Artificial
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Shear-Induced Hemolysis: Species Differences

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Abstract: The nonphysiological mechanical shear stress in blood-contacting medical devices is one major factor to device-induced blood damage. Animal blood is often used to test device-induced blood damage potential of these devices due to its easy accessibility and low cost. However, the differences in shear-induced blood damage between animals and human have not been well characterized. The purpose of this study was to investigate shear-induced hemolysis of human and three commonly used preclinical evaluation animal species (ovine, porcine, and bovine) under shear conditions encountered in blood-contacting medical devices. Shear-induced hemolysis experiments were conducted using two single-pass blood-shearing devices. Driven by an externally pressurized reservoir, blood single-passes through a small annular gap in the shearing devices where the blood was exposed to a uniform high shear stress. Shear-induced hemolysis at different conditions of exposure time (0.04 to 1.5 s) and shear stress (25 to 320 Pa) was quantified for ovine, porcine, bovine, and human blood, respectively. Within these ranges of shear stress and exposure time, shear-induced hemolysis was less than 2% for the four species. The results showed that the ovine blood was more susceptible to shear-induced injury than the bovine, porcine, and human blood. The response of the porcine and bovine blood to shear was similar to the human blood. The dependence of hemolysis on shear stress level and exposure time was found to fit well the power law functional form for the four species. The coefficients of the power law models for the ovine, porcine, bovine, and human blood were derived. **Key Words:** Shear stress—Hemolysis—Species differences—Exposure time.

The use of blood-contacting medical devices to treat or replace diseased organs of the cardiovascular, respiratory, and renal systems has saved or extended the lives of millions of patients with otherwise hopeless medical conditions. Novel and innovative ideas have been constantly conceived and proposed by physicians and engineers. Some of these ideas have been successfully adopted for development and entered the commercial market. These devices often introduce nonphysiological aspects to the circulation system that may cause blood trauma. The fluid-induced mechanical stresses through these devices are often nonphysiological and elevated. For example, the blood through ventricular assist devices (VADs) and artificial heart valves can be exposed to very high shear stress (>100 Pa) for a short period of time (<1 s) (1,2). For VADs, high shear stresses located at or near the rotating tips lead to blood damage (1,3). For artificial heart valves, blood damage is primarily caused by high wall shear stress, regurgitation jets, and turbulence (4). Several research groups used laser Doppler anemometry (4–6) or particle image velocimetry (7,8) to study the flow characteristics around heart valves and obtained shear stress thresholds of hemolysis (150 to 400 Pa) (5,6). The design of hinge and leakage gap width of heart valves is utilized to govern the magnitude of shear stresses generated in leakage flow fields through the valves (9). Thus, shear-induced blood damage has been one of the most important considerations during the conceptualization and development phases. Two interrelated steps are often taken: (i) to reduce shear-induced blood damage through analysis of blood flow in a device design; and (ii) to evaluate shear-induced blood damage of a physical device model.

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Numerous studies have shown that high mechanical shear stresses can cause a variety of blood damage mechanisms (10–13). The most studied aspect of shear-induced blood damage is hemolysis. The two dominant factors that determine shear-induced hemolysis are shear stress and exposure time. To relate the analysis of blood flow of a device to device-induced hemolysis from the design perspective, it is necessary to establish a quantitative relationship between hemolysis and flow-dependent factors: shear stress and exposure time. Although human blood has been used for studies of shear-induced blood damage, in vitro testing for hemo/biocompatibility of a blood-contacting medical device is more often performed using animal blood due to the easy accessibility and low cost compared with human blood and concerns of human blood-borne pathogen. For the obvious reason, preclinical evaluation of blood-contacting medical devices has been performed in animal subjects. Ovine, bovine, and porcine are commonly used species. While the use of animal blood and in vivo animal models for the in vitro testing and in vivo evaluation provides certain degree of confidence in device-related hemo/biocompatibility, clinical relevance and extrapolation of these nonhuman data remain ongoing discussions because of species differences in sensitivity of shear-induced blood damage (14,15), biology, and hematological and rheological properties (16–18). Although it is well recognized that there are species differences in these aspects between humans and animals, there are limited comparative data in the literature, in particular, mechanical shear-induced damage under conditions of high shear with short exposure time relevant to blood-contacting medical devices, which leads to the difficulty of interpretation of results from hemolysis experiments using blood of those animal species.

