From pioneering to implementing automated blood pressure measurement in clinical practice: Thomas Pickering's legacy

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Thomas G. Pickering spent most of his scientific career in carrying out research on clinical hypertension and blood pressure (BP) measurement. In our review of Pickering's seminal work, we first focused on white-coat hypertension and masked hypertension, two terms that he had introduced. Next, we highlighted the early publications of Pickering on diurnal BP variability and on the clinical application of self-measured BP. Pickering's work inspired many investigators worldwide and constituted a solid basis for further research. Pickering's original ideas led to algorithms for risk stratification involving white-coat hypertension and masked hypertension, diurnal BP variability, and self-measured BP. Recent studies validated Pickering's observations in terms of cardiovascular outcome and bridged the path from concept to application in clinical practice. *Blood Press Monit* 15:72–81 © 2010 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Introduction

Thomas G. Pickering spent his scientific career in carrying out research on behavioral cardiovascular medicine, clinical hypertension, and blood pressure (BP) measurement. His work inspired many investigators worldwide and stimulated research on BP measurement, particularly on the clinical application of 24-h ambulatory BP monitoring (ABPM) and the self-measurement of BP at home.

In 2002, Thomas G. Pickering wrote 'The addition of ABPM to conventional clinic measurements for defining BP status in clinical practice has added a new complexity to the process, because the separation of normotension and hypertension can be assessed independently by each of the two methods' [1]. The two groups of patients that arise from this classification and require special attention are individuals with white-coat hypertension and those with masked hypertension. Other focal points in Pickering's work were BP variability [2] and the assessment of BP by self-measurement [3–5].

White-coat hypertension

First studies on white-coat hypertension

In his study, which was published in *Journal Of The American Medical Association* in 1988 [6], Thomas Pickering

coined the term 'white-coat hypertension' to describe patients whose BP was elevated in the doctor's office, but not during daytime ambulatory BP measurement. For the first time, he assessed the prevalence of white-coat hypertension among 292 borderline hypertensive patients and 42 patients with established hypertension. He applied the 90th percentile of the distribution of awake ambulatory BP in healthy normotensive volunteers as a cutoff point. Using this threshold (134/90 mmHg), 21% of the patients with borderline hypertension and 5% of those with established hypertension had white-coat hypertension. Female sex, short duration of hypertension, and young age were factors associated with white-coat hypertension. Pickering predicted that by combining conventional measurement with ambulatory BP measurement, it would become possible to identify patients at a low risk, in whom the initiation of medical treatment might be questionable, and instead, a longer period of observation might be appropriate [6].

Mechanisms underlying white-coat hypertension

In 1983, Mancia *et al.* [7] reported that the doctor's arrival at the bedside induced an instantaneous rise in both systolic and diastolic BP [7]. White-coat hypertension is an alert reaction to the medical environment and to the

observer, who measures the BP. Thomas Pickering's group assessed office BP, ambulatory BP, and anxiety scores on three separate occasions, 1 month apart in 238 patients. They found that the white-coat effect (WCE) was a conditioned response to the medical environment and the physician's presence, rather than a function of the patient's trait of anxiety (Fig. 1) [8]. As the largest WCE occurred with the physician's measurement, Pickering's group [8], and later Myers *et al.* [9], proposed that WCE could be minimized by the use of automated BP devices for the measurement of BP in office settings in the absence of an observer. Pickering's group also reported that in a majority of people, worksite BP is consistently higher than home BP [10]. However, the WCE does not reflect generalized hyperactivity, because of the low correlation between the increment in BP the clinic and at work, both relative to the home BP [10].

From distributional to outcome-driven thresholds to diagnose white-coat hypertension

Inspired by Thomas Pickering's work, an international consortium established the International Database on

Ambulatory Blood Pressure Monitoring and published in 1994 a proposal for operational thresholds to define white-coat hypertension in clinical practice [11]. The database included 7069 recordings contributed by 24 clinical research groups. As few prospective outcome data in relation to the ambulatory BP were available, in 1994 [12–14], the consortium applied the 95th percentile of the ambulatory BP distribution in volunteers who were normotensive on conventional BP measurement. The proposed systolic/diastolic thresholds were 133/82, 140/88, and 125/76 mmHg for the 24-h, daytime, and night-time BP, respectively [11]. Similar to Thomas Pickering's publication of 1988 [6], the prevalence of white-coat hypertension in this database was 20–30%; its probability was greater in women, and it increased with age, but decreased if the patients had higher office BP, and if the diagnosis of hypertension was made after multiple office visits and multiple office BP assessments, or both.

