renal failure associated severe MALA and should be preferred above infusion of sodium bicarbonate alone.
In conclusion, although severe MALA has been proven to have a poor prognosis in general, interpretation of clinical neurological signs and prognostic estimations based on lactate, bicarbonate levels or APACHE II scoring should be interpreted with caution in individual cases.
Hypernatraemia due to sodium bicarbonate infusion can be limited by using early institution of continuous bicarbonate-buffered renal replacement therapy. Furthermore, adherence to known exclusion criteria in the prescription of metformin is stressed by this case of extreme MALA.

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CASE REPORT

Postpartum ovarian vein thrombosis: report of a case and review of literature

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ABSTRACT

Postpartum ovarian vein thrombosis (POVT) is an uncommon disease and it may complicate streptococcal group B infection of the vagina and endometrium. Obstruction of the right ureter is an uncommon complication of POVT. We present a case of POVT complicated by thrombus extension in the inferior vena cava and ureteral obstruction with urinary leakage, and outline the clinical presentation, radiological investigations useful in diagnosis and treatment of the disease process.

INTRODUCTION

There is an increased risk of thrombosis in pregnancy and puerperium.[1] Deep vein thrombosis complicates approximately 5 of 1000 pregnancies and pulmonary embolism is seen in 1 of 2000 pregnancies and the incidence of both is much higher in the puerperium. Compression of the inferior vena cava (IVC) by the uterus and hormonal changes underlie the thrombus formation in the deep veins of the lower limbs and pelvis. Changes in fibrinolysis and coagulation during pregnancy are possibly the most important factors (protein S deficiency; increased fibrinogen and concentration of factors II, VII, VIII, IX and X; increased platelet adhesion; and decreased fibrinolysis).[1] Underlying thrombophilia, such as antithrombin III deficiency, factor V Leiden, protein C or S deficiency can present for the first time as thrombosis in the postpartum period.[1,2] Postpartum ovarian vein thrombosis (POVT) is an uncommon disease that affects approximately 1 of 2000 deliveries or abortions and it may complicate streptococcal group A infection of the vagina and endometrium.[3] Obstruction of the right ureter is an uncommon complication of POVT.[4,5] We present a case of POVT complicated by thrombus extension in the IVC and ureteral obstruction.

CASE REPORT

A 33-year-old woman, gravida 1 para 1, presented five days after a normal vaginal delivery with right lower quadrant abdominal pain. She had had an uncomplicated pregnancy and was previously healthy. She had no chest pain or dyspnoea. She had no history of tobacco, alcohol or drug abuse. There was no clear tendency for thrombosis in her family. Physical examination showed an acutely ill and anaemic woman. The pulse was 100 beats/min, blood pressure was normal and temperature was 38.6°C. The findings of cardiopulmonary examination were unremarkable. Abdominal examination revealed right lower quadrant tenderness with no rebound tenderness and the right lumbar region was sensitive to palpation. Bimanual examination elicited cervical motion tenderness and right adnexal tenderness. There was no evidence of deep vein thrombosis in the lower extremities.
Laboratory examination showed a haemoglobin of 7.8 mmol/l, MCV 86 fl, white blood cell count $15.1*10^9$/l and C-reactive protein (CRP) 135 mg/l. Renal and liver function tests were normal. Urine and blood cultures were negative. Streptococcus group B was cultured from a vaginal smear. She had negative test results for antinuclear antibodies, anticardiolipin (IgM and IgG) antibodies and factor V Leiden. She had normal homocysteine and protein C and S levels.

An abdominal and pelvic ultrasound showed a thrombus (about 3 cm) in the right ovarian vein extending into the IVC (*figure 1*), also a moderate obstruction of the right ureter and rupture of a calyx and urinary leakage (*figure 2*). Computerised tomography (CT) confirmed the ultrasound results (*figure 3*). Findings on chest radiograph and electrocardiogram were normal.

The patient was treated with anticoagulants in the form of fraxiparine (low-molecular-weight heparin) together with the oral anticoagulant acinocumarol. Acinocumarol was continued for three months. A ten-day course of amoxycillin-clavulanic acid was also administered. She made a good recovery and was discharged from the hospital after five days. The ultrasound examination was repeated six months later and showed complete resolution of the thrombus and normalisation of the changes in the right kidney.

