Research article

Whole Blood Viscosity: Affordances and Re-evaluation of Sensitivity and Specificity for Clinical Use

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Over the years, whole blood viscosity (WBV), an indicator of thickness and stickiness of blood has been a laboratory marker for blood stasis, and useful for monitoring several disorders including cardiovascular diseases (CVD). However, the use of WBV in clinical practice is still limited by affordances, knowledge and attitude. With the development of extrapolated whole blood viscosity (eWBV) method from haematocrit and total serum protein level, what is yet to be established is the sensitivity and specificity of eWBV to address the limitations in clinical practice. The objective of this study was to highlight the discourse on sensitivity, specificity and affordances (accessibility and affordability) of eWBV to re-evaluate the utilization of WBV in clinical practice, especially in low-mid income communities. This was a observational study that used archived data from haematology and biochemistry routine laboratory tests associated with cardiovascular phenomena. Statistical analysis adopted the conventional paired-contingency table method for sensitivities and specificities to assess validity of eWBV in CVD. Reliability was affirmed by consistent significant differences in WBV levels between thrombocytopenia and thrombocytosis ($p < 0.005$). Calculated validities show that eWBV is ≥64% specific and ≤38% sensitive to cardiovascular phenomena. In conclusion, eWBV is generally less sensitive but more specific for CVD. One major significant finding from this study is that in patients with haematocrit and serum protein results, the risk of bleeding and monitor the effects of therapy can be assessed using specific and accessible eWBV at no extra cost in laboratory service. Being accessible at no extra cost translates to widespread affordance for this laboratory test.

Key words: aspirin, blood stasis, cardiovascular phenomena, clinical practice, laboratory medicine, therapeutic monitoring

Introduction

Monitoring of certain cardiovascular therapies such as antiplatelet therapy includes assessment of resistance, responsiveness and risk of side-effects using routine clinical laboratory methods. Antiplatelet therapies are commonly used in management of chronic diseases including prevention of stroke. According to the American College of Chest Physicians as well as American Heart and Stroke Associations,[1,2] guidelines recommend that in cases of atherothrombosis, stroke or transient ischemic attack, the patient can receive anti-

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platelet agents to prevent recurrence if there are no contraindications.[1-6]

In some patients, the desired effects are not attained when administering aspirin while in others there is the misnomer of aspirin resistance,[7] which can be confused with aspirin non-responsiveness. Furthermore, aspirin may be contraindicated in some patients while indicated in others.[8] Non-responsiveness and resistance to a drug, such as antiplatelet agents, are different phenomena,[9-11] and indeed, there is need for clarification on the definition of antiplatelet resistance in the context of a laboratory 'test' response to a drug.[12] This is regarding the expectation of therapeutic effect i.e. *blood thinning*,[13] which can be determined by a reduction in a patient's 'blood stasis' *vis-à-vis* whole blood viscosity (WBV).[14, 15]

At this juncture, it is pertinent to delineate that WBV is not normally assessed as part of chronic disease management, except at some reference laboratories and there is now extrapolated WBV (eWBV) method to enable testing in routine laboratories. Aggregometry for antiplatelet drug monitoring,[16, 17] is not commonly available outside reference laboratories and rarely accessible in regional health services. Thus, in terms of affordances (accessibility and affordability), there are patients who can afford the cost, but cannot access the service. With advancement in research, eWBV can now be determined from haematocrit and proteinaemia, thus removing the barrier of affordances and making the pathology test available in a clinical laboratory that performs routine haematology and liver function tests.

It is noteworthy that blood viscosity is a cardiovascular phenomenon, which may be associated with other phenomena. For instance, inflammation, metabolic syndrome, and platelet functions are three notable cardiovascular phenomena. Hence, it is hypothetical that laboratory tests for these three phenomena may validate eWBV.

