Ambulatory Arterial Stiffness Monitoring, As Good As Ambulatory Blood Pressure Monitoring?

이 해 영
서울대학병원 순환기 내과

SNUH 서울대학교병원
SEOUL NATIONAL UNIVERSITY HOSPITAL

The Korean Society of Cardiology

COI Disclosure

Hae-Young Lee

The authors have no financial conflicts of interest to disclose concerning the presentation

동맥 경화 검사 (Vascular biomarker)가 가져야 할 요건

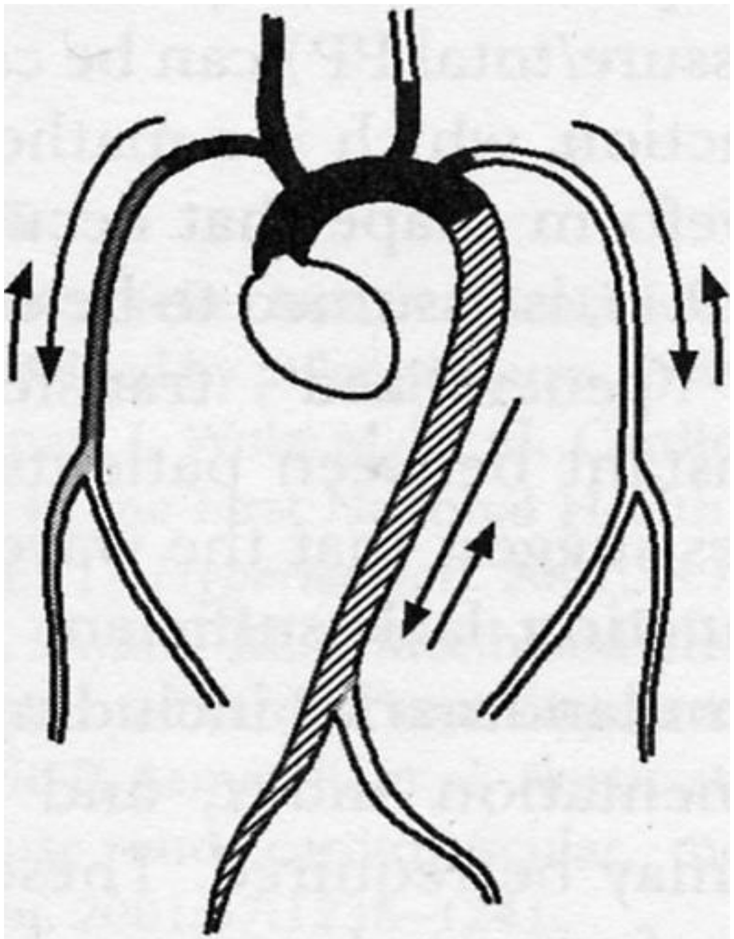
- 효능(Proof of concept)
  - 심혈관 사건 (기)발생자와 미발생자 사이 차이가 있는가?
- 예후 예측력 (Prospective validation)
  - 코호트 연구 등에서 사건 발생 예측력이 증명되었나?
- 추가 효능(Incremental value)
  - 기존의 위험 예측도에 더한 추가적인 예측력이 있는가?
- 검사 효과(Clinical utility)
  - 검사 결과로 치료 방침을 바꿀만한가?
- 치료 효과(Clinical outcomes)
  - 무작위 검사에서 검사에 따른 치료 결정으로 예후에 차이를 보았는가?
- 비용 대비 효과
- 검사의 용이성
- 검사 방법의 통일성
- 인종/성별/연령에 따른 정상치 보유

SNUH

‘Operator-independent’ 동맥경화도 검사

- Carotid-femoral pulse wave velocity
- Brachial-ankle pulse wave velocity
- Central hemodynamics/wave reflections

