Blood Pressure and Arterial Stiffness in Kenyan Adolescents with the Sickle Cell Trait

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Abbreviations:

ABPM: Ambulatory blood pressure monitoring

BP: Blood pressure

PWV: Pulse wave velocity

SCT: Sickle cell trait

ABSTRACT

The potential association between sickle cell trait (SCT) and increased arterial stiffness/blood pressure (BP) has not been evaluated in detail despite its association with stroke, sudden death and renal disease. We performed 24-hour ambulatory BP monitoring and arterial stiffness measurements in adolescents raised in a malaria free environment in Kenya.

Between December 2015 and June 2016, 938 randomly selected adolescents that had been continuous residents of Nairobi from birth were invited to participate in the study. Standard clinic BP measurement was performed followed by 24-hour ambulatory BP monitoring and arterial stiffness measurement using an Arteriograph device. SCT status was determined using DNA genotyping on contemporaneously collected blood samples. Of 938 invited, 609 (65%) provided complete data for analysis. SCT was present in 103 (17%). Mean 24-hour systolic and diastolic BP, SD was (116, 11.5) and (64, 7) mmHg respectively in SCT; and (117, 11.4) and (64, 6.8) in non-SCT. Mean pulse wave velocity (PWV), SD was (7, 0.8) and (7, 0.8) ms^{-1} respectively in SCT and non-SCT. No differences were observed in PWV and any clinic or ambulatory BP derived measures between those with and without SCT. These data suggest that SCT does not independently influence BP or PWV.

Keywords

Sickle cell trait; Hypertension; Blood Pressure; Arterial Stiffness

The sickle cell trait (SCT), common among populations of African descent(1) due to the protection it offers against malaria(2-4), has been associated with increased risk of cardiovascular and renal disease.(5-8) However the underlying mechanisms of this increased risk have not been elucidated clearly, hampering measures that can be implemented to reduce risk in carriers.

Individuals of African descent have relatively higher blood pressure (BP) compared to other ethnicities (9), and it is conceivable that increased BP or arterial stiffness, which have been shown to precede clinical events similar to those seen in SCT, could precede the events observed in SCT carriers.(8, 10, 11) Alternatively increased arterial stiffness and BP in individuals with SCT could result from the yet to be elucidated mechanisms that lead to cardiovascular and renal events.

Previous studies that assessed BP and/or arterial stiffness in individuals with SCT had several weaknesses; Rossi-Espagnet et al in a study conducted in Colombia in 1968 found no difference in BP between individuals with and without SCT.(12) However, BP measurements were performed only once at home visits; there was a poor response rate in men; and the data were susceptible to confounding by malaria, which SCT protects against(2-4) and is possibly related to BP.(13, 14) Bayramoglu et al found similar arterial stiffness indices in young Turkish adults with and without SCT, but the sample size was small.(15) Although the studies demonstrating increased cardiovascular and renal disease risk in SCT assessed BP at baseline, the BP measurements were done in the clinic/office, using manual or automated

methods.(7, 8) None of these studies utilized 24-hour ambulatory blood pressure monitoring (ABPM), considered the reference method for BP measurement(16, 17), raising the possibility that subtle but significant differences in BP could have been missed.(17) ABPM overcomes many of the limitations of office/clinic BP measurement.(17) ABPM also enables detection of masked hypertension (normal clinic BP but elevated 24-hour BP), a cardiovascular risk factor(18) that is more common in populations of African descent(19), the same population that has a high prevalence of SCT.

If arterial stiffness and/or BP are increased in young individuals with SCT they could become the target of interventions aimed at reducing future cardiovascular and renal events. We conducted a population-based study in Nairobi, Kenya to determine whether SCT influences arterial stiffness and BP among adolescents who have had minimal exposure to malaria.

