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Review article

The clinical importance of erythrocyte deformability, a hemorrheological parameter

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Summary. Hemorrheology, the science of the flow behavior of blood, has become increasingly important in clinical situations. The rheology of blood is dependent on its viscosity, which in turn is influenced by plasma viscosity, hematocrit, erythrocyte aggregation, and erythrocyte deformability. In recent years it has become apparent that the shape and elasticity of erythrocytes may be important in explaining the etiology of certain pathological situations. Thus, clinicians have become increasingly interested in hemorrheology in general and erythrocyte deformability in particular. In the course of time, many clinical studies have been performed, but no concise review has thus far been published. This article encompasses a review of the clinically based literature on this subject.

Key words: Erythrocyte deformability – Hemorrheology – Clinical

Introduction

Hemorrheology is the science of the flow behavior of blood. Its major field of interest is blood viscosity, i.e., the physical property of blood that is dependent on the friction of its components as they slide by one another. A function of blood flow is oxygen delivery; distribution and adequacy of flow are influenced by viscosity, which in turn is influenced by erythrocyte deformability (ED). We will first very briefly review viscosity, and then the phenomenon of ED will be described. Furthermore, the available measurement systems with their problems will be discussed, and finally hemorrheology and in particular ED in several clinical situations will be reviewed.

When pressure is applied to a fluid, layers of molecules slide upon one another and the fluid is said to be sheared. The fluid layers move with different velocities and the velocity gradient between two layers is called the shear rate. The force that causes the layers to slide over each other is called the shear stress. The ratio between shear stress and shear rate represents the fluid's viscosity. In so-called Newtonian fluids, fluids composed of small particles of equal size such as oil, viscosity behaves independent of shear rate and remains constant with increasing shear rate. Blood is a non-Newtonian fluid composed of a suspension of many elements of varying size. Blood viscosity is dependent on shear rate. As the velocity of flow decreases, the viscosity increases. In addition to the velocity of flow, shear rate is determined by the diameter of a vessel. The highest shear rates exist in the smallest vessels. For this reason blood viscosity must be measured at several shear rates. At very low shear rates the blood tickens exponentially as a consequence of erythrocyte aggregation, also known as rouleaux formation, which influences shear stress. When the shear rate increases, the aggregates will disperse and viscosity will decrease, a phenomenon called shear thinning. Other factors that influence blood viscosity through their influence on shear stress are hematocrit, plasma viscosity, and ED. The hematocrit is a very important determinant of blood viscosity, hemodilution decreasing viscosity significantly. Plasma viscosity is dependent on protein components, particularly fibrinogen. It influences blood viscosity at low shear rates through reinforcement of rouleaux formation.

A final important factor in blood viscosity is the shape and elasticity of the red blood cell. The study of ED is a field that has seen growing interest in recent decades. However, the fact that erythrocytes must change shape in order to be capable of passing the microcirculation has been known since 1675, when this phenomenon was first described [114].

Erythrocyte deformability

ED is an important physiological factor which plays an essential part in the delivery of oxygen to the tissues.

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Under normal conditions ED allows individual red blood cells whose mean resting diameter averages 7 μm to traverse nutritive capillaries with diameters no more than 3–5 μm, thus supplying the tissues with oxygen. Any decrease in deformability will result in impaired perfusion of the peripheral tissues [31, 74, 81, 110, 116].

Furthermore, Weed et al. [116] postulated ED to be a major determinant of red cell survival. This was later verified in other studies [81]. Passing through the spleen, the red blood cells must traverse extremely narrow endothelial slits with a diameter of 0.5–1.0 μm. Because of these slits the spleen acts as a highly effective filter. A certain reduction in ED may impair passage of these cells, leading to splenic sequestration and destruction.

Deformation of red blood cells also allows blood to remain fluid even at high hematocrits. Aarts et al. [7] reported that ED influences the platelet-vessel wall interaction in flowing blood in vitro. In case of decreased deformability they demonstrated increased platelet adherence to the arterial subendothelium and vice versa.

Finally, the ability of the cell to deform allows a reduction of the bulk viscosity in the larger vessels; In response to fluid shear forces erythrocytes deform from the resting biconcave into ellipsoid shapes and align themselves with their long axes parallel to the fluid stream [74, 81]. The membrane of the cell rotates around the cell's interior, a phenomenon known as "tank treading" [104], which allows the cell to participate in flow.