Rationale of carotid-femoral PWV measurement



Central Conduit Stiffness

= Characteristic Impedence

= Carotid- Femoral PWV

Peripheral (muscular) Conduit Stiffness

= Carotid- Brachial PWV

= Carotid- Radial PWV

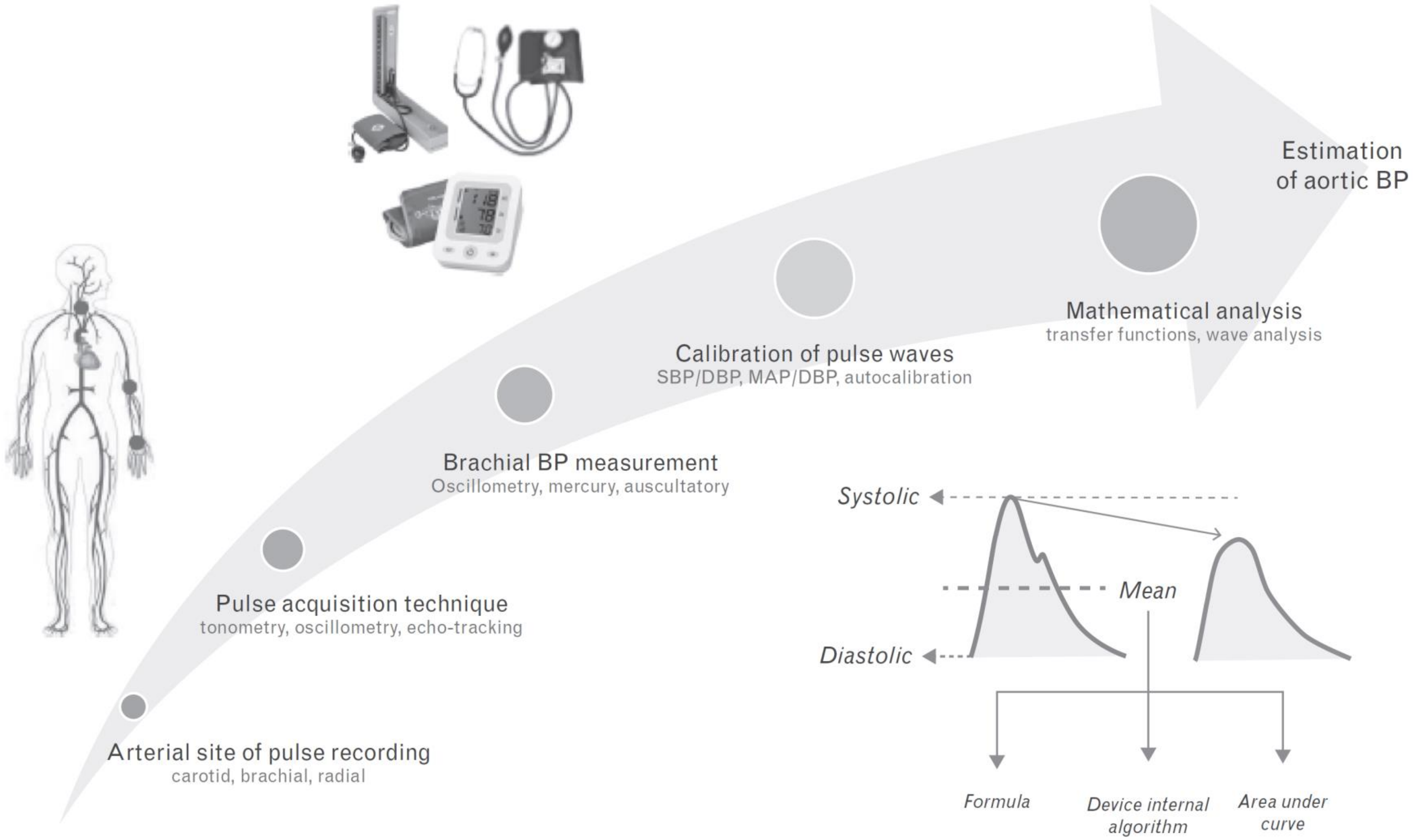
SNUH

Pros and cons of brachial-ankle PWV

- Brachial-ankle PWV의 단점
  - **혈관계가 좁은 하지의 동맥을 포함하므로 CfPWV에 비해 큰 값을 가짐 (**일본인 만 명을 대상으로 한 연구에서 baPWV 값이 14.0 m/s 이상인 경우 Framingham score에 의한 심혈관 위험도 예측에서 독립적인 예측인자였음**)**
  - **동일 혈관이 아닌 상지-하지 별개의 혈관 속도를 인위적으로 합친 측정치**
  - **Elastic artery인 대동맥 보다는 peripheral muscular artery의 경화도를 주로 반영?**
- Brachial-ankle PWV의 장점
  - **간편하고 비침습적인 방법: 의복을 착용한 상태에서 간편하게 측정 가능**
  - **혈압과 Ankle-brachial index를 동시에 측정 가능**
  - **말초 소동맥의 경화도 반영하므로 좌심실 비대 및 기능 저하의 평가인자로서는 carotid-femoral PWV보다 잠재적 우위성이 있을 가능성?**