METHODS

The study was a cross-sectional sample of residents of the Nairobi Urban Health and Demographic Surveillance System (20) in Kenya conducted from December 2015 to June 2016. The area has a population of approximately 70,000 and the prevalence of hypertension is high.(21) Nairobi, the capital city of Kenya was chosen for this study because of 2 reasons: First, Nairobi is located at high altitude (1800 meters above sea-level) and there is no evidence of malaria transmission.(22) This made it possible to study the effect of SCT on BP unconfounded by the presence of malaria. This was necessary because malaria could influence BP(14) and at the same time SCT protects against malaria(3, 4); Second, the population of Nairobi is composed of ethnic

groups originating in all parts of the country including those whose ancestral lands were endemic for malaria (e.g. Luhya, Luo, Teso, Mijikenda). The sickle cell gene frequency is much higher among these ethnic groups.(23) In order to increase our efficiency in recruiting participants with SCT we limited our recruitment to those who identified themselves as genetically derived from one of these ethnic groups.

Population-wide censuses are conducted 4 times a year within the study area.(20) Using census data we selected all children currently aged 11-17 years who had a continuous record of residence in the area since birth. Continuous residency was a requirement so as to minimize potential exposure to malaria as a result of migration. Trained staff visited all subjects who had been selected to participate in the study at their homes. Parents of the children were then asked to bring them to the nearer of two study clinics within the area to undergo study procedures. Subjects who failed to come to the clinic within 3 months of being requested to do so were considered to have refused to participate in the study.

Subjects first underwent an interview where they answered questions about their past medical history and their socioeconomic status based on the multi-dimensional poverty index.(24) Weight and height were measured using a validated SECA 874™ weighing machine and a portable stadiometer (SECA 213™) (SECA GMBH, Hamburg, Germany), respectively. Mid-upper arm circumference was measured in a standardized manner using TALC™ (Teaching Aids at Low Cost, Hertfordshire, UK) tapes. We then took a screening BP measurement using a validated automated Omron™ M10-IT

(Omron Healthcare Europe B.V, Hoofddorp, The Netherlands) BP machine. An appropriately sized cuff was placed on the non-dominant arm after the subject had been seated for at least 5 minutes. Three BP measurements were taken over a 5-minute period and the mean of the last 2 measurements was recorded as the screening BP value. All participants were subsequently fitted with an Arteriograph24™ device (Tensiomed Ltd, Budapest, Hungary) for 24-hour ABPM as well as pulse wave velocity (PWV) determination.(25) The devices, which have been calibrated in children(26), were programmed to take measurements every 20 minutes during daytime hours (0600-2200 hrs) and every 40 minutes at night (2200-0600 hrs).

Laboratory procedures

We collected 10ml of blood from participants for full blood count, determination of sickle hemoglobin status and serum electrolytes. After performing automated full blood counts using an ACT 5™ machine (Beckman Coulter Inc, Brea, CA), whole blood samples were frozen at -80ºC and then transported to the KEMRI-Wellcome Trust Research Programme laboratories in Kilifi, Kenya for determination of sickle hemoglobin status. DNA was extracted retrospectively from the frozen samples by use of Qiagen™ DNA blood mini-kits (Qiagen, Crawley, United Kingdom) and typed for sickle hemoglobin using polymerase chain reaction.

Serum and urine samples collected from participants were frozen at -80ºC within 4 hours of collection and later transported to Kilifi, Kenya for analysis. We determined sodium and potassium, urea and creatinine levels in these samples using ion electrophoresis and the jaffe method, respectively.(27) We additionally determined albumin levels in the urine samples by

immunoturbidometry using a Quantex™ microalbumin kit (Instrumentation Laboratory, Barcelona, Spain).

Statistical methods

Based on an expected minimum prevalence of 10% SCT in the ethnic groups we were studying, a systolic BP standard deviation of 15 mmHg, and 30% attrition due to poor quality ABPM data, we estimated that a total of 550 participants would provide 80% power to detect half of a standard deviation (7.5 mmHg) difference in 24 hour systolic BP between individuals with and without SCT.

