CHEMICAL ENGINEERING TRANSACTIONS Volume 24, 2011
Editor Sauro Pierucci
 ISBN 978-88-95608-15-0 ISSN 1974-9791
DOI: 10.3303/CET1124161

Modeling of Mechanical Blood Damage: a Discussion of Current Approaches and Alternative Proposals

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In artificial organs such as vascular prostheses and detoxification devices, blood is exposed to mechanical stresses that can damage red blood cells, possibly leading to membrane lysis. In this work a theoretical analysis of mechanical hemolysis in artificial organs is presented, by firstly considering the main features of the current modeling approaches in literature. Two alternative modeling approaches, based on a physical description of the hemolysis process, are then presented, discussed and compared with experimental data.

1. Introduction

Implantable vascular prostheses and artificial organs for extracorporeal blood purification represent nowadays a valid therapeutic tool in the case of natural organ failure treatments. In all of these devices, respect to the physiological artero-venous circulation, blood comes into contact with non biological surfaces and can be subjected to much higher mechanical forces for longer exposure times. This can eventually result in an RBC unsustainable deformation and cell lysis. The marker of red blood cells (RBCs) damage is the release of intracellular hemoglobin (Hb) into plasma, trough a partially damaged (sub-lytic trauma) or completely destroyed membrane (hemolysis). As a consequence, the commonly adopted standard for laboratory hemolysis assessments is the Index of Hemolysis (IH) defined as: $[\Delta Hb_p]/[Hb_{tot}]$, where $[Hb_p]$ and $[Hb_{tot}]$ are the plasma-free and whole blood hemoglobin (plasma+RBCs) concentrations, respectively (ASTM (1997)).
The design of biomedical devices in which blood undergoes a non-physiological flow must necessarily account for the aforementioned issues in order to ensure efficacy and hemocompatibility.
Several papers in the literature (Heuser and Opitz (1980), Paul et al. (2003), Wurzinger et al. (1986), Yeleswarapu et al. (1995), Beissinger and Laugel (1987)) have been devoted to the experimental assessment of the blood damage caused by circulation in in-vitro set-ups mimicking the flow configuration of biomedical devices. Nevertheless, experimental investigation of hemolysis is extremely difficult, because the fragility and variability of blood samples, pose ease-of-handling, reliability and repeatability issues and therefore there is an extreme variability in the reported results. Moreover, the scale-up of in-vitro experimental results to in-vivo applications is a challenging task. A mathematical model establishing a quantitative relationship between the flow conditions

Please cite this article as: Vitale F., Turchetti L. and Annesini M.C., 2011, Modeling of mechanical blood damage: a discussion of current approaches and alternative proposals, Chemical Engineering Transactions, 24, 961-966
DOI: 10.3303/CET1124161

and the resulting blood damage can be a valuable tool for the evaluation of the possible hemolytic effects of several classes of biomedical devices. The current approaches used in modeling shear-induced blood damage can be classified in two main categories: 1) threshold models (Goubergrits (2006)); 2) continuous models (Giersiepen et al. (1990)). Both of these approaches are based on empirical correlations relating scalar measures of stress intensity and duration to a conveniently defined blood damage scoring index. The major limitations of such approaches are related to their empirical nature, which does not take into account the physical phenomena involved in blood damage. Their derivation is based on data obtained by exposing blood to a time-constant, monodimensional stress, and therefore they do not apply directly to the actual solicitation experienced by blood flowing in complex ducts.

At the aim to overcome the limitations of current models, an alternative modeling approach, based on a "physical" description of the problem, is presented. More specifically, two model types are here presented. In a first model type, hemoglobin release is described as a diffusion process across the membrane, assuming a shear stress dependent hemoglobin permeability. In a second model type, hemoglobin release is assumed to be caused only by membrane breakdown, which occurs when red blood cells are solicitated for a time longer than a threshold value; the threshold exposure time is assumed to be gamma-distributed in the population of RBCs, with mean depending on the shear stress intensity.

The two model types are used to analyze literature data. The results of the analysis confirmed the potential applicability of the new modeling approaches for blood damage description.

2 Proposal of new models based on a physical description of RBC damage

2.1 Permeability model

Hb release can be observed also from unruptured RBCs subjected to shear stress (τ). Hence Hb should be capable of crossing RBC membranes when these are deformed. In this model the Hb transmembrane flux, N_{Hb}, is assumed to be proportional to the concentration difference between intracellular (Hb_{RBC}) and plasma free Hb (Hb_P):

$$N_{Hb} = \kappa \left(Hb_{RBC} - Hb_P \right) \quad (1)$$

where the membrane permeability κ for Hb is a function of intensity and duration of loading and membrane mechanical behavior. Focused experimental characterization aimed at completely elucidating this relationship should be carried out; nevertheless, according to experimental results of Ohta et al. (2002) a certain level of hemolysis occurs also in the field of low stresses, where RBC undergo small deformations. In light of these considerations and in this preliminary phase, an elastic mechanical behavior can be assumed for RBC membrane, and $\kappa = f(\tau)$. If a perfectly mixed finite blood volume V_B is subjected to the shear loading history $\tau(t)$, during the exposure time interval $[0,t]$, the free Hb time course is expressed by:

$$Hb_P(t) = Hb_{tot} - \left(Hb_{tot} - Hb^0{}_P\right) \quad \exp\left(-\frac{1}{\varphi} a_P \int_0^t \kappa\, dt\right) \tag{2}$$

where Hb_{tot} is the whole blood concentration, $Hb^0{}_p$ is the plasma-free Hb concentration before shearing, V_P is the volume of plasma, V_{RBC} and S_{RBC} are the RBC volume and surface, respectively, $a_P = S_{RBC}/V_P$ and $\phi = V_{RBC}/V_P$. In a constant shear stress experiment, eq. (2) can be easily integrated to obtain the expression of the Damage Index (DI):

$$DI = \frac{\Delta Hb_P}{Hb_{tot}} = \left[1 - \exp\left(-\kappa' t\right)\right]\left(1 - \frac{Hb^0{}_P}{Hb_{tot}}\right) \cong \left[1 - \exp\left(-\kappa' t\right)\right] \tag{3}$$

where $\kappa' = \kappa a_P/\phi$ and $Hb_P/Hb_{tot} \sim 10^{-4} << 1$. Eq. (3) can be used to correlate experimental data such as those reported by Wurzinger et al. (1986).

It is worth noting that a viscoelastic mechanical behavior of RBC membranes was observed by Jay (1973). The elastic behavior can be obviously considered as an approximation holding for small deformations, so that the model presented in this section is particularly suited for the description of sublytic damage in the range of low stresses. Nevertheless, by including appropriate expressions for the permeability, the model here presented could also account for membrane viscoelastic properties and extend its range of applicability to higher loading conditions, up to actual hemolysis.

2.2 Non-uniform threshold model

Data reported in literature regarding blood samples subjected to uniform shear stress experiments (Heuser and Opitz, 1980; Paul et al., 2003; Wurzinger et al.,1986) show that the amount of plasma-free Hb increases with stress duration, with a fast variation in proximity of a given exposure time value. In general, this value is lower when higher intensity stresses are applied. Nevertheless, a certain graduality in the increase of blood damage with increasing solicitation time can always be appreciated. This behavior could be modeled by considering the existence of a cellular age distribution within RBC population, as evidenced by Yeleswarapu et al. (1995), corresponding to a distribution of mechanical resistance properties.

Starting from an undeformed configuration, considering the application of a constant τ, it can be supposed that each RBC can stand the load without rupturing for a time t_{th}. Assuming that the variable t_{th} is distributed in the RBC population according to a probability density function $PDF(t_{th}|\tau)$ with parameters depending on τ, the fraction η of ruptured erythrocytes at time t (i.e. that have been exposed to the load for a time longer than their threshold value t_{th}) is given by

$$\eta(t,\tau) = CDF(t|\tau) = \int_0^t PDF(t_{th}|\tau)\, dt_{th} \tag{4}$$

where CDF is the cumulative distribution function corresponding to PDF. In order to be physically meaningful, $PDF(t_{th},\tau)$ has to satisfy two requirements: 1) it must be defined for $t_{th} \in [0;\infty)$; 2) $PDF(t_{th},\bar{\tau}) = 0$ for $t_{th} = 0$. The gamma PDF, which satisfies both constraints, will be considered hereafter.

Once the PDF defined, the time-course of Hb release in a batch of blood exposed for a time t to a constant shear stress is immediately derived as:

$$Hb_P(t) = \frac{\eta(t) n^{in}_{RBC} \hat{m}_{Hb\,RBC}}{V_P(t)} \tag{5}$$

where n^{in}_{RBC} is the erythrocyte count before shearing, $\hat{m}_{Hb\,RBC}$ is the mean Hb mass in one erythrocyte (normally in the range 27-32 pg) and $V_P(t)$ is the volume of plasma. Finally, the formulation of DI derived from eq.(5) is:

$$DI = \frac{\eta(t)}{1 - Hkt^0[1-\eta(t)]}\left(1 - \frac{Hb^0{}_P}{Hb_{tot}}\right) \cong \frac{\eta(t)}{1 - Hkt^0[1-\eta(t)]} \tag{6}$$

where Hkt^0 is the initial value of hematocrit. The non-uniform threshold model can be applied for the evaluation of the hemolysis process, characterized by the irreversible loss of integrity of the RBC membrane.