SNUH

Noninvasive estimation of aortic blood pressure



Noninvasive measurement underestimate actual SBP by ~4.5mmHg compared with 'gold standard' invasive catheter measurement

J of hypertension. 2016;34:1237-48

SNUH

Indirect, non-invasive methods for estimating central pressure

Method of waveform recording	Device	Company	Method of calibration	Method of estimation	Clinical applicability†
Radial tonometry	BPro[86,87]	HealthSTATS	Brachial–radial cuff BP	GTF (radial-aortic)	++
	SphygmoCor[12,88]	AtCor Medical	Brachial–radial cuff BP	(i) GTF (radial-aortic)	+
				(ii) Late systolic shoulder	+
	HEM9000AI[39,77]	Omron	Brachial cuff BP	(i) Algorithm	++
				(ii) Late systolic shoulder	++
Brachial cuff PVP	*ARCsolver[89,90]		Brachial cuff BP	GTF (brachial-aortic)	+++
	Centron cBP301[35,91]	Centron Diagnostics	Brachial cuff BP	GTF (brachial-aortic)	++++
	Vicorder[92]	Skidmore Medical	Brachial cuff BP	GTF (brachial-aortic)	+++
	XCEL	AtCor Medical	Brachial cuff BP	GTF (brachial-aortic)	+++
	Method of Sung *et al.*[42]		Brachial cuff BP	Algorithm	++
Suprasystolic brachial cuff PVP	Arteriograph[37,93]	TensioMed	Brachial cuff BP	Late systolic wave amplitude	+++
	Cardioscope II[36,94]	Pulsecor	Brachial cuff BP	Algorithm	++++

- Radial arterial tonometry: SphygmoCor, HEM9000AI
- High-sensitivity cuff oscillometry: ARCsolver device incorporated in Mobil-O-Graph

SNUH

중심 동맥압이 상완 동맥압에 비해 경동맥 비대/ 죽상 경화 예측에 우월함

Study	Population	CCA Phenotype	Methods	Central Correlation	Brachial Correlation	Comparison*
Boutouyrie[11]	167 HTN plus NL	Right diameter	Carotid†, USG	PP: 0.33; P<0.0001	PP: 0.09; NS	See text
		Right IMT		PP: 0.42; P<0.0001	PP: 0.27; P<0.001	
Roman[12]	3520 AI	Mean IMT	Radial†, USG	PP: 0.293; P<0.001	PP: 0.249; P<0.001	P<0.002
				SBP: 0.257; P<0.001	SBP: 0.196; P<0.001	P<0.001
		Mean mass		PP: 0.320; P<0.001	PP: 0.289; P<0.001	P<0.05
				SBP: 0.317; P<0.001	SBP: 0.264; P<0.001	P<0.001
		Plaque score		PP: 0.364; P<0.001	PP: 0.309; P<0.001	P<0.001
				SBP: 0.288; P<0.001	SBP: 0.221; P<0.001	P<0.001
Wang[13]	1272 HTN plus NL	Right IMT	Carotid†, USG	PP: 0.265; P<0.001	PP: 0.204; P<0.001	P<0.05
				SBP: 0.252; P<0.001	SBP: 0.225; P<0.001	n/a
DeLoach[16]	367 CKD	IMT	Radial†, USG	PP: 0.36; P≤0.0001	PP: 0.32; P≤0.0001	Not different
				SBP: 0.29; P≤0.0001		
		Plaque		χ^2; P<0.0001	χ^2; P<0.0001	
Norton[14]	462 black SA	Right IMT	Radial†, USG	PP: 0.49; P<0.0001‡		See footnote
				P2: 0.53; P<0.0001‡		
Neisius[15]	535 HTN plus NL	IMT	Radial†, USG	PP: 0.426; P<0.001	PP: 0.235; P<0.001	P<0.01
				SBP: 0.478; P<0.001	SBP: 0.417; P<0.001	P<0.01