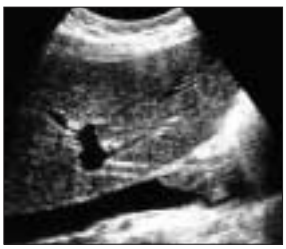

Figure 1
An abdominal and pelvic ultrasound showing thrombus in the IVC extending into the right ovarian vein

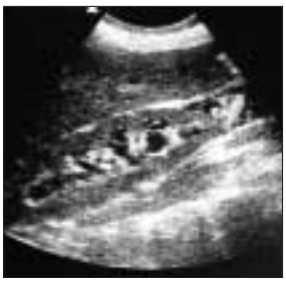

Figure 2
An abdominal ultrasound showing obstruction of the right pelvicalyceal system and rupture of calyx with urinary leakage

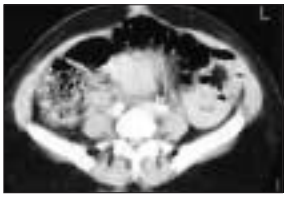

Figure 3
Computerised tomography of the abdomen showing a dilated right ureter next to a thrombosed right ovarian vein

DISCUSSION

The incidence of POVT is between 1:600 and 1:2000 deliveries.[1] Ovarian vein thrombosis has seldom been reported in nonpregnant patients.[6] POVT is a clinical entity characterised by lower abdominal or flank pain, fever and leucocytosis.[1,5] Of patients with POVT, 90% present within 10 days (1 to 17 days) after delivery.[1] The classical clinical picture is pain in the lower abdomen, and fever not responding to antibiotic treatment.[3]

A total of 80 to 90% of cases involve the right ovarian vein, while the left ovarian vein is involved in only 6%, and it is bilateral in 14% of the cases.[7]

A rare presentation of POVT is acute obstruction of the right ureter.[4,5] The obstruction of the left ureter as a presentation or complication of POVT has seldom been reported. Anatomically, the right ovarian vein crosses in front of the right ureter at the level of the L4 vertebra on its way to the inferior vena cava,[8] it is longer than the left and has multiple incompetent valves. The left ovarian vein does not cross the left ureter. Also, the left vein has retrograde blood flow, which probably prevents bacterial contamination.[8]

The most important reported aetiological factors are multiparity, puerperium, the postoperative period (e.g. caesarean section), infection (e.g. streptococcus group A or B, thrombophlebitis),[3] Crohn's disease[9] and malignant tumours.[10]

Other risk factors include systemic lupus erythematosus, antiphospholipid syndrome, presence of factor V Leiden, paroxysmal nocturnal haemoglobinuria, hyperhomocysteinaemia, protein C and S deficiency[1,2] and heparin-induced thrombocytopenia.[11] Thrombophilia screening testing in our patient turned out to be normal.

The current theory of POVT pathogenesis is based on the Virchow's triad of thrombosis, which consists of endothelial injury, stasis and hypercoagulability. Endometritis or infectious thrombophlebitis promotes endothelial injury. The most likely underlying causative factor in our patient is streptococcus group B infection of the vagina and /or the endometrium. This is a rare infection in the puerperium, but can rapidly develop into life-threatening puerperal sepsis, multiorgan infection and shock.[3]

The diagnosis of POVT can be established by ultrasound, CT scan or MRI examinations.[12-14] Kubik-Huch *et al.*[12] compared the radiological methods used in POVT and found the following sensitivities and specificities: Duplex ultrasonography (sensitivity 55.6%, specificity 41.2%), contrast-enhanced CT scan (sensitivity 77.8%, specificity 62.5%), magnetic resonant angiography (MRA) (sensitivity 100%, specificity 100%). Therefore, the MRA is recommended for the diagnosis of POVT, but because of the cost and speed, the contrast-enhanced CT scan is an accurate alternative. Ultrasound examination or CT scan is recommended

for the initial evaluation and is also a useful method for follow-up.[15] MRA can be reserved for doubtful situations. Initial ultrasound in our patient showed the thrombus in the ovarian vein, which was confirmed by CT scan. Laparoscopy can also be a useful alternative diagnostic method.[16]

POVT should be differentiated from the more common causes of lower abdominal pain in the postpartum period, most notably appendicitis, endometritis, pyelonephritis, urinary tract infection, adnexal torsion or abscess, intestinal volvulus and thrombosis of the renal veins.

