Original paper

Inter-arm Blood Pressure Difference in Type 2 Diabetic Patients and Ambulatory Blood Pressure Monitoring :A Clinical Dilemma

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Abstract

Background: Frequently coexistent condition in type 2 diabetes mellitus is hypertension and vice versa. Measurement of blood pressure by ambulatory blood pressure monitoring is superior to ordinary blood pressure . Blood pressure disparity reflects vascular diseases which diabetic patients liable for. Inconsistency in selecting the proper arm for blood pressure measurement may create a clinical dilemma in the presence of systolic and/or diastolic disparity.

Aim :We tried in this study to set proper steps in choosing the suitable arm for ambulatory blood pressure monitoring cuff fitting.

Material and Methods :Consecutive 140 type 2 diabetes mellitus patients aged 29 years and elder were examined by sequential ordinary blood pressure and simultaneous dual ambulatory blood pressure monitoring.

Results: Systolic disparity grade I was dominant (75.7%) as well as diastolic disparity grade I (86.4%). The mean systolic and diastolic blood pressure in the dominant arm was higher than that in the non-dominant arm with significant pressure differences (<0.001).Age and duration of diabetes had positive impacts on systolic and diastolic disparities while gender and Hemoglobin A1C had no impacts. Systolic and diastolic blood pressures were significantly different in both arms when studied over day-time, night-time, and 24-hours ambulatory monitoring. Systolic and diastolic differences in the dominant arm and the non-dominant arm had been shown to have significant mean differences with the mean ambulatory day-time blood pressure.

Discussion: Sequential method is an accepted modality and the arm with the higher systolic and/or diastolic blood pressure is the suitable arm for ambulatory monitoring and generally mirroring OBP.

Key words: type 2 diabetes mellitus, sequential office blood pressure, ambulatory blood pressure monitoring, systolic inter-arm blood pressure difference.

Introduction

The international diabetes federation had estimated that around 382 million individuals have diabetes and the prevalence of type 2 diabetes mellitus (T_2DM) is expected to rise dramatically over the ensuing years due to increasing longevity, industrialization, physical inactivity, and increasing obesity [1].High fatal and morbid outcome of this condition is mainly attributed to the chronic vascular complications [2]. Frequently coexistent condition in diabetic patients is hypertension and vice versa; studies had suggested an increased in the prevalence of hypertension in diabetic patients [3, 4] and that T_2DM was likely to develop in hypertensive than normotensive peoples [5].Hypertension serves to accelerate diabetic complications particularly cardiovascular and renal diseases [4]. Besides blood glucose optimizing, targeting blood pressure seems to prevent or retard the progression of diabetic complications [6, 7] taking into account that the target blood pressure in this group of patients should be lower than the

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traditional level applied for the general population [8]. The Seventh Report of the Joint National Committee on Prevention ,Detection, Evaluation, and Treatment of High Blood Pressure [8] and the American Diabetes Association [9] had recommended a blood pressure goal of 130/80 mm Hg or lower .Consequently, it is essential to detect even minor increments in blood pressure level. Measurement of blood pressure by ambulatory blood pressure monitoring (ABPM) appears to be superior as compared to office blood pressure (OBP) in the diagnosis and follow up of patients with hypertension [10], in predicting cardiovascular complications [11], and in correlating the blood pressure level with target organ damage [12, 13]. In addition, ABPM permits detection of masked hypertension and white coat hypertension that cannot be detected by casual OBP measurement [14, 15].

Difference in systolic and/or diastolic blood pressure between the arms is variously named as inter-arm pressure difference, between-arms pressure difference, or differential blood pressure sign and was first described in 1920 [16]. The exact prevalence of inter-arm blood pressure difference is variable [17] which probably reflects the limited reported studies and the variations in the inclusion criteria of these studies [18]. Knowing the clinical relevance of this sign to the blood pressure measurement is crucial and affects the decision in choosing the proper arm for blood pressure estimation and follow up.

One of the commonest dilemmas facing the operator on ABPM is in choosing the suitable arm for cuff placement. This is mainly due to the incomplete and conflicting recommendations by the universal guidelines. The European Society of Hypertension (ESH) and the European Society of Cardiology (ESC) [19] had recommended that the cuff of ABPM is to be worn on the non-dominant arm despite the earlier recommendation of that the causal OBP is to be measured in both arms and that the arm with the higher reading is taken as a baseline value when systolic inter-arm blood pressure difference is more than 10 mmHg. The American College of Cardiology (ACC) and American Heart Association (AHA) [20] had recommended that the blood pressure in the elderly should be measured in both arms and the arm with the higher reading is to be chosen for further monitoring. The National Institute for Clinical excellence (NICE) [21] had recommended fitting of ABPM cuff onto the non-dominant arm unless the inter-arm pressure difference is more than 20 mmHg for systole and/or more than 10 mmHg for diastole, in which case the arm with higher reading is chosen.

