

Device-Induced Hemostatic Disorders in Mechanically Assisted Circulation

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Abstract

Mechanically assisted circulation (MAC) sustains the blood circulation in the body of a patients undergoing cardiac surgery with cardiopulmonary bypass (CPB) or on ventricular assistance with a ventricular assist device (VAD) or on extracorporeal membrane oxygenation (ECMO) with a pump-oxygenator system. While MAC provides short-term (days to weeks) support and long-term (months to years) for the heart and/or lungs, the blood is inevitably exposed to non-physiological shear stress (NPSS) due to mechanical pumping action and in contact with artificial surfaces. NPSS is well known to cause blood damage and functional alterations of blood cells. In this review, we discussed shear-induced platelet adhesion, platelet aggregation, platelet receptor shedding, and platelet apoptosis, shear-induced acquired von Willebrand syndrome (AVWS), shear-induced hemolysis and microparticle formation during MAC. These alterations are associated with perioperative bleeding and thrombotic events, morbidity and mortality, and quality of life in MCS patients. Understanding the mechanism of shear-induced hemostatic disorders will help us develop low-shear-stress devices and select more effective treatments for better clinical outcomes.

Keywords

cardiopulmonary bypass, extracorporeal membrane oxygenation, ventricular assist device, mechanical shear stress, hemostatic disorder

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Introduction

Mechanically assisted circulation (MAC) includes all methods that can provide hemodynamic support for patients whose heart cannot provide adequately function due to cardiac failure or cardiopulmonary failure. MAC has been implemented in cardiopulmonary bypass (CPB), extracorporeal membrane oxygenation (ECMO) or extracorporeal life support (ECLS) and mechanical circulatory support (MCS). CPB is a technique in which the artificial blood pump and gas exchange device (oxygenator) completely take over the function of the heart and lung, and bypass both of them during aortic cross-clamping of cardiac surgery. ECMO or ECLS is a modified CPB technique in which the blood pump and oxygenator may partially or completely support the heart and/or lung for days to weeks for the management of patients in critical care suffering severe respiratory and cardiac failure. Ventricular assist devices (VADs) are used to provide MCS to patients who suffer from cardiac failure only. A VAD can be used to support left ventricle (LVAD) or right ventricle VAD (RVAD) or 2 VADs (BiVAD) for both ventricles for weeks to years. The total artificial heart (TAH) is a special form of MCS as a bridge to

transplantation or to be used for destination therapy for specific patients with biventricular heart failure.¹ It is estimated that over 400,000 (USA), 100,000 (Europe), and 36,000 (UK) cardiac surgeries are performed each year. Most of these procedures are performed on hearts under CPB support.² More than 10,000 patients have been treated with ECMO every year since 2016 around the world.³ And, more than 2,500 LVADs have been implanted annually over the last decade.⁴ The only FDA-approved TAH—Syncardia has been implanted almost 1800 times in the United States, Canada, and Europe.⁵

No matter which type of MAC, blood is constantly exposed to non-physiological shear stress (NPSS) due to mechanical

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pumping action and non-biological, artificial surfaces of the circuit components, such as blood pump, hollow fiber membrane oxygenator, filters, arterial and venous cannulas, tubing and connectors. These 2 factors have been shown to cause blood cell damage and protein activation, leading to activation of the contact system, coagulation cascade, fibrinolytic system, complement system and possibly weakened immune defense system.⁶⁻⁹ Although different anticoagulation strategies are used in patients with CPB or on ECMO or VAD support to prevent thrombosis, bleeding and thrombotic events in patients or circuitry remain frequent despite increasing knowledge of their pathogenesis and improvements in pump and oxygenator design, and the use of heparin-bonded surfaces.¹⁰⁻¹² The bleeding and thrombotic complications cannot be explained by type or severity of illness or the individual anticoagulation regimen. From the perspective of biomedical engineering, the non-physiological mechanical force acting on the blood's formed elements and proteins could induce structural and functional changes of these blood elements and proteins in varying degrees, including platelet activation, platelet receptor shedding, platelet apoptosis, von Willebrand factor (VWF) fragmentation, hemolysis, microparticle generation, impaired blood adhesion and aggregation. Platelet dysfunction, VWF fragmentation and hemolysis may contribute to both thrombosis and bleeding. In this article, we briefly review prevalence of thrombotic and bleeding complications in patients with MAC and discuss platelet physiology and acquired hemostatic dysfunction during MAC, including structural alterations and dysfunction of blood elements relevant to hemostatic function.

Prevalence of Bleeding and Thrombotic Complications

The prevalence of bleeding complications in patients undergoing cardiac surgery with CPB and on ECMO or LVAD support is summarized in Table 1. Excessive post-operative bleeding continues to be a concern for cardiac surgeons and anesthesiologists. More than 50% of adult patients experienced insignificant bleeding (<600 ml within 12 h), nearly 40% of patients had mild (601-800 ml) and moderate (801-1000 ml) bleeding and 10% patients had severe (1001-2000 ml) and massive bleeding (>2000 ml) after cardiac surgery.¹³ 2%-10% of patients experience re-exploration after cardiac surgery, which is associated with the need of transfusion and increased mortality (Table 1).^{10,14} The exact etiology of postoperative bleeding in cardiac surgery has not been elucidated completely, but postoperative bleeding and the need for blood product replacement to compensate for blood loss are associated with significant postoperative adverse events.

Bleeding in patients on ECMO is one of the most frequent complications, including bleeding at the gastrointestinal (GI), surgical site, peripheral/mediastinal cannula site, intracranial, and pulmonary hemorrhage. There were reports that 60% of V-A ECMO adult patients and 80% of V-V ECMO patients suffered from a bleeding event,¹¹ and 70% of children with ECMO had a bleeding event.¹⁵ According to the Extracorporeal

Life Support Organization (ELSO) registry in January 2020, the surgical site bleeding is the most common in all ECMO patients (cardiac/pulmonary support: neonatal 18%/6%, pediatric 17.9%/7.7% and adult 13.8%/6.4%).³ The other common bleeding complications include the mediastinal cannulation site bleeding during cardiac support (Neonatal/pediatric: 6.9%/6.6%), the pulmonary hemorrhage during pulmonary support (Neonatal/pediatric: 4.4%/5.8%) in neonatal and pediatric patients, and GI hemorrhage in all adult ECMO patients (Cardiac/pulmonary support: 4.1%/4.9%). The ECMO circuit clots are the main thrombotic events (6.6-30%). Bleeding during ECMO forces patients to receive a significant amount of blood transfusions and has negative impacts on patient outcomes (Table 1).

For patients on LVAD support, thromboembolic and bleeding events are common as well.^{16,17} Bleeding is the most common adverse event for LVAD patients. It has been reported that 20%-60% of LVAD patients experience bleeding complications after implantation.^{12,18} Bleeding and thrombotic complications continue to be associated with increased morbidity and mortality in patients with MCS, resulting in rise of hospital admission, procedure burden, transfusion requirement, morbidity, mortality and costs (Table 1).^{14,15,19,20} Bleeding (41.3%) is also the most common adverse event in the early phase (≤ 3 months) of the TAH implantation, and the incidence of GI hemorrhage is about 20% in patients with 6 months of TAH implantation.²¹

Shear Stress and Shear Rate Associated With MAC

Fluid shear stress refers to the stress coplanar component along with a fluid cross section. It arises from the shear force, the component of force vector parallel to the material cross section. Shear stress is a function of the local velocity gradient (shear rate 1/s) and local blood viscosity. For blood flowing in a circular tube, the shear stress is small at the center line of the vessel and the largest adjacent to the vessel walls because the velocity gradient is small at the center line but the largest at the wall.³⁷ Blood is a non-Newtonian fluid, and its viscosity is dependent on the local shear rate. However, the non-Newtonian characteristic is insignificant when shear rate is higher than 1000/s where blood flows under the normal physiological conditions.³⁸⁻⁴¹

The physiological shear rates of veins, large arteries and arterioles are about 20-200/s, 300-800/s, and 500-1600/s.⁴² Accordingly, the highest level of physiological shear stresses in the circulation is about 6.4 Pa (64 dyne/cm²) for blood with a viscosity of 0.004 N-s/m². However, NPSS is inevitably created due mechanical pumping action with MAC. The conventional roller pump used during CPB procedures can generate up to 900 Pa of instantaneous shear stress,⁴³ while the shear stresses in adult CPB oxygenators are much smaller (between 2.10-4.35 dynes/cm²).⁴⁴ NPSS also exists within the arterial cannula, depending on the cannula tip design and flow rates.⁴⁵ In contemporary ECMO and LVAD systems, continuous-flow rotary

Table 1. Bleeding Complication and Transfusion During MCS.