The most dangerous complications of POVT are:

- extension of the thrombus into the inferior vena cava[17] and renal veins[18] or iliofemoral veins;
- pulmonary embolism (3 to 33% of the cases),[19] sometimes septic emboli with potentially fatal consequences. With the use of anticoagulants, mortality has dropped from 25% to less than 5%;[2]
- multiorgan failure;
- acute obstruction of an ureter[5] and spontaneous kidney rupture;[3]
- approximately 25% of women who present with POVT have ileus;
- increased risk of ovarian infarction.[3]

Because this infrequently reported entity carries a risk of significant morbidity and mortality if inadequately treated, any woman who presents in the postpartum period with an unexplained lower abdominal pain, fever and leucocytosis should be evaluated by ultrasound or CT scan to make or refute the diagnosis of POVT. Anticoagulants are the mainstay of treatment. However, there is no uniform agreement regarding length of anticoagulation. Broad-spectrum antibiotic treatment should be immediately initiated after collection of cultures. Group A streptococcus is very sensitive to β-lactams. An antibiotic course of 7 to 10 days is usually sufficient.[15]

Treatment modalities for an extensive degree of thrombosis, such as POVT with free-floating thrombus in the IVC or failure to respond to standard medical therapy, are described in the literature and range from placement of an IVC Greenfield filter or hysterectomy and thrombectomy to ligation of the inferior vena cava. These are usually performed in conjunction with the continued administration of anticoagulants and antibiotics.[17, 20]

There are no recommendations for prophylaxis during a subsequent pregnancy and the recurrence rate for POVT is low.[2] However, if a patient is proved to have a hypercoagulable state, then prophylaxis is advocated.

In summery, POVT should be considered in any woman in the postpartum period with unexplained lower abdominal pain, fever and leucocytosis. An obstruction of the ureter is a well-known but seldom reported complication of POVT. For the initial evaluation CT or ultrasound examination is indicated.

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CASE REPORT

Severe maternal respiratory distress due to the amniotic fluid embolism syndrome in a twin pregnancy

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ABSTRACT

A 28-year-old female with a twin pregnancy at 29 6/7 weeks who was having premature uterine contractions developed acute respiratory failure due to sudden pulmonary oedema requiring mechanical ventilation. No evidence for venous thromboembolism, pulmonary infection or myocardial infarction was found. Subsequently a mild coagulopathy and foetal distress developed. Ultrasonography revealed oligohydramnios of one of the foetuses. A Caesarean section was performed and postoperatively mother and babies had an uneventful clinical course. By exclusion of other causes, we diagnosed severe maternal acute respiratory distress due to the amniotic fluid embolism syndrome in a twin pregnancy.

INTRODUCTION

The occurrence of the amniotic fluid embolism syndrome (AFES) is a rare and often fatal obstetric complication. This condition was first described by Meyer in 1926 as reported by Clark *et al.*[1] but it was not until 1941 before it became recognised as a clinical entity after the publication by Steiner and Lushbaugh.[2] Classically, AFES is a sudden event characterised by acute respiratory failure with severe maternal hypoxaemia, cardiovascular collapse and coagulopathy.[1] It has a reported incidence varying from 1 in 8000 to 1 in 80,000 pregnancies with a maternal mortality rate of up to 61%. In the USA, this condition is the most common cause of peripartum maternal death and is responsible for roughly 10% of all maternal deaths.[1] In 70% of cases AFES occurs during labour. The occurrence of AFES in twin pregnancy is extremely rare. Öney described the first case in 1982 at 39 weeks of pregnancy during normal labour.[3] In the USA national registry analysis, another twin gestation was reported in 1995, however not described in detail.[1] Recently a third case of AFES in twin pregnancy was described during preterm uterine contractions with ruptured membranes despite tocolytic therapy.[4] We report the occurrence of AFES in a twin pregnancy at 29 6/7 weeks during preterm uterine contractions with tocolytic therapy before vaginal loss of amniotic fluid.