*Statistical comparison of central vs brachial correlation

Roman MJ, Devereux RB. Hypertension. 2014;63:1148-1153

SNUH

중심 동맥압이 상완 동맥압에 비해
좌심실 질량 / 좌심실 비대 예측에 우월함

Study	Population	Phenotype	Methods	Central Correlation	Brachial Correlation	Comparison*
Covic[18]	51 ESRD	LV mass	Radial†, echo	SBP: 0.56; $P<0.001$	SBP: 0.35; $P=0.04$	n/a
Wang[13]	1272 HTN plus NL	LV mass/BSA	Carotid†, echo	PP: 0.286; $P<0.001$	PP: 0.219; $P<0.001$	$P<0.05$
				SBP: 0.410; $P<0.001$	SBP: 0.370; $P<0.001$	$P<0.05$
Roman[21]	3520 AI	LV mass/$Ht^{2.7}$	Radial†, echo	PP: 0.335; $P<0.001$	PP: 0.219; $P<0.001$	$P<0.005$
				SBP: 0.396; $P<0.001$	SBP: 0.370; $P<-0.001$	NS
		RWT		PP: 0.167; $P<0.001$	PP: 0.130; $P<0.001$	$P<0.02$
				SBP: 0.286; $P<0.001$	SBP: 0.250; $P<0.001$	$P<0.005$
Norton[14]	678 black SA	LV mass/$Ht^{1.7}$	Radial†, echo	PP: 0.41; $P<0.0001$‡		See footnote
				P2: 0.41; $P<0.0001$‡		
Neisius[15]	535 HTN plus NL	LV mass/$Ht^{2.7}$	Radial†, echo	PP: 0.385; $P<0.001$	PP: 0.189; $P<0.001$	$P<0.01$
				SBP: 0.391; $P<0.001$	SBP: 0.297; $P<0.001$	$P<0.01$
Wohlfahrt[25]	657 Czechs	LVH	ECG	SBP: AUC, 0.90±0.02	SBP: AUC, 0.83±0.03	$P<0.05$

