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Effect of Elevated Blood Pressure on Quality of Life in Children with Chronic Kidney Disease

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Abstract

Background—Although hypertension is known to have an adverse impact on health-related quality of life (HRQoL) in adults, little is known about the effects of hypertension and use of antihypertensive medications on HRQoL in hypertensive children with chronic kidney disease (CKD).

Methods—Cross-sectional and longitudinal assessment of impact of elevated blood pressure (BP) and antihypertensive medication use on HRQoL scores obtained in children enrolled in the Chronic Kidney Disease in Children Study. Blood pressure was measured both manually and by ambulatory blood pressure monitoring. HRQoL was assessed with the PedsQL survey.

Results—Study sample included 551 participants with sufficient data for cross-sectional and longitudinal analyses. Cross-sectional analysis of presence of prehypertension or hypertension and impact on HRQoL found mild associations between elevated BP and HRQoL scores with overall PedsQL parent and child scores averaging 79 versus 76.5 and 83 versus 78.5, respectively. However, no associations persisted under longitudinal multivariate analysis.

Conclusions—Despite apparent small effects of elevated BP on HRQoL at baseline, no association was found between the presence of elevated BP and HRQoL over time in children with

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mild to moderate CKD. In addition, antihypertensive medication use did not appear to have an impact on HRQoL in this population.

Keywords

Hypertension; PedsQL; pediatrics; antihypertensive medications

Introduction

Hypertension (HTN) is a common complication in children with chronic kidney disease (CKD) and contributes to increased morbidity and mortality in this population [1]. Fifty-four percent of children initially enrolled in the Chronic Kidney Disease in Children (CKiD) study had elevated blood pressures and/or a history of HTN and current antihypertensive medication use [2].

Various co-morbid conditions related to CKD can adversely affect health-related quality of life (HRQoL). Children with CKD report poorer overall HRQoL scores and poorer physical, school, emotional, and social functioning compared to healthy children [3]. Adult studies have shown a reduction in HRQoL in hypertensive patients to be associated with patient health comorbidities, awareness of diagnosis, and adverse effects from treatment [4]. For example, the African American Study of Kidney Disease and Hypertension (AASK) trial showed that African American adults with higher mean arterial pressure, longer duration of HTN, a larger number of antihypertensive medications, and more severe CKD had significantly lower HRQoL scores [5]. The AASK trial also found that physical aspects of quality of life were substantially reduced compared with mental components [5]. Similar studies in children are lacking and identifying associations between blood pressure and HRQoL in pediatric patients with CKD may be important with respect to targeting modifiable factors that can negatively impact these children's psychosocial development.

The primary aim of this study was to address this gap in the literature by determining if the presence of elevated blood pressures (BP), antihypertensive medication use, and/or duration of HTN were associated with decreased HRQoL in children with mild to moderate CKD.

Methods

The CKiD study is a multicenter longitudinal, observational cohort study of children with glomerular filtration rates (GFR) between 30–90 ml/min/1.73 m^2 determined by estimating GFR by Schwartz equation or measuring GFR by iohexol infusion at enrollment [6, 7]. Iohexol infusion was used to measure 508 GFRs and the remaining 43 GFRs were estimated by Schwartz equation [7]. The design and methods of the CKiD study have been previously reported [8]. The study protocol was approved by the Institutional Review Boards at all participating centers; informed consent and/or assent was obtained according to local requirements prior to inclusion in study.

Measurement of casual blood pressure

Casual blood pressure was measured at each CKiD visit (e.g. baseline, 6 months after enrollment and then yearly) by auscultation with an aneroid sphygmomanometer (Mabis

MedicKit 5, Mabis Healthcare, Waukegan, IL) [2]. Blood pressure was classified according to the National High Blood Pressure Educational Program Fourth Report as normotensive (BP <90th percentile and <120/80 mmHg), prehypertensive (BP ≥90th and <95th percentile or <90th percentile and >120/80 mmHg), or hypertensive (BP ≥95th percentile) [9]. BP index was calculated by dividing individual's measured casual BP by the 95th percentile systolic or diastolic BP for age, gender, and height.