CASE REPORT

A 28-year-old healthy female with a twin pregnancy (gravida 2 para 1) at 29 6/7 weeks was admitted to a general hospital elsewhere with premature uterine contractions. Vaginal examination revealed a cervix dilated to 2-3 cm; no amniotic fluid loss was seen. To decrease preterm uterine contractions maximal doses of fenoterol (2 g iv) were administered and indomethacin (100 mg supp.) was added as a tocolyticum. Betamethasone (12 mg iv) was added to accelerate foetal lung maturation. The patient's medical history revealed a previous twin pregnancy, which had ended in a partus immatures at 25 6/7 weeks after two weeks of tocolytic therapy. One of the children died shortly after birth, so this time she was transferred to our university centre because of the possible need of neonatal intensive care unit (NICU) facilities.

Upon arrival the patient was fully orientated, mildly pyretic (temperature of 37.6°C), with a heart rate of 136 beats/min and blood pressure of 100/70 mmHg. Cardiotocography (CTG) revealed no signs of foetal distress and ultrasound did not show any abnormalities and revealed normal quantities of amniotic fluid around both foetuses. Fenoterol was stopped because of the tachycardia and replaced by nifedipine (60 mg-30 mg-60 mg orally) as tocolyticum. Antibiotic treatment (amoxicillin/clavulanic acid 1000 mg/100 mg qid, iv) was started to prevent intra-uterine infection, and nadroparin calcium (2850 IU od, sc) was added for venous thromboprophylaxis. Twenty-four hours after the first dose of betamethasone the patient was given a second dose. There were no signs of pre-eclampsia. She had no allergic constitution.
After three days of bed rest, the patient became acutely dyspnoeic with a respiratory rate of 30 breaths/min and bilateral rhonchi. The haemodynamic parameters remained stable. Arterial blood gas analysis, without oxygen suppletion, showed a severe hypoxaemia (pH 7.46; PaO_2 7.2 kPA; 4.0 kPA, $PaCO_2$, bicarbonate 21.7 mmol/l, BE -0.3 mmol/l, and SaO_2 90%). The chest X-ray revealed central bilateral pulmonary oedema (*figure 1*). The electrocardiogram showed a sinus tachycardia of 120 beats/min; there were no signs of right-sided heart strain or ischaemia. CTG showed both foetuses in a tachycardia (180 beats/min and 190 beats/min). Treatment was started with oxygen via nasal spectacles, antibiotic treatment was changed to erythromycin (1 g qid, iv) and ceftriaxon (2 g od, iv) to treat a possible pneumonia. Serial duplex scanning of the lower extremities did not reveal thrombosis of the femoral and popliteal veins. The patient had no skin rash. In spite of treatment with oxygen her peripheral oxygen saturation decreased (88%) and she became even more tachypnoeic (50 to 60 breaths/min).