*Statistical comparison of central vs brachial correlation

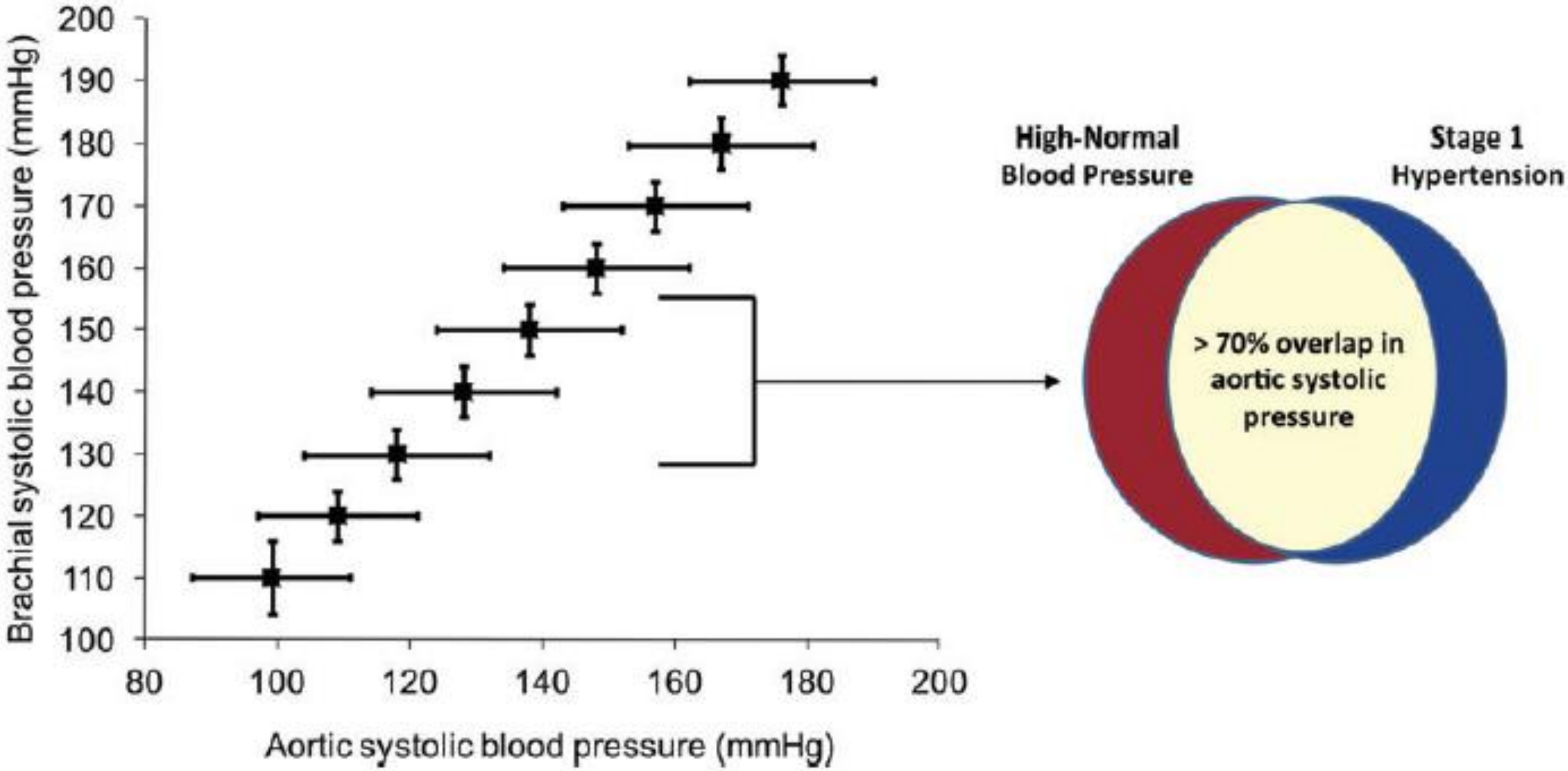
Roman MJ, Devereux RB. Hypertension. 2014;63:1148-1153

표적 장기 손상 예측에 대한 중심 동맥압 평가의 효용성

- 경동맥 비대, 좌심실 비대 등 심혈관 질환 미세 손상 지표와의 상관 관계가 상완 동맥보다 높음
- 고혈압 환자에서 Perindopril/Indapamide를 이용해 좌심실 비대를 호전시킨 REASON 연구에서는 좌심실 질량의 감소 정도가 중심 동맥압에서만 유의하였음
- 심혈관 사건 발생의 예측력이 보고됨
- 중심 동맥압 중심의 고혈압 약제 치료시 16%의 환자에서 약제 중지가 가능했다는 보고가 있음

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; 62:1138–1145.

고혈압 환자의 위험도 평가에
중심 동맥압이 Reclassification 효과가 있음



- Overlap in aortic SBP despite no overlap in brachial SBP, in healthy men and women (n = 5648).
- > 70% of individuals with high-normal BP had aortic SBP in common with individuals with stage 1 hypertension.

Hypertension 2008;51:1476–1482

SNUH

수축기 혈압의 변이 폭은 상완 동맥과 유사함

Variable	Mean	Range	SD	CV
Brachial SBP	136	163	28.2	20.5
Brachial DBP	81.2	107	16.2	20.0
Brachial PP	54.9	149	18.2	33.1
Brachial P2	123	158	32.4	26.3
Central SBP	123	136	28.4	23.1
Central DBP	82.3	109	16.5	20.0
Central PP	40.8	101	17.1	41.9
PPA	13.1	52	6.52	49.8
Central AI	130	186	30.6	23.5

SNUH

중심 동맥압 측정이 정립되기 위해 해결되어야 할 과제

- 중심 동맥압 측정 기기 사이의 측정치 차이가 큼
  - 경동맥 파형 분석 방식과 비교해 Omron (HEM9000AI) 기기의 중심 동맥압 측정치는 12mmHg 높게 표시되고, Sphygmocor 기기의 경우 7mmHg 낮게 표시됨.
- 중심 동맥압의 정상치가 정립되어 있지 않음
  - 상완동맥압의 140/90 mmHg에 대해 중심동맥압 125/90mmHg 수준이 상응된다는 보고가 있는 실정
- 연령/성별/신장/맥박 등 요인에 따라 상완 동맥압, 중심 동맥압의 차이가 영향받으나, 30%의 혈압 차이의 요인은 아직 설명되지 않음.
- 표적 장기 손상에 대한 높은 예측력이 10-12개의 맥박 결과를 평균해서 오는 정밀도에 의한 것이라는 유보적 견해도 있음