There has been a clarion call for the development of reproducible, simple and user-friendly bedside methods to determine antiplatelet responsiveness;[18] and assessment for bleeding risk is necessary before starting antiplatelet therapy.[19] Therefore, the relevance of this update is in the advancement of a method applicable and commonly available including in low-mid income countries or communities, but also potentially at patient' bedside for diagnostic decisions.

Objective: In the context of knowledge, attitude and, practice (KAP) gap, there is a void that can be viewed as:

- ***What is known***: WBV is a laboratory marker for blood stasis.[9-15]
- ***KAP gap***: WBV is speculated as being too sensitive and less specific for identifying blood stasis.[20]
- ***What is unknown***: sensitivity versus specificity of eWBV to specific CVD phenomena
- ***Proposition***: eWBV is neither too sensitive, nor a less routine CVD marker.

Materials and Methods

Study design and ethical clearance

This study followed a clinical laboratory observational method [21]. It is a clinical laboratory method based on evaluation of archived clinical pathology data; and observational study because it did not utilise experimental intervention but used archived laboratory results. The study was approved by the Human Research Ethics Committee of the University (H2014158).

Setting

Two datasets from electronic laboratory records of two health facilities were used. First dataset was obtained from Australian based South-West Pathology Service (SWPS) of the NSW Health Australia (Fig 1). Second dataset were collected from Wellness House Orange, a General Practice in regional NSW Australia.

Data

Information collected included routine laboratory test indices for assessing WBV and tests for inflammation, metabolic syndrome, and platelet function as three cardiovascular phenomena, which were previously assessed for association.[22-24]

- **Factors of WBV** – haematocrit and serum protein level
- **Inflammation** – white blood cell count (WBCC), erythrocyte sedimentation rate (ESR) and c-reactive protein (CRP). These laboratory test values increase with inflammation.
- **Metabolic syndrome** – blood glucose level, lipid profile. Abnormal values are associated with cardiometabolic syndrome and constitute risk for cardiovascular complications.
- **Platelet function** – platelets count. This test is currently the available closest indicator of blood stasis as a cardiovascular phenomenon.

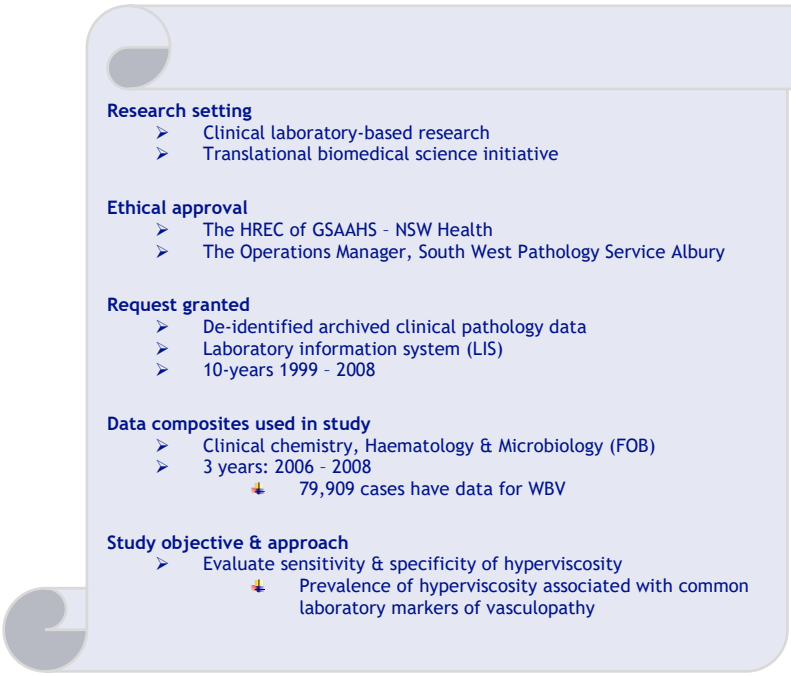


Figure 1: Summary of methods of the 10 years' dataset

Calculation method

First, the eWBV formula was used to generate the blood viscosity levels,[25] and for quick reference, WBV was derived digitally from haematocrit (HCT) and total serum protein level (TP). The translational procedure was as follows:

WBV = (0.17 x (P – 2.07)) + (0.12 x H)

- On excel, it is: eWBV = 0.17*(P–2.07) + (0.12*H)
- P = serum protein level
- H = haematocrit level
- * is multiplication a symbol in excel

Second, WBV sensitivity and specificity were evaluated with reference to determine validity, and this followed the 2-by-2 formula applicable for day-to-day clinical practice.[26, 27]

Statistics

In this study, reliability was defined as consistency,[28] and evaluation was second dataset if results would be consistent with previous observations in the first dataset. Validity meant sensitivity and specificity for the usefulness i.e., utility. Hence, the statistical analysis included to ascertain consistency as well as sensitivity and specificity of eWBV for the three indicated CVD phenomena i.e. inflammation, metabolic syndrome, and platelet function.

Consistency evaluation was done by assessing changes in eWBV levels with the inflammation, metabolic syndrome, and platelet function variables. The paired-contingency table method for sensitivities and specificities was adopted for validity determinations. The 1st and 4th quartiles were adopted as low and high values, respectively, in calculating sensitivities and specificities of the eWBV to inflammation, metabolic syndrome, and platelet function test parameters.

Results

The descriptive statistics of dataset 2 are shown in Table 1. The consistency assessment i.e. *reliability* results are shown in Fig 2, and eWBV is marginally associated with lipidaemia and WBCC i.e. similar to previous report.[24]

Table 1: Descriptive statistics of new dataset

	HbA1c (%)	*WBC×10⁹/L*	*Platelets ×10⁹/L*	*eWBV (208/Sec)*	*TG (mg/dl)*	*CHOL (mg/dl)*
Mean	7.976	7.366	252.351	11.808	118.449	103.090
Median	7.500	7.100	247.000	11.771	102.000	98.500
Mode	7.600	5.800	244.000	11.941	91.000	72.000
SD	2.938	2.242	72.730	0.723	42.827	27.605
Min	4.80	2.60	60.00	9.73	72.00	58.00
Max	44.00	18.10	509.00	14.49	300.00	170.00
N	245	245	245	245	100	100