As there are no published criteria for acceptable ABPM data in children, we used guidelines for completeness of ABPM data in adults from the International Database of Ambulatory blood pressure in relation to Cardiovascular Outcomes study.(28) Specifically, ABPM data were considered of acceptable quality if they met the following criteria: minimum 10 daytime and minimum 5 nighttime readings, where day was defined as 1000-2000 hrs and night as 0000-0600 hrs.(28) The same time periods were used to determine average daytime and nighttime blood pressures and to evaluate dipping status. Time weighting was applied in calculating average BP values for all time periods.(29)

We defined screen positives for hypertension as individuals whose mean of the last 2 clinic BP measurements was above the 95th percentile for their age, sex and height.(16) Confirmed hypertensives were those whose 24hr systolic

and/or diastolic BP averages respectively were above the 95th percentile for their sex, age and height.(16)

We categorized all subjects who were not on anti-hypertensive medication using the combination of clinic BP measurements and ABPM into four categories: sustained hypertensives (screen positive and confirmed hypertensive on ABPM); white coat hypertensives (screen positive, not confirmed hypertensive on ABPM); masked hypertensives (screen negative, confirmed hypertensive on ABPM) or normotensives (screen negative, not confirmed hypertensive on ABPM).(30)

Dipping status was defined using ABPM data only, using day and night periods as defined above. Subjects were classified using the following four categories, based on the night/day ratio of mean systolic and/or diastolic BPs: rising or absence of dipping (ratio ≥1.0); mild dipping (0.9 < ratio ≤1.0); dipping (0.8 < ratio ≤ 0.9); and extreme dipping (ratio≤0.8).(31)

Estimated glomerular filtration rate was calculated using the Schwartz formula.(32)

Summary statistics computed included means, medians and proportions as appropriate. Comparisons between SCT carriers and non-carriers were made using Student's t-test and χ^2 tests as appropriate. Data that were not normally distributed were log transformed prior to analysis. We compared ABPM and arterial stiffness measures between those with and without the sickle cell trait by Student's t-test. In addition we performed a multivariate

regression analysis testing the effect of sickle carrier status on mean 24-hour systolic and diastolic BP with sex, age, body mass index, pulse wave velocity and estimated glomerular filtration rate as covariates.

All analyses were conducted using Stata™ Version 12 software (College Station, Texas).

The Kenya Medical Research Institute's Ethical Review Committee approved the study. Written informed consent was obtained from parents of study participants. Participating children also provided written assent. The corresponding author had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

RESULTS

Of the 938 subjects requested to participate in the study, 686 (73%) completed enrollment (Figure 1). The 252 adolescents that were not recruited into the study were 0.6 years (95% CI 0.3-0.9) older than study participants, but with a similar sex distribution (53% female) to those that participated in the study. Genotype data was available for 644 subjects, 609 (95%) of who had complete ABPM data. Sickle cell trait (SCT) was present in 103 (15%) of participants. The proportion of participants with complete ABPM data did not differ by sickle cell trait (91% vs 90%, p=0.817) or any of the other demographic and clinical data collected. One participant had Sickle Cell Disease (Hemoglobin SS) and was dropped from analyses. None of the participants were previously aware of their sickle carrier status.

Mean clinic BP, SD among all participants was (98, 11) mmHg systolic and (64, 8) mmHg diastolic. The mean 24-hour BP, SD for all participants was (117, 11) mmHg systolic and (64, 7) mmHg diastolic. Mean 24-hour Pulse Wave Velocity (PWV), SD was (7, 0.8 ms^{-1}). Based on the data accrued, the study had >98% power to detect a 5 mmHg difference in systolic BP (0.4 standard deviations), a 4mmHg (0.5 standard deviations) difference in diastolic BP and a 0.4 ms^{-1} (0.5 standard deviations) difference in PWV between those with and those without SCT.