Over the next decade, several prospective outcome studies provided evidence validating the thresholds for

Fig. 1

Self-rated anxiety score before (pre) and after (post) blood pressure (BP) measurement in different conditions. On day 1, the research assistant (RA) measured BP outside the medical environment using a mercury sphygmomanometer (SPH). On day 2, the RA measured BP in the absence of a physician (MD) by manually triggering a device for ambulatory BP measurement (manually triggered device, MTD) first in the waiting room and later in the examination room before and after the MD measured BP using a SPH. Anxiety scores were obtained in normotensive participants (NT) and in patients with white-coat hypertension (WCH), masked hypertension (MH), and sustained hypertension (SH). Reproduced with permission [4].

the diagnosis of white-coat hypertension in terms of mortality and morbidity. In the first step, several studies showed that ambulatory BP was more predictive of an outcome than the BP obtained on conventional measurement [15–19]. In the Systolic Hypertension in Europe Trial (Syst-Eur) [19], to avoid problems with definitions and nomenclature, the WCE was analyzed as a continuous variable. The risk conferred by any level of conventional systolic BP at entry, declined by nearly one-fifth for every 10 mmHg increase in the WCE.

The International Database on Ambulatory blood pressure monitoring in relation to Cardiovascular Outcomes (IDACO) consortium assessed the risk associated with white-coat hypertension compared with normotension and sustained hypertension [19]. This meta-analysis of individual patient data included over 7000 people randomly recruited from four populations, and covered approximately 10 years of follow-up with more than 800 new cardiovascular endpoints. In multivariable-adjusted categorical analyses with normotension as the referent group (conventional BP < 140/90 mmHg and daytime ambulatory BP < 135/85 mmHg), white-coat hypertensive patients (conventional BP $\geq$ 140/90 mmHg and daytime ambulatory BP < 135/85 mmHg) had a slightly increased risk, but none of the hazard ratios reached significance ($0.63 \geq P \geq 0.09$; Fig. 2). These findings remained consistent if the Cox models were additionally adjusted for the daytime BP or when a lower cutoff (< 130/80 mmHg) was used for the daytime BP (Fig. 2) [20]. The same consortium reported outcome-driven thresholds for the ambulatory BP [21]. Approximate thresholds for an optimal level with the lowest cardiovascular risk were 115/75, 120/80, and 100/65 mmHg for the 24-h, daytime, and night-time BP, respectively. Rounded thresholds for normal ambulatory BP were 125/75, 130/85, and 110/70 mmHg, respectively, and those for ambulatory hypertension were 130/80, 140/85, and 120/70 mmHg, respectively. These findings suggest that to define white-coat hypertension, lower thresholds might have to be applied than those currently recommended in the guidelines.

Management of white-coat hypertension based on ambulatory monitoring

The ambulatory BP monitoring and treatment of hypertension (APTH) trial [22] showed that adjustment of antihypertensive treatment based on ABPM instead of conventional sphygmomanometry, may lead to less intensive drug treatment with preservation of BP control, general well-being, and inhibition of left ventricular enlargement. Antihypertensive drug treatment may be postponed in 25% of the hypertensive patients and multiple-drug treatment may be avoided in 15% of the hypertensive patients. The APTH results [22] do not imply that patients with white-coat hypertension should be left untreated. However, if no cardiovascular complications are present at diagnosis, treatment could be

limited to further follow-up and the implementation of cardiovascular hygienic measures, such as regular exercise, reduction of excessive alcohol and sodium intake, and weight reduction. Initial treatment should also account for other cardiovascular risk factors, such as smoking, hypercholesterolemia, and diabetes mellitus. Whether patients with white-coat hypertension are at a higher risk of developing sustained hypertension remains debatable, although recent evidence supports this contention [23].