TG: triglyceride; CHOL: total cholesterol

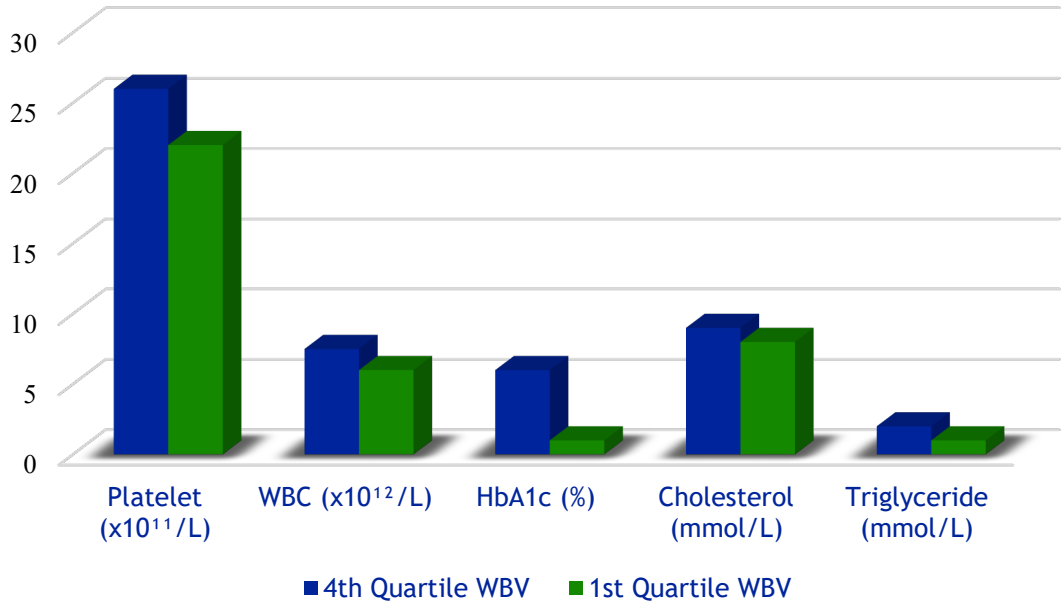
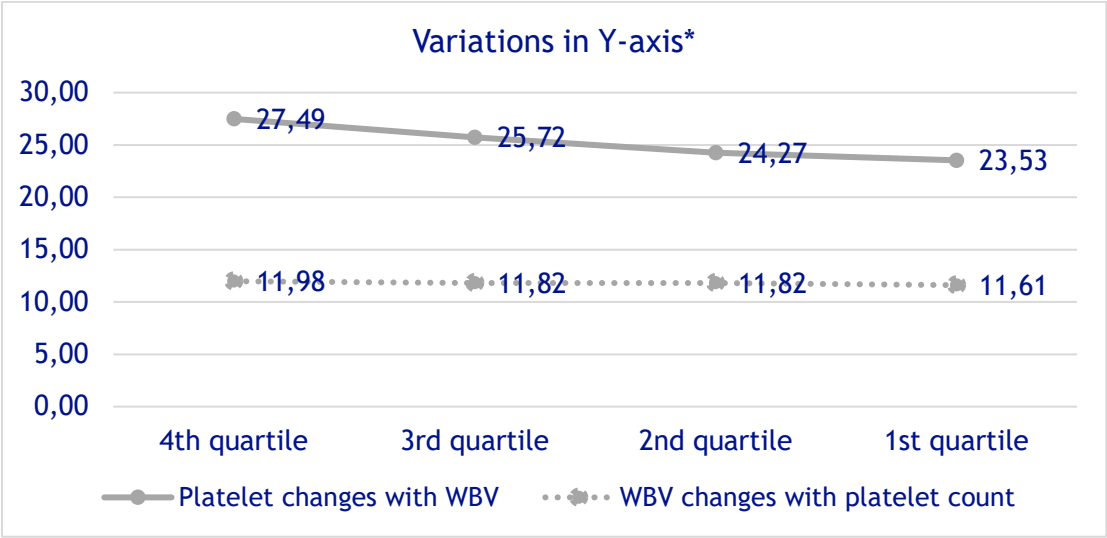


Figure 2: Differences in common clinical variables between quartile groups of WBV



**Platelets ×10⁹/L; and eWBV (208/Sec)*

Figure 3: Reliability of WBV changes with platelet count[29]

Consistent with previous report that platelets count reduced as blood viscosity decreased ($p < 0.001$) and eWBV level signify-cantly lower ($p < 0.005$) in thrombocytopenia compared with thrombocytosis,[22] results from the private general practice showed consis-tency that WBV increased with platelet count and vice versa (Figure 3).

Validity results show sensitivity and specificity of WBV for leukocytosis to be 15% and 69%, respectively. Higher specificity of 78% hypoviscosity to leukocytopenia was observed. Lipidaemia in the dataset were 62% and 38%, respectively for specificity and sensitivity but individual parameters are more specific and less sensitive. On platelet counts, the calcu-lated sensitivity and specificity of WBV for both sides of abnormal platelets showed higher specificity than sensitivity (Table 2).