The deformability of an erythrocyte is a consequence of three factors: (a) The large surface area-to-volume ratio, which is inherent to the biconcave disc shape; when the cell becomes spherical as a result of an increase in cell volume, as in hypotonically swollen cells or in the case of echinocytes and stomatocytes where the surface area is reduced, the erythrocyte will lose its advantageous surface area-to-volume ratio and a reduction of deformability will occur. (b) The viscoelastic properties of the membrane; the degree to which the membrane can be stretched has thus far not been elucidated. Some authors report that cell lysis occurs when the membrane is stretched over 10%–15% [69]. (c) The viscosity of the intracellular hemoglobin solution; in case of dehydration, as in hypertonically shrunken cells, there will be a reduction of deformability due to a higher mean cell hemoglobin concentration (MCHC) and thus a higher internal viscosity, in spite of an even more favorable surface area-to-volume ratio. It is the combination of these three features that allows the red blood cells to be flexible. It is thought that an abnormal increase in rigidity is caused by a change of any one or a combination of these factors [16, 19, 69, 80, 82].

Measurement of erythrocyte deformability

Ever since the clinical importance of ED became apparent, many methods of measuring this phenomenon have been developed. The most important problem many investigators still face is the difficulty of simulating the physiological situation. In large vessels the erythrocytes elongate in response to shear forces, whereas in the microcirculation the red cells "crawl" through a capillary. These two physiological situations should be kept in mind when one is measuring ED. The following techniques are presently used and generally accepted for the measurement of red cell deformability.

Erythrocyte filtration

Erythrocyte filtration is currently the most widely used technique. Since Reid et al. [95) developed their method, some variation of this technique has been used. In all cases the ability of red blood cells to pass a filter is measured either by the time required for passage of a certain volume of erythrocytes or by the pressure-flow relationship. Most often, polycarbonate membranes with pore sizes of 3–5 μm are used [61, 74]. Initially, whole blood was filtered. The filtration time often increased however, due to blockage of the pores by the more rigid leukocytes, platelet microaggregates, or erythrocyte aggregates [19, 61, 74, 110]. Thus, washed erythrocyte suspensions are now most often used [66, 110]. Although this method is quite time consuming, it is frequently used in deformability studies. The systems use gravity or applied positive or negative pressure filtration. All are regarded as comparable. Unfortunately, pore blockage due to contamination may still be a problem. The major disadvantage of these filtration systems is that minor deformability changes often remain undetected.

The relatively new Cell Transit Analyzer (ABX Rheology, Levallois, France), using a special 30-pore membrane, is regarded as one of the most efficient filtration systems available [45, 111, 120]. This computer-assisted system does not require washed cell suspensions. It measures the transit times of erythrocytes through a polycarbonate filter by changes in electrical conductance when pores are occupied by single erythrocytes. Fisher and co-workers [44] are working on improved hardware and new software to obtain more information from each red blood cell transit. This will make it possible to do more detailed studies of normal and pathological red blood cell mechanical behavior by means of the Cell Transit Analyzer.

Laser diffraction ellipsometry (erythrocyte elongation)

Laser diffraction ellipsometry (ektacytometry), combines viscometry with laser diffractometry: 10–25 μl of blood is suspended in a high-viscosity medium, usually polyvinylpyrrolidone (mol.wt. 360000) or dextran (mol.wt. 40000) in buffer, and subjected to well-defined shear stresses, thus producing a complete deformation spectrum. The erythrocytes are deformed to ellipsoids and diffract a helium-neon laser beam which passes through the test suspension [10, 11, 62]. The elliptical diffraction pattern obtained can be analyzed by a microprocessor-assisted quadrant detector (Technicon Instruments Corporation, Tarrytown, NY) [13, 48], or a videocamera can be used for pattern registration and subsequent computer analysis [52]. By changing the osmolality of the medium, deformability can be studied under hypo- and hypertonic conditions. When no stress is applied, or in case of no de-

formability, a circular diffraction pattern will be obtained. Upon increasing deformability lengthening ellipsoid forms will be registered. Ektacytometry is a quick method for measurement of ED, with good reproducibility, high precision, and narrow interassay variation [13,62,110]. Its major drawback is the high initial cost of an ektacytometer.

