Better Management of Cardiovascular Diseases by Pulse Wave Velocity: Combining Clinical Practice with Clinical Research using Evidence-Based Medicine

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Arterial stiffness measured by pulse wave velocity (PWV) is an accepted strong, independent predictor of cardiovascular events and mortality. However, lack of a reliable reference range has limited its use in clinical practice. In this evidence-based review, we applied published data to develop a PWV risk stratification model and demonstrated its impact on the management of common clinical scenarios. After reviewing 97 studies where PWV was measured, 5 end-stage renal disease patients, 5 hypertensives, 2 diabetics, and 2 elderly studies were selected. Pooling the data by the "fixed-effect model" demonstrated that the mortality and cardiovascular event risk ratio for one level increment in PWV was 2.41 (1.81-3.20) or 1.69 (1.35-2.11), respectively. There was a significant difference in PWV between survived and deceased groups, both in the low and high risk populations. Furthermore, risk comparison demonstrated that 1 standard deviation increment in PWV is equivalent to 10 years of aging, or 1.5 to 2 times the risk of a 10 mmHg increase in systolic blood pressure. Evidence shows that PWV can be beneficially used in clinical practice for cardiovascular risk stratification. Furthermore, the above risk estimates could be incorporated into currently used cardiac risk scores to improve their predictive power and facilitate the clinical application of PWV.

Keywords: Arterial stiffness; Cardiovascular risk; Evidence-based medicine

In recent decades the concept of evidence-based medicine (EBM) has been promoted by health professionals for its potential to bridge the gap between research and clinical practice. While some authors describe it as a revolutionary approach to clinical medicine, others argue it is a repackaging of old concepts in a new jargon.¹ Regardless of these opposing views, EBM is a systematic method of describing a problem, finding and appraising the appropriate information, and applying the information to individual patient care. In fact, all facets of clinical decision making, from diagnosis to management, could be facilitated by EBM in conjunction with a physician's professional skills and experience, as well as patient values and preferences.

Although pulse wave velocity (PWV) is one of the oldest parameters of aortic stiffness, its non-invasive automatic

measurement is a relatively new measurement of arterial stiffness. The measurement includes regional assessment of larger central arteries or smaller peripheral arteries. Central arterial stiffness has been established as a strong independent predictor of cardiovascular events and mortality, particularly in end-stage renal disease (ESRD),¹⁻³ hypertension,⁴⁻⁶ diabetes mellitus,^{7,8} and the elderly.⁹ Despite accumulating evidence that PWV detects cardiovascular disease (including coronary artery disease) and stroke,^{10,11} it is rarely used in clinical management, primarily due to lack of a reliable reference range. Diverse methodologies and a paucity of information from large longitudinal studies relating patients' outcome with different levels of PWV probably also limit its clinical use.

In this review, we analyzed and applied available published information on PWV for clinical decision making by using pertinent hypothetical clinical scenarios. Furthermore, we

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discuss the potential impact of arterial stiffness measured by PWV on patient management.

Clinical Scenarios

The following clinical scenarios were used to frame relevant questions regarding patient medications discussed in this review.

- Case 1.** A 45-year-old non smoking male with diabetes of 10 years (HbA1c=6.9%, total cholesterol=6, HDL=1 mmol/l) and an average daytime blood pressure of 135/80 mmHg without medication. The carotid-femoral PWV was 13.0 m/sec.
- Case 2.** A 55-year-old female, non-diabetic smoker with a history of hypertension and an average blood pressure of 160/95 mmHg over the preceding year. Her carotid-femoral PWV was 12.1 m/sec last year. Her current mean ambulatory blood pressure is 140/95 mmHg but her carotid-femoral PWV remained unchanged. Her total cholesterol was 5.5 (HDL=1.2) mmol/l.
- Case 3.** A 58-year-old male with ESRD on a regular hemodialysis program. His blood pressure had always been controlled with medication but recently it has been increased (average 150/90 mmHg). His most recent pre-dialysis carotid-femoral PWV was 9 m/sec.

Method

Framing the Relevant Clinical Questions

From the above clinical scenarios, the following questions emerged as the basis for this review:

- In patients with hypertension, diabetes or ESRD, how much risk of mortality is attributable to PWV and how could it be used in risk estimation for individual patients?
- How much benefit could be expected from reducing PWV in a given patient?
- Could benefits outweigh potential harms of treatment?

