The Role of Central Aortic Pressure in the Management of High Blood Pressure

Agenda

- Problem
- Central Aortic Pressure as a Predictor of Cardiovascular (CV) Events
- Central Aortic Pressure Threshold Values for Management Decisions
- How to Use Central Aortic Pressure
- Summary

Problem

Hypertension: Continued Adverse Socioeconomic Impact

Epidemiology (USA)

- Prevalence ≈45% of adults[1]
- Responsible for ≈500,000 deaths[2]
- CDC reports that hypertension is under control in only 24% of patients[2]

Economics

- Average annual medical expenditure attributable to hypertension = $9,089 per diagnosed patient[3]
- Relative to non-hypertensives: $1,920 higher annual adjusted incremental expenditure, 2.5x inpatient cost, 2x outpatient cost, and 3x prescription medication costs[3]
- Adjusted annual incremental cost = $131 billion/year higher for adults with hypertension relative to adults without hypertension[3]

1. CDC. Hypertension Cascade: Hypertension Prevalence, Treatment and Control Estimates Among US Adults Aged 18 Years and Older Applying the Criteria from the American College of Cardiology and American Heart Association's 2017 Hypertension Guideline—NHANES 2013–2016.; 2. CDC. Underlying Cause of Death, 1999–2018. CDC WONDER Online Database. Atlanta, GA: Centers for Disease Control and Prevention; 2018. http://wonder.cdc.gov/ucd-icd10.html. Accessed March 12, 2020; 3. Kirkland et al. Trends in Healthcare Expenditures Among US Adults With Hypertension: National Estimates, 2003–2014 J Am Heart Assoc. 2018;7:e008731. DOI: 10.1161/JAHA.118.008731.)

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Hypertension Management

Why are there ongoing problems with hypertension management?

- Various reasons: case finding (early diagnosis), continuity and continued follow-up of care, affordability of care, medication adverse effects and medication compliance, challenges in modifying lifestyle behavior

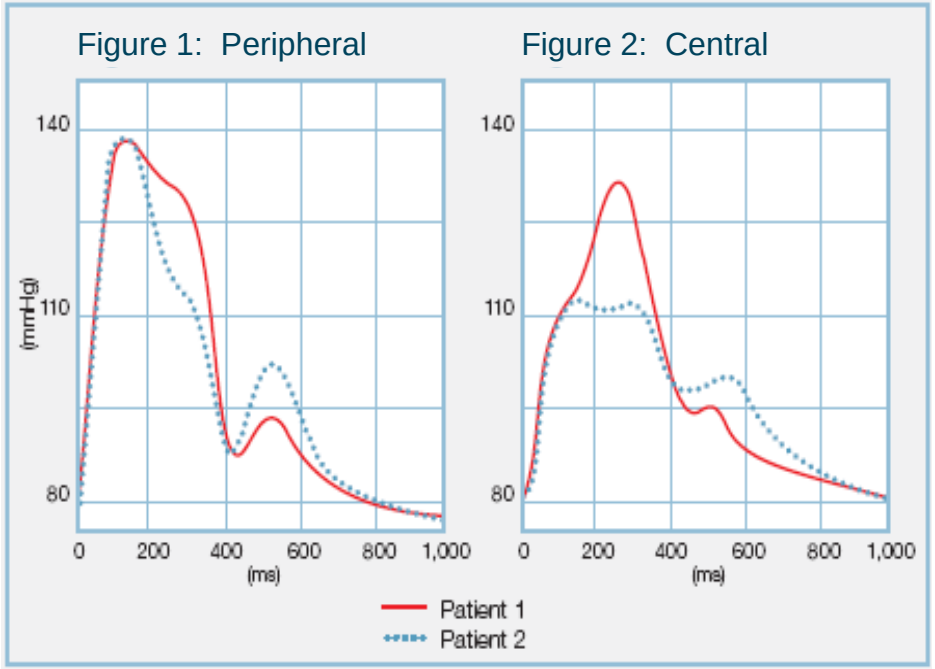
Additional issue: current monitoring based on brachial blood pressure