Studying patients with T_2DM by ABPM is particularly confusing, albeit critical for many reasons. This because the target blood pressure in this group of patients is recommended to be lower than that established for the general population (130/80 mmHg versus 140/90 mmHg) which makes the difference between the normal and target blood pressure levels is narrow and also because the recommended guidelines for selecting the proper arm is variable reflecting the variability in the prevalence and clinical relevance of inter-arm blood pressure difference. We tried in this study to set proper steps in choosing the suitable arm for ABPM cuff fitting

Patients and Methods

In this study, consecutive T_2DM (n=140) who attended outpatient clinic at merjan medical city, were studied by ABPM over a period of 2 year (December 2011 to December 2013). Patients were included in the database if they have current history of diabetes mellitus, inter-arm blood pressure difference of more than one mmHg in either systolic or diastolic blood pressure on sequential measurement, and potential indications for ABPM. Patients were excluded if they have one or more of the following features:

1. No current history of T2DM
2. Gestational diabetes or type 1 diabetes mellitus
3. Atrial fibrillation
4. Medically unsuitable patients e.g. paralyzed limb
5. Injury or infection at the site of cuff placement
6. Latex allergy

Baseline Interview

All the participants attended a pre-study appointment for routine medical history, physical examinations, and basic investigations.

Blood Pressure Measurement

All the participants included in this study passed through three steps of clinical preparation and examinations. The first step involved refraining from tobacco, coffee, or tea intake for 30 minutes. After seating the participants for at least 5 minutes with the back supported and the arms bare and at the heart level, mercurial blood pressure measurement in a sequential manner was undertaken; the blood pressure was taken in one arm (left or right, in no special order) and then in the other arm. Three readings were taken for each arm, averaged, and kept in the database. Diabetic participants with inter-arm blood pressure difference of more than one mmHg and potential indications for ABPM were given an appointment for the third step that included ABPM examination.

Figure 1 Contec® ABPM-50 device.

Ambulatory Blood Pressure Monitoring

A 24-hour blood pressure monitoring was obtained by using Contec® ABPM-50 device in which two portable monitors (Figure 1)worn on both arms for a total duration of 24 hours. Portable monitors were set to record the blood pressure profile each 30 minutes during the day and hourly overnight. At the time of fitting of the portable device, the difference between the initial values and those from causal BP measurements were not greater than 5 mmHg. When a larger blood pressure difference did happen, ABPM cuff was removed and fitted again as per guidelines of European Society of Hypertension and of the European Society of Cardiology [19]. The patient was asked to engage in a typical working week-day but to avoid excessive heavy physical exercise and, at the time of cuff inflation, to stop moving and talking and keep the arm still with the cuff at heart level. Each participant was given an event diary and was asked to provide information on symptoms and events that may influence blood pressure (e.g. caffeine or tobacco use and going to toilet), in addition to the time of any medication administration, meals, and wake and sleep time [19]. The measurements were then downloaded to a computer and a range of analyses was performed electronically. Grossly incorrect readings were cancelled electronically. The patient was asked to repeat the monitoring when less than 70% of blood pressure readings during day-time and night-time periods are not satisfactory.

Analysis of ABPM profile was undertaken according the standardized protocol of blood pressure (mean 24-hours, mean day-time, and mean night time) and interpreted in relation to diary information.

Statistical analysis

Statistical analysis was carried out using SPSS version 17. Categorical variables were presented as frequencies and percentages. Continuous variables were presented as (Means ± SD). Paired t-test was used to compare means between two dependent samples (paired of readings).

Wilcoxon signed ranks test was similar to paired t-test but used when differences between paired readings was none normally distributed. ANOVA test was used to compare means among three groups or more. Pearson's chi square (X2) test was used to find the association between categorical variables. A p-value of ≤ 0.05 was considered as significant.