In this study, shear-induced hemolysis of human and three commonly used animal species for hemo/biocompatibility testing was characterized under well-defined device-relevant shear stress and exposure time conditions using two novel Couette-type blood-shearing devices. The animal species differences in response to mechanical shear stress at device level were further verified using a clinical mechanical circulatory assist device.

MATERIALS AND METHODS

Blood-shearing devices

Two novel, custom-designed, flow-through Couette-type blood-shearing devices were used to obtain the experimental data of shear-induced hemolysis. One device for high shear stress conditions (150~320 P) (named as "Hemolyzer-H") is an axial flow-through Couette-type device supported by a pair of pin bearings, adapted from the adult Jarvik CF-VAD (Jarvik Heart Inc., New York, NY, USA). It consists of a rotating rotor spindle, instead of the impeller with blades, and the housing without the diffuser. The smallest gap between the rotor surface and outer housing is 0.1 mm. When the spindle is rotated, a uniform high shear stress region is generated in this gap. The other device for relatively low shear stress conditions (25~150 Pa) (named as "Hemolyzer-L") is a centrifugal flow-through Couette-type device supported with magnetic bearings, adapted from the CentriMag VAD (Thoratec, Pleasanton, CA, USA). A small gap is also created between the rotor and the housing wall. Computational fluid dynamics (CFD) simulations showed that a uniform high shear stress region can be generated inside the small gap of the two devices while the shear stresses elsewhere are relatively small. By adjusting the rotational speed of the rotor and axial flow rate, a variety of combinations of shear stress and exposure time can be generated when blood is forced to flow through the narrow gap of the shearing devices. The details of these two devices can be found in reference (19).

Clinical mechanical circulatory assist device

The CentriMag blood pump (Thoratec) was used in a circulatory flow loop to study the species differences in hemolysis at the device level with ovine, porcine, and bovine blood. The CentriMag is an extracorporeal circulatory support device providing hemodynamic stabilization for patients in need of circulatory support. It has a magnetically levitated centrifugal pump impeller and has been used clinically worldwide (20). The details of CentriMag can be found in reference (21). The flow loop consisted of a CentriMag blood pump, tubing, a resistance clamp, a heat exchanger, and a reservoir. The pump operated at 4000 rpm to produce a flow rate of 5.0 L/min.

Blood collection

Fresh heparinized (10 U/mL) blood from the three animal species was collected from local slaughter houses by cutting the neck blood vessel directly and used within the same day after being filtered with a blood transfusion filter (SQ40S, Pall Corporation, Port Washington, NY, USA). This collection method had been compared with venipuncture using large bore needle from live animals and no difference was found in terms of shear-induced hemolysis (19). The

hematocrit was adjusted to 30 ± 2% either by hemodilution with phosphate-buffered saline containing 0.5% bovine serum albumin or hemoconcentration via centrifugation. Bovine serum albumin was used due to its easy availability, and no adverse effects on experiments were observed. The quality of blood was controlled by assuring that the hematological and rheological properties were within the normal range. The rocker bead test (22) was also performed to assure that the variability for each blood preparation was minimized (19).

Human blood from healthy volunteers was collected via venipuncture in blood bags containing citrate anticoagulant and directly used in the experiments without adjusting hematocrit because of its high cost, limited amount, and potential infection risk. The hematocrit of human blood from all donors was 42 ± 4%. However, only blood with the normal hematological properties was used in the experiments. All procedures involving collection of human blood were approved by the institutional review board. All volunteers gave their written informed consent and were informed about the aims of the study in accordance with the Declaration of Helsinki.

Experiments

The hematocrit and viscosity of each blood preparation were measured by centrifugation with an Adams Micro-Hematocrit II centrifuge (Model No. 420556, BD, Franklin Lakes, NJ, USA) and by using a calibrated Cannon-Manning Semi-Micro viscometer (9721-Y56, Cannon Instrument Company, State College, PA, USA), respectively. Before each experiment, the blood-contacting surfaces were rinsed with normal saline. For single-pass experiments with the blood-shearing devices, the blood was pushed through the blood-shearing devices in single pass by a syringe pump (PHD 2000, Harvard Apparatus, Holliston, MA, USA). Plasma-free hemoglobin (PFH) after a single passage through the Hemolyzers was measured with spectrophotometry. The difference of PFH between the outlet blood sample and inlet blood sample was used to evaluate shear-induced hemolysis. The index of hemolysis (IH) (23) was used to present the experimental data:

$$IH = \frac{\left(1 - \frac{H_{ct}}{100}\right)\frac{PFH}{1000}}{H_b} \times 100$$