Masked hypertension

First reports on masked hypertension

In 2002, Thomas Pickering introduced the term 'masked hypertension' [1] to describe what other researchers called reverse white-coat hypertension [24,25], an elevated ambulatory BP in the presence of a normal office BP. The nomenclature proposed by Pickering [1] emphasizes that patients with masked hypertension are genuinely hypertensive, because of the superiority of ambulatory BP over office BP in predicting cardiovascular events. In this regard, Pickering showed in a cross-sectional study that patients with masked hypertension have more extensive target-organ damage (higher prevalence of carotid plaque and greater left ventricular mass) than true normotensive volunteers (Table 1) [26]. On the basis of this observation, Pickering suggested that masked hypertension should be taken seriously and excluded by ABPM in patients who have a normal clinic BP on repeated office visits, especially among patients with a family history of hypertension, or those with comorbid conditions, such as diabetes mellitus [1]. He did not propose the application of ABPM, to screen for masked hypertension at the population level [1].

Prognosis of masked hypertension: moving from cross-sectional to prospective studies

Pickering assessed the long-term prognosis of individuals with masked hypertension in an international database [4,27], which included data from his own group ($n = 1296$, [27]), the Ohasama population study ($n = 1277$, [27]), the Jichi Medical School-ABPM study ($n = 762$, [27]), and the Progetto Ipertensione Umbria Monitoraggio Ambulatoriale (PIUMA; $n = 2620$, [27]). In this heterogeneous database [4], 1272 participants had a normal clinic BP (< 140/90 mmHg), of whom 376 had a high daytime ambulatory BP (> 135/85 mmHg), whereas other individuals were normotensive by both criteria. The hazard ratio of cardiovascular events in patients with masked hypertension, relative to truly normotensive volunteers was 2.26 ($P < 0.0009$) [4], thus establishing, in a longitudinal cohort, the higher cardiovascular risk portended by masked hypertension over normotensive volunteers. This finding was later confirmed by the study conducted by the IDACO consortium, which assessed the risk of masked hypertension in 7030 participants randomly

Fig. 2

Hazard ratios for cardiovascular events according to the cross-classification of conventional and daytime ambulatory blood pressures. The analyses were based on (a) lower ($\geq 130/80$ mmHg) or (b) higher ($\geq 135/85$ mmHg) cutoff limits for ambulatory hypertension and were adjusted for cohort, sex, age, body mass index, serum cholesterol, smoking and drinking, history of cardiovascular disease, diabetes mellitus, and antihypertensive drug treatment. Squares are proportional to the number of events for each group. Horizontal lines denote the 95% confidence interval. MH, masked hypertension; NT, normotension; SH, sustained hypertension; WCH, white-coat hypertension. NT is the reference group (* $P < 0.01$; $^{\dagger}P < 0.001$). Reproduced with permission [20].

Table 1 Left ventricular and carotid arterial structure and function in study patients

Measurement	Patients with true normotension (n=234)	Patients with masked hypertension (n=61)	Patients with true hypertension (n=64)
Left ventricle			
Interventricular septal thickness (cm)	0.87 ± 0.11	0.96 ± 0.11***	0.97 ± 0.12***
Left ventricular internal dimension (cm)	4.80 ± 0.44	5.00 ± 0.44**	4.94 ± 0.50*
Posterior wall thickness (cm)	0.79 ± 0.11	0.90 ± 0.11***	0.92 ± 0.11***
Left ventricular mass (g)	134 ± 33	169 ± 40***	166 ± 43***
Left ventricular mass index (g/m ²)	73 ± 14	86 ± 16***	90 ± 18***
Left ventricular mass/height ^{2.7}	32 ± 6	38 ± 8***	40 ± 9***
Prevalence of LVH [n (%)]	1 (0.4)	4 (7)**	10 (16)**
Relative wall thickness	0.33 ± 0.05	0.36 ± 0.04***	0.37 ± 0.05***
Carotid artery			
Wall thickness (mm)	0.69 ± 0.16	0.79 ± 0.18***	0.85 ± 0.19***
Plaque [n (%)]	35 (15)	17 (28)*	17 (27)*