SNUH

ESC/ESH guideline에서의 PWV, Central BP의 위치

Index	Recommendation
cf PWV	Useful for risk stratification (IIa)
CAP and AIx	Not indicated at the moment; only exception is isolated systolic hypertension in the young (IIb)

Index	Level of evidence	Predictive value	Clinical utility	Ease of use	Methodological consensus	Reference values
cf PWV	A	++++	+++	+++	+++	Yes
CAP and AIx	B	+++	++	+++	+++	Yes (CAP)

Pulse wave analysis over 24 hours

- Simultaneous monitoring of
  - peripheral BP
  - Central arterial pressure
  - Arterial stiffness

  in ambulatory conditions over the 24 h.

Mobil-O-Graph PWA
By I.E.M. GmbH

BPLab
By OOO Petr Telegin

BPro
By HealthSTATS International

Mobil-O-Graph PWA

- Obtains pulse waves with a conventional upper arm BP cuff.
- Following inflation to DBP level, acquiring the pulse waveform over 10 s through a high fidelity pressor sensor.
- After digitalization by 12-bit A/D converter, a three-stage signal processing used to confirm signal quality.
- Aortic pulse wave generated by means of a generalized transfer function (ARCSolver) to compute vascular parameters.
- ARCSolver method uses
  - late systolic peak and a transfer function-like method.
- To estimate aortic PWV, this method utilizes parameters from PWA combined into a proprietary mathematical model, coupled with information on age and CAP

SNUH

BPLab

- During a step-by-step deflation of an upper arm cuff, brachial pulse wave forms obtained from oscillograms, digitalized and stored.
- Signal processing performed using a special mathematical algorithm (Vasotens transfer function)
- CAP and AIx derived from the analysis of the reconstructed central pulse wave.

BPro

- Acquires the radial pressure waveform through automated radial tonometry (EVidence-Based blood Pressure tonometry) at a frequency of 60 Hz
- A single radial waveform averaged from individual waveforms recorded consecutively for 10 s per block of waveforms.
- From the radial waveform, estimating CAP using an N-point moving average method
- **Accurately derive CAP and does not generate an aortic waveform.**

Main features and validations of 24h devices

Model	Technique	Main parameters	Validation of brachial BP measurement	Validation of PWA-derived parameters	Clinical studies
Mobil-O-Graph PWA	Oscillometric (ARCSolver) (*)	Brachial BP PWV CAP AIx	BHS SBP (B)/DBP (A) [18] BHS SBP (A)/DBP (A) [19] ESH passed [20]	SphygmoCor (6 studies: 3 PWV, 6 CAP, 4 AIx) [21–25] Cardiac magnetic resonance (1 study: PWV) [26] Intra-arterial (2 studies: 1 CAP, 1 AIx) [22, 27]	+++ (57 publications in Medline; 20 studies performed in ambulatory conditions)
BPLab	Osillometric Vasotens	Brachial BP PWV CAP AIx	BHS SBP (A)/SBP (A) [28] BHS SBP (A)/SBP (A) children [29] BHS SBP (A)/SBP (A) pregnant women [30]	SphygmoCor (3 studies: 1 PWV, 3 CAP, 3 AIx) [31–33]	++ (15 publications in Medline; 6 studies performed in ambulatory conditions)
BPro	Applanation tonometry EVBP method	CAP	ESH passed [34] AAMI passed [34]	SphygmoCor (4 studies: 4 CAP, 1 AIx) [35–58] Intra-arterial (2 studies: 2 CAP) [35, 36]	+ (8 publications in Medline; 3 studies performed in ambulatory conditions)
Arteriograph 24	Oscillometric	Brachial BP PWV CAP AIx	BHS SBP (A)/SBP (A) [39] AAMI passed [39]	SphygmoCor (8 studies: 5 PWV, 2 CAP, 6 AIx) [40–46] Complior (6 studies: 6 PWV) [41–43, 47, 48] Pulsepen (1 study: 1 PWV, 1 AIx) [49] Echotracking (1 study: 1 PWV) [48] Intra-arterial (4 studies: 1 PWV, 2 CAP, 1 AIx) [48, 50, 51]	+ (76 publications in Medline, but only 1 study performed over the 24 h)