MCS	Duration	Cases	Type	Bleeding (%)	Transfusion threshold	Transfusion	Mortality
CPB	1998.1-2007.12 (van Straten AH, et al. ²²)	10,025	Adult CABG	Re-exploration 5.3%	N/A	Donor blood 3.0, 2.1, 1.1, 0.9 unit in 4 groups	2.3% (30days), 11% (>30days)
	2000.11-2010.1 (Vivacqua A, et al. ²³)	18,891	Adult cardiac surgery	Reoperation for bleeding 3%	N/A	Intraoperative: PRBC 24.9%, platelet 7.9%	Re-exploring patient 8.5%, others 1%
	2004.1-2007.12 (Mehta RH, et al. ²⁴)	528,686	Adult CABG	Reoperation for bleeding 2.4%	N/A	Blood products 59.2%, PRBC 54%, platelet 22%	2.3%
	2010.10.1-12.31 (Colson PH, et al. ²⁵)	4,904	Adult cardiac surgery	Active bleeding after surgery 2.6%	N/A	Blood products 95%, PRBC 88%, platelet 48%	Incidence of death in ICU 7%
	2010.1-2011.3 (Klinge M, et al. ²⁶)	215	Adult cardiac surgery	Postoperative bleeding 26.5%	Hgb 10 g/dl	Need for transfusion 83.3%	8.8%
ECMO	2001.1-2017.12 (Doyle AJ, et al. ²⁷)	402	VV-ECMO 100%	17.7%, intracranial hemorrhage 14.2%	Hgb 8-9 g/dl	Total RBC 2,296 units, 0.66 → 0.44 RBC unit/ECMO day	27.6% (6 months)
	2005.1-2016.12 (Gumbretière G, et al. ²⁸)	509	VA-ECMO 81%	Thrombotic/hemorrhagic events 55.6%	Hgb 8 g/dl, platelets 50 × 10 ⁹ /L	PRBC 82.8%, 11.4 unit/patient; platelet 56.7%, 3.0 unit/patient	55.2% (6 months)
	2006.9-2015.11 (Santiago MJ, et al. ²⁹)	100	VA-ECMO 98%	76%, 52% (first 24 h), reoperation 39%	Hgb 10 g/dl, platelets 100 × 10 ⁹ /L	First 24 h: PRBC 85%, platelets 78%, plasma 83%	48%
	2010-2017 (Lansink-Hartgring AO, et al. ³⁰)	164	VA-ECMO 61%	45%	Hgb 6.9 g/dl, Platelets 50 × 10 ⁹ /L	RBC 85%	51%
	2012.12-2014.9 (Muszynski JA, et al. ³¹)	514	VA-ECMO 83.9%	Bleeding requiring a transfusion 65.8%	Hgb 10 g/dl	Platelet 43%	45.1% (in-hospital)
LVAD	2004.10-2009.5 (Schaffer JM, et al. ³²)	86	HM II 100%	Reoperation for bleeding 20%, GIB 28% (1 y)	Hgb 8-10 g/dl Platelet 100 × 10 ⁹ /L	Intraoperative: 11.6 unit, Postoperative: 12.6 unit in 48 h, 15.6 unit in first week	51% (1 year)
	2004.7-2014.6 (Quader M, et al. ³³)	666	HM II (83%), HW HVAD (5.1%), HM XVE (3.9%)	Reoperation for bleeding 22%	Intraoperative: HCT 18%, postoperative: HCT 21%	Blood products 92%, intraoperative 71.8%, postoperative 73%	13.2%
	2005.3-2006.5 (Miller LW, et al. ³⁴)	133	HM II 100%	Bleeding requiring surgery 31%	N/A	53% (Requiring ≥2unit PRBC)	32% (1 year)
	2006.12-2017.1 (Muslem R, et al. ³⁵)	83	HM II 77%, HM 3 23%	Bleeding event 54%, reoperation 47%	Hgb < 5 mmol/L, platelet >100 × 10 ⁹ /L in bleeders	Bleeders vs. non-bleeders: PRBC 7.8 vs. 1.3, platelets 0.6 vs. 0.03 unit	17% (1 year)
	2012.1-2016.6 (Malik S, et al. ³⁶)	205	HM II 100%	GIB 28%	N/A	GIB vs. Non-GIB: Blood products 29 vs. 13, PRBC 21 vs. 8, platelet 2 vs. 1 unit	37.6%, GIB vs. Non-GIB: 42% vs. 36%
TAH	1993.1-2002.9 (Copeland JG, et al. ¹)	81	SynCardia	102 bleeding events	N/A	18 events: 3 PRBC; 13 events: >8 PRBC	21% before transplantation
	2006.6-2017.4 (Arabia FA, et al. ²¹)	450	SynCardia	41.3%/7.1% (≤3 / >3 months)	N/A	N/A	34.1% (1 year)

CABG: Coronary artery bypass surgery; GIB: Gastrointestinal bleeding; HCT: hematocrit; HM: Heart Mate; HW: HeartWare; N/A: Not available; PRBC: Packed red blood cells.

pumps are exclusively used. Under common clinical ECMO operating conditions, the high-speed rotation of the impeller of a rotary pump can generate extremely high NPSS (>100 Pa) in some region, such as bladed regions of the impeller.⁴⁶ NPSS at this level can cause damages to blood cells and proteins. It was reported that the NPSS in the CentriMag pump (Abbott, Chicago, IL USA) can be over 150 and 500 Pa when operated for extracorporeal ventricular assist and arterio-veno ECMO support at a flow rate of 4.5 L/min against a pressure head of 150 mmHg and 350 mmHg, respectively.^{47,48} Gross-Hardt et al.⁴⁹ reported that the Revolution (LivaNova, London, UK), Rotaflow (Getinge, Gothenburg, Sweden), and i-cor (DP3) (Xenios AG, Heilbronn, Germany) pumps could generate NPSS higher than 150 Pa as well when these pumps are operated at a flow rate of 4 L/min against pressure head of 150 mmHg. The Impella axial pump (Abiomed, Inc., Danvers, MA, USA) is an intravascular micro-axial blood pump with a lower profile and higher rotation speed.⁵⁰ However, One *in-vitro* study showed that it had equivalent hemocompatibility with the CentriMag centrifugal pump.⁵¹ The implanted HeartMate II (Thoratec Corp., Pleasanton, CA, USA) and HeartWare HVAD (HeartWare International, Inc., Framingham, MA, USA) were reported to induce more than 200 Pa of shear stress at 4.5 L/min and 80 mm Hg.⁵² The latest clinical implanted HeartMate 3 (Abbott, St. Paul, MN, USA) has lower shear stress than HeartMate II and HVAD, but the artificial pulse can increase shear stress level.^{53,54}

Platelet Physiology

Platelets are released from megakaryocyte cells in the bone marrow and lungs, with size of 2–4 μm in diameter, lifespan of 7–10 days, and normal count of about $150\text{--}450 \times 10^3/\mu\text{l}$ in the human bloodstream, requiring a continuous platelet clearance and production of 100 billion platelets (70 million/min) daily to maintain a physiological platelet concentration.^{55–57} Although platelets are revealed to be versatile and significantly contribute to many other physiological and pathological processes such as tumor metastasis, anti-inflammatory and immune regulatory functions, the main function of platelets is to form hemostatic thrombi after vascular injury to prevent blood loss and maintain vascular integrity.^{58,59} Due to their small size, platelets circulate in blood and are pushed by larger red blood cells aside near the outer edge of the blood flow, allowing a majority of platelets in close proximity to the vessel wall and to arrive first and rapidly respond after the vascular damage.

