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MODELING OF HEMORHEOLOGICAL AND BIOCHEMICAL DATA: A NEW APPROACH TO UNDERSTAND HYPERTENSION

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ABSTRACT

Studies of clinical hemorheological data over the past three decades clearly signal a relationship between diseases (esp. cardiovascular disorders) and various hemorheological parameters. However, the literature related to these diseases doesn't even mention hemorheology as a possible tool of diagnosis, treatment, or prognosis. It is probably because most such studies have been 2-point determinations of hemorheological parameters in a few human volunteers in which several parameters also likely to affect blood viscosity have not been monitored. Thus, their findings have been inconclusive, often contradictory and hence not clinically useful. Our study presents the statistical analysis and mathematical modeling of a vast database, consisting of 1168 records of individuals, collected over a five-year period, each comprising 39 health-indicating parameters-biochemical, hemorheological, and clinical in normal and diseased persons. The results of multivariate regression of data subsets in male and female, further classified into normal, pre-hypertensive and hypertensive- suggest that there exists a definite degree of association between BP, specific hemorheological and other biochemical parameters related to blood. These relationships have been derived here in the form of specific mathematical equations, which vary among each of the subgroups. The role of each variable has been determined in terms of its contribution to the variability it caused in the response variable. The adjusted R^2 of each derived model has also been determined and models with adjusted R^2 above 0.38 are reported and are found to be clinically relevant. This exploratory study might suggest ways of applying innovative mathematical modeling to biomedical data so as to draw scientifically robust and clinically meaningful conclusions from it. It also points to the need of identifying additional parameters that might be implicated in HT and which have not been covered in this study.

Keywords: Mathematical modeling, Blood viscosity, Hypertension, Hemorheology.

INTRODUCTION

Clinical hemorheological studies conducted in the past three decades have established that low values of hemorheological (HR) parameters indicate wellness, while their elevation could be caused by stress, infection, cardiovascular ailments like hypertension (HT)[1], atherosclerosis[2], and myocardial infarction[3]; metabolic disorders like diabetes[4] , X-syndrome[5] or by tumor/cancer.[6] A

growing body of knowledge has established diagnostic, prognostic[7] and therapeutic significance of hemorheological parameters in several ailments/diseases, e.g., a study carried out as a follow up of the famous MONICA Project on Scottish population suggested that Plasma viscosity (PV) may have considerable potential to predict death from all causes in middle-aged men.[8] However, the most notable contributions of clinical hemorheology (Cl HR) have been made in the field of cardiovascular medicine, especially HT. The relationship between Blood Pressure (BP) and Blood Viscosity (BV) has been a topic of investigation among clinical hemorheologists for the past three decades, beginning with the pioneering work of Dintenfass, who , in 1981 concluded that "hypertension not only is accompanied by increased and abnormal blood viscosity factors (in particular, by increased rigidity of red cells and increased consistency of artificial thrombi); but that the rigidity of red cells and a breakdown of the auto regulatory control of viscosity (through malfunction of viscoreceptors) might be most important in the etiology of essential HT".[9] Although the causative relationship between BV and BP and the presence and role of viscoreceptors have not been substantiated through later studies, it has been shown that HT is accompanied by an abnormal enhancement in one or more of the BV parameters viz. Whole Blood Viscosity at low (WBVl) or high (WBVh) shear rate, Plasma Viscosity (PV), Red Cell Rigidity (RCR), Red Cell Aggregation (RCA), Plasma Fibrinogen (PF) and Hematocrit (HCT).[10-13] However, the application of clinical hemorheological concepts in clinical practice has been severely limited by the inconsistent, and often contradictory nature of findings in this field; e.g., the vital role of certain BV parameters as shown in earlier publications has been proved to be negligible in subsequent studies, while certain new parameters have been added to the list of causative or related factors.[14-18] Expert opinion has also been found to be divided on the nature of relationship between BP and BV. While some compared it with "the chicken and egg"[19], others termed BP and BV as "two chickens from similar eggs"[20]. In fact, the cause and effect relationship between BV and BP is still a speculation, which could only be confirmed through large scale longitudinal studies using time series data, statistical experiments being nearly infeasible here. Present data is not even adequate to conclusively demonstrate any directional association between BV parameters and BP.