where H_{ct} is the hematocrit value of the blood expressed in %, PFH is the concentration of plasma-free hemoglobin (unit: mg/dL), and H_b is the hemoglobin concentration of the whole blood (unit: g/dL) (19). The unit of IH is %. Hematocrit is related with blood viscosity (24), which is proportional to shear stress. In this study, we adjusted the rotational speed of rotors of Hemolyzers with respect to viscosity of blood to achieve the same shear stresses applied to the blood of the four species. The IH value was normalized to the H_b of the whole blood. Therefore, the difference of hematocrit of human blood and the blood of the other three species had a relatively small impact to the shear-induced hemolysis in this study. The experiments and measurements were performed in the same way as those described in detail previously (19). All of the single-pass shearing experiments were conducted at room temperature.

Device-induced hemolysis of the three animal species by the CentriMag blood pump was evaluated using a recirculating flow loop with animal blood. The experiments were carried out according to the recommended practice for assessment of hemolysis in continuous flow pumps specified by the American Society of Testing and Materials (ASTM F1841-13) (25).

Data analysis

For the experiment design, the meaningful difference was chosen as 0.5 (in log scale) and the experimental domain was set to be $25 < \tau < 320$ Pa and $0.04 < t < 1.5$ s. The uniform experimental design was used to select the experimental conditions (26). With the type I error rate of 0.05 and power of 90%, 29 experimental conditions were selected for human, bovine, and porcine blood based on our previous experimental study on ovine blood (19). Three separate experimental runs were carried out for each condition and all of the experiments were arranged in random order. Data under each experimental condition were averaged and are presented as mean ± standard deviation. A multivariate linear regression analysis was performed to fit the power law model with the data of shear-induced hemolysis for the four species. The correlation coefficient was applied to indicate correlation of experimental data with fitted data from the model. *F*-test (26) was implemented to test the hypothesis of the power law model for the experimental data.

RESULTS

Figure 1 shows experimental data of shear-induced hemolysis of the four species and three-dimensional (3D) maps of shear-induced hemolysis against shear stress and exposure time. The 3D maps of shear-

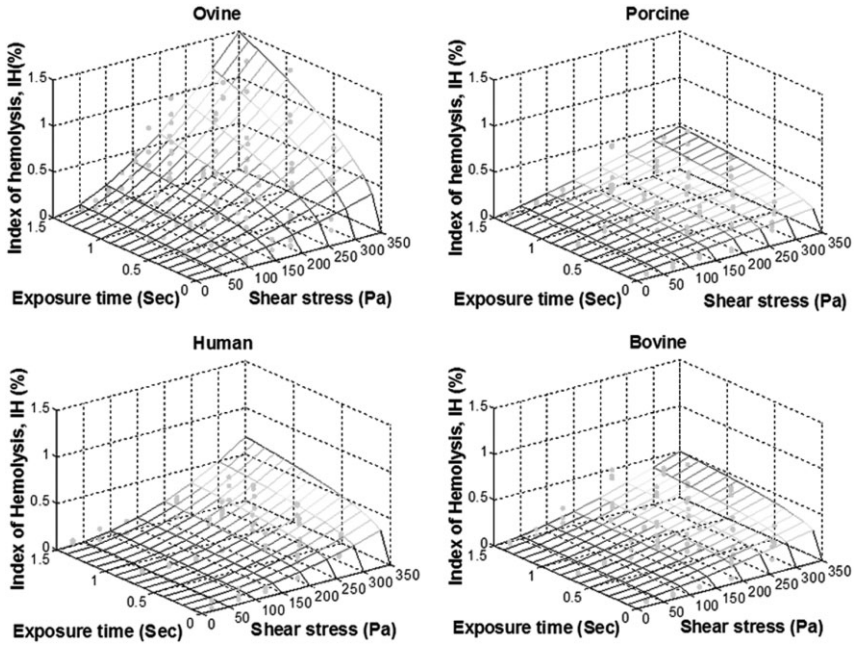

FIG. 1. The experimental data points of shear-induced hemolysis of the four species and three-dimensional (3D) maps of shear-induced hemolysis against shear stress and exposure time from the fitted power law models.

induced hemolysis were created using data calculated from their respective fitted power law models. Table 1 lists the coefficients of the power law models of shear-induced hemolysis for the four species and the correlation coefficient of fitting the experimental data with the power law model. The correlation coefficients indicate the power law model fitted well the experimental data for the four species. Table 2 lists the results of using the *F*-test to verify the hypothesis of the power law model for the experimental data. The resulting *F* values all were larger than the respective acceptance criterion for the power law model for the experimental data for the four species.