1. Platelet Granules

Platelet has 3 main secretory granules—alpha (α) granules, dense granule and lysosomes. The α -granules (50–80 per platelet) mainly contain fibrinogen, fibronectin, von Willebrand factor (VWF), platelet factor 4 (PF4), P-selectin, plasminogen activator inhibitor-1 (PAI-1). The dense granules (3–8 per platelet) have adenosine triphosphate (ATP), adenosine

diphosphate (ADP), P-selectin, calcium, and others. The lysosomes (0–3 per platelet) contain some acid hydrolases. Upon activation, platelets secrete contents of these granules, which play an important role in inflammation, angiogenesis, hemostasis and thrombosis.^{60,61} When the endothelial cells of a blood vessel are damaged by injuries or pathological alterations, the subendothelial structures, including basement membrane, collagen and microfibrils are exposed and trigger sudden platelet activation and adhesion. Subsequent to platelets activation, for example, α -granule secretion results in P-selectin expression on the platelet surface, releases of VWF and coagulation factors.⁶² ADP is secreted from dense granules to further amplify platelet activation.⁶³ Various soluble stimuli released from platelets strengthen platelet adhesion and recruit more platelets into the growing thrombus, leading to platelet aggregation.

2. Membrane Glycoproteins

Platelet membrane consists of at least 9 glycoproteins (GP), named GPI to GPIX. Among them, GPIb-IX-V complex is the platelet receptor for VWF, the second most abundant receptor complex on the human platelet surface. As the mediator of the interaction of platelets with the subendothelial collagen, VWF tethers platelets via the GPIb-IX-V complex to the site of vascular injury and initiates both hemostasis and pathological thrombosis. This is the first step of platelet adhesion at the site of vessel injury, and also facilitates fibrinogen binding to GPIIb/IIIa to help platelet aggregation.⁶⁴ But at low shear stress, platelet adhesion is independent of GPIb-IX-V complex.⁶⁵ High shear stresses change the conformation of VWF, leading to a high-affinity ligand between VWF and GPIb-IX-V complex.⁶⁵ Because primary hemostasis is initiated by VWF tethering platelets via GPIb-IX-V complex, a dysfunction in either VWF or platelets could increase the risk of bleeding.

GPVI is a receptor for collagen. The interaction of platelet GPVI with collagen results in platelet activation and adhesion as well. The initial interaction between VWF and GPIb-IX-V is rapidly reversible and insufficient for stable adhesion. Firm platelet adhesion on collagen under high shear requires intracellular signaling from GPVI, and is reinforced by release of soluble mediators, such as ADP and thromboxane A_2 (TXA_2), and by the generation of thrombin.^{66,67}

GPIIb/IIIa is a receptor for fibrinogen, the most abundant platelet adhesion receptor on the platelet surface. The unactivated GPIIb/IIIa can bind only immobilized fibrinogen, but the activated GPIIb/IIIa can also capture soluble fibrinogen and other ligands, resulting in platelet aggregation.⁶⁸ Platelet GPIIb/IIIa is usually activated via inside-out and/or outside-in signaling mechanisms. The common inside-out activation cascade is triggered by binding of thrombin to proteinase-activated receptor 1 (PAR1) on the platelet membrane, leading to increased affinity of GPIIb/IIIa to fibrinogen and other ligands.⁶⁹ Thrombin is generated by the exposure of tissue factor to the coagulation system on the vessel injury area. The outside-in activation of GPIIb/IIIa is initiated by interactions of the GPIIb/IIIa extracellular domain with fibrinogen and other

ligands, leading to the generation of a complex cascade of intracellular signaling processes that mediate irreversible stable adhesion, spreading, aggregation of platelets, and subsequent thrombus growth.^{70,71} Platelet aggregation through platelet GPIIb/IIIa binding to fibrinogen is the final step in platelet activation.⁷² Platelet activation leads to a remarkable increase in the affinity of GPIIb-IIIa for fibrinogen. The active form of GPIIb/IIIa can be quantified by measuring the binding of the antibody PAC-1 (phosphatase of activated cells 1).⁷³

Shear-Induced Platelet Adhesion and Aggregation

Platelet adhesion, activation and aggregation play a pivotal role in thrombus formation at sites of vascular injury. Circulating platelets become adherent and activated at the site of damaged or diseased vessel wall, and form aggregations that promote coagulation and prevent blood loss after injury.⁷⁴ Three different pathways trigger this complex process, including exposure of subendothelial matrix proteins (collagen and VWF), exposure of tissue factor, and mechanically-induced platelet activation.^{75,76} Among them, shear-dependent platelet activation is possibly initiated by binding of plasma VWF to platelets through GPIb α , leading to platelet secretion and GPIIb/IIIa-dependent aggregation.^{77,78} A recent study showed that shear stress can induce prominent procoagulant activity with increased phosphatidylserine externalization (PSE) and thrombin generation, but without GPIIb/IIIa activation. The latter may result from platelet cross-activation by biochemical agonists, such as ADP and thrombin.⁷⁹ Shear stress may directly activate platelets without the help of exogenous agonists.⁸⁰ Human platelets can express a mechanosensitive Ca²⁺ entry pathway that is activated by arterial shear stress *in vitro*.⁸¹ The phosphoinositide 3-kinases (PI3 K)/protein kinase B (Akt) signaling pathway is also involved with shear-induced platelet activation.⁸² However, platelets may be damaged by shear stresses ranging from 10 Pa to 50 Pa.⁸³

When blood comes in contact with foreign substances by extracorporeal circuitry, the protein adsorption rapidly occurs in a few seconds; next, platelets may adhere to adsorbed proteins within the first minute, and then platelets aggregate leading to blood coagulation and thrombus formation. The protein adsorption includes albumin, fibrinogen, VWF, thrombin, factor XII, etc. depending on physicochemical properties of both surfaces and proteins. Platelets can adhere to an artificial surface through platelet interaction with these surface adsorbed proteins. Fibrinogen is the key protein in the platelet adhesion. Thus, non-activated platelets can become activated through protein adhesion and aggregation. The latter also occurs through the adsorption of proteins and other byproducts of contact/ complement system activations. Platelet aggregation is mainly through the interaction between platelet GPIIb/IIIa and fibrinogen, ultimately forming a firm platelet plug that can prevent bleeding.^{74,84-86}

Beside hemodilution, hypothermia and blood loss during CPB procedures or ECMO support, thrombocytopenia is

common in patients undergoing CPB due to complete bypassing lungs in which more than 50% of total platelet production take place.⁵⁵ CPB also causes structural and biochemical changes in platelets due to shear forces created by blood pumps.⁸⁷ These changes could exacerbate platelet clearance and consumption in the circulation. In ECMO patients, platelet consumption also occurs, resulting in platelet count drop. Platelets adhere to the fibrinogen which initially is absorbed by the circuit surfaces, resulting in a time-dependent platelet activation and persistent and progressive platelet dysfunction during ECMO.^{88,89} The impaired secretion of α - and dense granules caused relevant platelet dysfunction in patients with V-V ECMO.⁹⁰ The reduced platelet adhesion, decreased platelet activation, and reduced platelet aggregation were reported in adult patients during ECMO treatment.⁹¹ In simulated LVAD systems, our *in-vitro* studies demonstrated that high shear stress induced platelet activation, increased the platelet adhesion on fibrinogen, reduced platelet adhesion capacity with VWF and collagen, and reduced both ristocetin- and collagen-induced platelet aggregation.^{67,92} Some clinical studies also showed severely impaired ristocetin-induced platelet aggregation, which may contribute to an increased tendency of bleeding in the LVAD patients.^{93,94} However, high shear rates ($\geq 10,000/s$) can cause vWF-mediated activation-independent platelet adhesion and aggregation, followed by stable aggregation in LVADs.⁹⁵ Thus, acquired platelet dysfunction contributes to risks of bleeding and thrombosis during MCS.

Shear-induced platelet activation, adhesion, aggregation and platelet-mediated thrombosis relative to MCS devices may be simulated by computational fluid dynamics (CFD) using multi-scale strategies with particle-based methods, helping researchers investigate and predict device thrombogenicity.⁹⁶⁻⁹⁸ The device thromboresistance optimization methodology can further optimize the thromboresistance performance of any MCS device during the research and development (R&D) stage, thereby reducing the R&D costs and shortening the development cycle.⁹⁹⁻¹⁰¹

Shear-Induced Platelet Receptor Shedding

The receptor shedding is a process of irreversible removal of transmembrane cell surface receptors by proteolysis of the receptor at a position close to the extracellular surface of the plasma membrane. It releases a soluble ectodomain fragment and preserves a membrane-associated remnant fragment. Ectodomain shedding is a ubiquitous control mechanism for rapid and irreversible downregulation of receptor expression and regulating cellular transmembrane proteins.¹⁰² Metalloproteinase-mediated ectodomain shedding of platelet receptors has been recently recognized as a mechanism for regulating platelet function.¹⁰³ GPIb α and GPVI are the 2 key platelet receptors that bind vWF and collagen, respectively, and initiate hemostasis at sites of vascular injury. Several biochemical pathways that induce shedding of GPIb α and/or GPVI have been identified.^{104,105} While these pathways might be dependent or independent of platelet activation, the loss of these functional

receptors may result in defective platelets. Defects affecting normal expression and function of GPIIb/IIIa (Bernard-Soulier syndrome) or GPVI result in mild or more severe bleeding. Linking these defects to the bleeding is complicated by co-existing abnormalities in these patients. Animal studies demonstrated that genetic disruption of normal GPIIb/IIIa and/or GPVI or inhibition using antibodies or other inhibitors impaired adhesion capacity of platelets on subendothelial matrix (vWF or collagen) and attenuated thrombotic propensity of platelets.