While factors like variations in study design and methodology partly account for such variation in observations and inferences, a major reason behind this discrepancy could be the insufficient sample size employed for several of these reported studies. Moreover, most of the BV parameters exhibit overlapping ranges of values for normal (control) and diseased individuals and a wide range of inter-individual variation. Most such studies have been pre-treatment and post-treatment observations of HR parameters during which several other factors that might affect these parameters (e.g.; smoking, disease status, lipid profile) have not been monitored. As a result, in spite of a plethora of research material available in this field, clinical applications of hemorheological concepts for diagnosis, prognosis or treatment have not been made possible. International guidelines (for example, Joint National Commission-JNC[21]) about treatment of hypertension (the ailment most studied by hemorheologists), do not have a word about BV and related parameters. The present study was undertaken to address the above-mentioned issues and attempt to evolve better defined, mathematically accurate relationships among blood pressure, HR parameters and other related hematological parameters. This study uses a vast database of clinical, HR and biochemical parameters and innovative mathematical modeling techniques to draw conclusions which will be scientifically robust as well as clinically meaningful.

MATERIALS AND METHODS

The database used for analysis in this paper has been compiled as a part of an earlier study entitled Early Detection Project (EDP) at the Hemorheology Laboratory of the erstwhile Inter-Disciplinary Programme in Biomedical

Engineering at the School (now Department) of Biosciences and Bioengineering, Indian Institute of Technology Bombay (IITB), Mumbai, India. Spanning over a period from January 1990 to April 1996, it consists of 1168 records, each with 39 parameters, which encapsulate the biochemical, hemorheological and clinical status of the individuals-mainly students, faculty, staff and their family members visiting IITB Hospital for routine checkups or treatment of common ailments. This laboratory has pioneered research in this field by conducting the baseline hemorheological studies in the Indian population and correlating the BV parameters with various disease conditions.[22-26] Several papers demonstrating important relationships between BV parameters and essential HT, based on part of this database and published in reputed journals testify its scientific soundness.[27-30] However, for the first time, the entire database has been compiled, organized and subjected to rigorous mathematical analysis during the present study. Some of the conclusions resulting from this analysis are reported in this paper.

Profile of the sample

In all, 39 parameters have been noted for each respondent. They include age, gender, habit (smoking , alcohol consumption), blood groups, disease state, health indicators (e.g.; pulse, systolic blood pressure (BP1), diastolic blood pressure (BP2) and biochemical parameter like Serum Proteins (SP), Serum Albumin (SALB), Serum Fibrinogen (SFIB), Hematocrit (HCT), Erythrocyte Sedimentation Rate (ESR), Serum Cholesterol (SC), Serum Triglycerides (STG), Hemoglobin (HB), Platelet Aggregation (PLA), along with various HR parameters (Whole Blood Viscosity-WBV measured over eight different shear rates, Plasma Viscosity- PV- measured over three different shear rates, using a Contraves 30 viscometer, and Red Cell Aggregation - RCA).