Measurement of ambulatory blood pressure

Ambulatory blood pressure monitoring (ABPM) was conducted at study visits done at year 1, 3, and 5 after baseline using the SpaceLabs 90217 device (SpaceLabs Healthcare, Issaquah, WA). Blood pressure measurements were collected every 20 minutes during the day and night, and the child and family kept a diary recording wake, sleep, and any medications given while wearing the monitor [10]. HTN by ABPM was defined by systolic or diastolic BP index >1 (subject's mean systolic or diastolic BP/95th% BP for gender and height) or systolic or diastolic BP load >25% [11].

Measurement of HRQoL

HRQoL was evaluated in all children using the 23-item Parent and Child Report Pediatric Inventory of Quality of Life Core Scales (PedsQL™, Version 4.0) [12, 13]. The PedsQL assesses the problem frequency within the domains of physical, emotional, social, school, and overall functioning. This study focused on HRQoL domains of physical, school, and overall functioning. Responses are summed and linearly transformed into a score ranging from 0–100, with higher scores suggesting a better HRQoL.

Statistical analysis

Data analysis included cross-sectional description of the sample at the first available study visit. To investigate the hypothesized relationship between hypertension and HRQoL domain scores in children with CKD, a cross-sectional analysis compared HRQoL scores by prehypertensive and hypertensive status defined as either: 1) systolic and/or diastolic BP ≥ 90th percentile for age, sex, and height, or 2) self-reported diagnosis of hypertension combined with current antihypertensive medication use. Similar analysis of ABPM data used systolic or diastolic load ≥ 25% in place of BP ≥ 90th percentile. Wilcoxon rank-sum tests were used to compare HRQoL scores between groups.

We then utilized longitudinal measurements in the cohort to analyze the impact of a change of 0.05 in BP index or 5% in BP load on HRQoL domain scores. For each of the six different HRQoL outcomes as measured by PedsQL (Parent and Child Overall, Physical, and School), and each of four main predictors of interest (Systolic and Diastolic BP Index and ABPM Load), a median regression model was used controlling for potential confounders including age, sex, African-American race, Hispanic ethnicity, maternal education, low birth weight, height z-score, GFR baseline and annual rate of change, duration of CKD, and nephrotic range proteinuria (urine protein to creatinine ratio > 2 mg/mg).

To analyze if the presence of HTN or no HTN impacted HRQoL domain scores in children with CKD, longitudinal measurements were also performed. Dichotomous HTN was interacted with age in order to assess the effect of HTN over time. Additionally, to determine whether antihypertensive medications affected HRQoL, a categorical variable for number of medications (none, 1, or 2 or more) was included in all models. Confidence intervals were obtained by bootstrapping with 2000 replicates at the subject level to account for clustering of observations.

Results

Data on blood pressure and quality of life were available for 551 subjects, contributing a total of 2,376 visits. Ambulatory blood pressure measurements were available for 396 of these subjects, with 673 total visits. Descriptive statistics of subjects at their first visit are found in Table 1. A higher number of subjects had a non-glomerular etiology for CKD compared to subjects with a glomerular etiology for CKD, 434 (79%) versus 117 (21%) subjects, respectively. Of the 548 subjects with known blood pressure status, 384 (69.7%) were normotensive with 236 of these subjects on antihypertensive medications; 164 (29.8%) had elevated blood pressures with 101 of these subjects on antihypertensive medications; and 3 of the 551 subjects were missing blood pressure status (Table 2). At the first visit with ABPM data available, 155 (39%) of 396 subjects had either a systolic or diastolic load of 25% or higher. Of the 551 subjects included in the analysis, 318 (58%) did not have complete follow-up, including 172 (31%) renal replacement therapy (dialysis or transplant) events, 143 (26%) with loss to regular follow-up (withdrawal, age-out, etc.), and 3 deaths. Of the CKiD cohort of 510 subjects with a least one post-baseline visit, 350 of 506 (69%, 4 with missing data) had a negative GFR annual slope. GFR did decline over the observed follow-up period.