The role of shear stress in platelet receptor shedding has not been well defined. Only a few studies have been carried out to examine the shear-mediated platelet receptor shedding either in the context of platelet-surface interaction¹⁰⁶ or direct shear effect.¹⁰⁷ NPSS induces not only platelet activation and hemolysis, but also the shedding of platelet receptors.^{75,106,108-112} Activated platelets in the circulation increase the risk of thrombosis. But shedding of platelet receptors could significantly affect initiation and development of the thrombus. An in-vitro study showed that induction of GPVI cleavage caused specific down-regulation of collagen-induced platelet aggregation.¹¹² Loss of the platelet GPIIb/IIIa and GPVI may contribute to ablated platelet adhesion/aggregation. This may be a protective mechanism for down-regulating platelet adhesiveness during elevated shear stress, thereby reducing the level of platelet activation and thrombus formation.^{75,102,113}

NPSS has been considered to contribute to the shedding of 3 specific platelet receptors—GPIIb/IIIa, GPVI, and GPIIb/IIIa.^{67,108,110,114} Platelet receptor shedding is regulated by endogenous membrane-associated proteinases—platelet sheddases. The major sheddases for GPIIb/IIIa and GPVI are members of the a disintegrin and metalloproteinase (ADAM) family—ADAM17 and ADAM10. ADAM17 cleaves GPIIb/IIIa, ADAM10 primarily cleaves GPVI, and both ADAM10 and ADAM17 cleave GPV.¹¹⁵ Plasmin can proteolyze GPIIb/IIIa.¹¹⁶ Shear-induced GPIIb/IIIa shedding is dependent on GPIIb/IIIa-VWF interaction, calpain, and metalloproteinase activations.¹⁰⁶ Moreover, shear-induced GPVI shedding did not require VWF interaction with GPIIb/IIIa, GPIIb/IIIa engagement, or platelet activation, and is metalloproteinase-dependent after exposure of platelets to NPSS in vitro.⁷⁵ Beside ADAM-induced GP shedding, direct mechanical damage is partially responsible for NPSS-induced receptor shedding. Because the ADAM inhibition couldn't completely suppress the NPSS-induced loss of the GPIIb/IIIa and GPVI. This phenomenon could be explained as resulting from both the NPSS-induced GP shedding by mechanical forces and ADAM-induced glycoprotein shedding by triggering an intracellular signaling.¹¹⁷

Loss of the platelet surface receptors GPIIb/IIIa and GPVI has been reported in heart failure patients.^{113,118,119} Some early clinical studies showed that GPIIb/IIIa levels decreased during 120-min CPB and then gradually return to pre-bypass level.¹²⁰ But no significant change in platelet GPIIb/IIIa expression throughout CPB, and a significant decrease in levels soon after CPB was reported.^{87,121} These may indirectly suggest the existence of platelet receptor shedding by CPB procedure. A recent clinical study confirmed a decrease in platelet GPIIb/IIIa surface

expression after adult CPB.¹²² Our results also showed CPB-associated platelet activation and concomitant receptor shedding in pediatric patients with CPB.¹²³ Similarly, increased platelet GPIIb/IIIa and GPVI shedding is already present in patients before ECMO placement and remain significantly elevated after on ECMO support.^{113,119} The increase in soluble GPVI levels was found in CF-VAD and ECMO patients as compared with healthy donors, indicating device-related shedding in patients on LVAD or ECMO support.¹¹³ For LVADs, in-vitro studies demonstrated that NPSS induce both activation and shedding of the GPIIb/IIIa, GPVI and GPIIb/IIIa on the platelet surface occur simultaneously and increase with increasing shear stress level and exposure time. Plasma soluble GPIIb/IIIa also increased with increasing shear stress level. Platelet receptor shedding may lead platelet dysfunction and influence the coagulation system.¹⁰⁸⁻¹¹⁰ In a study on LVAD patients, platelet GPIIb/IIIa shedding was observed to be a preexisting condition and increase post-implantation in those patients who experienced bleeding events.¹¹⁸ Loss of the platelet receptors GPIIb/IIIa and GPVI in LVAD patients may contribute to hemorrhagic complications.^{113,119} Therefore, on the one hand LVADs can induce platelet activation and enhanced platelet adhesion, which may lead to an elevated risk of thrombosis, but on the other hand they can also cause the loss of platelet receptors and reduced platelet adhesion capacities, which may lead to hemostasis dysfunction and elevated propensity of bleeding.

Shear-Induced Platelet Apoptosis

Apoptosis is a physiologic process of cell death to control the number of cells and eliminate unwanted cells. Platelet apoptosis can be induced by physiologic compounds (such as phosphatidylserine (PS) and thrombin), chemical stimuli, NPSS (mechanical rheological forces) and platelet storage. NPSS (117–388 dynes/cm²) were reported to induce not only platelet activation but also apoptosis.¹⁰⁷ It's believed that mechanoreceptors on platelets transmit activation and apoptotic signals to the cell interior, including P-selectin express on the platelet surface, depolarization of mitochondrial membrane potential, activation of cytosolic enzyme caspase-3, microparticle formation and PS translocation from the inner to the outer plasma membrane leaflet.¹⁰⁷ The damaged platelets by NPSS may be recognized as “unwanted” cells by the reticuloendothelial system and then are removed from the circulation. Additionally, the GPIIb/IIIa–VWF interaction initiates platelet adhesion and thrombus formation under pathophysiologic flow conditions, but it also induces apoptotic events in human platelets which occurs independently of platelet activation.¹²⁴ GPIIb/IIIa may act as one of mechanoreceptors transmitting apoptotic signals inside the platelet.¹⁰⁷ Our study confirmed platelet apoptosis existed in continuous-flow-LVAD patients who developed bleedings within 1 month post-implantation and was associated with endogenous reactive oxygen species (ROS) generation triggering the intrinsic pathway of platelet apoptosis.¹²⁵

Shear-Induced Acquired von Willebrand Syndrome (AVWS)

VWF is a multimeric plasma glycoprotein, synthesized by endothelial cells and megakaryocytes in a multimerized form from identical single-chain subunits into disulfide-linked multimers. Each subunit has a single A1 domain that is the binding site for platelet GPIIb α and collagen IV, a A3 domain that binds to collagens I and III, and a C4 domain that is binding site for the platelet-integrin α IIB β 3 (glycoprotein GPIIb/IIIa).^{126,127} vWF is stored at the Weibel-Palade bodies in the endothelial cells and the α -granules in platelets. Endothelial cells secrete VWF to maintain basal levels of VWF in plasma (approximately 10 μ g/mL in humans). After release into blood, Ultra-large VWF multimers (up to 20,000 kDa) bonded to the endothelial cell surface are rapidly cleaved by the metalloprotease ADAMTS-13 into smaller forms and release into the circulation. Soluble VWF cannot interact with platelets in the absence of injury.^{65,128} But, it can noncovalently link with blood clotting factor VIII to protect factor VIII from degradation.^{126,129} The absence of VWF results in low activity level of the factor VIII. A majority of VWF is cleared by macrophages in the liver, spleen and vascular endothelial cells and its circulating half-life ranges from 6 to 24 h.^{95,130} VWF plays a major role in primary hemostasis by acting as a bridging molecule between vascular injury and circulating platelets in blood, recruiting platelets to injured vessel wall. Upon vascular damage, subendothelial collagen is exposed. VWF can bind with exposed collagen at the A3 domain and become tethered to the vessel wall. Its A1 domain then binds to the platelet receptor GPIIb-IX-V complex, simultaneously triggering intracellular signaling cascades leading to platelet aggregation and thrombus formation.⁶⁴ The adhesiveness of VWF is determined by its multimeric size. High-molecular-weight (HMW) multimers (5000–10,000 kDa) are the most effective to interact with collagen and platelet receptors.¹³¹ The GPIIb α -VWF interaction also induces apoptotic events in human platelets.¹²⁴