Table 1 displays the characteristics of the participants according to SCT carrier status. The mean, SD 24-hour systolic and diastolic BP in subjects with SCT was (116, 11.5) and (64, 7) mmHg. In subjects without SCT the corresponding 24-hour BP values were (117, 11.4) and (64, 6.8) (p=0.8551 and 0.9691 for comparison between SCT carriers and non-carriers). There were no statistically significant between-group differences in estimated glomerular filtration rate, clinic BP, clinic PWV and 24-hour PWV. There were no between-group differences in the prevalence of masked hypertension, white coat hypertension, or non-dipping status. Urinary sodium and potassium were 19.5 mmol/L (95%CI 1.4-37.6, p=0.0352) and 13.5mmol/L (CI 5.8-21.2, p=0. 0006) lower in SCT carriers than in non-carriers.

Figure 2 displays distribution of 24-hour, daytime and nighttime blood pressures in study participants by SCT carrier status. All measures were similar for SCT carriers and non-carriers.

Table 2 displays the results of regression analyses examining whether SCT influenced 24-hour systolic and diastolic BP adjusted for age, sex, body mass index, glomerular filtration rate and pulse wave velocity. While age, sex, body mass index and glomerular filtration rate were all associated with 24-hour systolic BP, there was no association between SCT and 24-hour BP measures. Pulse wave velocity displayed the strongest association with both systolic and diastolic BP. Additional adjustment for urinary sodium and potassium levels made no material difference to the results.

DISCUSSION

It has previously been hypothesized that the excess risk of cardiovascular disease observed in African populations may be result from pleiotropic effects of genetic polymorphisms that protect them from common infections during childhood. An elegant example of this is variants of the *APOL1* gene, which while reducing the risk of trypanosomiasis, increase the risk of hypertension associated chronic kidney disease.(33) Malaria has exerted the strongest known selective pressure on the human genome, SCT being prominent among the polymorphisms under positive selection.(34) Given the previously documented excess cardiovascular and renal events observed in both sickle cell disease and SCT, we hypothesized that individuals with SCT would have different BP compared to those without SCT.

In this detailed study of BP phenotypes and arterial stiffness among children who were selected because they had had little exposure to malaria throughout childhood, we did not find any differences between those with and without SCT. Because the exposure measurement was a genetic trait

acquired at conception and the participants were ascertained to have remained in the same malaria-free environment since birth we believe that this study suggests that a direct effect of SCT on BP and indices of arterial stiffness is highly improbable within the first 11-17 years of life.

Estimated glomerular filtration rate and urine albumin to creatinine ratio were the same in SCT carriers and non-carriers in this study. In a study conducted among blacks in the US showing increased renal events in SCT carriers, most participants were recruited at 45 years of age and above(8), much older than the population we recruited in this study. We however found significantly lower urine electrolyte levels in SCT carriers, which could be attributed to hyposthenuria (impaired urinary concentrating ability) that has previously been described in SCT.(35)

While we failed to detect any meaningful effect of SCT on BP and arterial stiffness, the results of this study do have important implications; first it seems unlikely that increased BP and arterial stiffness precede or are involved in the pathogenesis of cardiovascular and renal events in individuals with SCT. In view of this, studies of other biomarkers that could predict the development of chronic kidney disease in individuals with SCT are warranted. Because individuals with SCT form a significant proportion of the population in many developing as well as developed countries, early identification of risk factors in this sub-group of individuals could have significant population-wide benefits.

An alternative to the hypothesis that genetic variations protective against infectious diseases predispose to cardiovascular disease is that in some instances the infectious diseases themselves may have long-term consequences in survivors including the development of hypertension.(14) One robust way to test such hypotheses is by utilizing mendelian randomization techniques in which BP is compared in individuals with and without genetic variants that are associated with the infectious disease. An important prerequisite for using these variants is that they should not affect the outcome (BP) in the absence of the infectious disease (malaria). The results of this study suggest that SCT does not influence BP in the absence of malaria and can therefore be used as an instrumental variable in MR studies to test the malaria-high blood pressure hypothesis.(14) SCT is a particularly attractive candidate for such studies as it is relatively common in areas with malaria and displays a very strong protective effect against mild as well as severe malaria(2, 4) thus reducing sample size requirements for such studies. Confirmation of the hypothesis would represent a paradigm shift in understanding the pathogenesis of hypertension in many developing country settings where malaria is endemic.(36)

A major strength of this population-based study was the use of ABPM, which is considered the reference standard for blood pressure measurement in children.(16) The study was well powered to detect very small differences in BP and PWV. We also used health and demographic surveillance system records that were prospectively collected in order to ascertain residence in a

non-malaria zone, there being no better method of doing this in sub-Saharan Africa.