Unadjusted cross-sectional analysis of PedsQL scores and hypertensive status suggested several statistically significant, though not clinically meaningful, differences between hypertensive status (defined, as described above, as elevated BP or self-reported hypertension plus BP medication use) and HRQoL scales (Table 3). With casual BP measurements, both parent- and child-rated overall HRQoL was lower among hypertensive children ($p=0.01$ and 0.03 respectively), though the magnitude of the difference in median scores was minor (3 and 2 points respectively). Parent-rated school HRQoL was a median 10 points lower among hypertensive children ($p=0.003$), though this was only 5 points lower for child ratings ($p=0.052$). Neither parent- nor child-rated physical HRQoL was significantly lower among hypertensive children. Using the definition of hypertension based on ambulatory rather than casual measurements, all three parent-rated scales were lower among hypertensive children compared to normotensive children, with the greatest difference on the overall scale (84.5 vs. 78, $p< 0.001$). Children rated themselves lower only on the school subscale (75 vs. 65, $p=0.007$).

Median regression models incorporating longitudinal data where the primary predictor is either presence of prehypertension or HTN, defined as systolic and/or diastolic BP $\geq 90^{th}$ percentile, systolic and/or diastolic ABPM load >25%, or self-reported HTN plus use of antihypertensive medications, or no presence of HTN. These models did not find a

significant relationship between HTN and HRQoL over time (Table 4). Largest effect was presence of HTN on Child Physical HRQoL with corresponding decrease in HRQoL of 12.49 points (95% CI, −21.74 to −2.26).

Median regression models incorporating longitudinal data and continuous rather than dichotomous BP measurements did not find a relationship between casual BP index or ABPM load on HRQoL (Table 5). For instance, using systolic BP index as the primary predictor and parent overall HRQoL as the outcome with covariates listed above, an increase of 0.05 in systolic BP index was associated with a corresponding decrease in HRQoL of 0.24 points (95% CI, −0.93 to 0.41). The largest effect magnitudes were seen on parent and child school HRQoL, though no effects reached statistical significance in these adjusted models.

At baseline, 339 subjects were on BP medications (see Table 2), including 53% being on an angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB). Median regression analysis did not find any association between number of antihypertensive medications used and HRQoL (see Table 6a and 6b).

Discussion

The goal of this study was to determine if elevated BP and/or antihypertensive medication use had a negative impact on HRQoL in children with CKD. As opposed to findings in studies conducted in hypertensive adults, this analysis in children found that while the presence of HTN or history of HTN on antihypertensive medications was associated with lower parent and child HRQoL scores, these differences in PedsQL scores were not clinically significant, and did not persist over time.

Over the past two decades from 1990 through 2010, the incidence of CKD in children has steadily increased, with HTN as a common complication and a potentially modifiable risk factor for disease progression [14–16]. End-organ disease, medication adverse effects, and labeling phenomenon due to HTN are all factors that may contribute to poorer self-related health and reduction in HRQoL [17–19]. Determining what features of CKD and cardiovascular disease impact HRQoL is of great interest to better understand how providers may customize care to be patient-centered with a focus on psychosocial and emotional issues with hopes of improving overall health.

The lack of a relationship between HTN and HRQoL in children with mild to moderate CKD may be due to children having fewer limiting physical and cardiovascular co-morbidities compared to adults. Older adults with cardiovascular disease, including congestive heart failure, myocardial infarction, and/or angina, reported lower physical and mental health HRQoL scores [4]. Although children with HTN tend not to have as severe cardiovascular disease as seen in adults, investigation of predictors of cardiovascular events in the CKiD cohort has previously revealed significantly elevated median carotid intima-media thickness (cIMT) that was 0.02 mm larger (95% confidence interval, 0.01–0.05) compared to healthy controls and 17% had LVH [20, 21]. Determination of the impact of HTN on end-organ damage in children with CKD and the association with HRQoL is

difficult since etiology of findings, such as proteinuria and impaired cognition, are often multifactorial.