Micropipette aspiration

In this method segments of, or entire erythrocytes are aspirated into glass capillaries 1–5 μm in diameter. ED is determined by the measured amount of negative pressure necessary to aspirate the cell. Although this is a precise method for single cell deformability measurements and provides much information on the viscoelastic properties of the membrane, it is difficult and time consuming, and therefore rarely used [19,61,79,81,110].

Taylor factor

The Taylor factor, empirically derived and calculated from hematocrit, plasma viscosity, and high shear whole blood viscosity, is claimed to reflect ED [25,26,89]. The Taylor factor is thus calculated:

$$T = 1 - \frac{(\text{plasma viscosity} : \text{high shear blood viscosity})^{0.4}}{\text{hematocrit}}$$

As has been the case in viscometry, many different methods have been developed for the measurement of ED. In the past several decades measurement techniques have been developed, from centrifugal packing and bulk viscometry, through primitive filtration systems, to the computerized Cell Transit Analyzer and laser diffraction ellipsometry. It should be realized that most clinical studies here described made use of a variety of methods. Furthermore, many of the existing methods were modified by the different authors. To be able to compare different clinical investigations, the materials and methods used should be comparable. This was realized by the International Committee for Standardization in Hematology; guidelines were developed in 1986 to ensure uniformity in measurement of blood viscosity and ED [61]. In spite of the guidelines, many studies have been published in which these were not followed. Generally, filtration and ektacytometry are considered the optimal measurement techniques.

Clinical Significane of erythrocyte deformability

Initially, ED was looked upon mainly from a biochemical and physicochemical point of view. In the past 20 years an increasing number of clinical studies have been and are being performed (Table 1). Below, a review is presented of the relevant studies thus far performed on ED in various clinical disorders. Classification has been done by organ system. In all studies mentioned, except when stated differently, a *filtration method* was used to determine ED.

Table 1. Clinical studies on erythrocyte deformability

Disorder	ED	Technique	Reference
Hemolytic anemias	⇩	Filtration	88
Hereditary spherocytosis	⇩	Ektacytometry	4
Hemoglobin C-C disease	⇩	Ektacytometry	4
Unstable hemoglobin disorder	⇩	Ektacytometry	4
Autoimmune hemolytic anemias	⇩	Ektacytometry	4
Glucose-6-dehydrogenase deficiency	=	Ektacytometry	4
Pyruvate kinase deficiency	⇩	Ektacytometry	4
Sickle cell disease	⇩	Ektacytometry	6,12,71
β-Thalassemia	⇩	Filtration	115
Malaria	⇩	Filtration	5,22,87
Septicemia	⇩	Filtration	59,78
Myocardial infarction	⇩	Filtration	28,32
Peripheral occlusive arterial disease	⇩	Filtration	7,33,96
	=	Ektacytometry	7
	=	Viscometry	7
Aortic valve disease	=	Filtration	17
Starr-Edwards valve replacement	⇩	Filtration	17
Raynauds's syndrome	⇩	Filtration	27,77
Cerebral vascular accident	⇩	Filtration	15,73,90
Transient ischemic attack	⇩	Filtration	42,73
Lacunar strokes	⇩	Filtration	107
Multiple sclerosis	=	Filtration	93
	⇩	Filtration	108
Diabetes mellitus	⇩	Micropipette	79,105
	⇩	Filtration	37,63,64,92
Diabetes mellitus			
– complications	=	Filtration	76
+ complications	⇩	Filtration	76
Postmenopause	⇩	Filtration	46
Ovariectomy	⇩	Filtration	47
Normal pregnancy	=	Filtration	103
Gestational diabetes	=	Filtration	103
Insulin-dependent diabetes and pregnancy	⇧	Filtration	103
Essential hypertension and pregancy	=	Filtration	103
Hypothyroidism	=	Filtration	68
Parathyroid hormone	⇩	Filtration	14
Renal failure	⇩	Filtration	9,23,67
	⇩	Ektacytometry	9
Dialyzed patients	⇩	Filtration	60
Nondialyzed patients	=	Filtration	60
Nephrotic syndrome	⇩	Filtration	18
Several liver diseases:	⇩	Ektacytometry	8
(alcoholic liver disease,	⇩	Filtration	8
chronic active hepatitis,	⇩	Viscometry	8
extrahepatic cholestasis, primary biliary cirrhosis)			
Surgery	⇩	Filtration	29,85
Cardiopulmonary bypass	⇩	Filtration	34,54,55
Physical activity	⇧	Filtration	35,40,38
Obesity	⇩	Filtration	40
Psychoemotional stress	⇩	Filtration	40
Marathon running	⇩	Filtration	97
Bed rest	⇧	Filtration	41,65
Blood storage	⇩	Filtration	51,118