- Variable precision and reliability of measuring brachial BP (patient and health care provider factors)
- Brachial BP is a surrogate for central (i.e., aortic) blood pressures, which represent the actual pressures that are transmitted to organs effected by hypertension (e.g., heart, brain, kidney)
- Cuff brachial blood pressure measurement “is not so much a surrogate, but a compromised measure that is recorded because of technical limitations.” (Cheng et al)[1]

1. Cheng et al. Derivation and validation of diagnostic threshold for central blood pressure measurements based on long-term cardiovascular risks. J Am Coll Cardiol. 2013;62:1780-7.

Additional Clinical Tools for Management: Non-Invasive Measurement of Central Aortic Pressure

- Non-invasive pulse wave analysis (PWA) is a technique that transforms the data from peripheral arterial pressure waveforms obtained into an evaluation of central aortic pressures
- Calculations are performed through a generalized transfer function that corrects for pressure wave amplification in the upper limb
- Variables produced:
  - Central aortic systolic and diastolic pressures
  - Central aortic pulse pressure (systolic minus diastolic pressure)
  - Augmentation pressure (difference between (a) reflected wave added to incident wave, and (b) incident pressure during systole)
  - Augmentation index (augmentation pressure divided by the pulse pressure)
- Peripheral (brachial) blood pressures are highly correlated to central pressures
  - Brachial systolic pressure is higher than central aortic systolic pressure
  - Diastolic pressures are similar



The SphygmoCor® XCEL System

Dual Arterial Pressure Monitoring System

- Obtains brachial pressures immediately followed by measurement of central aortic pressures
- Performed in the same session
- The only FDA cleared medical device for non-invasive central arterial pressure waveform analysis in adults

Brachial and Central Aortic BP Measurement in the Same Session with the Same Equipment

Arterial Waveform Capture

- A cuff is applied on the upper arm in the standard position
- The cuff is partially inflated to record the brachial waveforms
- These waveforms are detected by sensing changes in the pressure inside the cuff related to arterial pulsation
- The ascending aortic waveform is subsequently derived using a validated mathematical transfer function*

Brachial and Central Aortic BP Measurement in the Same Session with the Same Equipment

*Generalized transfer function cleared by FDA

Central Aortic Pressure Predicts End-Organ Damage and Cardiovascular Events

Central BP Predicts End-Organ Damage and Cardiovascular Risk

End-organ damage associated with hypertension is directly related to central pressures as these, rather than peripheral pressures, are the pressures that are transmitted to vital organs

Central systolic pressures

- Correlated to but incompletely predicted by peripheral systolic pressures
  - correlation coefficients 0.6 to 0.97
- Multiple studies indicate that central BP is at least as predictive for CV risk and end-organ damage as peripheral blood pressure with some studies indicating superiority
- Data supports central systolic pressure as an independent predictor of CV risk

Objective of hypertension management

- Data provide rationale for goal of lowering central systolic pressures to values (or thresholds) that correspond to the targets set for peripheral systolic pressures for the purpose of reducing vascular risk

Elevated Central BP is Associated with End-Organ Damage

Study Objective: determine relationship of blood pressures to organ damage

Subjects: N= 1,169, ≥ 16 years old, randomly recruited from Johannesburg, South Africa

Brachial BP (mm Hg)	**Optimal** <120/80	**Normal/High Normal** ≥120/80 + <140/90		**Hypertension** ≥140/90 or Treatment
Aortic Systolic BP (mm Hg)	-	**<112**	**≥112**	-
Unadjusted Values				
eGFR (ml/min/1.73m^2) (n)	128±32 (244)	126±32 (108)	111±26 (149)	103±28 (443)
LVMI (g/m^2) (n)	35.5±10.2 (181)	38.2±11 (82)	44.0±12.1 (109)	47.5±15.8 (318)
Adjusted Values				
eGFR (ml/min/1.73m^2) (n)	118±29 (244)	115±27 (108)	108±26 (104)	112±30 (443)
LVMI (g/m^2) (n)	40.0±14.3 (181)	40.7±13.2 (82)	44.5±12.6 (109)	44.0±14.6 (318)

Central pressure added relevant data determining risk of end-organ damage

eGFR: estimated glomerular filtration rate; LVMI left ventricle mass index
Multivariate adjustment for age, sex, BMI, diabetes mellitus and/or an HbA1c>6.1%, regular tobacco use, regular alcohol intake and pulse rate.