Symptom burden is another factor that has been shown to negatively impact HRQoL in adults with advanced CKD and on dialysis.[22, 23]. To study the impact of symptom burden in children with chronic medical conditions, Kim et al classified children into 3 groups, those with low-, moderate-, or high-symptoms, and assessed the impact on quality of life [24]. Children who reported the most problems with symptoms had the lowest HRQoL scores [24]. Roumelioti et al found a strong association between trouble sleeping, low energy, and lower HRQoL scores in children with mild to moderate CKD [25]. Similar to findings in our analysis, Roumelioti did not find a relationship between HTN, antihypertensive medication use, symptom burden, and HRQoL [25]. Whereas chronic HTN is often thought to be an asymptomatic condition with a lower symptom burden that may have less of an impact on HRQoL, studies in both adults and children suggest this is not the case [26, 27]. One pediatric study evaluated 343 hypertensive children without CKD and found the majority were not symptom free [28]. Most common symptoms included headache, trouble falling asleep, tiredness, chest pain, abdominal pain, school failure, and poor concentration [28]. As we did not specifically question participants regarding HTN-related symptoms, we cannot comment on whether a lack of such symptoms might have contributed to a lack of effect of HTN on HRQoL. Alternatively, other CKD-related symptoms may dominate, masking the effect of symptoms specific to HTN.

Evaluating if there is an effect of antihypertensive medications on HRQoL is important since many children with CKD require medications to adequately control their blood pressure within the goal of $<90^{th}$ percentile for age, gender, and height or <130/80, whichever is lower [29]. Studies have shown that aggressive control of BP slows the progression of CKD, though studies assessing the impact of therapy on HRQoL are lacking [14]. In this study, our analysis of subject's use of antihypertensive medications did not negatively affect child or parent HRQoL domain scores. Use of an ACE inhibitor or ARB antihypertensive medication is recommended as first line therapy for HTN in children with CKD [17, 29]. More than half of the CKID subjects were on an ACE inhibitor or ARB, which tend to have a lower symptom burden than other antihypertensive medications, such as beta blockers [19].

Limitations of this study include the observational study design and the fact that the population may not be generalizable to all children with mild to moderate CKD. In particular, the CKiD cohort racial distribution and cause of CKD may differ from the general population of youth with kidney disease. Another limitation of this analysis is that it may not be possible to discern an independent effect of HTN on HRQoL due to the many other factors that are present in children with CKD. For instance, higher pill burden, poor linear growth, poor school functioning have all been associated with lower HRQoL [3, 6, 30]. However, the study also has notable strengths, including a large population of children with mild to moderate CKD whose blood pressures were measured by casual and ABPM measurements and PedsQL scores that were repeated longitudinally.

Conclusion

No clinically meaningful association was found between presence of elevated blood pressures/HTN and decreased HRQoL at baseline or between changes in HTN and HRQoL over time in children with mild to moderate CKD. In addition, antihypertensive medication use was not associated with decline in HRQoL in this population.

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Table 1

Baseline demographics of subjects

Characteristic	Median [IQR] or n (%)
Covariates	
Total number of subjects	551
Age, years	11.5 [7.9, 15.1]
Male sex	342 (62%)
African-American	124 (23%)
Hispanic	80 (15%)
Maternal Education	
High School or less	229 (43%)
Some college	146 (27%)
College or more	163 (30%)
Low birth weight	101 (19%)
Height z-score	−0.7 [−1.4, 0.0]
GFR[a], ml/min/1.73 m^2	44.6 [33.4, 58.0]
Duration of CKD, years	6.4 [3.1, 10.3]
Glomerular CKD diagnosis	117 (21%)
Nonglomerular CKD diagnosis	434 (79%)
Urine Protein/Creatinine, mg/mg	0.4 [0.2, 1.1]
Urine Protein/Creatinine > 2, mg/mg	69 (13%)

IQR = interquartile range, n = number of subjects,

[a]GFR = glomerular filtration rate measured by iohexol or estimated by Schwartz equation [7]:

$$\mathrm{eGFR} = 39.8 * [\mathrm{ht(m)/Scr}]^{0.456} [1.8/\mathrm{cysC}]^{0.418} [30/\mathrm{BUN}]^{0.079} 1.076^{\mathrm{male}} [\mathrm{ht(m)}/1.4]^{0.179},$$

$$\mathrm{CKD} = \mathrm{chronic\ kidney\ disease}.$$

Table 2

Diagnosis of hypertension, antihypertensive medication use, and baseline blood pressures