Under normal circulation conditions, VWF exists in a compact globular (collapsed) conformation. It is essentially inert at the low shear rates of veins and normal arteries, and does not stimulate platelet adhesion.¹³² VWF multimers circulating in blood also do not bind the platelet GPIIb-IX-V complex but can be induced by elevated shear stress. Platelet adhesion is strongly dependent on VWF at shear rates $>1,000/s$.¹²⁶ Shear-induced conformational changes in VWF may contribute to the regulation of VWF binding to platelet GPIIb.^{126,133} Force-sensing mechanisms of VWF are the key to its function in hemostasis and its role in thrombosis.¹³⁴ NPSS can change VWF multimers from a globular shape to an elongated rope-like structure.¹³⁵ Structural changes of VWF molecule induced by NPSS expose the A2 domain^{136,137} and promote proteolytic cleavage by ADAMTS-13 and multimeric binding to platelets GPIIb α through A1 domain.¹³⁸ The VWF-platelet binding also increases proteolytic cleavage by ADAMTS-13.¹³⁹ As a result, VWF multimers are degraded into smaller multimers. The loss of large multimers of plasma VWF may increase the bleeding

tendency associated with AVWS by down-regulation of VWF's hemostatic potential.¹²⁶

AVWS became a clinical concern in 1990s after realizing the association between GI bleeding and aortic stenosis.¹⁴⁰ The severity of the stenosis (transvalvular gradients) was negatively correlated with the percentages of the HMW-VWF multimers.¹⁴¹ NPSS across the stenotic valve lead to increased fragmentation of HMW-VWF multimers.¹⁴² Aortic valve replacement reverses the bleeding disorder. A similar AVWS is observed in LVAD patients. Nearly all patients with continuous flow LVADs suffer from AVWS diagnosed by the decrease in or absence of HMW vWF multimers.¹⁴³⁻¹⁴⁶ Therefore, AVWS is considered as one of the reasons for increased bleeding complications, such as epistaxis, GI and non-surgical hemorrhage, in patients with VAD. The loss of large multimers reduced collagen binding capacity (VWF: CB) and ristocetin cofactor activity (VWF: RCo) in LVAD patients early in the postoperative period after LVAD implantation, persistent during LVAD support, and resolves after LVAD explantation or heart transplantation.^{144,147,148} Similarly, gastrointestinal bleeding can stop after removal of the LVAD.^{137,149} ECMO patients also showed a decreased collagen binding capacity to VWF antigens, a decreased VWF: RCo/VWF: Ag ratios, a decreased VWF: CB/VWF: Ag ratios, and loss of HMW-VWF multimers.^{90,113,150,151} AVWS is also reversible in ECMO patients after ECMO removal.¹⁵⁰ It is clear that the designs of contemporary LVADs or ECMO systems and long-term support affect hemostatic factors.^{93,147,152} It is known that artificial surface of the ECMO and LVAD systems plays an important role in the activation of platelets. It is possible that artificial surfaces could disrupt HMW-VWF multimers. It is widely considered that NPSS, generated around the impellers of rotary pumps, in the arterial/venous cannulas and in the circuits for hemoconcentration or continuous renal replacement therapy (CRRT) during MCS, can result in loss of HMW-VWF multimers, subsequently leading to AVWS and increase risk of bleeding complications. A reduced pump speed cannot effectively decrease VWF degradation.¹⁵³ Supplementation with factor VIII/vWF concentrate is necessary in life-threatening bleeding episodes during ECMO and LVAD.¹⁵⁴ Device explantation or transplantation can completely resolve the AVWS. However, AVWS is universal to all patients on ECMO and LVAD, possibly CPB, we believe that AVWS is a factor to increased bleeding, but not determining factor. Platelet defects are the key factor to bleeding in these patients.

Shear-Induced Hemolysis

Hemolysis was a key issue during the early stage of development and clinical use of MCS and is associated with increased blood product transfusion requirements, increased incidence of acute kidney injury, increased mortality and morbidity, impending oxygenator failure in ECMO and pump thrombosis in ECMO and LVAD.^{155,156} Although sub-clinical hemolysis is still generated by contemporary devices, hemolysis has become less an issue in patients on LVAD or ECMO support unless

there is thrombosis inside the device. High shear stress and high shear rate generated by flow through the extracorporeal circuit can induce erythrocyte lysis and release free hemoglobin, depending on shear stress level and exposure time. The shear stress thresholds of hemolysis are considered between 150 Pa to 400 Pa.⁸³ High shear stress can cause red blood cell either slipper or parachute deformation, and also leads to pores in the erythrocyte membrane to grow and hemoglobin to leak out.^{157,158} Plasma-free hemoglobin (PFH) can bind directly to vWF, thereby increasing the affinity of the vWF A1 domain for the GPIb receptor on the surface of platelets.¹⁵⁹ PFH can also block the cleavage of VWF by ADAMTS-13.¹⁶⁰ Therefore, a reduction of VWF cleavage by high-level PFH can cause thrombosis in LVAD patients.¹⁶¹ An in-vitro study showed that PFH (≥ 50 mg/dL) effectively augmented platelet adhesion (even at low shear stress) and micro-thrombus formation on fibrinogen, extracellular matrix, and collagen at high shear stress.¹⁵⁹ ADP release from damaged red blood cells and ROS production by hemoglobin also activate platelets.^{162,163} Additionally, as a potent nitric oxide (NO) scavenger, PFH binds quickly and irreversibly to NO which inhibits platelet activation in circulation.^{164,165} The exhaustion of NO may result in thrombosis.¹⁶⁶ In an in-vitro study, heparin weakly inhibited the action of free Hb.¹⁵⁹ This may be explained by the fact that there are still clot forms in the ECMO circuit despite the continuous use of heparin.

Shear-Induced Microparticle Formation

Microparticles in blood are small membrane vesicles derived from a variety of cell types, sizing 0.1-1 micron in diameter. Blood pumps used in CPB, ECMO and LVAD systems can generate high shear stress that may lead to the production of microparticles from shear-sensitive cells, such as platelets. Platelet-derived microparticles (PMP) are strongly procoagulant because they contain PS and tissue factor (TF). There was a report that cardiac surgery on CPB induced an increase amount of PMPs in systemic blood and pericardial blood.¹⁶⁷ An in-vitro study showed that more PMPs were generated in the neonatal ECMO system with a centrifugal pump compared with a roller pump, perhaps because centrifugal pumps have a dynamic shear stress.¹⁶⁸ Our in-vitro experiment also demonstrated PMPs generation with an increasing trend over time in the pediatric ECMO system.¹¹⁴ Patients with LVAD had significantly increased microparticles from platelets, leukocytes, and endothelial cells, which may increase risk of developing thromboembolic complications.¹⁶⁹ LVAD patients had higher level of PS⁺ microparticles and patients who developed an adverse event had significantly higher PS⁺ microparticles than patients with no events.¹⁷⁰

Conclusions

MAC saves lives of millions of patients who suffer heart failure, respiratory failure, and cardiopulmonary failure or who undergo cardiac surgery. In these patients, the survival rate

increases, and the post-operative complications decrease year after year. However, postoperative bleeding and thrombotic complications remain biggest challenges for clinicians and patients. The exposure of blood to artificial surfaces of the circuit and NPSS can induce platelet activation, which increases the risk for thrombotic events, but NPSS also causes platelet receptor shedding, AVWS and platelet apoptosis, which lead to hemostasis dysfunction. In addition, anticoagulation is must to prevent the circuit from clotting. So, patients undergoing MCS simultaneously face high risks of thrombosis and bleeding. The whole key is finding the balance between preventing clotting due to the circuit without inducing the risk for hemorrhagic complications by NPSS. Therefore, based on knowledge of shear-induced hemostatic disorders, it is necessary to modify circuit material and design for bioengineers, develop low-shear-stress blood pumps, oxygenators and canulas for manufacturers, optimize anticoagulation therapy and strengthen clinical management for clinicians, aiming to reduce bleeding and thrombotic complications and improve clinical outcomes in patients with MCS.

Authors' Note

Wang: concept/design, data collection, and drafting manuscript; Griffith: concept/design and critical revision; Wu: concept/design, critical revision, and approval.