The database covers a very wide age-range (14-83 years), although majority of the respondents are closer to 40 years of age (average age 41.67 years). The female component of the database is comparable to the male component in most parameters like age, blood group distribution and biochemical values. The average BP of the entire database (127.27 /83.89 mm of Hg) and also that of its male (127.97/85.14 mm of Hg) and female (125.46/82.36 mm of Hg) components are close to the normal value of 120/80 mm of Hg, reported in the literature, signifying preponderance of normal controls in the sample. About 16% of male subjects indulge in smoking, alcohol consumption or both, while the corresponding value for females is 1%. The distribution of blood groups in the database is consistent with other reports related to Indian population. The incidence of HT among the database studied is found to be higher in males as compared to females (21.45% and 13.10% resp.); while the corresponding figures for Diabetes Mellitus (DM) in these sexes are 15.24% and 12.46 % resp. Most biochemical parameters are found to lie within the normal range. Plasma Viscosity (PV) shows 100% variation between maximum and minimum reported values (1.02 to 2.02cp), both in males and females. The average plasma viscosity in females is slightly higher than that reported in males (1.40 cp against 1.385 cp); the difference is not statistically significant. On the contrary, the Whole Blood Viscosity at high shear rate (WBVh) is significantly higher in males than in females (5.47 cp against 4.48 cp, $p<0.01$). The higher PV in females may be attributed to a higher percentage of females reporting elevated PF values and is consistent with earlier reported studies. The greater association of males with alcohol and smoking, along with higher HCT in males can, at least partly explain the higher value of WBV among them, in spite of the near normal value of PV. The various HR parameters included in this database, plasma viscosity (PV) and whole blood viscosity (WBV) have been determined at different shear rates using a Contraves 30 viscometer. RCA has been calculated from the following formula:

$$RCA = (WBVl/PV1)*45/HCT \quad \ldots\ldots\ldots\ldots (1)$$

Where WBVl is Whole Blood Viscosity determined at 0.512 sec $^{-1}$, PV1 is Plasma Viscosity determined at 20.4 sec $^{-1}$, and HCT is Hematocrit.[31]

All the biochemical parameters pertaining to blood have been determined using internationally

accepted standard biochemical methods and equipments. The hematological parameters were measured using SYSMEX KX-21 Automatic Hematology Analyzer (Sysmex, Japan). The guidelines specified by the International Committee for Standardization of Hemorheology (ICSH) have been strictly adhered to in determination of various hemorheological parameters. The mathematical equations related to BP and HR parameters were derived through multiple regression. *Mathematical modeling of the data*: The mathematical modeling based on the statistical concept of correlation, not implying any directional causality, which forms the cornerstone of this study is outlined below. Medical diagnosis uses logic as its basis with the premise that when causality of pathology is unclear, the presence or absence of certain symptoms suggests the presence or absence of certain diseases. What is implied here is that a significant correlation between the symptomatic observation and the presence of certain disease may be used as a predictive tool to help contemplate actions to treat that malady. Correlation, a statistical measure of the association between two variables or sets of data, is an expression of the strength of relationships between the two, not necessarily implying causation. In business, for example, a correlation is generally present between the demand for a product and the price at which it is offered to be sold. Thus correlations may be used to indicate a predictive relationship which may be exploited in practice. However, statistical dependence, as might be indicated by observing a correlation, is not sufficient to imply a *causal relationship*. Indeed, a causal relationship directly implies that A *causes* B. Mere correlation may be observed when the causes underlying the correlation, if any, may be indirect or unknown. So correlation may be taken as evidence for a possible causal relationship but it cannot indicate what the causal relationship might be. But even so, the situation does not remain desperate for too long. As medical science progresses, we keep on discovering better and better symptoms (conditions observed to be strongly correlated with certain diseases) or biochemical markers and exploit their implicative capacity. For instance, Glycated hemoglobin (*hemoglobin A1c)* is now used to diagnose diabetes quite reliably as it is found to be strongly correlated with fasting plasma glucose (FPG).[32] The present study has utilized a modeling approach that has looked into the *quantitative* relationship between blood viscosity and some other variables and hypertension, by statistically studying the association between the established indicator(s) of hypertension (BP1 and BP2) and a large number of blood viscosity-related and other biochemical variables that in practice are comparatively easy to measure. Associations between each of the most important hemorheological indicators (WBVh and PV) and these biochemical variables have also been studied in a similar manner. Beyond merely studying association as commonly measured by correlation between the "response" and a speculated set of selected "explanatory variables", this exploratory study has used stepwise regression and a large set of subject data with sufficient diversity to develop a number of quantitative models. These models are parsimonious and preserve only those explanatory variables that are sufficient to explain the observed variation in the response (such as systolic or diastolic blood pressure) up to a specified level of statistical significance. Admittedly, since the set of possible explanatory variables could not be made exhaustive, nor data for all such possible variables could be measured, the predictive capability of such multi-regression models cannot still be claimed to be ideal: Adjusted R^2 for these models range from 0.35 to 0.72, indicating that in future studies, the explanatory variables set should be expanded to improve the predictive value of such potentially powerful models.