Searching for the Evidence

The MEDLINE and EMBASE databases were searched for relevant studies using “pulse wave velocity” or “arterial distensibility” or “arterial compliance” in combination with “cohort” as study type (yield: 35 articles) or “prognosis” as a MeSH term or a text word (yield: 62 articles). The retrieved papers were screened for their relevance to the framed questions, resulting in 12 papers after exclusion of irrelevant, biased and repeated publications.

Critical Appraisal

For cohort studies, the quality of studies was evaluated with particular focus on the following questions:

- Was there a representative sample of patients at a well-defined point?
- Was follow-up sufficiently long and complete?
- Were all potentially important prognostic factors assessed?
- What was the effect size (considering the 95% confidence interval [CI])?

Table 1. Summary of studies evaluated.

Study	Participants	Age range	Follow-up period	Outcome	Group	N	No. of events	Relative Risk (RR)
Boutouyrie et al. ⁵	Essential hypertensives	51 ± 12	5.7 years	CV events	All			Adjusted
					G1: PWV<10	348	17	1
					G2: PWV=10 to 12.3	349	38	1.22 (0.91-1.65)
					G3: PWV>12.3	348	54	1.49 (0.82-2.71)
					Low risk group			Adjusted
					G1: PWV<10	348	10	1
					G2: PWV=10 to 12.3	349	23	1.82 (1.25-2.65)
					G3: PWV>12.3	348	24	3.31 (1.56-7.05)
Blacher et al. ³	ESRD on hemodialysis	51.5 ± 16.3	72 ± 41 months	All-cause mortality	G1: PWV<9.4	81	6	Adjusted
					G2: PWV=9.4 to 12.0	80	16	1
					G3: PWV>12.0	80	51	3.57 (0.21-9.46)
								4.31 (2.22-7.91)
*Shoji et al. ⁸	Diabetic ESRD	55.4 ± 10.5	63 ± 23 months	All-cause mortality	Low (<8.5)	129	27	1
					High (≥8.5)	136	54	1.90
*Blacher et al. ¹⁶	Geriatric patients	67.6 ± 11.0	38 ± 19 months	CV events				Adjusted
					L: PWV<10	171	53	1
					H: PWV>10	89	47	2.02 (0.90-4.55)

* Used different method for PWV. RR demonstrates risk of PWV grades (G).
CV, cardiovascular; ESRD, end-stage renal disease; PWV, pulse wave velocity.

Table 2. Comparison of adverse outcome risks after univariate analysis adjustment.

Study groups	Year	N	Follow-up (months)	Outcome	PWV	Systolic blood pressure	Age
Essential hypertensives ⁵	2002	1045	68.4	CHD events	Each 3.5 m/s increase RR= 1.42 (1.10-1.32)		Each 10 years RR= 1.42 (1.12-1.81)
				All CV events	RR= 1.41 (1.17-1.70)		RR= 1.47 (1.23-1.76)
Essential hypertensives ⁴	2001	1980	112 ± 53	CHD mortality	5 m/s PWV OR=2.35 (1.76-3.14)	Each 10 mmHg OR=1.26 (1.12-1.42)	Each 10 years OR= 2.32 (1.78-3.01)
				All-cause mortality	OR= 2.14 (1.71-2.67)	OR= 1.17 (1.08-1.28)	OR= 2.12 (1.78-2.53)
Essential hypertensives ⁶	2003	1715	94.8	Stroke mortality	Each 4 m/s PWV RR=1.72 (1.48-1.96)	Each 10 mmHg RR= 1.20 (1.06-1.34)	Each 10 years RR=2 (1.60-2.40)
Older than 70 ⁹	2001	141	30	CV mortality	Each 1 m/s PWV RR=1.19 (1.03-1.37)	Each 1 mmHg RR= 1.03 (1.0-1.06)	Each year RR=1.05 (0.98-1.13)
ESRD ¹⁵	2005	305	70	CV mortality	Each 1 m/s PWV RR=1.30 (1.23-1.38)	Each 1 mmHg RR=1.01 (1.00-1.03)	Each year 1.07 (1.09-1.55)

CV, cardiovascular; CHD, coronary heart disease; ESRD, end-stage renal disease; PWV, pulse wave velocity.

Risk Analysis

The relative risk (RR) of mortality in levels of PWV was summarized. Adjusted risk ratios for a 1 standard deviation (SD) change in PWV was either quoted or extracted from other reported indices like odds ratio (OR). Similar risk estimates for systolic blood pressure and age, the main determinants of PWV, were added to the table for better comparison. The 2-by-2 tables were reconstructed according to the information in the text, tables and graphs in order to define the absolute risks and number-needed-to-treat (NNT). While the patient classifications were not based on consistent cutoff points in the studies, they were categorized into low (G1), moderate (G2) and high (G3) risk for analysis. The pooled RR of mortality for the grades of PWV and weighted mean difference of PWV in survived and deceased groups were calculated using the fixed effect model.