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References

1. Copeland JG, Smith RG, Arabia FA, et al. Cardiac replacement with a total artificial heart as a bridge to transplantation. *N Engl J Med*. 2004;351(9):859-867.
2. O'Shaughnessy D, Gill R. *Cardiothoracic Surgery*. In: Key N, Makris M, Lillcrap D, eds. *Practical Hemostasis and Thrombosis*. Wiley-Blackwell; 2016:299-313.
3. *ECLS Registry Report, International Summary*. Extracorporeal Life Support Organization; 2020:1-37.
4. Teuteberg JJ, Cleveland JC Jr, Cowger J, et al. The Society of Thoracic Surgeons Intermaacs 2019 Annual Report: the changing landscape of devices and indications. *Ann Thorac Surg*. 2020; 109(3):649-660.

5. Arabia FA. SynCardia total artificial heart opportunities and challenges moving forward. *Artif Organs*. 2019;43(11):1051-1052.
6. Li S, Price R, Phiroz D, Swan K, Crane TA. Systemic inflammatory response during cardiopulmonary bypass and strategies. *J Extra Corpor Technol*. 2005;37(2):180-188.
7. Millar JE, Fanning JP, McDonald CI, McAuley DF, Fraser JF. The inflammatory response to extracorporeal membrane oxygenation (ECMO): a review of the pathophysiology. *Crit Care*. 2016;20(1):387.
8. Radley G, Pieper IL, Ali S, Bhatti F, Thornton CA. The inflammatory response to ventricular assist devices. *Front Immunol*. 2018;9:2651.
9. Janatova J. Activation and control of complement, inflammation, and infection associated with the use of biomedical polymers. *ASAIO J*. 2000;46(6):S53-S62.
10. Petrou A, Tzimas P, Siminelakis S. Massive bleeding in cardiac surgery. Definitions, predictors and challenges. *Hippokratia*. 2016;20(3):179-186.
11. Lotz C, Streiber N, Roewer N, Lepper PM, Muellenbach RM, Kredel M. Therapeutic interventions and risk factors of bleeding during extracorporeal membrane oxygenation. *ASAIO J*. 2017; 63(5):624-630.
12. Kormos RL, Cowger J, Pagani FD, et al. The Society of Thoracic Surgeons Intermacs Database Annual Report: evolving indications, outcomes, and scientific partnerships. *Ann Thorac Surg*. 2019;107(2):341-353.
13. Dyke C, Aronson S, Dietrich W, et al. Universal definition of perioperative bleeding in adult cardiac surgery. *J Thorac Cardiovasc Surg*. 2014;147(5):1458-1463 e1.
14. Biancari F, Mikkola R, Heikkinen J, Lahtinen J, Airaksinen KE, Juvonen T. Estimating the risk of complications related to re-exploration for bleeding after adult cardiac surgery: a systematic review and meta-analysis. *Eur J Cardiothorac Surg*. 2012;41(1): 50-55.
15. Dalton HJ, Reeder R, Garcia-Filion P, et al. Factors associated with bleeding and thrombosis in children receiving extracorporeal membrane oxygenation. *Am J Respir Crit Care Med*. 2017; 196(6):762-771.
16. Crow S, John R, Boyle A, et al. Gastrointestinal bleeding rates in recipients of nonpulsatile and pulsatile left ventricular assist devices. *J Thorac Cardiovasc Surg*. 2009;137(1):208-215.
17. Kurien S, Hughes KA. Anticoagulation and bleeding in patients with ventricular assist devices: walking the tightrope. *AACN Adv Crit Care*. 2012;23(1):91-98.
18. Leebeek FWG, Muslem R. Bleeding in critical care associated with left ventricular assist devices: pathophysiology, symptoms, and management. *Hematology Am Soc Hematol Educ Program*. 2019;2019(1):88-96.
19. Ranucci M, Bozzetti G, Ditta A, Cotza M, Carboni G, Ballotta A. Surgical reexploration after cardiac operations: why a worse outcome? *Ann Thorac Surg*. 2008;86(5):1557-1562.
20. Voruganti DC, Shantha GP, Inampudi C, Alvarez P, Giudici MC, Briasoulis A. Gastrointestinal hemorrhage among LVAD recipients. A nationwide inpatient sample study. *J Heart Lung Transplant*. 2019;38:S195.
21. Arabia FA, Cantor RS, Koehl DA, et al. Interagency registry for mechanically assisted circulatory support report on the total artificial heart. *J Heart Lung Transplant*. 2018;37(11):1304-1312.
22. van Straten AH, Hamad MA, van Zundert AJ, Martens EJ, Schonberger JP, de Wolf AM. Preoperative hemoglobin level as a predictor of survival after coronary artery bypass grafting: a comparison with the matched general population. *Circulation*. 2009;120(2):118-125.
23. Vivacqua A, Koch CG, Yousuf AM, et al. Morbidity of bleeding after cardiac surgery: is it blood transfusion, reoperation for bleeding, or both? *Ann Thorac Surg*. 2011;91(6):1780-1790.
24. Mehta RH, Sheng S, O'Brien SM, et al. Reoperation for bleeding in patients undergoing coronary artery bypass surgery: incidence, risk factors, time trends, and outcomes. *Circ Cardiovasc Qual Outcomes*. 2009;2(6):583-590.
25. Colson PH, Gaudard P, Fellahi JL, et al. Active bleeding after cardiac surgery: a prospective observational multicenter study. *PLoS One*. 2016;11(9):e0162396.
26. Klingele M, Enkel J, Speer T, Bomberg H, Baerens L, Schafers HJ. Bleeding complications after cardiac surgery, before anticoagulation start and then with argatroban or heparin in the early postoperative setting. *J Cardiothorac Surg*. 2020;15:27.
27. Doyle AJ, Richardson C, Sanderson B, et al. Restrictive transfusion practice in adults receiving venovenous extracorporeal membrane oxygenation: a single-center experience. *Crit Care Explor*. 2020;2(1):e0077.
28. Guimbretiere G, Anselmi A, Roisne A, et al. Prognostic impact of blood product transfusion in VA and VV ECMO. *Perfusion*. 2019;34(3):246-253.
29. Santiago MJ, Gomez C, Magana I, et al. Hematological complications in children subjected to extracorporeal membrane oxygenation. *Med Intensiva*. 2019;43(5):281-289.
30. Oude Lansink-Hartgring A, de Vries AJ, Droogh JM, van den Bergh WM. Hemorrhagic complications during extracorporeal membrane oxygenation—The role of anticoagulation and platelets. *J Crit Care*. 2019;54:239-243.
31. Muszynski JA, Reeder RW, Hall MW, et al. RBC transfusion practice in pediatric extracorporeal membrane oxygenation support. *Crit Care Med*. 2018;46(6):e552-e559.
32. Schaffer JM, Arnaoutakis GJ, Allen JG, et al. Bleeding complications and blood product utilization with left ventricular assist device implantation. *Ann Thorac Surg*. 2011;91(3):740-747; discussion 747-9.
33. Quader M, LaPar DJ, Wolfe L, et al. Blood product utilization with left ventricular assist device implantation: a decade of statewide data. *ASAIO J*. 2016;62(2):268-273.
34. Miller LW, Pagani FD, Russell SD, et al. Use of a continuous-flow device in patients awaiting heart transplantation. *N Engl J Med*. 2007;357(9):885-896.
35. Muslem R, Caliskan K, van Thiel R, et al. Incidence, predictors and clinical outcome of early bleeding events in patients undergoing a left ventricular assist device implant. *Eur J Cardiothorac Surg*. 2018;54(1):176-182.
36. Malik S, Malik SA, Ulmer LL, et al. Gastrointestinal bleeding with left ventricular assist devices (LVAD): locating the leak and