A potential limitation of this study was the limited age range of subjects recruited, necessitated by the fact that there were no long-term residency records for older individuals. Most demographic surveillance systems in Africa were established in the late 1990's to early 2000's.(37) Recruiting older individuals would have compromised data on residency status in childhood, the period when malaria risk is highest. In addition, older subjects would be more likely to have acquired additional risk factors for hypertension, including chronic kidney disease that would have confounded the analyses. While BP differences are likely to be larger at older ages, it is known that differences in adult BP emerge in childhood(38, 39) and that childhood BP levels are predictive of adult BP.(40) The absence of even a small difference in carefully measured BP and arterial stiffness in our study of adolescents therefore suggests that it is very unlikely such differences would emerge in future.

Although the study was well powered to detect differences in continuous variables such as mean nighttime and daytime BP, we were underpowered to detect differences in the prevalences of categorical variables such as masked hypertension and white coat hypertension. This could form the basis of future studies.

An additional limitation of this study is the fact that as with many BP measurement devices, validation studies for the Arteriograph24™ have only been done in adults.(25) It is however unlikely that measurement error

significantly influenced the result, as the oscillometric principle used by the device has been validated in children and is particularly suited for pediatric ambulatory BP studies.(16, 41)

Non-responders in this study were slightly older than those who participated, but the 0.6-year difference is unlikely to have significantly biased our results. We also observed no significant differences between those that provided acceptable ABPM data and those that did not suggesting that the data presented are representative of the larger population of individuals with sickle cell trait.

In summary, we have demonstrated that the presence of sickle cell trait does not influence BP and arterial stiffness in Kenyan adolescents.

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Table 1: Characteristics of study subjects according to sickle trait status, Nairobi, Kenya 2015-2016

Characteristic	SCT Noncarrier (N=567)			SCT Carrier (N=103)			p-value
	No.	%	Mean (SD)	No.	%	Mean (SD)	
Female sex	323	57		49	48		0.08
Complete ABPM data	516	91		93	90		0.82
White coat hypertension[a]	23	44		3	3.2		0.59
Masked hypertension[a]	37	7.2		8	8.6		0.63
Non dipping BP pattern[a]	17	3		2	2		0.55
Age, years			13.2 (2.2)			13.8 (2.3)	0.093
BMI[b]			19 (3)			19 (3)	0.63
MUAC, cm			23.2 (3.6)			23.5 (3.8)	0.41
Hemoglobin, mg/dL			13.2 (1.5)			13.4 (1.6)	0.15
White cell count			5.5 (1.5)			5.6 (1.3)	0.78
Platelet count			310 (87)			305 (95)	0.64
Serum sodium (mmol/L)			139 (6)			139 (6)	0.94
Serum potassium (mmol/L)			4.9 (0.6)			5.0 (0.8)	0.093
Socioeconomic status (MDPI score)			2.2 (1.3)			2.1 (1.3)	0.55
Clinic BP, mmHg							
Systolic			98 (11)			99 (13)	0.31
Diastolic			64 (8)			64 (9)	0.32
Pulse wave velocity (ms^{-1})			7 (0.8)			7.1 (0.8)	0.26
eGFR ($mls/min/1.73m^2$)			110 (15)			108 (14)	0.12
UACr			3.6 (18)			3.5 (8)	0.96
Urine sodium (mmol/L)			136 (73)			119 (45)	0.031
Urine potassium (mmol/L)			48 (31)			36 (23)	0.0001