Discussion

Reliability

Internal consistency assessed the changes in eWBV levels with multiple variables. Based on dataset from private general practice, results affirm consistencies reported[22-24] – that is, WBV may increase with cholesterolaemia, glycosy-lated haemoglobin, leucocytosis, and thrombo-cytosis (Figure 2). Hence it is pertinent to reiterate some points advanced in previous reports that eWBV increased with the level of inflammation, but this was not statistically significant between sub-populations of nega-tive versus positive CRP/ESR results.[30] When eWBV was compared among cases with leuco-cytosis and/or leucopenia, non-significant as-sociation between leucocytosis and hyper-viscosity was observed and this was supported by the low correlation.[24] With reference to platelets as index of platelet function test, *reliability* evaluation showed that as WBV increases with platelet count it is significantly lowered in thrombocytopenia compared with thrombocytosis.[22]

Validity

Validity is sensitivity and specificity,[26] which refers to usefulness and utility. The crux of this discourse is considering leukapheresis to be therapy in leukocytosis-based hyperviscosity and platelet count as an accessible platelets function test. Hence, the extent that high and low WBV are sensitive and/or specific to paradigms of the cell counts was determined and the results show WBV to be more specific and less sensitive to these phenomena (Table 2). Putting the results into perspective, platelets count does not fully reflect the level of blood stasis and this is supported by reports of an association between platelet hyper-activity and antiplatelet therapy.[31]

Gender-specific differences in platelet func-tion and response to antiplatelet therapy are speculated, hence the quest for more specific evidence base.[32] While laboratory monitoring of antiplatelet medication helps to predict individual responsiveness,[33] the significance of this paper is in advancement of sensitivity and

Table 2: Calculated sensitivities and specificities of eWBV to established tests

Established laboratory tests of cardiovascular phenomena		Sensitivity	Specificity
Platelet (150-450 ×10⁹/L)	Thrombocytosis	15%	70%
	Thrombocytopenia	10%	64%
WBC (4.5-11 × 10⁹/L)	Leucocytosis	15%	69%
	Leukopenia	38%	78%
Lipidaemia	Triglyceride > 2.28 mmol/L	17%	97%
	Total cholesterol >5.17 mmol/L	8%	98%
Glycaemic control	HbA1c >6.5%	3%	98%

specificity of an often overlooked test.

Further, significance of this discourse is on accessibility of eWBV, bearing in mind that blood viscosity test is not readily available or accessible but eWBV can be extrapolated from haematocrit and serum protein levels,[25, 34] just as INR is generated for prothrombin time. Therefore, affordances may not be an issue in providing blood viscosity test but what is needed is awareness.

Note on study limitation:

Several studies have reported inconsistent results possibly due to the objectives and protocols. For instance, cognizance was taken that serum protein level excludes fibrinogen, but this was deemed not a major issue since the estimated formula is more specific and less sensitive. Correlation of mean arterial pressure with WBV has been reported to be different,[35, 36] but differences in genders' haematocrit were noted as not being compensated in one.[35] Further, this study focused on platelets and associated routine laboratory tests with recourse to 'blood thinning' effect of antiplatelet therapy. Notwithstanding this limited focus, the validity of assessing level of blood stasis for antiplatelet contraindication in thrombocytopaenia or indication in thrombocytosis is presented to advocate evidence-based prescription. It has been reported that WBV strongly correlates with blood salicylate level and international normalized ratio;[22, 37] therefore, this report is corroborative.

Conclusion

This paper advances the discourse on sensitivity and specificity, as well as affordances in terms of accessibility and affordability of eWBV with a view to re-evaluate utilization of WBV in clinical practice. This report highlights a clinical laboratory tool for evidence-based medical practice to manage cardiovascular phenomena, especially antiplatelet therapy. The results show that eWBV is generally more specific and less sensitive to common CVD phenomena. In particular, the laboratory tool showed a minimal sensitivity to thrombocytosis and higher than specificity to thrombocytopenia. The potential of adopting eWBV is for the benefit of patients' care with emphasis on affordances, reliability and validity. The long-term and universal utility is that patients who have haematocrit and serum protein level results i.e., from accessible routine laboratory tests, can have their WBV level determined.

Acknowledgments

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Data Availability

Data supporting the results reported in the manuscript have been previously published as referenced. However, any further request can be made through the authors

Conflicts of Interest

None to declare

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