ED, Erythrocyte deformability; ⇩, decrease; ⇧, increase; =, equals

General differences in erythrocyte deformability

As with many other physiological phenomena, there are interindividual differences in erythrocyte filterability which result in a relatively wide normal range. Erythrocytes from newborn infants were found to be less deformable than those from adults; this appeared to be due to the larger volume of the fetal erythrocyte [98]. These results were not confirmed using an ektacytometer [21]. In children reduced deformability was found when compared with adults [24].

Sutera et al. [113] described the deformability changes related to cell age by means of a rheoscope. In a rheoscope, direct microscopic observations can be made of red cells at various shear stresses. Ninety percent of the older cells were still capable of tank treading. All those cells deformed less than their younger counterparts. This was suggested to be caused by a loss of surface area. Aging of normal erythrocytes is thought to be accompanied by a decrease in cell volume, and therefore by an increase in MCHC and internal viscosity [13, 53].

Metabolic changes

Impairment of energy supply to a cell will change its mechanical properties. The biconcave shape of the erythrocyte is maintained by an energy-requiring process [86]. Weed et al. [117] showed ATP depletion to decrease ED. The authors demonstrated a 400% increase in intracellular Ca^{2+} during 24-h of incubation in serum. It was suggested that hemoglobin and nonhemoglobin proteins, which are soluble within metabolically intact cells, may become insoluble in case of ATP depletion and Ca^{2+} accumulation. It was hypothesized that a gel is formed, located at the interface between the cell's interior and the membrane, thereby changing the cell shape. After reincubation with adenosine, the ATP level, cell shape, and mechanical properties of the cell were restored to normal. LaCelle [69] observed that hypoxia also reduced ED. He interpreted this to be a consequence of hemoglobin binding of ATP, with resultant gel formation. Hakim and Macek [49] confirmed LaCelle's results in different species. Using the micropipette method, LaCelle and Smith [70] demonstrated decreased ED when extracellular pH was reduced, but were not able to duplicate this with the filter technique. Clearly, metabolic changes influence ED. However, most of the studies mentioned above were performed with older versions of filtration systems. The modern measurement techniques could be useful in detecting less pronounced changes in ED following minor decreases in pH, ATP, and oxygen tension.

Blood disorders

Hemolytic anemias

In 1964, using a primitive filtration technique, Nicolau et al. [88] reported a reduction of ED in several hemolytic blood disorders and suggested that flexibility changes might play an important role in the red cell's pathology. Using ektacytometry, blood from patients with *hereditary spherocytosis (HS)* showed varying proportions of nondeformable erythrocytes (10% – 30%); the percentage was generally found to correlate with the severity of the disease [4]. A significantly higher percentage of nondeformable erythrocytes was found in patients with *hemoglobin C-C* and *unstable hemoglobin disorders* (60% – 80%) [4]. In case of *autoimmune hemolytic anemias* a large variation of impaired deformability was reported (10% – 70%) [4]. This seemed to be due to membrane loss as a result of partial phagocytosis of the antibody-coated red cells by macrophages [81]. The deformability of red cells from patients with *glucose-6-phosphate-dehydrogenase deficiency* was near normal, while patients with *pyruvate-kinase deficiency* showed small subpopulations (10% – 15%) of nondeformable cells [4].

In the ektacytometer the red cells from patients with *sickle cell disease* exhibit a unique diffraction pattern: a horizontal ellipse superimposed on a vertical ellipse. This is explained by the fact that irreversibly sickled cells (ISC) do not align themselves parallel to the direction of flow, but move in a direction perpendicular to the flow, rotating around their long axis without deforming [12]. This was thought to be the explanation for the vaso-occlusive crises in sickle cell disease. However, Ballas et al. [6] and Lande et al. [71], both using ektacytometry, found a strong positive correlation between the frequency and severity of crises with ED and hemoglobin concentration. It was postulated that the more deformable the sickled erythrocytes are, the greater their adherence to vascular endothelium and the more they cause vaso-occlusive crises. A slight decrease in ED has been demonstrated in patients with minor and intermediate *β-thalassemia* [115].