RESULTS AND DISCUSSION

Each of the male and female volunteer databases was divided into three groups-

a. Normal-Control 'N'-(SBP < 120 mm Hg and DBP < 80 mm Hg),
b. Pre-HT 'X' (SBP = 121- 139 mm Hg and /or DBP = 81- 90 mm Hg), and
c. Hypertension 'HT' (SBP > 140 mm Hg or DBP > 90 mm Hg).

No distinction was made on the basis of those receiving treatment and those not receiving it. The classification was made solely on the basis of BP. In all, six groups were made. For each group, four equations were derived with BP1 (systolic blood pressure), BP2 (diastolic blood pressure), PV and WBVh as independent variables. Of the 24 derived models, 14 equations, each with adjusted $R^2 > 0.38$ have been reported below:

MALE NORMAL CONTROL (Male- 'N')

BP1 = 55.31+ 0.772 BP2 – 0.068 AGE +0.0154 SC …….. (2)

(Adjusted $R^2 = 0.4397$)

BP2 = 8.677 +0.552 BP1 +0.56 WBVh +0.042 AGE ……. (3)

(Adjusted $R^2 = 0.4359$)

WBVh = - 4.2769 + 0.133 HCT + 2.75 PV ....(4)

(Adjusted $R^2 = 0.5502$)

MALE PREHYPERTENSIVE (Male-'Pre-HT')

WBVh = - 4.6307 + 0.137 HCT + 2.85 PV….(5)

(Adjusted $R^2 = 0.5399$)

MALE HYPERTENSIVE (Male-'HT')

BP1 = 14.675 +1.48 BP2 + 0.51 AGE +8.6 WBVh – 1.21 HCT – 19.0 PV …….. (6)

(Adjusted $R^2 = 0.4965$)

BP2 = 60.33 +0.243 BP1 ……. (7)

(Adjusted $R^2 = 0.3848$)

PV = 0.9277 +0.106 WBVh - 0.0139 HCT +0.00046 STG + 0.037 SALB +0.0030 BP2 ....(8)

(Adjusted $R^2 = 0.3852$)

WBVh = - 1.1153 + 0.115 HCT + 2.8 PV +0.0137 BP1 – 0.026 BP2 – 0.0135 AGE – 0.15 SALB …..(9)

(Adjusted $R^2 = 0.6087$)

FEMALE NORMAL CONTROL (Female- 'N')

WBVh = - 3.68 + 0.128 HCT + 2.01 PV +0.00235 STG – 0.0093 AGE +0.19 SALB – 0.0018 SC …... (10)

(Adjusted $R^2 = 0.6808$)

FEMALE HT (Female- 'HT')

BP1 = 31.292 +1.36 BP2 – 1.58 HCT + 0.58 AGE +5.3 WBVh ……. (11)

(Adjusted $R^2 = 0.5656$)

BP2 = 100.02 +5.01 WBVh – 18.6 PV …. (12)

(Adjusted $R^2 = 0.4737$)

PV = 1.644 +0.137 WBVh - 0.014 BP2 + 0.098 SALB +0.00060 STG …… (13)

(Adjusted $R^2 = 0.6348$)