Booysen et al. Aortic, but not brachial blood pressure category enhances the ability to identify target organ changes in normotensives. J Hypertension 2013;31:1124-30.

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Central BP Relates to CV Mortality

1,272 normotensive and untreated hypertensive (SBP ≥140 or DBP ≥90 mmHg) participants

Baseline values correlated to laboratory and clinical outcomes over a period of up to 10 years

Hazard ratios and 95% CI for all-cause and CV mortality by univariate analysis.

	All-Cause Mortality		CV Mortality	
	Women	**Men**	**Women**	**Men**
Brachial Systolic BP (per 10 mm Hg)	1.15 (1.04-1.27)	1.11 (1.00-1.22)	1.30 (1.08-1.55)	1.33 (1.11-1.60)
Central Aortic Systolic BP (per 10 mm Hg)	1.23 (1.12-1.36)	1.11 (1.01-1.23)	1.51 (1.27-1.80)	1.35 (1.50-1.59)

Elevated central pressure were associated with increased risk of CV and all-cause mortality

Wang et al. Central or peripheral systolic or pulse pressure: which best relates to target organs and future mortality? J Hypertension 2009; 27: 461–467.

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Central BP Relates to CV Mortality

Multivariate Cox proportional hazards regression models relating incidence of cardiovascular mortality to dual blood pressure components of SBP-B, PP-B, SBP-C, and PP-C (HR = Hazard Ratio)

		HR/10 mm Hg (CI)	HR/SD increment (CI)
Model 2	Brachial Systolic BP	0.957 (0.787–1.164)	0.902 (0.567–1.434)
	Central Aortic Systolic BP	**1.336 (1.107–1.612)***	**2.002 (1.276–3.140)***

Central pressure was an independent predictor of CV risk

***p<0.05**

All adjusted for age, sex, heart rate, BMI, current smoking, fasting plasma glucose levels, cholesterol/HDL ratio, carotid-femoral pulse wave velocity, LVM, IMT, and eGFR

Wang et al. Central or peripheral systolic or pulse pressure: which best relates to target organs and future mortality? J Hypertension 2009; 27: 461–467.

Central BP Predicts CV Events

Study

- Design: meta-analysis from International Database of Central Arterial Properties for Risk Stratification.
- Objective: examine thresholds for central aortic systolic BP (cSBP) associated with clinical outcomes and whether cSBP, either alone or in combination with brachial systolic BP (bSBP) improved risk stratification
  - 5,576 subjects (mean age 54.2 years, 54% women)

Results

	Central Systolic Normotension (NT)		Central Systolic Hypertension (HT)	
	Brachial NT	Brachial HT	Brachial NT	Brachial HT
Number at risk	2403	277	209	2687
Systolic BP thresholds, mm Hg				
Central	<120	<120	≥120	≥120
Brachial	<130	≥130	<130	≥130
Primary end-point				
HR (95% CI)	1 (reference)	1.30 (0.58–2.94)	2.28 (1.21–4.30)‡	2.02 (1.41–2.91)†
Secondary end points				
Mortality HR (95% CI)	1 (reference)	1.03 (0.44–2.43)	0.54 (0.20–1.51)	1.05 (0.74–1.48)
Cardiac end-point HR (95% CI)	1 (reference)	1.26 (0.62–2.60)	1.15 (0.56–2.36)	1.37 (0.97–1.91)*
Cerebrovascular end-point HR (95% CI)	1 (reference)	2.21 (0.62–7.97)	3.71 (1.37–10.06)*	2.60 (1.35–5.00)*

*p<0.01
†p<0.001
‡p<0.05

relative to the reference group

Conclusion

"Irrespective of the brachial blood pressure status, central hypertension increased cardiovascular and cerebrovascular risk indicating the importance of controlling central hypertension."