BMI=Body mass index; eGFR=estimated glomerular filtration rate; MDPI=multi-dimensional poverty index; MUAC=mid upper arm circumference; UACr=Urine albumin to creatinine ratio

[a]Data on white coat, masked hypertension and non-dipping pattern are based on the 609 individuals that had complete ABPM data

[b] BMI is calculated as $Weight(kg)/height(m)^2$

Table 2: Predictors of mean 24-hour systolic and diastolic BPs among adolescents in Nairobi, Kenya, 2015-2016[a]

Characteristic	24-hour SBP			24-hour DBP		
	β	95% CI	p-value	β	95% CI	p-value
Age, years	0.6	0.07, 1.1	0.027	0.008	–0.3, 0.3	0.96
Male Sex	2.4	0.4, 4.3	0.016	–0.06	–1.3, 1.2	0.92
BMI[b]	0.6	0.2, 1	0.001	0.2	–0.09, 0.4	0.21
eGFR (mls/min/1.73m^2)	0.08	0.01, 0.15	0.017	0.01	–0.03, 0.05	0.58
PWV (ms^{-1})	2.8	1.6, 4.1	<0.001	2.7	1.9, 3.5	<0.001
Sickle carrier status	0.1	–2.4, 2.6	0.923	0.4	–1.1, 2	0.58

SBP=systolic blood pressure; DBP= diastolic blood pressure; BMI=Body mass index; eGFR=estimated glomerular filtration rate; PWV= pulse wave velocity

[a]Multivariate analyses were conducted using data from participants that had complete Ambulatory BP Monitoring data (N=609)

[b]BMI is calculated as Weight(kg)/height(m)^2

Figure 1 Legend: Study flow chart of participants in sickle trait–blood pressure study in Nairobi, Kenya 2015-2016.

Figure 2 Legend: 24-hour ABPM measures by sickle cell trait (SCT) carrier status in Nairobi, Kenya 2015-2016. For each category of 24-hour, day and night measures, the plots on the left are for systolic blood pressure and those on the right are for diastolic blood pressure. Error bars represent 95% Confidence Intervals.