PWV Method

PWV is measured by placing pressure sensitive transducers over different arteries (e.g., the right carotid and femoral arteries for carotid-femoral PWV). Dividing the distance separating the sensors by the time corresponding to the transmission time of the pulse wave (defined by the start of the rising phase of the pulse wave) from one site to the other determines the PWV. It is a non-invasive, inexpensive, rapid measurement of arterial stiffness which could be easily performed in an office.

While distance measurement between the probes affects PWV measurement,¹² it is of considerable importance to investigate the method of measurement, or possible adjustments, when studies are compared. However, since the impact is systematic in the measurement, using relative statistics or ratios is not significantly influenced by this factor.

Result

Study Analysis

The 14 eligible studies included:

- Five reports evaluated ESRD patients. All were performed by a group at F. H. Manhes Hospital, Paris, a gradually increasing study population during progressive research phases.^{2,3,13-15} Because these were multiple reports on the same population, the most recent and most complete reports were applied. The average follow-up time was 78 ± 48 months, indicating a relatively short follow-up for some subjects. While in one of their serial reports the proportion of subjects with diabetes was not homogenous across the tertiles of PWV, this factor was not considered in their multivariate analysis. Despite this limitation, other aspects of their study were methodologically acceptable.
- Five reports evaluated hypertensive patients, all by a group from Broussais Hospital, Paris, who evaluated stroke in one study,⁶ and overall and cardiovascular mortality in three others.^{4,16,17} The latest report contained the greatest number of patients and the longest follow-up and was selected for review.¹⁷ The fifth article evaluated coronary events.⁵

Table 3. Weighted mean difference (WMD) in carotid-femoral PWV between living and deceased groups.

Study or sub-category	Living N	Living Mean (SD)	Deceased N	Deceased Mean (SD)	Weight %	WMD (fixed) 95% CI
<i>General (non-specified risk)</i>						
Essential hypertensives ⁵	947	11.40 (3.10)	97	12.80 (3.20)	2.17	-1.40 (-2.07, -0.73)
General population ⁷	97	9.70 (0.50)	22	11.10 (1.40)	2.75	-1.40 (-1.99, -0.81)
Laurent ⁴	20	12.00 (1.80)	30	14.00 (2.90)	0.57	-2.00 (-3.30, -0.70)
Subtotal (95% CI)	1064		149		5.49	-1.46 (-1.88, -1.04)
Test for heterogeneity: $\text{Chi}^2 = 0.73$, $\text{df} = 2$ ($P = 0.69$)						
Test for overall effect: $Z = 6.83$ ($P < 0.00001$)						
<i>High risk</i>						
ESRD ¹⁰	110	10.40 (2.40)	70	13.80 (3.00)	1.39	-3.40 (-4.23, -2.57)
Diabetes ⁷	218	10.40 (0.40)	179	13.00 (0.60)	91.67	-2.60 (-2.70, -2.50)
Glucose intolerance ⁷	37	9.80 (0.70)	18	12.20 (1.70)	1.45	-2.40 (-3.22, -1.58)
Subtotal (95% CI)	365		267		94.51	-2.61 (-2.71, -2.51)
Test for heterogeneity: $\text{Chi}^2 = 3.74$, $\text{df} = 2$ ($P = 0.15$)						
Test for overall effect: $Z = 50.56$ ($P < 0.00001$)						

ESRD, end-stage renal disease; PWV, pulse wave velocity.

Although all these study cohorts were heterogeneous for diabetes, this factor was controlled by multivariate analysis and other aspects of their research methodology were acceptable.

- Two papers evaluated patients with diabetes, one with ESRD⁸ and one in the general population.⁷ Unfortunately a different PWV method of measurement was used and their results could not be directly applied to the above clinical scenarios. However, their results were used for the risk analysis phase in this review.
- Two studies evaluated the prognostic value of PWV in the elderly.^{9,18} These results could not be extrapolated to our hypothetical cases whose ages are less than 70.