Cheng Y, Thijs L, Aparicio LS, Huang Q, Wei F, et al. Risk stratification by cross-classification of central and brachial systolic blood pressure. Hypertension. 2022;79:00–00. DOI:10.1161/HYPERTENSIONAHA.121.18773.

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Central Pressure Threshold Values for Management Decisions

Threshold Values for Central Aortic Systolic BP and CV Outcomes

Study

Objective: determine thresholds for prediction of CV outcomes

Design

- Derivation cohort (1,272 individuals, *median follow-up of 15 years*)
  - Determined diagnostic thresholds based on brachial BP cut-offs with a bootstrapping method (resampling by drawing randomly with replacement) and an approximation method.
- Validated with an independent cohort (validation cohort, 2,501 individuals, *median follow-up of 10 years*)

Results (Proposed Threshold Values for Central Aortic Pressure)

Optimal: <110/80 mmHg

Prehypertension: 110-129 / 80-89 mm Hg

- corresponding to “elevated” and Stage 1 hypertension (2017 Guidelines)

Hypertension: ≥130/90 mm Hg

- corresponding to Stage 2 hypertension (2017 Guidelines)

Cheng et al. Derivation and validation of diagnostic threshold for central blood pressure measurements based on long-term cardiovascular risks. J Am Coll Cardiol. 2013;62:1780-7.

Threshold Values: Associations of Systolic Pressures with MACE*

Prospective study

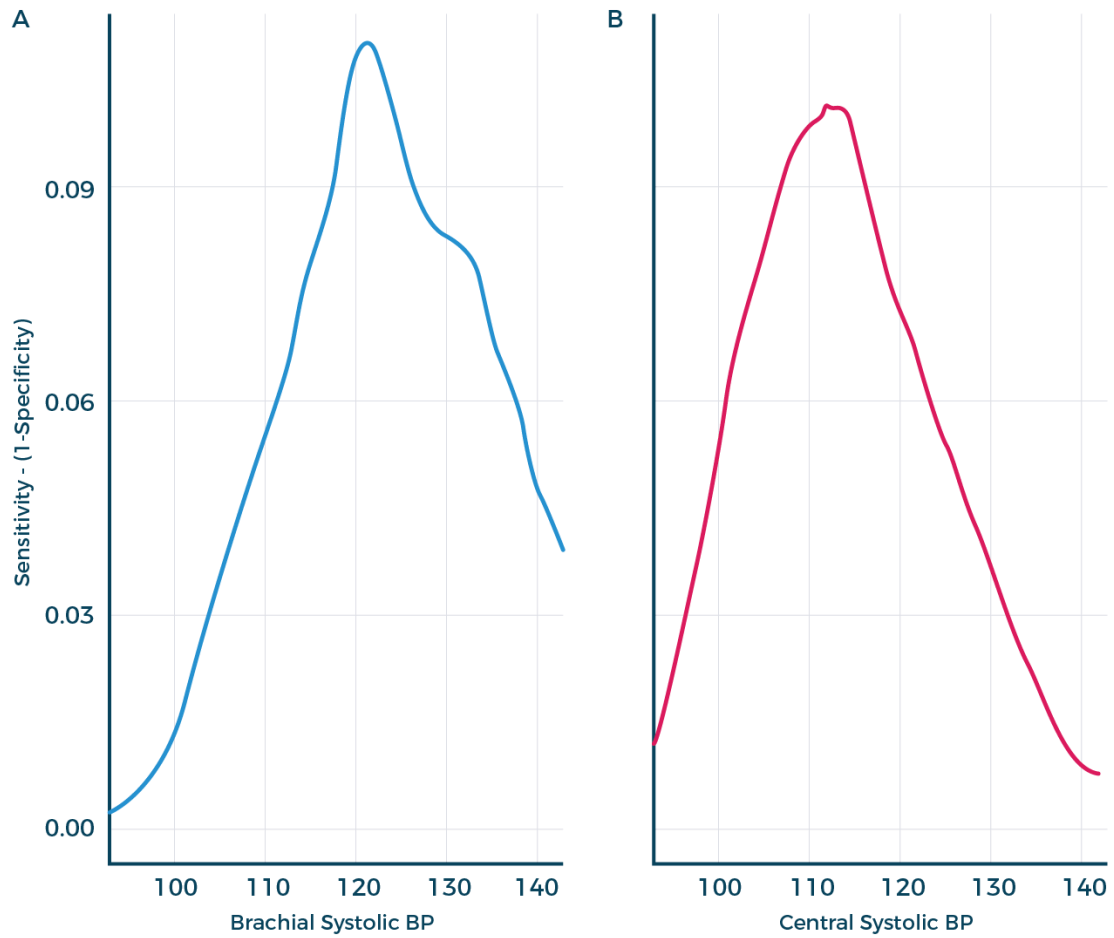
- 13,461 patients using available central blood pressure measurements and follow-up data from administrative databases
- 1,327 MACE, median follow-up ≈9 years)