The data presented in Fig. 1 clearly show that liberated hemoglobin from the ovine blood cells was two to three times higher than that from the human, bovine, and porcine blood when subjected to nonphysiological shear stress at the levels of 100 to 350 Pa. It can be seen in Table 1 that the coefficient β, which reflects the response of hemolysis to exposure time, was larger for the ovine than the other three species. The coefficient α for shear stress was similar between the human and ovine, but larger than those of the porcine and bovine.

To further understand the differences in shear-induced hemolysis for the four species, the curves of hemolysis versus exposure time for the four species at three levels of shear stresses were plotted in Fig. 2. When subjected to a relatively low shear stress of <50 Pa (Fig. 2A), liberated hemoglobin from blood cells of the four species was similar and small (<0.06%). However, it increased slightly with exposure time. When the applied shear stress increased to the level of >150 Pa (Fig. 2C), it can be seen that shear-induced hemolysis was much higher for the ovine than the other three species. It is interesting to note that curves of hemolysis versus exposure time for the human, bovine, and porcine blood almost overlapped with each other and had a similar response trend to the increasing exposure time.

Figure 3 shows the curves of hemolysis versus shear stress for the four species at three exposure

TABLE 1. *Parameters of the power law model for the four species*

$$IH_{\text{flow}}(\%) = A \times \tau^{\alpha} \times t^{\beta}$$

Species	A	α	β	Correlation coefficient (*R*)
Ovine	1.228×10^{-5}	1.9918	0.6606	0.8445
Porcine	6.701×10^{-4}	1.0981	0.2778	0.8634
Human	3.458×10^{-6}	2.0639	0.2777	0.6821
Bovine	9.772×10^{-5}	1.4445	0.2076	0.7162

times. At a relatively short exposure time of 0.05 s (Fig. 3A), liberated hemoglobin from blood cells of the four species was similar and exhibited the same trend with increasing shear stress. When the exposure time increased to 0.5 and 1.0 s (Fig. 3B,C),

TABLE 2. *The result of* F*-test for model fitness*

Species	*F* value	*P* value	Accept or reject
Ovine	$F_{43, 81} = 1.4305$	0.0831	Accept
Porcine	$F_{27, 58} = 1.7369$	0.0398	Accept
Human	$F_{27, 58} = 1.5304$	0.0880	Accept
Bovine	$F_{27, 58} = 1.6794$	0.0499	Accept

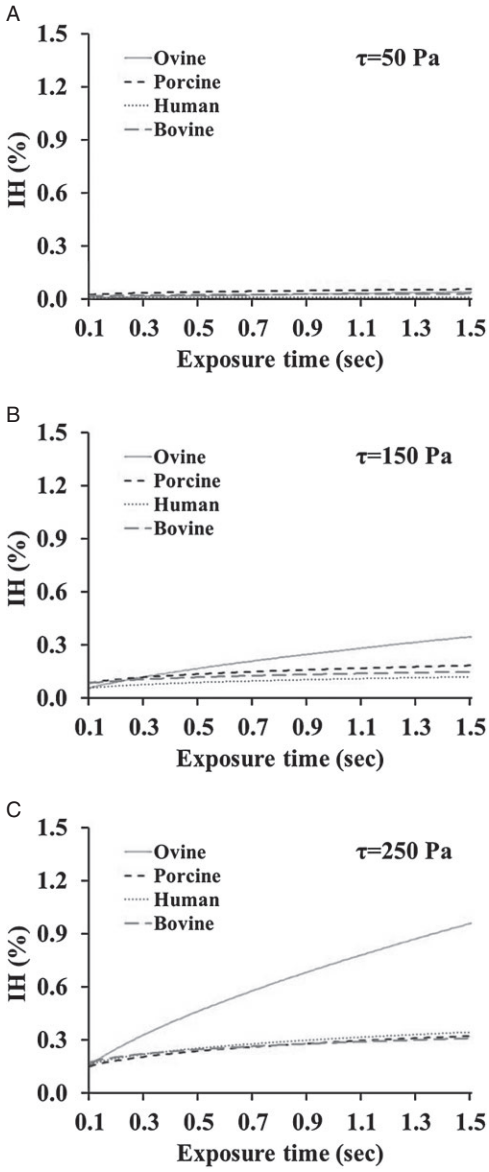

FIG. 2. The curves of hemolysis versus exposure time for the four species at three levels of shear stresses: (A) 50 Pa, (B) 150 Pa, and (C) 250 Pa.