Results

Between December 2011 and December 2013, 191 T_2DM patients eligible for the study were included in the database. Of these, we excluded 23 individuals (12.1%) due to absence of inter-arm blood pressure difference, 17 (9.5%) individuals due to intolerance of ambulatory technique, 5 (2.6%) individuals due to missing records, and 5 (2.6%) individuals due to unsatisfactory results, leaving a cohort of 140 study participants each contributing a single sequential clinic and simultaneous ambulatory blood pressure assessment.

Since all of the participants were right-handed, the term dominant referred to the right arm and the term non-dominant arm referred to the left arm. This obligate designation was to compare our study with the recommendations of the universal guidelines.

As a part of our inclusion criteria, all the studied participants had inter-arm pressure systolic and/or diastolic blood pressure difference. We enrolled T_2DM with variable duration and glycosylated hemoglobin levels (Table 1).

Table 1. Distribution of patients according to the level of HBA1c and duration of diabetes

Variable	Mean ±SD	Range
Duration (years)	4.55 ± 2.77	1-11
HbA1C	8.18 ± 0.92	6-11

The mean age of the participants was 42.05 (± 13.64) years with an age range from 19 to 74 years. Of them, 76.4% were male.

Clinic blood pressure (CBP) measurement in a sequential manner was undertaken for all the participants in both arms. Measurements are repeated thrice for each arm, averaged and then recorded for future analysis. The means of systolic and diastolic blood pressure as well as the means of the systolic and diastolic differences are derived.

After CBP, systolic inter-arm blood pressure difference had been graded into three levels (Table 2); grade I was the dominant (Figure 2).

Likewise, grade I diastolic inter-arm blood pressure difference was the dominant category (Table 2and Figure 3).

The means of systolic and diastolic CBP was significantly different between the dominant and the non-dominant arm (Table 3).

Table 2. Classification of systolic and diastolic inter-arm blood pressure difference

Systolic inter-arm pressure difference	Grade I	1 –9 mm Hg
	Grade II	10 –19 mmHg
	Grade III	≥ 20 mmHg
Diastolic inter-arm pressure difference	Grade I	>1 – < 10 mm Hg
	Grade II	> 10 mmHg

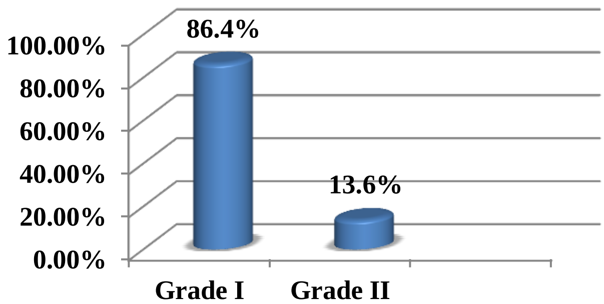

Figure 2. Distribution of diabetic patients according to the systolic inter-arm blood pressure difference.

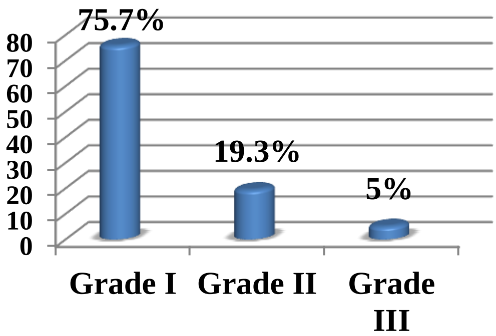

Figure 3. Distribution of diabetic patients according to the diastolic inter-arm blood pressure difference.

Table 3. Mean difference of systolic and diastolic blood pressure

Variable	Categories	N	Mean ± S.D	Paired t-test	df	P value
Clinic diastolic blood pressure	Dominant	140	86.95± 6.25	10.43	139	<0.001
	Non-dominant	140	82.93± 7.03			
CBP systolic	Dominant	140	147.72 ± 11.88	13.39	139	<0.001
	Non-dominant	140	141.11 ± 10.66			

Df=degree of freedom

The correlation between systolic clinic blood pressure and means of age of the diabetic patients had shown a significant difference (Table 4)

Gender of diabetic patients had no impact on systolic clinic blood pressure difference (Table 5) like glycosylated hemoglobin while duration of diabetes had a positive impact (Table 7).

Like in clinic systolic blood pressure, there were a positive impact of increasing age and duration of diabetes on clinic diastolic blood pressure (table 4,7) while the level of glycosylated hemoglobin and gender of patients had shown no significant impact (table 6) .

All the participants after that underwent simultaneous ambulatory blood pressure monitoring by fitting two ambulatory monitors on their arms for a period of 24 hours. Mean day-time and mean night-time readings as well as median 24-hours readings were obtained.