Hazard ratio for risk of MACE* (for 1 SD increase)

- Central SBP 1.16 (95% CI 1.09-1.22)
- Brachial SBP 1.15 (95%CI 1.09-1.22)
- Modeling data (AUC) for risk indicated a slightly higher risk using cSBP vs. brachial SBP that was statistically significant

Conclusion

- Central and brachial SBPs of 112 mm Hg (95% CI, 111.2–114.1) and 121 mm Hg (95% CI, 120.2–121.9) were identified as optimal BP thresholds.



Optimal brachial and central systolic blood pressure thresholds.

Youden index according to **(A)** brachial systolic blood pressure (BP) and (B) central systolic BP. Youden index is the maximal value obtained, a brachial systolic BP threshold of 121mmHG (95%CI, 120.1-121.9 mmHG) and a central systolic BP threshold of 112 mmHG (95% CI, 111.2-114.1 mmHG).

*MACE: Major Adverse Cardiovascular Events

Lamarche et al. Prediction of cardiovascular events by type I central systolic blood pressure. A prospective study. Hypertension 2021;77:319-327.

How to Use Central Aortic Pressure in Management Decisions

Optimizing Hypertension Pharmacotherapy

Incorporation of PWA into the treatment paradigm for hypertension (i.e., in addition to brachial pressure monitoring) can provide clinically relevant value to patient care:

1. Confirmation of hypertension so that initiation of medication is more likely to be the correct decision for an individual patient