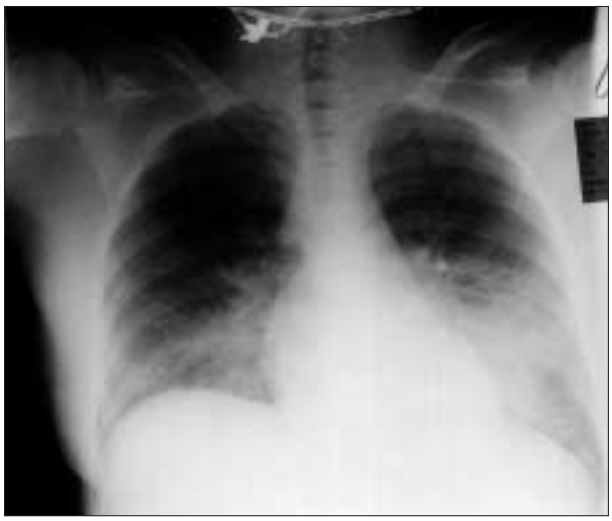

Figure 1
Acute central bilateral pulmonary oedema

The patient was transferred to the intensive care unit (ICU) for treatment of respiratory failure.
After intubation and initial alveolar recruitment she was subsequently ventilated with pressure-controlled inverse ratio ventilation (PC-IRV 34/20 cm H_2O, F_IO_2 0.6), which improved oxygen saturation to 99% within a few hours. A central venous catheter was inserted in the right internal jugular vein. Central venous pressure was 11 mmHg. Since the patient was haemodynamically stable no pulmonary artery catheter was inserted. On the third day after admission to the ICU she developed fever (38.3°C), a leucocytosis ($17*10^9$/l) and mild coagulopathy (APTT 52 sec, INR 1.43, and platelet count $175*10^9$/l). CTG then showed foetal distress and abdominal ultrasound revealed an oligohydramnion around the first foetus. Clinically the moment of rupture of the membranes had not been identified. On the suspicion of an intra-uterine infection a Caesarean section was performed at 30 5/7 weeks. She delivered twins (one male, one female) who were taken to the NICU. After that crucial intervention the patient made a quick and uneventful recovery with complete resolution of the pulmonary oedema and was extubated two days later on the fifth day of ICU admission. Extensive laboratory tests and cultures obtained from mother and infants all remained negative (*table 1*). Histology of the placenta showed no signs of chorioamnionitis. By exclusion of other causes, we made the clinical diagnosis of acute respiratory distress due to acute pulmonary oedema based upon the amniotic fluid embolism syndrome.

DISCUSSION

The differential diagnosis for severe acute respiratory failure during pregnancy includes septic shock, aspiration pneumonia, acute myocardial infarction, pulmonary embolism, placental abruption, pre-eclampsia, complication of tocolytic therapy with β-sympathomimetics as well as the amniotic fluid embolism syndrome (AFES). In 1988, a national registry for AFES cases was established in the USA. Analysis of this registry by Clark *et al.*[1] suggests that AFES is clinically, haemodynamically and haematologically undistinguishable from anaphylaxis and septic shock. AFES appears to be initiated after maternal intravascular exposure to foetal tissue. Variations in nature and severity of the clinical syndrome may be dependent on variations in antigenic exposure and in individual response. According to Green *et al.* the diagnosis of AFES is based on its clinical presentation and supportive laboratory studies.[5] The finding of squamous cells in the maternal pulmonary circulation, once considered pathognomonic, is neither specific nor sensitive for the diagnosis of AFES. Kostamovaara *et al.* showed that squamous cells can also be detected in nonpregnant patients and even in males.[4]

Table 1
Serological tests, cultures and histology obtained from mother and infants

SEROLOGY OF MOTHER	
CMV	Negative
EBV	Negative
HSV IgM	Negative
Rubella	
IgG	Positive
IgM	Negative
Mycoplasma pneumoniae	<1:40
Legionella	Negative
Lues	
VDRL	Negative
TPHA	Negative
Chlamydia	
PnIgG	Negative
PnIgA	Negative
CULTURES FROM MOTHER	
Multiple blood cultures	No micro-organism
Sputum cultures	No micro-organism
Vagina culture	*Candida albicans* ++
β-haemolytic streptococcus	Negative
HISTOLOGY OF THE PLACENTA	
No signs of chorioamnionitis	
CULTURES OF INFANTS	
Blood cultures	Negative
Skin cultures	Negative

CMV = cytomegalovirus, EBV = Epstein-Barr virus, HSV = herpes simplex virus, Ig = immunoglobulin, VDRL = venereal disease research laboratories, TPHA = treponema pallidum haemagglutination