Twenty-Four-Hour Ambulatory Pulse Wave Analysis
in Hypertension Management: Current Evidence and Perspectives.
Curr Hypertens Rep. 2016;18:72

SNUH

Accuracy of 24h pulse wave analysis

- In most studies, measurements of PWV, CAP, and AIx were in accordance with the reference standard.
- Cuff-based method seems to be the most promising technique, given the fact that it is affordable, convenient, and easy-to-use.
- Oscillometric devices with autocalibration function can estimate central SBP with a very high degree of accuracy [test-reference difference and 95 % confidence interval:−0.77 (−3.27, 1.73) mmHg].
- All studies were performed in resting conditions.

SNUH

24시간 동맥경화도 측정의 정확도

- Comparing the Mobil-O-Graph with the gold standard SphygmoCor, mean difference in estimated aortic SBP of only 0.1mmHg and a difference in aortic Aix of 1.2%.
- An acceptable accuracy between PWV measured by the Mobil-O-Graph and PWV derived from the invasive intra-aortic catheter measurements
  – Moderately higher PWV values in Mobil-O-Graph

SNUH

Reproducibility of 24h pulse wave analysis

- Reproducibility or 24-h ambulatory CAP taken at least 1-week apart in 30 consecutive subjects.
  - Acceptable reproducibility of both 24-h CAP (2.6 and 3.2 %) and 24-h brachial BP (2.7 and 3.3 %).
- Highly reproducible PWV and AIx, with average variation coefficients of 1.5 and 11.4 %, respectively, and intraclass correlation coefficients always >0.8.
- Reproducibility of a new interesting index, the Pulse Time Index of Norm (PTIN)
  - Percentage of a 24-h period during which the PWV does not exceed the 10 m/s threshold
  - Similar during the first and second recording, either in normotensives (86.5 vs. 87.3 %) or in HT pts (57.5 vs. 57.4 %)
  - Excellent intraclass correlation coefficients (0.98 for normotensives and 0.95 for hypertensives)

SNUH

Clinical studies based on Mobil-O-Graph

- Significantly lower systolic CAP than peripheral SBP either during the day (124.1 ± 15.7 vs. 133.9 ± 16.3 mmHg) or during the night (114.4 ± 14.5 vs. 121.5 ± 15.2 mmHg).
- Nocturnal fall in systolic CAP was lower than peripheral SBP fall
- 24-h central and brachial SBP were superior to conventional office BP in predicting BP-related cardiac damage (LVH and LV diastolic dysfunction)
- 24-h ambulatory central SBP was also more closely associated with LVH than 24-h brachial SBP (r = 0.51 vs. r = 0.40).
  - Ambulatory PWV provides additional information to cfPWV regarding the association of arterial stiffness with the retinal vessel calibers.