- identifying outcomes. *J Clin Gastroenterol*. 2019;53(5):e202-e207.
37. Varga-Szabo D, Pleines I, Nieswandt B. Cell adhesion mechanisms in platelets. *Arterioscler Thromb Vasc Biol*. 2008;28(3):403-412.
 38. Taylor TW, Yamaguchi T. Three-dimensional simulation of blood flow in an abdominal aortic aneurysm—steady and unsteady flow cases. *J Biomech Eng*. 1994;116(1):89-97.
 39. Perktold K, Peter R, Resch M. Pulsatile non-Newtonian blood flow simulation through a bifurcation with an aneurysm. *Biorheology*. 1989;26(6):1011-1030.
 40. Johnston BM, Johnston PR, Corney S, Kilpatrick D. Non-Newtonian blood flow in human right coronary arteries: transient simulations. *J Biomech*. 2006;39(6):1116-1128.
 41. Ballyk PD, Steinman DA, Ethier CR. Simulation of non-Newtonian blood flow in an end-to-side anastomosis. *Biorheology*. 1994;31(5):565-586.
 42. Kroll MH, Hellums JD, McIntire LV, Schafer AI, Moake JL. Platelets and shear stress. *Blood*. 1996;88(5):1525-1541.
 43. Mulholland JW, Shelton JC, Luo XY. Blood flow and damage by the roller pumps during cardiopulmonary bypass. *J Fluids Struct*. 2005;20(1):129-140.
 44. Hendrix RHJ, Ganushchak YM, Weerwind PW. Contemporary oxygenator design: shear stress-related oxygen and carbon dioxide transfer. *Artif Organs*. 2018;42(6):611-619.
 45. Menon PG, Antaki JF, Undar A, Pekkan K. Aortic outflow cannula tip design and orientation impacts cerebral perfusion during pediatric cardiopulmonary bypass procedures. *Ann Biomed Eng*. 2013;41(12):2588-2602.
 46. Chen Z, Jena SK, Giridharan GA, et al. Flow features and device-induced blood trauma in CF-VADs under a pulsatile blood flow condition: a CFD comparative study. *Int J Numer Method Biomed Eng*. 2018;34(2):10.1002/cnm.2924.
 47. Chen Z, Zhang J, Li T, Tran D, Griffith BP, Wu ZJ. The impact of shear stress on device-induced platelet hemostatic dysfunction relevant to thrombosis and bleeding in mechanically assisted circulation. *Artif Organs*. 2020;44(5):E201-E213.
 48. Fraser KH, Zhang T, Taskin ME, Griffith BP, Wu ZJ. A quantitative comparison of mechanical blood damage parameters in rotary ventricular assist devices: shear stress, exposure time and hemolysis index. *J Biomech Eng*. 2012;134(8):081002.
 49. Gross-Hardt S, Hesselmann F, Arens J, et al. Low-flow assessment of current ECMO/ECCO₂ R rotary blood pumps and the potential effect on hemocompatibility. *Crit Care*. 2019;23:348.
 50. Apel J, Paul R, Klaus S, Siess T, Reul H. Assessment of hemolysis related quantities in a microaxial blood pump by computational fluid dynamics. *Artif Organs*. 2001;25(5):341-347.
 51. Roka-Moiia Y, Li M, Ivich A, Muslmani S, Kern KB, Slepian MJ. Impella 5.5 versus Centrimag: a head-to-head comparison of device hemocompatibility. *ASAIO J*. 2020;66:1142-1151.
 52. Thamsen B, Blumel B, Schaller J, et al. Numerical analysis of blood damage potential of the HeartMate II and HeartWare HVAD rotary blood pumps. *Artif Organs*. 2015;39(8):651-659.
 53. Wiegmann L, Thamsen B, de Zelicourt D, et al. Fluid dynamics in the HeartMate 3: influence of the artificial pulse feature and residual cardiac pulsation. *Artif Organs*. 2019;43(4):363-376.
 54. Bourque K, Cotter C, Dague C, et al. Design rationale and pre-clinical evaluation of the HeartMate 3 left ventricular assist system for hemocompatibility. *ASAIO J*. 2016;62(4):375-383.
 55. Lefrancais E, Ortiz-Munoz G, Caudrillier A, et al. The lung is a site of platelet biogenesis and a reservoir for haematopoietic progenitors. *Nature*. 2017;544:105-109.
 56. Thon JN, Italiano JE. Platelets: production, morphology and ultrastructure. *Handb Exp Pharmacol*. 2012;(210):3-22.
 57. van der Meijden PEJ, Heemskerk JWM. Platelet biology and functions: new concepts and clinical perspectives. *Nat Rev Cardiol*. 2019;16:166-179.
 58. Xu XR, Zhang D, Oswald BE, et al. Platelets are versatile cells: new discoveries in hemostasis, thrombosis, immune responses, tumor metastasis and beyond. *Crit Rev Clin Lab Sci*. 2016;53(6):409-430.
 59. Li Z, Delaney MK, O'Brien KA, Du X. Signaling during platelet adhesion and activation. *Arterioscler Thromb Vasc Biol*. 2010;30(12):2341-2349.
 60. Heijnen H, van der Sluijs P. Platelet secretory behaviour: as diverse as the granules... or not? *J Thromb Haemost*. 2015;13(12):2141-2151.
 61. Laffan MA, Manning RA. Investigation of haemostasis. In: Bain BJ, Imelda B, Mike L, eds. *Dacie and Lewis Practical Haematology*. Elsevier; 2017.
 62. Haley KM, Recht M, McCarty OJ. Neonatal platelets: mediators of primary hemostasis in the developing hemostatic system. *Pediatr Res*. 2014;76(3):230-237.
 63. Offermanns S. Activation of platelet function through G protein-coupled receptors. *Circ Res*. 2006;99:1293-304.
 64. Arya M, Lopez JA, Romo GM, et al. Glycoprotein Ib-IX-mediated activation of integrin alpha(IIb)beta(3): effects of receptor clustering and von Willebrand factor adhesion. *J Thromb Haemost*. 2003;1(6):1150-1157.
 65. Berndt MC, Shen Y, Dopheide SM, Gardiner EE, Andrews RK. The vascular biology of the glycoprotein Ib-IX-V complex. *Thromb Haemost*. 2001;86(1):178-188.
 66. Nieswandt B, Watson SP. Platelet-collagen interaction: is GPVI the central receptor? *Blood*. 2003;102(2):449-461.
 67. Chen ZY, Oswald BE, Sullivan JA, et al. Platelet physiology and immunology: pathogenesis and treatment of classical and non-classical fetal and neonatal alloimmune thrombocytopenia. *Ann Blood*. 2019;4:29-29.
 68. Shattil SJ, Hoxie JA, Cunningham M, Brass LF. Changes in the platelet membrane glycoprotein IIb/IIIa complex during platelet activation. *J Biol Chem*. 1985;260:11107-11114.
 69. Mehrbod M, Trisno S, Mofrad MR. On the activation of integrin alphaIIb beta3: outside-in and inside-out pathways. *Biophys J*. 2013;105(6):1304-1315.
 70. Fullard JF. The role of the platelet glycoprotein IIb/IIIa in thrombosis and haemostasis. *Curr Pharm Des*. 2004;10(14):1567-1576.
 71. Huang J, Li X, Shi X, et al. Platelet integrin alphaIIb beta3: signal transduction, regulation, and its therapeutic targeting. *J Hematol Oncol*. 2019;12(1):26.
 72. Saboor M, Ayub Q, Ilyas S, Moinuddin AS. Platelet receptors; an instrumental of platelet physiology. *Pak J Med Sci*. 2013;29(3):891-896.