Values are mean ± SD or number of participants (%). LVH indicates left ventricular hypertrophy. Significance of the difference with the normotensive group: * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$. Reproduced with permission [26].

recruited from four populations [20]. In multivariable-adjusted continuous analyses, with true normotension as the reference, the hazard ratios associated with masked hypertension and true hypertension were 1.62 (1.35–1.96; $P < 0.0001$) and 1.80 (1.59–2.03; $P < 0.0001$), respectively (Fig. 2).

Similarly, Lurbe *et al.* [28] extended Pickering's observation of the higher risk of masked hypertension to adolescents and children. In a nested case-control study of 592 youths aged between 6 and 18 years, they compared echocardiographic left ventricular mass among children with persistent masked hypertension and normotensive controls. They found that participants with masked hypertension had a higher left ventricular mass index and included a higher percentage with a left ventricular mass index above the 95th percentile in this pediatric population, as compared with normotensive controls [28]. Thus, even in children and adolescents, masked hypertension carries a high risk, being a precursor of sustained hypertension and left ventricular hypertrophy [28].

Diurnal blood pressure variability

Seminal studies on diurnal blood pressure variability

In a seminal study of ABPM, Pickering compared the 24-h BP in normal individuals, patients with borderline hypertension, and those with established hypertension [2]. One of the most striking findings of this study was that the three groups of individuals generally showed similar and parallel changes of their BP during their daily activities. All individuals had their highest BP readings during work or at the clinic, and the lowest readings during sleep (Fig. 3). The noted nocturnal fall in BP during sleep is among the components of BP variability that have received immense attention from both physiologists and clinicians. In 1988, O'Brien *et al.* [29] reported for the first time that an abnormal circadian BP profile with decreased night-time dipping might be associated with a higher risk of stroke. Subsequently, numerous studies have corroborated this assertion [30].

Fig. 3

Average values of systolic blood pressure taken under different circumstances with an ambulatory blood pressure recorder in normotensive participants and in patients with borderline hypertension (conventionally measured diastolic blood pressure 90–95 mmHg) and established hypertension (> 95 mmHg). Reproduced with permission [2].

Moving from concept to mathematical and outcome-driven criteria for nocturnal dipping

In an international database established in the 1990s [31], the night-to-day BP ratio depended less on the BP level than the nocturnal fall in BP did. The ratio may, therefore, be preferable for characterizing dippers as opposed to nondippers. The mathematical definition of nondipping, that is, a night-to-day BP ratio equal to or higher than unity (100%), corresponded nearly with the 95th percentiles of the ratios in normotensive volunteers. The application of this criterion to both systolic and diastolic BP resulted in an overall prevalence of nondipping of 3.2%, with a distinct age-related increase [31].

The IDACO consortium [32] recently reported risk estimates independently associated with the daytime and night-time BP in 7458 participants enrolled in prospective population studies in six countries. Median follow-up

was 9.6 years. Adjusted for daytime BP, the night-time BP predicted total ($n = 983$; $P < 0.0001$), cardiovascular ($n = 387$; $P < 0.01$), and noncardiovascular ($n = 560$; $P < 0.001$) mortality. Conversely, adjusted for night-time BP, the daytime BP predicted only noncardiovascular mortality ($P < 0.05$), with lower BP levels being associated with increased risk. Both daytime and night-time BPs consistently predicted all cardiovascular events ($n = 943$; $P < 0.05$) and stroke ($n = 420$; $P < 0.01$). Adjusted for night-time BP, the daytime BP lost prognostic significance only for cardiac events ($n = 525$; $P \geq 0.07$). Adjusted for the 24-h BP, the night-to-day BP ratio predicted mortality, but not fatal combined with nonfatal events. Thus, in the IDACO database [32], the predictive accuracy of daytime and night-time BP and the night-to-day BP ratio depended on the disease outcome under study, and differed for fatal outcomes compared with the composite of fatal and nonfatal diseases (Fig. 4). For fatal endpoints, night-time BP performed better than daytime BP, and the night-to-day BP ratio predicted mortality. By contrast, for fatal combined with nonfatal outcomes, the daytime BP performed equally well as the night-time BP and the night-to-day BP ratio lost its prognostic accuracy. Thus, the available evidence supports the concept that the ambulatory BP should be recorded over the entire day, as both the night-time and daytime BP levels carry prognostic information. The 24-h BP levels rather than the dipping pattern should continue to inform clinical decisions [32].