Malaria

Several authors [5, 22, 87] reported red blood cells from patients infected with *Plasmodium falciparum* to have reduced deformability. Nash et al. [87] described a loss of deformability in cells containing ring forms of the parasite when aspirated into a micropipette. More mature parasites caused a greater loss of flexibility, probably due to the presence of the parasite itself. These forms in particular might contribute to the microvascular occlusion and subsequent organ damage seen in severe cases of malaria.

Septicemia

Hurd et al. [59] reported a reduction in ED in sepsis. This effect was suggested to be responsible for the reduced blood flow to several organs despite an increase in cardiac output. Machiedo et al. [78] confirmed these findings and found a negative correlation between ED and oxygen free radical formation, as measured by malonyldialdehyde. It was hypothesized that free radicals generated during sepsis might play a role in the decrease in deformability. A direct relation was found between changes in ED and the severity of multiple organ failure.

Antioxidant therapy by means of *α-tocopherol* was shown to prevent an alteration in red blood cell deformability in septic patients. Again, this implicated free oxygen radicals as a possible mediator in the reduction in ED [94]. In this study patients who had undergone antioxidant therapy had no peripheral shunting, improved organ perfusion, and improved survival rates. It might be interesting to investigate the effect of modern drugs used in septicemia, such as monoclonal antibodies.

Cardiovascular disorders

Several authors have suggested that hemorrheological disturbances play a crucial role in coronary and/or arterial disease. Thus, an extensive amount of work has been done on the relation between hemorrheological parameters and cardiovascular disorders.

Dodds et al. [28] studied hemorrheological variables in 43 patients after acute *myocardial infarction* and found a significant drop in deformability within the first 12 h after infarction. During the first day a significant rise was seen. When subsequent hemodynamic complications occurred, particularly cardiogenic shock, a greater drop was observed. Hematocrit decreased in the week after infarction. In contrast to the expected decrease in blood viscosity, an increase was found during this period, most likely due to an increase in plasma fibrinogen content. As a result of these changes the blood flow in the ischemic area around the central area of infarction might be reduced even more and lead to extension of the infarction size. Dormandy et al. [32] confirmed these results and found the early minimum deformability value to be a good indicator of the patient's subsequent clinical course.

Reid et al. [96] reported diminished deformability in 44 patients with *peripheral occlusive arterial disease.* The cells from the patients with gangrene or rest pain showed the largest decrease. Ehrly and Landgraf [33] reported similar results. They showed that the oxygen tension in the ischemic muscle tissue of claudicants was reduced by about 50% as compared with controls even if the total blood flow as measured plethymographically was normal. Bareford et al. [7], however, found no loss of ED measured by ektacytometry and viscometry in 32 patients with peripheral occlusive arterial disease compared with 32 controls.

Regarding patients with coronary and/or arterial disease, conflicting results regarding ED have been published. Possibly, such factors as history of infarction, hypertension, age, and additional disease (diabetes, hypercholesterolemia) may play a role in these findings. Clearly, more well-defined, randomized investigations need to be performed in the future to elucidate the role of ED in these diseases.

Blood filterability has also been found to be impaired in patients with *aortic valve disease* and with *aortic valve replacements* [17]. In these patients the decrease in filterability is most likely based on mechanical damage of red blood cells.

A deterioration of deformability has been reported in patients with *Raynaud's syndrome.* Here, intervention with prostaglandin E_1 showed no improvement in deformability [77]. However, blood flow and ED improved significantly after plasma exchange [27]. The removal of an unknown plasmatic factor was postulated.

Neurological disorders

Cerebrovascular diseases

Many investigators have established diminished ED in patients with cerebral vascular disorders [15, 42, 73, 90, 107]. Lorient-Roudaut et al. [73] found impaired ED in 100 patients with cerebrovascular accidents (CVA) and transient ischemic attacks (TIA). It was stated that this depended mainly upon a plasmatic factor, since washing of the erythrocytes resulted in an improvement of deformability. Boisseau et al. [15] confirmed these results and found that deteriorated ED can be regarded as an indicator of the severity and prognosis of CVA. The drop in deformability was found to be larger in a subgroup with severe CVA and became progressively worse up to day 8, whereafter an improvement began in recovering patients. Ernst et al. [42] described decreased ED accompanied by a rise in plasma viscosity and erythrocyte aggregation in patients with TIA. They speculated that hemorrheological disturbances might predispose to the development of stroke by decreasing cerebral blood flow.