The mean systolic blood pressure of the day-time study(extending from 11 PM to 8 AM) and the night-time study (extending from 8 AM to 11 PM) was significantly different between the two arms (Table 9). The same results were obtained after analysis of the whole 24-hour blood pressure monitoring (Table 11).

Like in ambulatory systolic blood pressure, the mean diastolic blood pressure of the day-time study, the night-time study, and the whole-day study was significantly different between the two arms (table 8 & 10)

Table 4. Association between age and clinic systolic and diastolic blood pressure

Variable	Systolic difference	N	Mean ± S.D	test	P value
Age (years)	Grade I	106	43.45 ± 13.26	6.758	0.002
	Grade II	27	34.33 ± 13.23		
	Grade III	7	50.57 ± 9.50		
Variable	Diastolic difference	N	Mean ± S.D	test	P value
Age (years)	Grade I	121	42.53± 14.25	2.40	0.018
	Grade II	19	50.58± 7.90		

Table 5. Association between sex and clinic systolic differences

Characteristics	Systolic difference			χ^2	P-value
	Grade I(%)	GradeII (%)	Grade III(%)		
Gender				0.534	0.766
Male	80 (75.5)	22 (81.5)	5 (71.4)		
Female	26 (24.5)	5 (18.5)	2 (28.6)		

Table 6. Association between sex and clinic diastolic blood pressure

Characteristics	Diastolic difference		Fisher-exact test	P-value
	Grade I (%)	Grade II(%)		
Gender			0.189	0.782
Male	90 (74.4)	15 (78.9)		
Female	31 (25.6)	4 (21.1)		

Table 7. Association between clinic systolic and diastolic difference and HbA1c and duration of diabetes

Variable	Systolic difference	N	Mean ± S.D	t-test	P value
HbA1c	Grade I	106	8.22 ± 0.9	2.482	0.087
	Grade II	27	8.21 ± 1.05		
	Grade III	7	7.42 ± 0.43		
Duration of diabetes	Grade I	106	4.54 ± 2.80	7.554	0.001
	Grade II	27	3.79 ± 2.03		
	Grade III	7	8.14 ± 1.86		
Variable	Systolic difference	N	Mean ± S.D	t-test	P value
HbA1c	Grade I	121	8.23 ± 0.94	0.977	0.33
	Grade II	19	8.01 ± 0.83		
Duration of diabetes	Grade I	121	4.96 ± 3.44	-6.050	0.001
	Grade II	19	10.76 ± 6.07		

Table 8. Day and night-time diastolic blood pressure in the two arms

Variable	Categories	N	Mean ± S.D	Paired t-test	df	P value
Day-time diastolic blood pressure	Dominant	140	85.34± 6.25	8.47	139	<0.001
	Non-dominant	140	82.03± 6.87			

Table 9. Day and night-time systolic blood pressure in the two arms

Variable	Categories	N	Mean ± S.D	Paired t-test	df	P value
Day-time systolic blood pressure	Dominant	140	145.40 ± 11.25	12.32	139	<0.001
	Non-dominant	140	139.31 ± 10.42			
Night-time systolic blood pressure	Dominant	140	144.19 ± 10.58	11.45	139	<0.001
	Non-dominant	140	138.30 ± 9.99			

Table 11. Median 24-hour systolic blood pressure in the two arms

Variable	Categories	N	50^{th} (median)	Z	P value
24-hour systolic blood pressure	Dominant	140	143.00	-9.095	<0.001
	Non-dominant	140	138.00		
Wilcoxon signed ranks test					

Table 10. Whole day, night time diastolic blood pressure in the two arms

Variable	Categories	N	50^{th} median	Z	P value
24-hour diastolic blood pressure	Dominant	140	87.00	-7.85	<0.001
	Non-dominant	140	84.00		
Night-time diastolic blood pressure	Categories	N	Mean±SD	Paired t-test	p-value
	Dominant	140	84.56± 6.09	8.76	<0.001
	Non-dominant	140	80.91± 6.77		

Table 12. Association between day-time systolic blood pressure and systolic difference in the dominant arm and non-dominant arm

Variable	Systolic difference	N	Mean ± S.D	F-test	P value
Day-time systolic blood pressure	Grade I	106	143.95 ± 11.19	3.95	0.021
	Grade II	27	149.4 ± 11.33		
	Grade III	7	152.0 ± 4.93		
Day-time systolic blood pressure	Grade I	106	140.0 ± 10.48	3.136	0.047
	Grade II	27	139.0 ± 10.17		
	Grade III	7	130.0 ± 5.71		