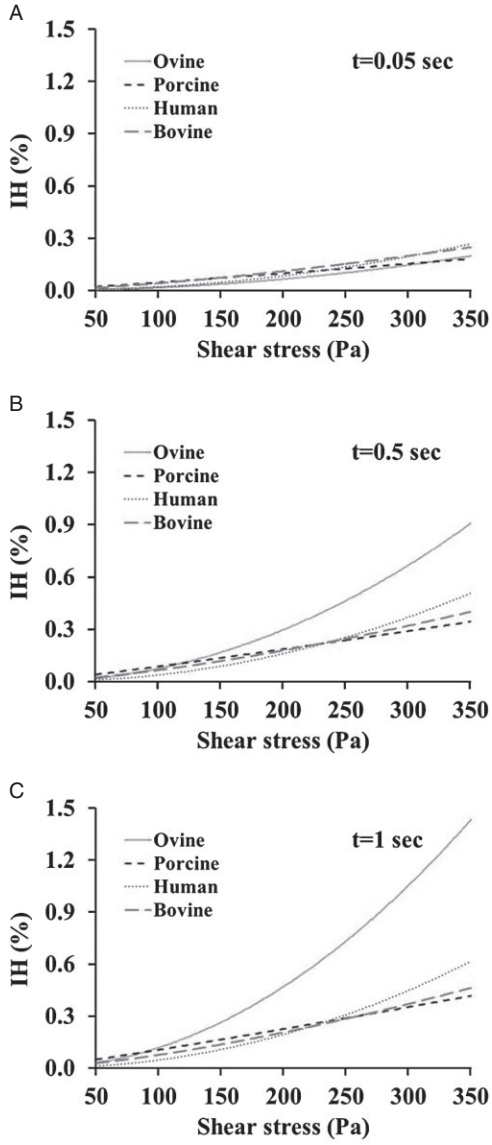

FIG. 3. The curves of hemolysis versus shear stress for the four species at three exposure times: (A) 0.05 s, (B) 0.5 s, and (C) 1 s.

shear-induced hemolysis was much higher for the ovine than for the other three species. The curves of shear-induced hemolysis versus shear stress for the bovine and porcine blood overlapped with each other and had a very similar response trend with the increasing shear stress.

The data of the device-induced hemolysis experiment for the three animal species are depicted in Fig. 4. The concentration of the PFH liberated from red blood cells (RBCs) of the three animal species in the circulatory flow loop by the CentriMag blood pump was converted to the normalized index of hemolysis (NIH) (25). The rotational speed of the CentriMag blood pump was set at 4000 rpm to produce a flow rate of 5.0 L/min, resulting in a pres-

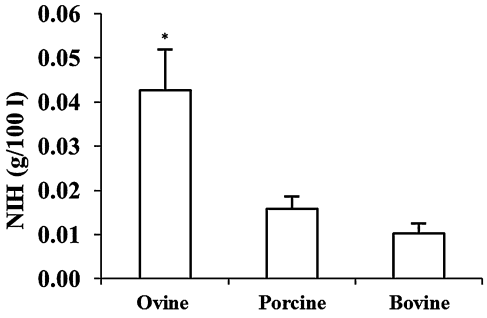

FIG. 4. Normalized indices of hemolysis (NIH) of the ovine, porcine, and bovine caused by the CentriMag blood pump in a circulatory flow loop with animal blood. The asterisk (*) represents significant difference ($P < 0.05$) between the shear-induced NIH of ovine and that of porcine and bovine.

sure head of ~330 mm Hg. Shear-induced NIH at the device level for the ovine was significantly higher than those for the bovine and porcine ($P < 0.05$). Although the NIH values for bovine and porcine blood were relatively close, they were still significantly different.

DISCUSSION

Shear-induced hemolysis of the four species (human, ovine, bovine, and porcine) was quantified after being exposed to a range of shear stresses of 25 to 320 Pa for 0.04 to 1.5 s. These levels of shear stresses and exposure times commonly exist in blood-contacting medical devices, such as VADs, hemodialysis systems, blood oxygenators, and heart valves. The data indicated that the ovine blood was much more susceptible to shear-induced damage than the blood of the other three species. The hemolysis data caused by the CentriMag blood pump in a circulatory flow loop with the ovine, bovine, and porcine blood supported this observation. Specifically, the NIH value of the ovine was the highest among the three animal species. The power law relationship was found to fit well the experimental results and the coefficients of the power law mode were derived between hemolysis and shear stress/exposure time for the ovine, porcine, bovine, and human blood (Table 1 and Fig. 1).