The morning surge in blood pressure

Thomas Pickering mentored several young Japanese investigators, who have contributed immensely to the

research in ABPM. Examples of his tuition are the studies dealing with the morning surge in BP, that is, the rise in BP on wake up. Several studies under his supervision showed that it is a predictor of cardiovascular complications. For instance, Japanese hypertensive patients with a mean age of 72 years had a higher risk of multiple brain infarcts and stroke, if the morning surge in systolic BP was above the 90th percentile [33]. Wizner *et al.* [34] assessed the short-term and long-term repeatability of the morning surge, using continuous definitions and previously published thresholds. The BP changes in the morning were poorly reproducible, irrespective of whether they were analyzed as a continuous or categorical variable. Nevertheless, prospective outcome studies confirmed that the morning surge in BP is a predictor, albeit weak, of the outcome [33].

The IDACO consortium studied the prognostic significance of the morning BP surge in 5645 participants randomly recruited from eight countries [35]. The sleep-trough and the preawakening morning surge were the differences of the morning BP with the lowest night-time BP and the preawakening BP, respectively. Multivariable-adjusted hazard ratios were computed, comparing the risk in ethnic-specific and sex-specific deciles of the morning surge relative to the average risk in the whole study population. During follow-up (median, 11.4 years), 785 deaths and 611 fatal and nonfatal cardiovascular events occurred. While accounting for covariables and the night-to-day ratio of systolic pressure, the hazard ratio of all-cause mortality was 1.32 (95% confidence interval, 1.09–1.59; $P = 0.004$) in the top decile of the systolic sleep-trough morning surge (≥ 37.0 mmHg). For cardio-

Fig. 4

Kaplan-Meier survival function estimates for total mortality (a) and for all cardiovascular (CV) events (b) by category of the night-to-day ratio of systolic blood pressure. P values are for trend across the four categories. Incidence was adjusted for cohort, sex, age, body mass index, smoking and drinking, serum total cholesterol, history of cardiovascular disease, diabetes mellitus, and antihypertensive drug treatment. Reproduced with permission [32].

vascular and noncardiovascular deaths, these hazard ratios were 1.18 (0.87–1.61; $P=0.30$) and 1.42 (1.11–1.80; $P=0.005$), respectively. For all cardiovascular, cardiac, coronary and cerebrovascular events, the hazard ratios in the top decile of the systolic sleep-trough morning surge were 1.30 (1.06–1.60; $P=0.01$), 1.52 (1.15–2.00; $P=0.004$), 1.45 (1.04–2.03; $P=0.03$), and 0.95 (0.68–1.32; $P=0.74$), respectively [35]. Analysis of the preawakening systolic morning surge and diastolic morning surge generated consistent results. Thus, a morning surge above the 90th percentile significantly and independently predicted cardiovascular outcome and might contribute to risk stratification by ABPM [35].

Self-measurement of blood pressure

Self-measurement as an alternative to ambulatory monitoring

In 1971, investigators from Leuven promoted the use of BP self-measurement at home for clinical research [36]. The development of cheap and properly validated devices for BP self-measurement, over the past 20 years, has made this technique available for clinical application. BP self-monitoring offers several well-recognized advantages over the more complex approach of ambulatory monitoring [37,38]. The greater number of readings and the absence of the WCE contribute to a better diagnostic accuracy, compared with conventional sphygmomanometry [39,40]. If automated devices are used, self-recorded BP values are free of observer bias. Moreover, self-measurement of BP increases adherence to antihypertensive treatment [41] and allows reducing the number of clinic visits required for the diagnosis and treatment of hypertension [42].