Table 13. Association between day-time diastolic blood pressure and diastolic difference in the dominant arm and non-dominant arm

Variable	Systolic difference	N	Mean ± S.D	t-test	P value
Day-time diastolic blood pressure	Grade I	121	83.98 ± 6.30	5.005	<0.001
	Grade II	19	75.78 ± 7.74		
Day-time diastolic blood pressure	Grade I	121	84.13 ± 6.07	6.106	<0.001
	Grade II	19	74.13 ± 7.60		

The association between the day-time systolic blood pressure and clinic systolic inter-arm blood pressure differences had shown significant differences in both the dominant and non-dominant arms (Table 12).

Like that in systolic association, the association between the day-time diastolic blood pressure and clinic diastolic inter-arm blood pressure differences had shown significant differences in both the dominant and non-dominant arms (Table 13).

Discussion

Diabetes mellitus and hypertension are frequently coexistent diseases. Hypertension serves to accelerate the cardiovascular complications when accompanied diabetes mellitus and vice versa [3-5]. The main objectives in the management of these coexistent conditions are to optimize the blood glucose and targeting blood pressure [6, 7] taking into account that the blood pressure target in diabetic patients is lower than the level recommended for the general population, that is, 130/80 mm Hg [8]. The range between the normal and target blood pressure will therefore be slight, but critical and in the presence of inter-arm blood pressure difference, this would undoubtedly create clinical dilemma.

The study protocol had intentionally designed a sequential rather than simultaneous blood pressure estimation to simulate the actual daily practice in taking blood pressure. The sequential nature, however, might give rise to spurious high inter-arm blood pressure differences. This phenomenon was demonstrated in a recent study by Martin, who attributed the apparent disparity in office blood pressure to white coat effect [22]. In his study, blood pressure was sequentially measured for 710 participants and the results were compared with day-time ambulatory results. He concluded that the differences between the clinical readings and that of ambulatory reading were not significant for the dominant and non-dominant arms and attributed that to white coat effect. In our study and to the contrary to the latter study, blood pressure was measured thrice for each arm to reduce spurious discrepancy [23, 24] as per guidelines of optimal blood pressure measurements [19]. Despite conflicting data of which method for blood pressure measurement is ultimate, studies had suggested that inter-arm blood pressure difference is prevalent even when the ideal steps are followed [18].

In our study, the mean systolic blood pressure (± SD) in the dominant arm (147.72 mm Hg (± 11.88)) was higher than that in the non-dominant arm(141.11(± 10.66 mm Hg) with significant (P <0.001) systolic inter-arm blood pressure differences. Diastolic blood pressure analysis had shown similar findings (86.95 ± 6.26) mm Hg, dominant arm versus 82.93 ±7.03) mm Hg, non-dominant arm) with significant difference (P < 0.001). Reported studies had shown that inter-arm blood pressure difference is associated with peripheral artery disease and coronary artery disease [25, 26]. Most importantly, studies had demonstrated that systolic difference of 10 mm Hg or more was intensely correlated with greater cardiovascular fatal outcome and all-cause mortality [27-29]. Diabetic patients are prone to macrovascular complications which might explain the significant inter-arm blood pressure difference in our study.

Grade I systolic inter-arm blood pressure difference was the dominant grade (75.7%) and was followed by grade II (19.3%) and then grade III (5%). On the other hand, diastolic grade I inter-arm blood pressure difference was the dominant rhythm (86.4%) and was followed by grade II (13.6%). Despite different study design and inclusion criteria, these findings are consistent with Clark et al in a meta-analysis of four old studies that demonstrated a mean prevalence of 19.6% for systolic differences above 10mmHg and 4.2% for systolic differences above 20mm Hg [18]. In that study also, Clark showed a prevalence of diastolic inter-arm blood pressure difference of 8.1% in patients with a difference ≥ 10mm Hg.

In our study, age and duration of diabetes had a positive impact on systolic and diastolic clinic blood pressure differences while gender and magnitude of glycosylated hemoglobin had poor correlation. In a study conducted on 11,140 patients with T_2DM, Zoungas had concluded that age and diabetic duration were linked to macrovascular complications and risk of death [30]. This would explain why age and diabetic duration had a positive impact on systolic and diastolic inter-arm blood pressure difference in our study.