   Scenario: Concurrent elevation in brachial and central pressures

2. Avoiding initiation of medication when white coat hypertension is suspected

   Scenario: Elevated brachial pressure and normal central pressures

3. Confirmation that increased treatment may not be needed

   Scenario: Borderline high peripheral pressures and normal central pressures

4. Targeting when to consider reduction of medication

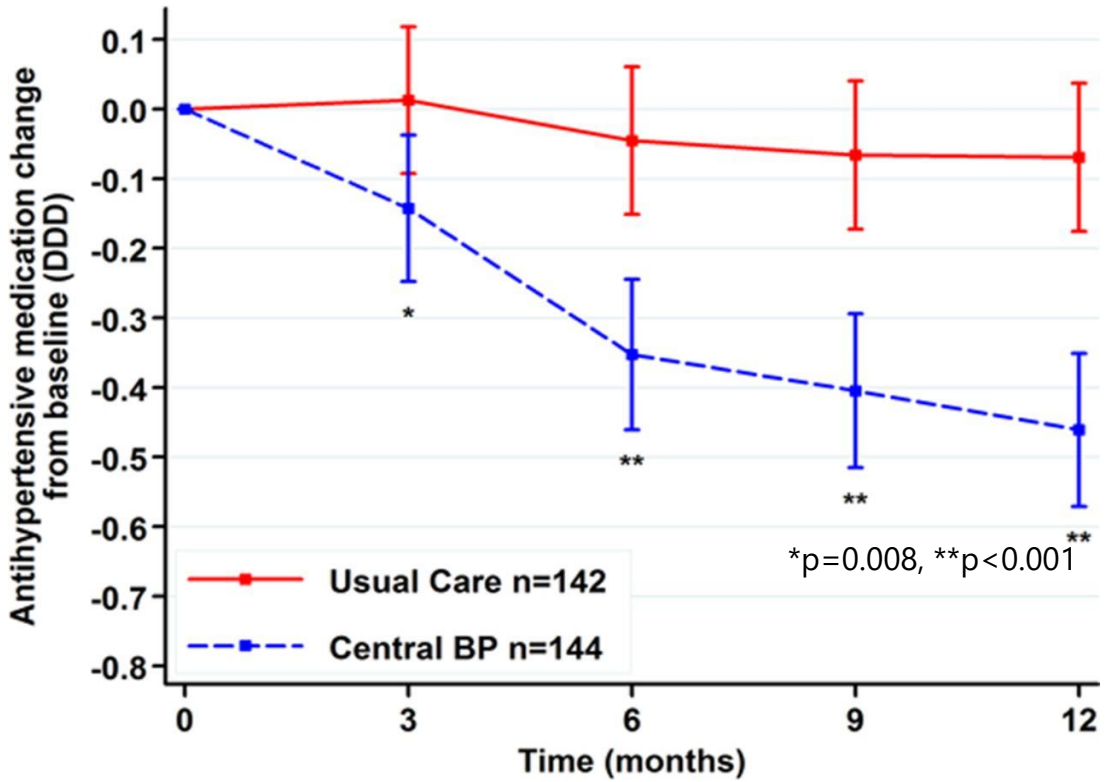
   Scenario: Normal peripheral and low central pressures, or extended period of normal peripheral and normal central pressures (particularly in the setting of medication tolerance issues)

Using Central Arterial Pressure to Guide Hypertension Management

BP Guide Study

- 286 hypertensive patients randomized to best-practice brachial BP management* +/- PWA
- Hypertension management guided by PWA resulted in significantly less medication needed to maintain brachial BP control
- 16% of PWA guided patients had complete cessation of medication vs. only 2% of usual care
- No adverse effects on LV mass, aortic stiffness, or quality of life in the PWA guided treatment cohort

Between-group change in daily defined dose (DDD) of antihypertensive medications.



*Best-practice usual care included office, home, and 24-hour ambulatory blood pressure

Sharman et al. Randomized trial of guiding hypertension management using central aortic blood pressure compared with best-practice care. Principal findings of the BP Guide Study. Hypertension 2013;62:1138-45.

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Morbidity from Hypertension Medications

- Overtreatment may occur if office-based cuff measurements are misleadingly high
- Potential consequences of over-treatment
  - Adverse effects specific to the medication class (e.g., cough with ACE inhibitors)
  - Adverse effects common to all anti-hypertensive medications (i.e., hypotension)
- Elderly patients are likely more susceptible to hypotension and associated adverse consequences
- Association of BP with CV events appears to be bimodal with higher rates at both low and high blood pressures.[1]
- Several studies have noted an increased mortality in elderly patients related to lower treated blood pressure.[2,3]
- Reduced kidney function was associated with lower BP in a study in older subjects.[4]
- Older hypertensive patient have an increased risk of postural hypotension, balance and gait impairment, confusion, and dizziness.[5]
- Increased risk for injuries related to falls may result from overly aggressive treatment of hypertension.[5]