Characteristic	Median [IQR] or n (%)
Subjects with self-reported diagnosis of hypertension and on antihypertensive medications	242 (45%)
All antihypertensive medication use	
Any	339 (62%)
ACEi/ARB	292 (53%)
Other	47 (9%)
Subjects with known BP status[a]	548
Normotensive on BP medications	236 (43%)
Elevated blood pressures on BP medications	101 (18%)
Blood Pressure	
Systolic BP Index[b]	0.88 [0.82, 0.94]
Diastolic BP Index[b]	0.84 [0.75, 0.94]
Systolic or Diastolic BP percentile ≥ 90	164 (30%)
Systolic ABPM Load[c]	11 [3, 30]
Diastolic ABPM Load[c]	11 [4, 26]
ABPM Systolic or Diastolic load[c] ≥25%	155 (39%)

IQR = interquartile range, n = number of subjects, ACEi = Angiotensin-converting-enzyme inhibitor, ARB = Angiotensin receptor blocker, BP = blood pressure,

[a] BP status unknown for 3 of the 551 subjects (2 in medication group and 1 in no medications),

[b] BP index = casual BP divided by the 95th percentile systolic or diastolic BP for age, gender, and height,

[c] ABPM loads from first available visit.

Table 3

Baseline comparisons of parent and child HRQoL outcomes by normotensive versus prehypertensive/ hypertensive status

HRQoL Outcome	Casual BP Normotensive (n=242) Median [IQR]	Casual BP Pre- and Hypertensive (n=309) Median [IQR]	p-value
Parent Overall	79 [66, 90]	76 [62, 87]	0.01
Parent Physical	84 [69, 97]	84 [66, 94]	0.27
Parent School	70 [50, 85]	60 [45, 80]	0.003
Child Overall	79 [68, 88]	77 [65, 84]	0.03
Child Physical	84 [72, 94]	81 [69, 94]	0.16
Child School	70 [55, 80]	65 [50, 75]	0.052
	ABPM Normotensive (n=151)	ABPM Hypertensive (n=245)	p-value
Parent Overall	84.5 [68, 92]	78 [62, 88]	0.0009
Parent Physical	91 [75, 100]	86 [69, 97]	0.009
Parent School	70 [60, 90]	65 [50, 85]	0.005
Child Overall	82 [69, 90]	79 [68, 87]	0.14
Child Physical	84 [72, 94]	84 [75, 94]	0.86
Child School	75 [60, 85]	65 [55, 80]	0.007

HRQoL = Health related quality of life, BP = blood pressure, n = subjects, IQR = interquartile range, ABPM = ambulatory blood pressure monitoring

Table 4

Summary of longitudinal median regression models comparing HRQoL by blood pressure status over time

QOL Outcome	HTN[a] or Normotensive (CI)	HTN[a] X Age (CI)
Parent Overall	−6.59 (−12.83, 0.43)	0.45 (−0.07, 0.98)
Parent Physical	−2.02 (−10.18, 4.85)	0.22 (−0.29, 0.89)
Parent School	−9.21 (−20.29, 0.13)	0.46 (−0.20, 1.33)
Child Overall	−7.55 (−16.33, 1.90)	0.57 (−0.08, 1.22)
Child Physical	−12.49 (−21.74, −2.26)	0.97 (0.26, 1.59)
Child School	−6.53 (−18.12, 9.67)	0.46 (−0.71, 1.27)

HRQoL = health related quality of life, HTN = hypertension, CI = confidence interval,

[a]HTN = hypertension that includes prehypertension, hypertension, and/or self-reported HTN plus use of antihypertensive medications.

Table 5

Summary of longitudinal median regression models comparing HRQoL and continuous blood pressure values over time

BP Predictor HRQoL Outcome	Systolic BP Index[a] per 0.05 (CI)	Diastolic BP Index[a] per 0.05 (CI)	Systolic ABPM Load per 5% (CI)	Diastolic ABPM Load per 5% (CI)
Parent Overall	−0.24 (−0.93, 0.41)	−0.39 (−0.81, 0.07)	−0.10 (−0.72, 0.39)	−0.33 (−0.86, 0.34)
Parent Physical	−0.13 (−0.86, 0.66)	−0.09 (−0.67, 0.32)	0.22 (−0.48, 0.60)	0.00 (−0.73, 0.63)
Parent School	−0.56 (−1.42, 0.46)	−0.47 (−1.09, 0.11)	−0.45 (−1.23, 0.36)	−0.20 (−1.02, 0.53)
Child Overall	0.27 (−0.31, 0.82)	−0.12 (−0.52, 0.28)	0.08 (−0.45, 0.40)	−0.17 (−0.60, 0.34)
Child Physical	0.13 (−0.55, 0.82)	−0.19 (−0.58, 0.33)	−0.08 (−0.61, 0.36)	−0.13 (−0.72, 0.41)
Child School	−0.24 (−1.17, 0.56)	−0.50 (−1.12, 0.04)	−0.32 (−1.04, 0.17)	−0.73 (−1.22, 0.08)