In a study conducted by Lane et al on 400 volunteers to estimate the mean and frequency of the clinically significant blood pressure disparities, age was the single most significant factor influencing the results while sex had shown no significant correlation [31]. These findings were in keeping with our results. In another study, Martin et al had found weak association between clinic systolic/diastolic blood pressure differences and the age and sex of the participants [22]. Similarly, Oh in a study conducting on 464 patients without prior cardiovascular disease had concluded that after simultaneous automatic blood pressure measurements, the absolute systolic and diastolic difference was not associated with increasing age [32]. Age disagreement in the latter two studies was inconsistent with our findings.

In agreement with our study, Clack et al in a cross-sectional study involving 101 type 2 diabetic patients to estimate systolic and diastolic differences in this group of patients had found that systolic difference ≥10mmHg or diastolic difference ≥5 mmHg was not significantly correlated to glycosylated hemoglobin and other variables [33].

Systolic and diastolic blood pressures were significantly different in both arms when studied over day-time, night-time, and 24-hours ambulatory monitoring. Persistence of significant difference between the two arms over this period of time denoted that the disparity in blood pressure is genuine and is not due to white coat effect or other factors. Systolic and diastolic inter-arm blood pressure differences in the dominant arm and the non-dominant arm had been shown to have significant mean differences with the mean ambulatory day-time systolic blood pressure. The order of means was increasing in the dominant arm and decreasing in the non-dominant arm. This could be interpreted into that the mean day-time blood pressure would be highest when the dominant arm is used in patients with large inter-arm blood pressure difference and highest when the non-dominant arm is used in patients with small inter-arm blood pressure difference. Murphy and O'Shea [34]compared the readings of the arm exhibiting the higher manual blood pressure with that obtained via 24-hours ambulatory monitoring in 10 volunteers exhibiting systolic difference of more than 10 mm Hg. The manual blood pressure was 16 ± 6 mmHg higher in the right arm as compared with left, but the mean 24-hours ambulatory blood pressure was only 6 ± 0.7 higher in the right arm with a significant difference between the two readings (P = 0.025). The findings were similar for diastolic blood pressure. They concluded that around one third of the average reading may be attributed to white coat effect generated by inconsistency in selecting the suitable arm for blood pressure measurements. In the latter study and in comparison with our study, however, the sample size was small (10 versus 140 individuals) and the characteristics of the participants were different (volunteers referred primarily for blood pressure estimation versus patients with diabetes, a well-known predisposing factor for macrovascular complications).

In a study of Martin, after comparison of sequential blood pressure measurements with day-time blood pressure results, he found no significant difference between the dominant and non-dominant arms and attributed that to white coat effect [22].The disagreement in the latter study as compared with our study can be explained also by the fact that our participants were diabetics who were at high risk for the development of vascular complication.

Conclusions and Recommendations

Type 2 diabetic patients seem to have significant systolic and diastolic inter-arm blood pressure difference even when sequential, albeit ideal blood pressure method is used .Increasing age and diabetic duration seem to affect systolic and diastolic blood pressure differences while sex and glycosylated hemoglobin seem not. According to our study, we believe that the proper steps of clinic and ambulatory blood pressure examination in type 2 diabetic patients exhibiting systolic/diastolic inter-arm blood pressure differences should involve the following points:

1. Sequential blood pressure measurement is an accepted modality if the examination of the blood pressure is to be repeated three times for each arm and then averaged.
2. The arm with the higher systolic and/or diastolic blood pressure is the suitable arm for ambulatory monitoring and generally mirroring the clinic blood pressure.
3. In patients with large systolic or diastolic inter-arm blood pressure difference, using the dominant arm for ambulatory monitoring will result in high blood pressure readings. Using the non-dominant arm in this case will result in low blood pressure readings.
4. In patients with small systolic or diastolic inter-arm blood pressure difference, using the non-dominant arm for ambulatory monitoring will result in high blood pressure readings. Using the dominant arm in this case will result in low blood pressure readings.

Strengths and Limitations

One of the powerful points in this study was that it was conducted on diabetic patients who were already candidates for ambulatory monitoring. Giving the fact that the target blood pressure in diabetic patients had to be lower than that set for the general population, the study had compared manual versus ambulatory methods of blood pressure measurements under standardized steps to find out the suitable arm for blood pressure monitoring in diabetic population. Estimates of the differences might be inaccurate due to enrollment of a relatively small number of diabetic patients. In addition, the study was conducted in specialized center that applications of the recommendation to primary care might be difficult.

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