Figure 1

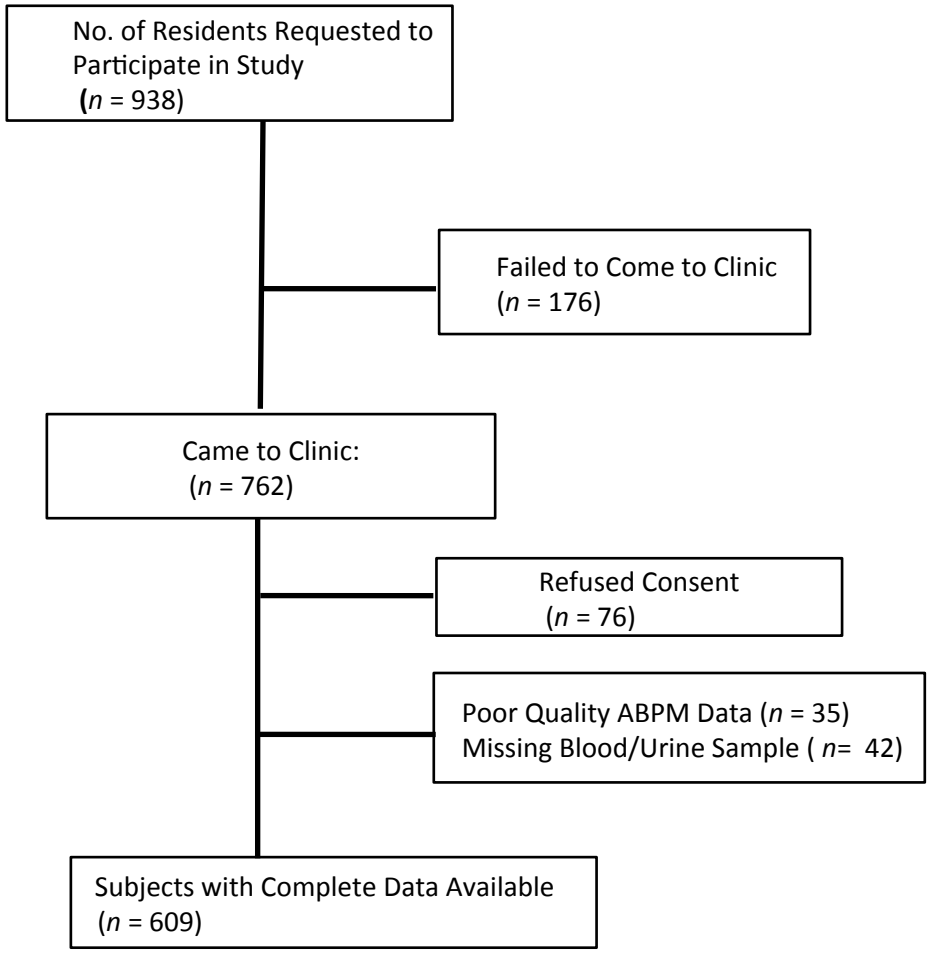
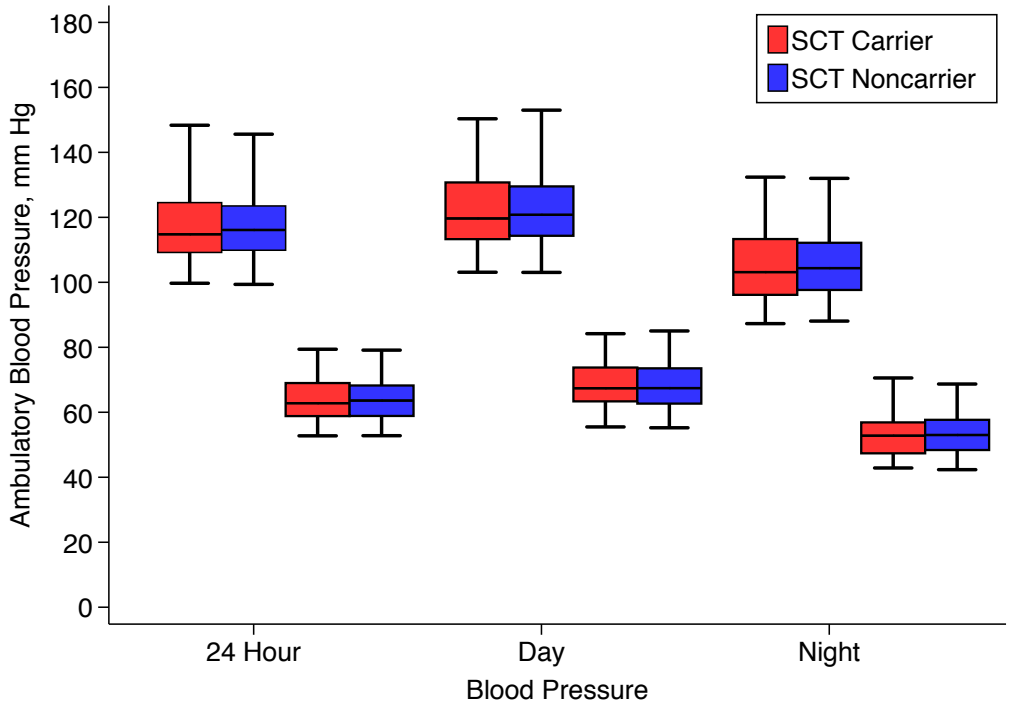

No. of Residents Requested to Participate in Study (n = 938)
Failed to Come to Clinic (n = 176)
Came to Clinic: (n = 762)
Refused Consent (n = 76)
Poor Quality ABPM Data (n = 35)
Missing Blood/Urine Sample (n= 42)
Subjects with Complete Data Available (n = 609)

Figure 2


SCT Carrier
SCT Noncarrier
Ambulatory Blood Pressure, mm Hg
180
160
140
120
100
80
60
40
20
0
24 Hour
Day
Night
Blood Pressure