HRQoL = health related quality of life, BP = blood pressure,

[a]BP index = casual BP divided by the 95th percentile systolic or diastolic BP for age, gender, and height, CI = confidence interval

Table 6a

Blood pressure medication usage at baseline and over time regardless of blood pressure status

	No BP meds (n)	1 BP med (n)	2 or more BP meds (n)
Baseline (n=551)	38.5% (212)	41.7% (230)	19.8% (109)
All visits (n=2376)	36.0% (855)	44.5% (1058)	19.5% (463)

BP = blood pressure, n = number of subjects

Table 6b

Effect of blood pressure and number of antihypertensive medication use on HRQoL

Systolic BP Predictor on BP medication HRQoL Outcome	**Systolic BP Index[a] per 0.05 1 med (CI)**	**Systolic BP Index[a] per 0.05 2+ meds (CI)**	**Systolic Load ABPM per 5% 1 med (CI)**	**Systolic Load ABPM per 5% 2+ meds (CI)**
Parent Overall	1.57 (−1.95, 3.84)	0.77 (−4.02, 3.97)	1.81 (−3.89, 6.02)	4.16 (−3.63, 9.56)
Parent Physical	2.14 (−0.72, 5.38)	0.62 (−4.09, 5.41)	4.26 (−0.60, 10.34)	1.53 (−4.72, 10.43)
Parent School	0.22 (−4.27, 3.95)	−2.12 (−7.59, 2.96)	−1.54 (−8.17, 5.04)	1.48 (−8.51, 9.82)
Child Overall	1.44 (−1.15, 3.43)	−1.15 (−4.75, 1.85)	2.03 (−1.43, 6.00)	1.72 (−4.96, 5.93)
Child Physical	2.03 (−0.78, 4.35)	−1.79 (−5.47, 1.81)	1.20 (−1.76, 6.87)	−0.99 (−5.24, 6.58)
Child School	1.84 (−2.13, 4.70)	−0.37 (−6.19, 3.88)	−0.98 (−5.27, 6.02)	2.56 (−4.21, 9.65)
Diastolic BP Predictor on BP medication HRQoL Outcome	Diastolic BP Index[a] per 0.05 on 1 med (CI)	Diastolic BP Index[a] per 0.05 2+ meds (CI)	Diastolic Load ABPM per 5% 1 med (CI)	Diastolic Load ABPM per 5% 2+ meds (CI)
Parent Overall	1.66 (−1.94, 3.75)	1.10 (−4.25, 3.95)	0.64 (−3.99, 5.56)	4.34 (−4.09, 9.39)
Parent Physical	2.25 (−0.85, 5.30)	0.84 (−4.32, 5.45)	4.26 (−0.71, 10.10)	2.54 (−4.69, 10.56)
Parent School	0.49 (−4.44, 3.72)	−2.49 (−7.83, 2.78)	−0.89 (−7.90, 5.42)	1.15 (−9.06, 9.98)
Child Overall	1.15 (−1.22, 3.29)	−1.44 (−4.64, 1.63)	2.58 (−1.56, 5.88)	0.78 (−5.05, 5.80)
Child Physical	1.74 (−0.91, 4.20)	−1.81 (−5.42, 1.83)	1.11 (−1.75, 6.64)	−1.42 (−5.65, 6.81)
Child School	1.71 (−2.47, 4.64)	−0.87 (−6.19, 3.62)	−0.50 (−5.36, 5.72)	2.88 (−4.46, 8.88)

HRQoL = health related quality of life, BP = blood pressure,

[a]index = Casual BP divided by the 95th percentile systolic or diastolic BP for age, gender, and height, ABPM = ambulatory blood pressure monitoring, CI = confidence interval,