Multiple sclerosis

Pollock et al. [93] measured the deformability of erythrocytes in 15 patients with multiple sclerosis in remission and detected no significant difference in deformability when compared with volunteers. Simpson et al., however, performed similar measurements in multiple sclerosis patients with varying degrees of locomotor difficulties. Here, a significant decrease in ED was established. It was suggested that these results might explain the signs of impaired microcirculatory flow found in patients suffering from multiple sclerosis [108].

Endocrinological disorders

Diabetes mellitus

ED is impaired in diabetes mellitus [37, 76, 79, 92, 105]. Schmid-Schönbein and Volger [105] and McMillan et al. [79], who used the micropipette method, found the observations of reduced deformability to be independent of the diabetic's age, duration of diabetes, and the presence of complications. In more recent studies other authors [76, 92] found a reduction in ED in diabetics with vascular complications only when compared with diabetics without these complications.

Juhan et al. [63, 64] observed that the abnormal deformability in insulin-dependent diabetics (IDD) could be rapidly reversed by an infusion of insulin even when hyperglycemia was maintained. The deformability of ery-

throcytes from healthy donors was reduced when they were incubated in the plasma of uncontrolled IDD, but it was normal in plasma from IDD controlled by a 24-h infusion of insulin. They suggested that insulin has a direct action on ED, possibly through the membrane receptors for insulin. The platelet hyperaggregation observed in IDD also disappeared when the glucose level was corrected. Platelets from normal subjects showed hyperaggregation in the presence of red cells from uncontrolled IDD. It was concluded that the effect of insulin on platelet aggregation was at least partially mediated by erythrocytes.

Estrogens

Gelmini et al. [46] found ED to be reduced in postmenopausal women compared with premenopausal women. This might partially explain the increased incidence of cardiovascular diseases in women after the menopause. Solerte et al. [109] studied the hemorrheological changes during the menstrual cycle in healthy women and found a significant rise in fibrinogen, blood, and plasma viscosity and decreased ED during the follicular and ovulatory phase compared with the mid and late luteal phase. A positive correlation was found between estradiol and the rheological variables, indicating that ovarian hormonal activity influences blood flow in women. This was confirmed by Gelmini et al. [47], who found a persistence of low estrogen and a decrease in deformability in patients 3 weeks after hysterectomy and ovarietomy compared with hysterectomized, nonovariectomized patients.

Rogers et al. [103] studied erythrocyte filtration longitudinally in *normal and high-risk pregnancy.* ED remained stable in controls, gestational diabetics, and essential hypertensives. Insulin-dependent diabetics, however, had elevated and widely varying ED compared with controls during pregnancy.

According to Költringer et al. [68], *hypothyroidism* resulting from thyroidectomy does not affect ED. However, an increase in blood viscosity and erythrocyte aggregation was seen, of both which returned to normal after substitution therapy. No studies have been performed in patients with hyperthyroidism.

Parathyroid hormone (PTH) caused a significant decrease in ED [14]. This effect was Ca^{2+} dependent and was partially reversed by the calcium blocker verapamil. It was suggested that PTH enhances calcium entrance into the erythrocyte.

Urogenital disorders

Renal failure

Several authors have demonstrated reduced ED In patients suffering from acute or chronic renal failure [9,23,60,67]. Studying deformability in dialyzed and nondialyzed uremic patients, Inauen et al. [60] reported a negative correlation between serum creatinine and red cell deformability. Nondialyzed patients had normal ED, dialyzed patients showed impaired ED. However, there were no differences in pre- and post-dialysis filtration times. Later, Bareford et al. [9], using filtration and ektacytometry, also reported decreased ED in chronic renal failure patients. In this study dialysis caused a complete or partial correction. A positive correlation was found with the degree of renal failure. Lerche et al. [72] investigated patients with end-stage renal failure under recombinant human erythropoietin therapy by means of the micropipette technique. After several weeks of treatment significant rises in hematocrit, whole blood viscosity, and ED were observed. It was hypothesized that the deformability impairment in these patients might also be attributed to disturbed erythropoiesis.