Rationale for Incorporating Central Aortic BP to Optimize Pharmacotherapy

1. Bangalore et al. J-curve revisited: An analysis of blood pressure and cardiovascular events in the Treating to New Targets (TNT) Trial. Eur Heart J. 2010; 31(23): 2897–2908. 2. Kovesdy et al. Blood pressure and mortality in U.S. veterans with chronic kidney disease. A cohort study. Annals Intern Med. 2013; 159(4):233–242. 2.Sim et al. Impact of achieved blood pressures on mortality risk and end-stage renal disease among a large, diverse hypertension population. JACC. 2014; 64(6):588–597. 4. Cushman et al. Effects of intensive blood-pressure control in type 2 diabetes mellitus. N Engl J Med. 2010; 362(17):1575–1585. 5. Aronow et al. ACCF/AHA 2011 expert consensus document on hypertension in the elderly: a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus documents developed in collaboration with the American Academy of Neurology, American Geriatrics Society, American Society for Preventive Curr Hypertens Rep. Cardiology, American Society of Hypertension, American Society of Nephrology, Association of Black Cardiologists, and European Society of Hypertension. JACC. 2011; 57(20):2037–2114.

Summary

New Paradigm of Incorporating Central Pressures: Not a New Concept

Analogies to Advancement in Medical Evaluation

- Fasting blood glucose followed by introduction of HbA1C
- Electrocardiograms followed by introduction of echocardiogram
- COPD Guidelines: FEV_1 only, followed by incorporation of COPD exacerbations

Every-Day Analogies

- 2-factor identification
- Dead-bolt lock in addition to regular latch and lock

Common Sense Practice of Medicine

- BP measurement needs to be correct and confirmed
- Brachial pressures and central aortic pressures should be considered as part of management of all patients requiring blood pressure management, but particularly those with renal and/or cardiac disease

Economic Implications

- Reduced additional costs for confirmation of white coat hypertension (reduced ABPM, repeated office visits)
- Avoidance of medication costs for treatment when elevation in brachial blood pressure (untreated and treated hypertension) is not reflective of the usual physiologic state
- Reduced costs due to avoidance of medication adverse effects (medication specific, hypotension)
- Earlier treatment when there is confirmation of hypertension with associated reduction in socioeconomic costs due to subsequent reduced morbidity
- Guidance to attempting trials of medication reduction in treated patients who may have low or low-normal central pressures and normal brachial pressures

Summary and Conclusions (1)

Hypertension

- Responsible for continued morbidity and high socioeconomic costs despite the widespread availability and use of cuff brachial artery measurements for diagnosis and monitoring.

Brachial blood pressure monitoring

- Elevated pressure predicts CV events, mortality, and organ damage (e.g., LVH, intima-medial thickness and reduced GFR).
- Lowering elevated brachial BP reduces the risk of CV events and improves survival.

Central aortic systolic pressure monitoring

- Elevated pressure predicts CV events, mortality, and organ damage (e.g., LVH, intima-medial thickness and reduced GFR).
- Correlated to but incompletely predicted from brachial systolic pressures.
- Risk of adverse outcomes with elevated central pressure is higher that brachial pressure in multiple studies and uniformly at least as high as brachial pressure in others.
- Central systolic pressure is independently predictive of CV events and therefore provides additional risk information.

Conclusion

- Lowering elevated central systolic pressures should be an objective of hypertension management.

Summary and Conclusions (2)

Central Pressures

- Threshold values for the diagnosis and treatment of elevated central pressures have been defined.

Incorporation of central pressures into hypertension management has the following advantages:

- Confirmation of hypertension so that initiation of medication is more likely to be the correct decision for an individual patient *(concurrent elevation in brachial and central pressures)*.
- Avoiding initiation of medication when white coat hypertension is suspected *(elevated brachial pressure and normal central pressures)*.
- Confirmation that increased treatment may not be needed *(borderline high peripheral pressures and normal central pressures)*.
- Targeting when to consider reduction of medication *(normal peripheral and low central pressures, or extended period of normal peripheral and normal central pressures particularly in the setting of medication tolerance issues)*.

Conclusions

- Incorporation of central aortic pressure monitoring should be a part of the care of all patients with hypertension.
- The Dual Arterial Pressure SphygmoCor XCEL system provides both peripheral and central pressures in the same office-based setting and therefore represents a cost-effective addition to BP management.