WBVh = - 9.689 + 4.44 PV + 0.105 BP2 – 0.52 SALB ……. (14)

(Adjusted $R^2 = 0.7278$)

The above set of equations shows that of the various biochemical and HR parameters, only a few have strong explanatory relationship with BP and that relationship is not unique: it differs among between normal population, borderline hypertensive and HT patients. The first two equations covering the Normal Control dataset reveal that apart from the obvious correlation between systolic and diastolic blood pressure, BP in normotensive individuals is correlated with age and serum cholesterol. Slight increase in BP with age has been reported in several studies. Serum cholesterol has been a known culprit in HT. Our model suggests that the process of elevation of BP with increasing levels of serum cholesterol might begin even in normotensive population, which, if unchecked, might culminate in HT. The next equation shows association of whole blood viscosity with plasma viscosity and hematocrit, a fact fundamental to the science of hemorheology. We would recall that HCT has been shown to directly contribute to whole blood viscosity in various earlier clinical and modeling studies.[33,34] Interestingly, model (5) representing the behavior of whole blood viscosity at higher shear rate in male borderline HT patients is almost the replica of model (4) in male normal population. WBVh has mainly been shown, in both cases, to be function of PV and HCT.

Model (6) reveals that the systolic blood pressure in male HT patients is, apart from diastolic BP and age, related to the most important HR parameters, viz., PV and WBVh (along with HCT, which also contributes to WBV). Consistent with the models of WBVh in normal and borderline male hypertensive populations, the one related to male HT patients (model 9) shows association of the response variable with PV and HCT. However, in addition, this model with adjusted $R^2 = 0.6087$ also shows its correlation (although feeble) with BP1, BP2, age and SALB. PV, another important

hemorheological parameter has been shown to be associated with BP2, WBVh, HCT, SALB, and STG in hypertensive males. Serum albumin, the main constituent of serum proteins also contributes to plasma viscosity. Total cholesterol and triglycerides, the well-known culprits in HT may also be acting through elevation of BV as indicated by several studies. Thus, the probability of co-occurrence of changes in BV- related and BP- related parameters in hypertensive males has been demonstrated by these equations.

In female population, models describing changes in WBVh have been constructed with reasonable degree of confidence in normal controls and HT patients. PV and SALB have been implicated both in models (10) and (11); the former has additional parameters – HCT, STG, AGE and SC also contributing to it. Of clear significance are models describing behavior of BP in female HT populations. Like in male population, hemorheology-related parameters- WBV, PV and HCT have been shown to influence BP changes in females. Similarly, PV is shown to be associated with WBVh, BP2, SALB and STG. Recall that PV, HCT and SALB all are known to be the building blocks which make up the viscosity of the whole blood and have obvious correlation with it. Its relationship with diastolic BP only reinforces validity of other proposed models.

The adjusted R^2 values for all these equations vary between 0.3848 and 0.7278, thereby validating the well-known fact that regulation of BP and BV is a much complex process, involving several other parameters, many of them may be difficult to enlist, quantify and measure. For example, the auto regulatory mechanism of BP involves the role of diet, physical activity, age, hormones and various enzymes. Similarly, WBV and PV are known to be affected by several factors, viz., diet, state of hydration, stress, smoking etc. This study, however, reveals which parameters among those recorded (see profile of the sample above) are most significantly related to it.

The following table encapsulates the summary of our findings in terms of the main response variables and the parameters shown to be closely associated with them thus; BP in HT patients, irrespective of their gender has been shown closely associated with age, PV and WBVh, with age and WBVh being influential even in normal male population. Thus, the probability of changes in hemorheological parameters influencing changes in BP has been established by these equations. The process might be initiated even when the BP is within the normal range, but which might continue with increasing BP. On the other hand, changes in plasma viscosity in both male and female hypertensive patients have been shown to be influenced by diastolic pressure, apart from its known associations with WBVh, STG and SALB. WBVh, the most important hemorheological parameter has been shown by our models to be mainly dependent on HCT and PV. However, in normal female dataset, it has also been shown to be associated with STG, SC, SALB and age, which is a major departure from the behavior observed in normal male dataset. In fact, this model closely resembles that found in male HT patients. Most interestingly, its association with BP has been shown in both male and female HT patients.