Patients with *nephrotic syndrome* are known to have an increased risk of thrombosis. It was shown that the mean value of glycosylated hemoglobin A 1c was significantly increased [18]. An inverse correlation was found with ED, which was significantly lower in patients.

Hepatobiliary disease

Bareford et al. [8] investigated erythrocytes, by means of filtration, viscometry, and ektacytometry, from patients with *alcoholic liver disease, chronic active hepatitis, extrahepatic cholestasis, and primary biliary cirrhosis,* all with grossly abnormal liver function. All methods showed impaired deformability. Larger numbers of codocytes and acanthocytes and an increase in mean cell diameter were found, which appeared to be a major determinant of the deformability disturbance.

Other factors associated with changes in erythrocyte deformability

Surgery

Several investigators have reported reduced ED following surgery. Dodds et al. [29] demonstrated a postoperative decrease in ED in patients after arterial surgery and varicose vein stripping, with the lowest flexibility reached in both groups on the first postoperative day. Fibrinogen content and blood viscosity at low shear rates rose to a maximum on the fifth day. According to Müller and Musikic [85], disturbed hemorrheological conditions may cuse improper healing due to impaired blood flow.

Cardiopulmonary bypass (CPB)

Ekeström et al. [34] reported that marked decreases in ED are seen in patients who have undergone open heart surgery. Their study revealed a progressive deterioration of ED, reaching a minimum by the second to the third day postoperatively. The contact between the patient's blood and the materials of the extracorporeal circuit was postulated to be associated with severe blood damage, for no correlation between deformability reduction and duration of CPB was detected. Hirayama et al. [54,55], however, did establish a significant correlation between these parameters. These factors might thus be partially

responsible for postoperative complications. Al-Khaja et al. [3] measured the cutaneous blood flow with laser doppler flowmetry in patients undergoing open heart surgery. They demonstrated a reduction in the microcirculation after surgery. It was postulated that damage to red cells as a consequence of CPB could contribute to this reduction. However, it should also be recognised that the prolonged hypothermia that exists after CPB might be responsible for this reduction in cutaneous blood flow. Hirayama et al. reported an association between the occurrence of pulmonary dysfunction [57], bleeding tendency [56], and arrhythmia requiring treatment more than 24 h postoperatively [58] and impaired ED following CPB.

In all previously mentioned studies a bubble oxygenator was used. Recently, it was demonstrated that the type of oxygenator used is of importance [50]. A greater drop in deformability was seen when a bubble oxygenator was used compared with a hollow-fiber membrane oxygenator. This was thought to be due to a larger blood-gas interface and oxygen free radical formation in the bubble oxygenator. The administration of 0.5–1.0 g/kg body wt. urea has been reported to limit the amount of red cell damage due to CPB [102, 119]. It was suggested that urea decreases mechanical hemolysis by increasing the pliability of the membrane.

Physical activity

Physical activity seems to be beneficial for blood rheology. Ernst et al. [35, 40] studied the effect of cardiovascular risk factors and found that regular physical activity improves ED and the blood and plasma viscosity. Furthermore, prolonged psychoemotional stress and obesity lead to a loss in blood fluidity and erythrocyte flexibility. In stable patients with intermittent claudication who were submitted to standardized regular exercise an improvement of rheological parameters and walking distance was observed [38].

In marathon runners, Reinhart et al. [97, 99] found a reduction in red cell deformability after a 100-km run with subsequent preferential removal of older cells. Still, the mean filtration values appeared to be higher than in normal nonrunning individuals. A slight stomatocytosis was observed after the run compared with a control day; this change in morphology appeared to be due to a change in the red cell membrane itself.

Bed rest

In patients with bone fractures prolonged bed rest was observed to improve all hemorrheological variables [41]. In patients with sickle cell disease, the increase in deformability after bed rest was associated with decreased hemolysis [65].

Blood storage

Decreased deformability in stored erythrocytes has been reported by several authors [51, 118]. ED progressively decreased with storage of blood cells in acid-citrate dextrose solution at 4°C for 6–8 weeks. A dramatic reversal was demonstrated after restoration of the ATP level through incubation with adenosine [51].