A clinically or subclinically consumptive coagulopathy of unknown aetiology almost invariably accompanies AFES.[6] There is no diagnostic test for AFES. The diagnosis is therefore made by exclusion of other causes.[7]
In any individual patient, the haemodynamic, pulmonary or haematological disturbances can dominate the presentation or be entirely absent, which makes the clinical presentation very variable.[8] One factor that is consistently related to the occurrence of AFES is a tear in the foetal membranes. The occurrence of AFES has been described during first trimester suction curettage, a time when the total volume of amniotic fluid is relatively low. Apparently, AFES can result from simple exposure to even small volumes of foetal tissue. According to the USA national registry, five patients had the onset of the syndrome with intact membranes. These findings suggest that certain conditions may permit exposure of foetal tissue to the maternal vasculature and may increase the risk of AFES.
In our patient the diagnosis of AFES was made after exclusion of other causes. Sepsis or septic shock was not supported by any positive cultures or serological parameters. Pneumonia was not supported by positive cultures and less probable with the rapid resolution of pulmonary oedema and the subsequent absence of infiltrates. Acute myocardial infarction was not supported by elevated enzymes or typical electrocardiographic disturbances. Deep venous thrombosis was made unlikely by the absence of thrombosis by serial duplex scanning of both lower extremities. A normal central venous pressure made pulmonary embolism less probable especially during concomitant high ventilation pressures. Tocolytic therapy with fenoterol was an unlikely cause because the elimination half-life of fenoterol is three hours and the administration of the drug was stopped more than 48 hours before onset of the acute respiratory failure. Anaphylaxis was clinically highly unlikely. Finally, there were no signs of pre-eclampsia or placental abruption.
We believe this case represents one of the atypical presentations of AFES in which severe hypoxaemia was the presenting symptom followed by a mild consumptive coagulopathy. Our patient did not develop haemodynamic disturbances. Respiratory distress is found to be the first symptom in 51% of patients, hypotension in 27%, and coagulopathy in 12%.[6] The acute development of bilateral pulmonary oedema has recently been recognised to follow a biphasic model. If even a small volume of amniotic fluid enters the maternal circulation, the initial haemodynamic response consists of acute pulmonary hypertension and vasospasm complicated by severe hypoxaemia and right-sided heart failure, followed by a second phase of more sustained left ventricular failure.[6] The first phase might be due to the introduction of a potent vasoconstrictor arising from the amniotic fluid, and the second phase is thought to be due to a direct myocardial depressant also from the amniotic fluid. The responsible substance might be endothelin, which has been found in high concentrations in the amniotic fluid.[6] In conclusion, AFES should be considered as a differential diagnosis in pregnant patients or immediate postpartum patients with acute profound haemodynamic, pulmonary or haematological disturbances. Physicians should maintain a high index of suspicion. The therapy for AFES is nonspecific and directed towards ventilatory and circulatory support and correction of the coagulopathy.
The occurrence of AFES in twin pregnancy is very rare.

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ANSWER TO PHOTO QUIZ (ON PAGE 330)
HYPERTENSION IN NEUROFIBROMATOSIS

The differential diagnosis of the combination neurofibromatosis and hypertension is in order of frequency:
1. Renal artery stenosis due to a neurofibroma that compresses the renal artery, sometimes even bilaterally.
2. Pheochromocytoma coexisting with neurofibromatosis. The incidence of pheochromocytoma in patients with neurofibromatosis is about 1%, thus much higher than in patients with hypertension without neurofibromatosis.
3. 'Coarctation' of the aorta due to neurofibromas in the vessel wall, narrowing the aorta.
4. Renal artery aneurysm occurring with neurofibromatosis. Such a lesion can cause a functional stenosis based on the whirls of the blood stream or a mechanical stenosis by suppressing the renal artery itself or a side branch of the renal artery.

Our patient had already had two years attacks of palpitations, excess sweating and headache, and laboratory investigations revealed increased concentrations of adrenaline and noradrenaline. On the arteriogram of the renal artery a pathological structure richly vascularised on top of the left kidney was seen (see *figure 2*).
The patient was prepared for surgery with α- and β-adrenergic blockade and indeed the tumour appeared to be a pheochromocytoma. After the operation the attacks disappeared but the blood pressure remained too high, though clearly lower than preoperatively. Careful reinspection of the arteriographic picture suggested that there was also a renal artery stenosis and a second operation was performed. A neurofibroma was compressing the renal artery and after removal the blood pressure normalised (120-135/80-85 mmHg).