Thomas Pickering repeatedly underlined the importance of the self-monitoring of BP at home [3–5]. He pointed out that physicians must accept the fact that BP measurement could no longer be restricted to the idiosyncratic environment of the physician's office [3]. In 1984,

Pickering's group compared BP measurements taken in the clinic by physicians and by the patient at home with 24-h ambulatory measurements [43]. Home BP readings were consistently lower than clinic measurements, and correlated more closely with the 24-h ambulatory BP level than the clinic readings (Fig. 5) [43]. Pickering was instrumental in the development of practice guidelines for the use of home BP monitoring in clinical practice through the American Society of Hypertension, the European Society of Hypertension, and the American Heart Association [5,44,45].

Mathematical and outcome-driven thresholds for the self-measured blood pressure

In an attempt to define diagnostic thresholds for the self-measured BP, we performed two meta-analyses, in collaboration with a large number of researchers [46,47], which were based on aggregate data extracted from published articles [46] and on individual patient data that were made available to the International Database of Self-Recorded Blood Pressures, respectively [47].

In 1998, we reviewed 17 studies including a total of 5422 participants [46]. Within each study, we computed an operational threshold for the self-measured BP separating normotension from hypertension either by the mean + 2 standard deviations or by the 95th percentile of the self-recorded BP in participants who were normotensive according to their office BP. For the sake of comparability with the contemporary literature, we also extracted the thresholds derived by the regression approach [48] or the percentile method [49,50], from published studies. The former consists of calculating the regression line between the self-recorded BP and the clinic BP in individual patients to estimate the self-recorded BP that corresponds with a clinic BP of 140 mmHg systolic or 90 mmHg diastolic. The percentile method first involves the calculation of the percentile of the clinic BP that corresponds to 140 mmHg systolic or 90 mmHg diastolic,

Fig. 5

(a) Office diastolic blood pressure vs. average 24-h diastolic blood pressure recordings; (b) self-measured diastolic blood pressure at home vs. average 24-h diastolic blood pressure recordings. Lines of identity have been drawn. Reproduced with permission [43].

Fig. 6

Mean systolic and diastolic blood pressures measured at physician's office, at the patient's home, and by daytime ambulatory monitoring. Error bars indicate SEs. *P* values are for differences between patients randomized to treatment based on blood pressure measurement at the physician's office vs. at home. Significance of the between-group difference: **P* ≤ 0.05; †*P* ≤ 0.01; ‡*P* ≤ 0.001. HBP, home blood pressure; OBP, office blood pressure. Reproduced with permission [51].

and later the determination of the self-recorded BP that ranks at the same percentile value [46]. The reference values for the self-recorded systolic/diastolic BP as derived from the mean + 2 standard deviations (137/89 mmHg) and the 95th percentile (135/86 mmHg) of the distribution in normotensive volunteers were concordant within 2 mmHg systolic and 3 mmHg diastolic. The cutoff points derived using the regression and percentile methods were considerably lower, 129/84 and 125/79 mmHg, respectively [46].

Thirteen research groups contributed individual data of 4668 untreated participants to the International Database [47], of which 2401 were normotensive on office measurement. The mean self-recorded BP in normotensive participants averaged 115.4 mmHg systolic and 70.7 mmHg diastolic. The 95th percentiles of their self-recorded BPs were 136 mmHg systolic and 86 mmHg diastolic in the morning, 139 and 86 mmHg in the evening, and 137 and 85 mmHg over the whole day. Of 1773 patients with definite systolic hypertension on office measurement, 16% had a self-measured systolic BP below 137 mmHg (the 95th percentile of the self-measured systolic pressure in normotensive participants). Similarly, 25% of those with definite diastolic hypertension had a self-measured diastolic BP below 85 mmHg (the 95th percentile of the self-measured diastolic pressure in normotensive participants). The probability that participants with definite hypertension had a self-measured BP below these thresholds (white-coat hypertension) was 34% (diastolic) to 62% (systolic) greater in women than in men. It was two-to-three-folds greater if fewer than three

office BP readings had been averaged to diagnose hypertension, and it increased by 50% (diastolic) to 126% (systolic) if the self-measured BP had been measured on more than 3 days as opposed to a fewer number of days. In contrast, for every 10-mmHg increment in the systolic office BP, the probability of isolated office systolic hypertension decreased by 35%; for every 5-mmHg increment in the diastolic office BP, the probability of isolated office diastolic hypertension decreased by 36%. Finally, the probability of isolated office systolic hypertension decreased by 31% for every 10-year increment in age [47].