Drugs and erythrocyte deformability

Since the importance of normal ED for the microcirculation has become apparent, the hemorrheological effects of several drugs and other chemical substances have been tested [75] (Table 2). However, many of those studies were short term and/or uncontrolled. Many investigators have attributed a favorable effect to the xanthine derivative *pentoxifylline* (PTX) regarding all hemorrheological variables in several patient groups [20, 83–85, 91, 106]. Often, marked improvement of the clinical course was seen during therapy with PTX.

In sickle cells, PTX and *citiedil citrate* were reported to have a protective effect in vitro [112]. However, citiedil citrate induced the formation of stomatocytes at concentrations of 10 μmol/l and higher. The protective effect of PTX was also demonstrated by Dodson et al. [30], using ektacytometry, when it was added with the Ca^{2+} ionophore A 23187, which causes loss of cell water, cell volume, and consequently loss of cell deformability. The calcium channel blocker *diltiazem* exhibited the same effect as PTX. Diltiazem has also been reported to improve hemorrheology in patients [39]. Other calcium blockers (*cinnarizine, flunarizine*) appeared to enhance ED as well [75].

Isoxuprine, a drug with vasodilating characteristics, is currently being used for its effect on erythrocyte deformability. Aarts et al. reported an increase in the flexibility of erythrocytes, estimated by the Taylor value, after the administration of *isoxsuprine* in vitro [1] and in vivo [2].

Ernst et al. [36, 43] observed an increase in ED in volunteers and patients with hyperlipoproteinemia after treatment with *fish oil* (n-3 fatty acids: eicosapentenoicacid and docosahexenoicacid).

Opioids [100, 101] have been demonstrated to induce a reduction of ED. The in vitro effect of opioids was dose dependent and reversible by naloxone. No studies have been performed on the influence of anesthesia on ED.

Table 2. Studies on the influence of drugs on erythrocyte deformability

Drug	ED	Technique	Reference
Pentoxifylline	⇧	Filtration	20, 83, 84, 85, 91, 106
	⇧	Ektacytometry	30
Citiedil citrate	⇧	Filtration	112
Diltiazem	⇧	Filtration	39, 30
Cinnarizine	⇧	Filtration	75
Flunarizine	⇧	Filtration	75
Isoxuprine	⇧	Taylor factor	1, 2
Fish oil	⇧	Filtration	36, 43
α-Tocopherol	⇧	Filtration	94
Opioids	⇩	Filtration	100, 101

ED, Erythrocyte deformability; ⇩, decrease; ⇧, increase; =, equals

Conclusion

The clinical importance of hemorrheology is increasing rapidly. Many pathophysiological phenomena may possibly be explained by abnormalities in flow characteristics of different organ systems. As the importance of ED within the rheological profile has been underestimated by clinicians, this review aims to summarize the clinical studies thus far performed.

Since the viscosity of the hemoglobin solution is an important determinant of ED, it can be expected that hemoglobin disorders, such as in sickle cell anemia are associated with disturbed deformability. Here, the reduction in ED is clearly a consequence of the underlying disorder and may play a role in the etiology of the known complications in these patients, such as spleen infarctions and sludging phenomena in the microcirculation.

Hemorrheology has been studied extensively in several vascular disorders. However, in the case of cardiovascular disorders in particular, quite often older measurement techniques were used, which, as mentioned earlier, may have contributed to the conflicting results. Nevertheless, many patients are currently being treated with hemorrheologically active drugs. In cerebrovascular disorders more uniform results have been reported, all indicating reduced deformability. Even so, the question of the role of ED in the etiology of vascular diseases has yet to be answered.

Finally, malaria, septicemia, renal failure, and cardiopulmonary bypass all seem to be associated with decreased deformability. Thus far, in only a few of these disorders was it possible to partially elucidate the role of ED in the pathogenesis. The question again remains whether decreased ED is cause or consequence of the underlying disease. In view of the rapidly advancing technology and developments in measurement techniques, it may be possible to perform well-defined, randomized, double-blind studies in the very near future. It should be realized that to make results comparable there must be an international consensus as to the techniques used.

Presently, no hemorrheological test are employed in the diagnosis and/or staging of patients with any disease. Although there is some evidence that changes in rheological profiles may contribute to the pathogenesis of certain diseases, thus far the clinical importance of these techniques has not been established. However, manipulation of hemorrheology is becoming increasingly important in patient treatment.

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