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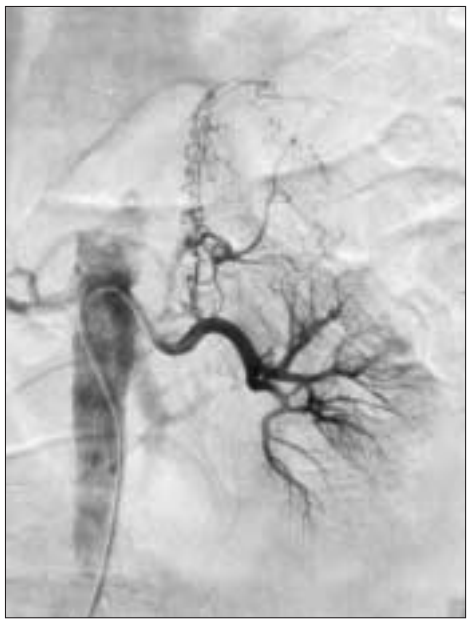

Figure 2

A colour version of this photo quiz can be found on our website www.njmonline.nl.

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The Netherlands Journal of Medicine publishes papers in all relevant fields of internal medicine. In addition to reports of original clinical and experimental studies, reviews on topics of interest or importance, case reports, book reviews and letters to the Editor are welcomed.

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Language
The language of the Journal is English. English idiom and spelling is used in accordance with the Oxford dictionary. Thus: Centre and not Center, Tumour and not Tumor, Haematology and not Hematology.

Preparation of manuscripts
Type all pages with double spacing and wide margins on one side of the paper. To facilitate the reviewing process number the pages; also we would appreciate seeing the line numbers in the margin (Word: page set-up - margins - layout - line numbers). Divide the manuscript into the following sections: Title page, Abstract, Introduction, Materials and methods, Results, Discussion, Acknowledgements, References, Tables and Figures with Legends.

A *Covering letter* should accompany the manuscript, identifying the person (with the address, telephone and telex numbers, and e-mail address) responsible for negotiations concerning the manuscript: the letter should make it clear that the final manuscript has been seen and approved by all authors. Conflicts of interest, any commercial affiliations, consultations, stock or equity interests should be specified. In the letter 1-3 sentences should be dedicated to what this study adds. All authors should sign the letter.

The *Title page* should include authors' names, degrees, academic addresses, address for correspondence including telephone, fax and e-mail, and grant support. Also the contribution of each author should be specified.
The title should be informative and not exceed 90 characters, including spaces. Avoid use of extraneous words such as 'study', 'investigation' as well as priority claims (new, novel, first). Give a running title of less than 50 characters. If data from the manuscript have been presented at a meeting, list the name, date and location of the meeting and reference and previously published abstracts in the bibliography. Give a word count (including references, excluding tables and legends) at the bottom of this page.

Abbreviations: Measurements should be abbreviated according to SI units. All other abbreviations or acronyms should be defined on the first appearance in the text. Use a capital letter for proprietary names of substances and materials. At first mention of a chemical substance, use the correct chemical designation as well as the generic name.

The *Abstract*, not exceeding 200 words, should be written in a structured manner and with particular care, since this will be the only part of the article studied by some readers. In original articles, the abstract should consist of four paragraphs, labelled Background, Methods, Results, and Conclusions. They should briefly describe the problem being addressed in the study, how the study was performed and which measurements were carried out, the most relevant results, and what the authors conclude from the results.

The *Introduction* should be brief and set out the purposes for which the study has been performed.

The *Materials and methods* should be sufficiently detailed so that readers and reviewers can understand precisely what has been done without studying the references directly. The description may be abbreviated when well-accepted techniques are used.

The *Results* should be presented precisely without discussion.

The *Discussion* should directly relate to the study being reported. Do not include a general review of the topic, but discuss the pertinent literature.

Acknowledgement: All finding sources should be credited here. Also a statement of conflicts of interest should be put here.

References should be numbered consecutively (in square brackets) as they appear in the text. Type the reference list with double spacing on a separate sheet. References should