Summarizing and Applying the Evidence

All included studies showed an increasing mortality risk with increased PWV. A summary of the reported risk estimates for each grade of PWV is illustrated in tables 1 and 2. Data from the studies were pooled using the fixed effect model and for one level of increment in PWV grades produced RR of 2.41 (1.81-3.20) and 1.69 (1.35-2.11) for all-cause mortality and cardiovascular events, respectively ($P < 0.00001$) (figure 1). Although pooled RR for two level increment in PWV was 4.59 (2.61-8.05) with a significant P value (0.00001), the tests ($I^2 = 77\%$ and $P = 0.04$) demonstrated heterogeneity which made pooling inappropriate.

Comparison of the reported mean PWV from 6 studies showed a significant difference between PWV in survived and deceased subjects; the overall mean difference was

determined to be 1.46 (95% CI, 1.04-1.88) and 2.61 (95% CI, 2.51-2.71) for the low and high risk groups, respectively (table 3). Assuming that reducing PWV by better control of conventional cardiovascular risk factors, as well as non-classic ones, would decrease cardiovascular risk outcomes as much as an increase in PWV would increase risk, we calculated relative and absolute risk reduction and NNT to prevent a death (table 4). From this analysis it can be demonstrated that in a high risk group, such as ESRD, if PWV is reduced from the highest grade (G3, e.g., 13) to the lowest (G1, e.g., 9.2), or even to the moderate grade (G2, e.g., 11.5), approximately 2 patients need to be treated to prevent a death. PWV reduction from G2 to G1 (e.g., 10.5 to 9) for 8 patients for 6 years would also save one life in this population. Although the theoretical benefit in hypertensives is not as profound as the predicted benefit in the ESRD group, it is still convincing. For instance NNTs to save one life by reducing PWV from 13 to 11.5 or 9.5 was calculated at 9 or 27 patients, respectively. Treatment of less than 17 patients to reduce PWV from 11.5 to 9.5 for a similar duration would also prevent a death. Likewise, reducing PWV of 5 diabetic patients to the low level over 5 years of treatment would also save one life. Although the translation from risk to benefit is optimistic, the treatment may be less effective in practice, but it could facilitate clinical decision making. Furthermore, available evidence, although limited, from longitudinal studies is consistent and demonstrates RR of 0.71 (0.6 to 0.86) for all-cause mortality and 0.79 (0.69-0.93) for cardiovascular mortality as a consequence of a decrease in PWV of 1 m/s.¹⁹ Hence, clinical intervention with the intention of reducing PWV by at least one grade seems reasonable.

Review: PWV longitudinal studies
 Comparison: 01 PWV, CV events and mortality
 Outcome: 01 Risk of mortality

Figure 1. Pooled, weighted RR for one level increment in PWV grade using the fixed effect model in terms of all-cause mortality and cardiovascular events.

Potential Risks of Treatment

The possible benefit of treatment should be considered alongside the possible risks. Therapeutic trials based on cardiovascular mortality have shown that systolic blood pressure reduction requires normalization of both large artery stiffness and wave reflections.²⁰⁻²² Clinical trials suggest angiotensin converting enzyme inhibitors and angiotensin receptor blockers as the leading candidates for treatment of “arterial pulse hypervelocity” and wave reflection attenuation. They are also very well tolerated with few adverse effects and good long-term compliance.^{23,24} Other medications are less effective long term, even with a comparable reduction in blood pressure.^{15,25}

Relationship of PWV with Systolic Blood Pressure and Age

Comparison of the RRs for these factors after adjustment by multivariate analysis (table 2) shows the risk of a 1 SD increment in PWV is equivalent to 10 years of aging. It is also approximately 1.5 to 2 times the RR of 10 mmHg increase in systolic blood pressure.

Clinical Scenarios Resolution

Case 1. While not clearly hypertensive, assessment by the Coronary Heart Disease (CHD) Event and Stroke Risk Calculator²⁶ demonstrated this patient has a 12.6% 10-year CHD risk which is equal to a 16.75% cardiovascular event risk within 10 years. Without the PWV information there is no treatment indication. However, since his PWV was at least 1 SD more than the low risk tertile (an equivalent of 10 years of aging), reassessment demonstrated a risk of 19.7% for coronary

and 26.2% for cardiovascular events. According to recent international guidelines, every patient with a 10-year cardiovascular risk of 20% (equivalent to 15% CHD risk) or greater should be treated.²⁷ Hence, medical treatment (targeting arterial function by reducing blood pressure, blood glucose, lipids, and renal function) is justified for this patient regardless of his blood pressure.