Management of hypertension based on self-measurement

In the Treatment of hypertension based on Home or Office blood Pressure (THOP) trial [51], antihypertensive drug treatment was adjusted in a stepwise manner based on either the self-measured diastolic BP at home (an average of six measurements each day, during 1 week; 203 patients) or the average of three sitting diastolic readings at the doctor's office (197 patients). If the diastolic BP guiding treatment was above (> 89 mmHg), at (80–89 mmHg), or below (< 80 mmHg) the target, one physician blinded to the patients' randomization, intensified antihypertensive treatment, left it unchanged or reduced it, respectively.

The target BP was the same in the two treatment groups. At the end of the study (median follow-up, 350 days), more patients who were randomized to self-measurement had stopped antihypertensive treatment (25.6 vs. 11.3%; *P* = 0.14). The final office, home, and 24-h ambulatory BPs were higher (*P* < 0.001) in patients randomized to

self-measurement than in those treated according to the office BP. The baseline-adjusted systolic/diastolic differences between these two groups averaged: office, 6.8/3.5 mmHg; home, 4.9/2.9 mmHg; and 24-h ambulatory, 4.9/2.9 mmHg, respectively (Fig. 6). Left ventricular mass and reported symptoms were similar in the two groups [51]. The THOP trial [51] confirmed that the cutoff limit for the diastolic BP should be lower for home than office measurement.

In the randomized Home versus office blood pressure MEasurement: Reduction of Unnecessary treatment study (HOMERUS) [52,53], the office BP and the self-measured BP guided antihypertensive drug treatment in the control and experimental group, respectively. In contrast to the THOP trial [51], HOMERUS patients randomized to office BP measurement, did not record their BP at home [52]. The patients underwent ABPM at entry and at closeout. By using a standardized treatment schedule, the investigators had to reach in their patients the target BP levels of 120–139 mmHg systolic and 80–89 mmHg diastolic. This goal was similar in both treatment groups [53]. A blinded physician at the coordinating center took the treatment decisions. The stated hypothesis [52] was that at the end of the 1-year follow-up period, patients in both groups would have the same BP, at the expense of more medication in the office BP group.

The patients randomized to self-measurement ($n = 216$) used less medication than those ($n = 214$) allocated to office BP measurement (1.47 vs. 2.48 drug steps; $P < 0.001$) with lower costs (\$3222 vs. \$4420 per 100 patients per month; $P < 0.001$), but without significant differences in systolic and diastolic BP in office measurement (1.6/1.0 mmHg; $P = 0.25/0.20$), in changes in left ventricular mass index (-6.5 vs. -5.6 g/m²; $P = 0.72$), or in median urinary microalbumin excretion (-1.7 vs. -1.5 mg/24 h; $P = 0.87$). Nevertheless, the 24-h ambulatory BP was higher (125.9/77.2 vs. 123.8/76.1 mmHg; $P < 0.05/0.05$) in the self-measurement than the office group [53].

Perspectives

We showed that Pickering's work lies at the heart of many subsequent studies on white-coat hypertension and masked hypertension, diurnal BP variability, and the use of the self-measured BP. His concepts have now been validated in terms of cardiovascular outcomes and are routinely being used in day-to-day clinical practice. This is by no means the end of a fascinating stream of research. For instance, randomized clinical trials should test the hypothesis that reacting immediately to self-measured BP by means of telemedicine or that restoring the diurnal BP profile might be beneficial in terms of the prevention of cardiovascular morbidity and mortality. In this respect, Thomas G. Pickering's premature death might not be the end of an era, but might provide the motivation to continue his work, in the interest of many patients.

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