SNUH

Novel findings following 24 hour pulse wave analysis

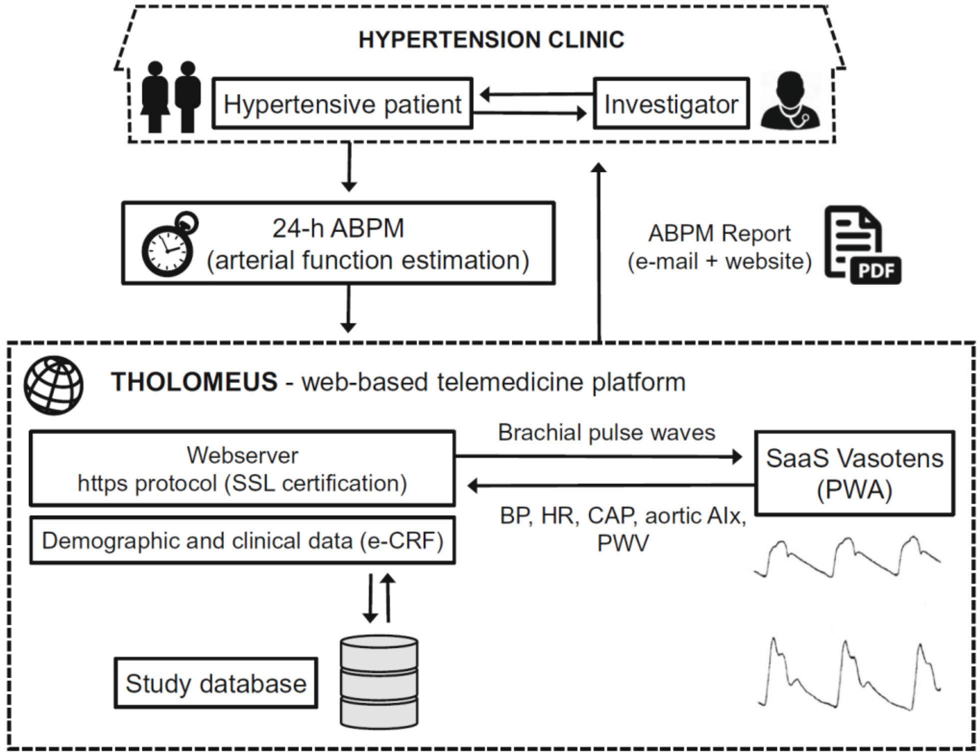
- PWV decreases from day to night (0.7 m/s), whereas AIx increases (2.3 %).
- Ambulatory AIx significantly declined after high-intensity interval training, but not after moderate continuous training.
- Strong relationship of 24-h BP variability with CAP and arterial stiffness, which is largely independent from the average 24-h BP level.
- Good correlation ($r = -0.72$) between PTIN (Pulse Time Index of Norm) and LVMI, indicating that PTIN may represent an interesting marker of end organ damage in hypertension.

SNUH

Outcome-Based Evidence for 24-h PWA: the VASOTENS Registry

- VASOTENS (Vascular health ASssesment Of The hypertENSive) Registry.
-

  International, multicenter, observational, non-randomized,
- prospective study, approximately 2000 subjects referred to 20 hypertension clinics worldwide for routine diagnostic evaluation and follow-up of hypertension of any severity or stage will be recruited.



- Each subject will be submitted every 6 to 12 months to an ABPM performed with a BPLab monitor, with simultaneous assessment of brachial BP, PWV, CAP, and Aix.
- Subjects will be followed up for a minimum of 2 years.

SNUH

Current advantages of PWA assessment over 24 h

- Easy-to-use (particularly cuff-based techniques)
- Techniques are largely operator-independent
- Evaluation in daily life conditions
- Repeated and prolonged measurement
- Evaluation of the effect of activity vs. sleep
- Evaluation of antihypertensive treatment
- Affordability: in most cases devices are cheaper than those used for monitoring at rest
- Potentially useful for early screening of arterial damage in many conditions (e.g. arterial hypertension, diabetes, at high CV risk, etc.)

SNUH

Current limitations of PWA assessment over 24 h

- Accuracy
  - Validation studies performed only at rest
  - No standardized validation protocols
  - Lack of non-invasive reference ‘gold’ standard
  - Intra-arterial validation studies not feasible
  - Validation is device-dependent: generalization not possible
- Possible artifacts due to the dynamic conditions
- Limited information on reproducibility in ambulatory conditions
  - No reference values in ambulatory conditions
- Lack of outcome-based validation (no long-term prospective data)
- Limited clinical evidence

SNUH

요약 및 결론

- 24-h PWA appears to be a potentially promising tool for evaluating vascular function, structure, and damage in daily life conditions and promoting early screening in subjects at risk.
- 24시간 동맥경화도 측정계의 경우 Gold standard 동맥경화도 측정계와 비교해 acceptable한 정확도를 보인다.
- Accuracy and quality of the evidence collected so far seems to be strongly device-dependent and results could not be considered interchangeable between devices.
- Long-term follow-up (outcome) studies, such as the VASOTENS Registry, are needed to show the predictive value of the parameters provided by the various devices and to answer the many technical and clinical questions still open.

SNUH