Case 2. The patient’s systolic blood pressure is acceptable although her diastolic blood pressure is just above the target point. Since the patient was not diabetic, risk assessment was performed using the CHD Event and Stroke Risk Calculator.²⁶ The 10-year risk of CHD was 12.6% which is compatible with a cardiovascular risk of 16.8% without taking the PWV result into account. However, adding 10 years to her age represents 1 SD difference with the low grade PWV, and the estimated 15.5% CHD risk (20.7% cardiovascular risk) supports treatment.

Case 3. Since PWV did not suggest an excess risk and considering this patient’s history of controlled blood pressure, his high blood pressure was likely to be a white coat effect and a 24-hour monitoring for the patient was ordered. The result demonstrated an average daytime blood pressure of 135/85 and a lack of nighttime blood pressure dipping. Hence, no further blood pressure medication is required. Nevertheless, the observed non-dipping in blood pressure represents an expected

Table 4. Assessment of treatment benefit.

Study	Treatment goal	RRR	ARR	NNT	Treatment duration
<i>Study 1 (cardiovascular events)</i> All study group	G3 to G1*	69%	11%	9.1	5.7 years
	G3 to G2	29.7%	4.6%	21.7	
	G2 to G1	55%	6%	16.7	
Low risk group	G3 to G1	76%	11%	9.1	6 years
	G3 to G2	44%	5%	20	
	G2 to G1	63%	6%	16.7	
<i>Study 2 (mortality)</i>	G3 to G1	88%	57%	1.75	6 years
	G3 to G2	69%	44%	2.27	
	G2 to G1	63%	13%	7.7	
<i>Study 3 (mortality)</i>	High to low	53%	19%	5	5.2 years

* G1, G2, and G3 are groups of pulse wave velocity (see table 1).

RRR, relative risk reduction; ARR, absolute risk reduction; NNT, number-needed-to-treat.

vascular risk in a patient with ESRD which could possibly be improved by timing adjustment of his current medication.

Discussion

This evidence-based review confirms PWV as a robust and important indicator of vascular disease and supports its role as a routine investigation in clinical practice. Therefore, the clinical utilization of this cardiovascular disease indicator should result in better management of patients with established risk factors.

The definitions of hypertension, hypercholesterolemia and diabetes have been reevaluated over recent years because evidence has indicated a significant morbidity and mortality among people with a blood pressure, lipid and glucose below the previously defined levels for disease description. For instance, the vascular risk associated with blood pressure exhibits a close and continuous association, at least to a systolic blood pressure as low as 110 mmHg,^{28,29} so that a threshold of 140/90 mmHg is neither a sensitive (71%) nor specific (54%) predictor of cardiovascular risk.²⁸ In addition, evidence from published trials supports medical intervention for high risk patients irrespective of initial blood pressure.^{30,31} This uncertainty remains true for diabetes and hypercholesterolemia, and the controversy about where to start treatment has lead to moving from a “goalposts” definition to a risk assessment approach. As a result, the clinical application of cardiovascular risk calculators has become increasingly important in routine clinical practice, a trend encouraged by EBM. While this review used PWV data in risk assessment for a series of common case scenarios, PWV is not incorporated in current cardiovascular risk calculations. However, with accumulating data such a development should soon be achievable.

Based on the impact of an elevated PWV on cardiovascular prognosis, it is expected that reducing PWV, regardless of the intervention, would dramatically decrease cardiovascular events and mortality. This prediction is supported by the reduction in both cardiovascular and all cause mortality in a cohort study involving ESRD patients following a decrease in aortic PWV.¹⁹ In this study, 70% of patients with appropriate blood pressure reduction, but who maintained elevated PWV, had a reduced survival time. This evidence clearly shows the critical deleterious role of increased stiffness and morbid arterial remodeling.³²

Angiotensin converting enzyme inhibitors and angiotensin receptor blockers are currently the leading candidates for reduction of PWV in clinical practice^{23,25,33-35} despite little improvement in arterial compliance with short-term treatment. Interestingly, administration of lipid-lowering agents^{36,37} and a type of oral hypoglycemic agent had a significant effect in reducing PWV in normolipidemic and normotensive individuals.³⁸ Of most importance, although PWV improves with blood pressure treatment, the medication impact on PWV is apparently independent of blood pressure reduction.

Conclusion

Measurement of aortic PWV is an established surrogate measurement of vascular damage, as well as a useful methodology to evaluate treatment benefits. While the analysis of published studies using a particular methodology (Complior) has allowed the development of a useful calculation of risk, the amalgamation of a comprehensive population database using several active research centers would be ideal.

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