3 Comparison with experimental data: results

3.1 Permeability model

The application of the permeability model requires the definition of a mathematical expression for membrane permeability. Here, the following empirical relation will be considered:

$$\kappa'(\tau) \cong a[\exp(b\tau) - 1] \tag{7}$$

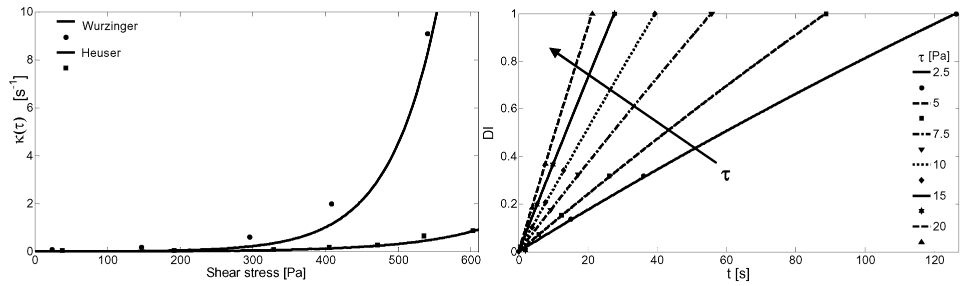
Literature data of blood damage obtained by rotational viscometer experiments (Heuser and Opitz, 1980; Wurzinger et al., 1986) are analysed by eq. (3) and (7). As for data obtained by Poiseuille flow experiments (Beissinger and Laugel, 1987), the radial distribution of shear stress and residence time in the capillary are taken into account and experimental data are compared with the cup-averaged damage index at the outlet section, calculated by taking into account eq. (7):

$$DI = \frac{4}{R^4}\int_0^R \{1 - \exp[-\kappa'(\tau(r))t(r)]\}(R^2 - r^2)dr \tag{8}$$

The results and the optimal values of parameters a and b obtained for each data set are reported in Figure 1 and Table 1, respectively.

Table 1: Optimal values for parameters of membrane permeability function $\kappa'(\tau)$

Data set	Blood	$a \cdot 10^3$ [s^{-1}]	$b \cdot 10^3$ [Pa^{-1}]
Wurzinger (1986)	Human	2.5	15
Heuser (1980)	Porcine	2.6	9.6
Beissinger (1984)	Human	2	310



(a) (b)

Figure 1:Fitting of experimental data with the permeability model: a) Rotational viscometer data (Heuser and Opitz,1980; Wurzinger et al.,1986); b) Poiseuille flow data (Beissinger and Laugel, 1986).

Figure 1a shows, as points, the optimal κ' values obtained for each constant τ data set reported by Heuser and Opitz (1980); lines in the same figure are obtained by fitting eq. (7) to these data. As for the Poiseuille flow experiments reported by Beissinger and Laugel (1986), each data set does not correspond to a single value of τ; therefore, a *DI* Vs. residence time plot is used instead. In order to obtain a clearer figure, each *DI* data set in Figure 1b is scaled to the respective highest value.

This preliminary analysis of the applicability of the permeability model shows that the expressions used for membrane permeability and damage index show an acceptable agreement. In order to improve the predictive capability of the model, a further extensive analysis of membrane deformation under mechanical loading, including the characteristic RBCs viscoelastic properties, is required. The membrane rupture condition, in fact, is physically related to a threshold strain rather than load. Such a refinement of the model will result in the formulation of more suitable expression for the membrane permeability function, which will allow to extend the range of validity to higher loading conditions and to take into account also the breakdown condition.

3.2 Non-uniform threshold model

The expression of DI in eq.(6) is fitted to data at constant τ from Heuser (1980), by using the unknown values of the mean μ and variance σ^2 of the $PDF(t_{th}|\tau)$ as adjustable parameters. Assuming that the variance of t_{th} is τ-invariant (homoscedasticity hypothesis) data sets corresponding to different τ were fit with different μ, but with a single σ^2 value . Results are shown in Table 2 and in Figure 2. It may be stated that, in this preliminary test, the model seems in fair agreement with the considered data sets. The choice of the distribution and the hypothesis of homogeneity of σ^2 should be verified with a proper statistical test on a higher number of data. For this reason and at the aim of obtaining further indications and validation of the approach, a larger number of reliable, consistent and comparable experimental data would be required.

Table 2: Values of estimated mean failure membrane times for different values of τ. Variance of the distribution σ^2 = 20.4 s^2

τ [Pa]	132	262	378	443	498	552	610
μ [s]	6.92	6.74	6.14	5.43	4.92	4.06	3.71

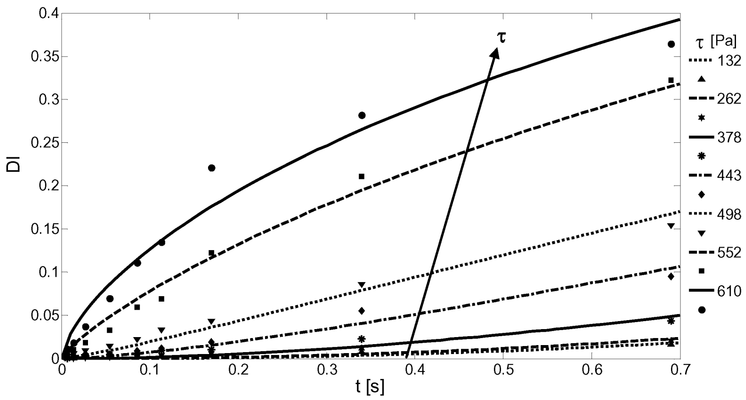


Figure 2: results of multiple data sets parameter estimation for eq.(6) on Heuser (1980) data. Values of the parameters are reported in Table 2.

Acknowledgements

The authors wish to thank Prof. Matteo Pasquali and Eng. Sarah Meloni for their useful suggestions and contribution.

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