CONCLUSIONS

Clinical Hemorheology, in spite of three decades of excellent research, has not succeeded in influencing the clinical practice of the cardiovascular diseases. The research inputs have not been acknowledged even at the conceptual level, as seen from the near absence of hemorheological interpretation of etiology and treatment of these diseases in standard textbooks or international guidelines [21, 35]. One possible reason is the separation of biomedical engineering (of which Clinical Hemorheology is a part) and clinical streams in research and practice of medicine. Moreover, the discrepancy in the conclusions about the exact role of each of the BV parameters in its contribution to BV and the complexity of the BV-BP relationship has also played an important role it.

Inadequate sample size is one of the major limitations of earlier studies on this subject. Although many difficulties related to the application of statistical methods outlined above are relevant to this study, the probability of

reaching more reliable inferences has been enhanced by the vastness of this database. The strong positive correlation between blood pressure and WBVh, PV and HCT, along with age; reinforce some findings of the earlier studies. In fact, WBVh and PV have emerged as the most powerful independent variables that are shown to be correlated to blood pressure. Age has been shown to be related to both blood viscosity as well as blood pressure. It occurs in five of the thirteen models described above. SALB, a factor relatively less reported in clinical literature has been found to occur in five models, while STG, the well-known culprit occurs in three models related to hemorheological parameters as response variables. It might be indirectly implicated through SP in one more model. Several epidemiological and smaller studies have reported that smoking may cause elevations in STG, WBVh, SC, and PF. Leads like this need to be probed further through a more focused study of patient habits.

Finally, in addition to a better use of statistical tools, clinical hemorheological observations could be interpreted in a "clinically more relevant" manner, if more focused, longitudinal studies involving careful follow-up (to help affirm hypothesized causalities) is carried out in healthy volunteers *and* patients and the changes occurring in response variables as well as dependent variables are carefully monitored. The low value of adjusted R^2 in several equations derived in this study implies that several parameters likely to be associated with SBP and DBP have not been included in it. Hence, future studies should include parameters such as family history, HDL_Cholesterol, LDL, Cholesterol, ratio of HDL/LDL, Body Mass Index (BMI), Blood Sugar Fasting (BSF), Blood Sugar Past Partum (BSPP) (as diabetes is a significant risk factor in HT) so that more reliable predictions about associations between SBP, DBP (response variables) and biochemical-clinical parameters (dependent variables) could be revealed using appropriate statistical models.

Nevertheless, the present approach has already established the high utility of blood viscosity-a property relatively easy to measure in practice-as being a dependable predictor of hypertension. Establishing causality of hypertension (not attempted here)-the quest of many modern studies of arterial maladies-would require either longitudinal studies of subjects of varied characteristics, or conducting statistically designed experiments where the speculated "causes" are varied in accordance with plans such as factorial experiments, the resulting data analyzed by methods such as ANOVA.

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Table 1: Summary of association among main response variables and other parameters

Response variable	Group	Parameters closely associated with response variable
BP	MALE N	AGE/ WBVh/ SC/
	MALE HT	AGE/ WBVh/ HCT/PV
	FEMALE HT	AGE/WBVh/HCT/PV
PV	MALE HT	WBVh/STG/SALB/BP2/HCT
	FEMALE HT	WBVh/STG/SALB/BP2
WBVh	MALE N	HCT/PV
	MALE BORDERLINE	HCT/PV
	MALE HT	HCT/PV/BP1/BP2/AGE/SALB
	FEMALE N	HCT/PV/STG/SC/AGE/SALB
	FEMALE HT	PV/BP2/SALB

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