As one of the important parameters for evaluating shear-induced blood damage of blood-contacting medical devices, hemolysis has been extensively studied in the last four decades. Many research groups have attempted to derive the model of hemolysis with respect to shear stress and exposure time. The power law model (27), cumulative power law model (28), and power law combined with threshold model (29) have been proposed. The most widely used model is power law model. The power law relationship of hemoglobin released by RBCs of human to shear stress and exposure time ($A = 3.62 \times 10^{-5}$, $\alpha = 2.416$, $\beta = 0.785$) was first proposed by Giersiepen et al. (27). The A of Giersiepen et al.'s model was one order higher than that of our human hemolysis model ($A = 3.458 \times 10^{-6}$, $\alpha = 2.0639$, $\beta = 0.2777$) (Table 1). The α and β of both models are in the same order. Giersiepen et al.'s model was based on the experimental data obtained using a shearing device with mechanical seals, which could cause secondary blood damage and might overestimate shear-induced blood damage (19). Few shear-induced hemolysis models of the ovine, bovine, and porcine blood are available. In this study, the quantitative models of shear-induced hemolysis were derived for the ovine, bovine, and porcine blood. These models may be used for comparative analysis of CFD prediction of shear-induced hemolysis of those species in blood-contacting devices (30).

The vulnerability of RBCs of different species associated with shear stress and exposure time is diverse. The interpretation of the published hemolysis data of distinct species is difficult, owing to lack of quantitative comparison of hemolysis based on species as well as the differences in experimental conditions. The device-induced hemolysis of the human blood is most significant for evaluation of blood-contacting devices compared with that of other species as eventually those devices will be utilized in patient's bodies. However, few experiments used human blood due to the risk of infection, limited availability, and relatively high cost (23). The ovine, bovine, and porcine are commonly used in preclinical evaluation of animal species. Therefore, it is crucial to understand the differences in sensitivity of RBCs of human and these animal species. Many studies only focused on the hemolysis of single species (23,27,31). In this study, shear-induced hemolysis of the three animal species and human was conducted under the same conditions with the same devices. It was demonstrated that shear-induced hemolysis of the ovine blood was much higher than those of bovine, human, and porcine blood. Our data are consistent with the result of Jikuya et al.'s study of erythrocyte destruction rate of the ovine, human, and bovine (14). Thus, the ovine may be recommended for evaluation of hemolysis in initial stage of device design and optimization because RBCs of the ovine are most sensitive to shear stress. Hemolysis index of the porcine blood exposed to the shear stress of 310 Pa for 1.2 s was 0.47% from our data, which was very close to that of the porcine blood under similar shearing conditions in another study (23). Other

studies demonstrated that the properties of the porcine blood are more similar to those of human blood than those of bovine blood (32). However, RBCs of the porcine were even more vulnerable to shear stress than the human (32,33), which matched our data of the porcine and human blood under shear stress level less than 240 Pa for 0.5 and 1 s (Fig. 3B,C). Nonetheless, the RBC sensitivities of the human, bovine, and porcine to shear-induced damage are still very close to each other under the device relevant conditions (shear stress from 25 to 320 Pa, exposure time from 0.04 to 1.5 s) in this study. Therefore, both the bovine and porcine might be good animal models for evaluation of shear-induced hemolysis for blood-contacting medical devices.

CONCLUSION

Shear-induced hemolysis of the human and three commonly used animal species (ovine, bovine, and porcine) was characterized when subjected to a wide range of constant shear stresses with controlled exposure times. Under the low shear stress range (<50 Pa) with short exposure time (<0.05 s), the characteristics of shear-induced hemolysis for the four species were similar. However, the ovine blood was much more vulnerable to hemolytic damage when the applied shear stress was above 150 Pa with an exposure time over 0.5 s compared with the other three species' blood. The human, bovine, and porcine blood exhibited very similar hemolytic characteristics when subjected to the shear stress from 25 to 320 Pa with the exposure time from 0.04 to 1.5 s. The functional relationship of hemolysis of the human, ovine, bovine, and porcine with respect to shear stress and exposure time was found to fit well the power law functional form. The coefficients of the power law models for the ovine, porcine, bovine, and human blood were derived and could be used in prediction of device-induced hemolysis of those species with computational fluid dynamics modeling.

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