73. Ngo ATP, Sheriff J, Rocheleau AD, et al. Assessment of neonatal, cord, and adult platelet granule trafficking and secretion. *Platelets*. 2020;31(1):68-78.
74. Andrews RK, Berndt MC. Platelet physiology and thrombosis. *Thromb Res*. 2004;114(5-6):447-453.
75. Al-Tamimi M, Tan CW, Qiao J, et al. Pathologic shear triggers shedding of vascular receptors: a novel mechanism for down-regulation of platelet glycoprotein VI in stenosed coronary vessels. *Blood*. 2012;119(18):4311-4320.
76. Shadden SC, Hendabadi S. Potential fluid mechanic pathways of platelet activation. *Biomech Model Mechanobiol*. 2013;12(3):467-474.
77. Cosemans JM, Schols SE, Stefanini L, et al. Key role of glycoprotein Ib/V/IX and von Willebrand factor in platelet activation-dependent fibrin formation at low shear flow. *Blood*. 2011;117(2):651-660.
78. Ju L, Chen Y, Zhou F, Lu H, Cruz MA, Zhu C. Von Willebrand factor-A1 domain binds platelet glycoprotein Ibalpha in multiple states with distinctive force-dependent dissociation kinetics. *Thromb Res*. 2015;136(3):606-612.
79. Roka-Moiia Y, Walk R, Palomares DE, et al. Platelet activation via shear stress exposure induces a differing pattern of biomarkers of activation versus biochemical agonists. *Thromb Haemost*. 2020;120(5):776-792.
80. Brown CH III, Leverett LB, Lewis CW, Alfrey CP Jr, Hellums JD. Morphological, biochemical, and functional changes in human platelets subjected to shear stress. *J Lab Clin Med*. 1975;86(3):462-471.
81. Ilkan Z, Wright JR, Goodall AH, Gibbins JM, Jones CI, Mahaut-Smith MP. Evidence for shear-mediated Ca(2+) entry through mechanosensitive cation channels in human platelets and a megakaryocytic cell line. *J Biol Chem*. 2017;292(22):9204-9217.
82. Chen Z, Li T, Kareem K, Tran D, Griffith BP, Wu ZJ. The role of PI3K/Akt signaling pathway in non-physiological shear stress-induced platelet activation. *Artif Organs*. 2019;43(9):897-908.
83. Morsi YS, Sakhaeimanesh AA. Flow characteristics past jellyfish and St. Vincent valves in the aortic position under physiological pulsatile flow conditions. *Artif Organs*. 2000;24(7):564-574.
84. Bartolo LD, Curcio E, Drioli E. *Blood-Membrane Interactions*, in *Membrane Systems—For Bioartificial Organs and Regenerative Medicine*. Walter de Gruyter GmbH; 2017:119-137.
85. Barstad RM, Ovrum E, Ringdal MA, et al. Induction of monocyte tissue factor procoagulant activity during coronary artery bypass surgery is reduced with heparin-coated extracorporeal circuit. *Br J Haematol*. 1996;94(3):517-525.
86. Ma YQ, Qin J, Plow EF. Platelet integrin alpha(IIb)beta(3): activation mechanisms. *J Thromb Haemost*. 2007;5(7):1345-1352.
87. Weerasinghe A, Taylor KM. The platelet in cardiopulmonary bypass. *Ann Thorac Surg*. 1998;66(6):2145-2152.
88. Cheung PY, Sawicki G, Salas E, Etches PC, Schulz R, Radomski MW. The mechanisms of platelet dysfunction during extracorporeal membrane oxygenation in critically ill neonates. *Crit Care Med*. 2000;28(7):2584-2590.
89. Gemmell CH, Ramirez SM, Yeo EL, Sefton MV. Platelet activation in whole blood by artificial surfaces: identification of platelet-derived microparticles and activated platelet binding to leukocytes as material-induced activation events. *J Lab Clin Med*. 1995;125(2):276-287.
90. Kalbhenn J, Schlagenhauf A, Rosenfelder S, Schmutz A, Zieger B. Acquired von Willebrand syndrome and impaired platelet function during venovenous extracorporeal membrane oxygenation: rapid onset and fast recovery. *J Heart Lung Transplant*. 2018;37(8):985-991.
91. Balle CM, Jeppesen AN, Christensen S, Hvas AM. Platelet function during extracorporeal membrane oxygenation in adult patients: a systematic review. *Front Cardiovasc Med*. 2018;5:157.
92. Chen Z, Zhang J, Kareem K, et al. Device-induced platelet dysfunction in mechanically assisted circulation increases the risks of thrombosis and bleeding. *Artif Organs*. 2019;43(8):745-755.
93. Klovaite J, Gustafsson F, Mortensen SA, Sander K, Nielsen LB. Severely impaired von Willebrand factor-dependent platelet aggregation in patients with a continuous-flow left ventricular assist device (HeartMate II). *J Am Coll Cardiol*. 2009;53(23):2162-2167.
94. Hudzik B, Kaczmarek J, Pacholewicz J, Zakliczynski M, Gasior M, Zembala M. Monitoring hemostasis parameters in left ventricular assist device recipients—a preliminary report. *Kardiochirurgia Torakochirurgia Pol*. 2016;13(3):224-228.
95. Mehta R, Athar M, Girgis S, Hassan A, Becker RC. Acquired Von Willebrand Syndrome (AVWS) in cardiovascular disease: a state of the art review for clinicians. *J Thromb Thrombolysis*. 2019;48(1):14-26.
96. Soares JS, Gao C, Alemu Y, Slepian M, Bluestein D. Simulation of platelets suspension flowing through a stenosis model using a dissipative particle dynamics approach. *Ann Biomed Eng*. 2013;41(11):2318-2333.
97. Zhang P, Gao C, Zhang N, Slepian MJ, Deng Y, Bluestein D. Multiscale particle-based modeling of flowing platelets in blood plasma using dissipative particle dynamics and coarse grained molecular dynamics. *Cell Mol Bioeng*. 2014;7:552-574.
98. Zhang P, Zhang L, Slepian MJ, Deng Y, Bluestein D. A multiscale biomechanical model of platelets: correlating with in-vitro results. *J Biomech*. 2017;50:26-33.
99. Marom G, Chiu WC, Crosby JR, et al. Numerical model of full-cardiac cycle hemodynamics in a total artificial heart and the effect of its size on platelet activation. *J Cardiovasc Transl Res*. 2014;7(9):788-796.
100. Girdhar G, Xenos M, Alemu Y, et al. Device thrombogenicity emulation: a novel method for optimizing mechanical circulatory support device thromboresistance. *PLoS One*. 2012;7(3):e32463.
101. Chiu WC, Tran PL, Khalpey Z, et al. Device thrombogenicity emulation: an in silico predictor of in vitro and in vivo ventricular assist device thrombogenicity. *Sci Rep*. 2019;9:2946.
102. Andrews RK, Karunakaran D, Gardiner EE, Berndt MC. Platelet receptor proteolysis: a mechanism for downregulating platelet reactivity. *Arterioscler Thromb Vasc Biol*. 2007;27(7):1511-1520.
103. Qiao JL, Shen Y, Gardiner EE, Andrews RK. Proteolysis of platelet receptors in humans and other species. *Biol Chem*. 2010;391(8):893-900.

104. Gardiner EE, Arthur JF, Kahn ML, Berndt MC, Andrews RK. Regulation of platelet membrane levels of glycoprotein VI by a platelet-derived metalloproteinase. *Blood*. 2004;104(12):3611-3617.
105. Bergmeier W, Piffath CL, Cheng G, et al. Tumor necrosis factor- α -converting enzyme (ADAM17) mediates GPIIb/IIIa shedding from platelets in vitro and in vivo. *Circ Res*. 2004;95(7):677-683.
106. Cheng H, Yan R, Li S, et al. Shear-induced interaction of platelets with von Willebrand factor results in glycoprotein Iba/IIb shedding. *Am J Physiol Heart Circ Physiol*. 2009;297(6):H2128-H2135.
107. Leytin V, Allen DJ, Mykhaylov S, et al. Pathologic high shear stress induces apoptosis events in human platelets. *Biochem Biophys Res Commun*. 2004;320(2):303-310.
108. Chen Z, Mondal NK, Ding J, Gao J, Griffith BP, Wu ZJ. Shear-induced platelet receptor shedding by non-physiological high shear stress with short exposure time: glycoprotein Iba/IIb and glycoprotein VI. *Thromb Res*. 2015;135(4):692-698.
109. Chen Z, Mondal NK, Ding J, et al. Activation and shedding of platelet glycoprotein IIb/IIIa under non-physiological shear stress. *Mol Cell Biochem*. 2015;409(1-2):93-101.
110. Chen Z, Koenig SC, Slaughter MS, Griffith BP, Wu ZJ. Quantitative characterization of shear-induced platelet receptor shedding: glycoprotein Iba/IIb, glycoprotein VI, and glycoprotein IIb/IIIa. *ASAIO J*. 2018;64(6):773-778.
111. Gardiner EE, Al-Tamimi M, Andrews RK, Berndt MC. Platelet receptor shedding. *Methods Mol Biol*. 2012;788:321-339.
112. Stephens G, Yan Y, Jandrot-Perrus M, Villeval JL, Clemetson KJ, Phillips DR. Platelet activation induces metalloproteinase-dependent GP VI cleavage to down-regulate platelet reactivity to collagen. *Blood*. 2005;105(1):186-191.
113. Lukito P, Wong A, Jing J, et al. Mechanical circulatory support is associated with loss of platelet receptors glycoprotein Iba/IIb and glycoprotein VI. *J Thromb Haemost*. 2016;14(11):2253-2260.
114. Sun W, Wang S, Chen Z, et al. Impact of high mechanical shear stress and oxygenator membrane surface on blood damage relevant to thrombosis and bleeding in a pediatric ECMO circuit. *Artif Organs*. 2020;44(7):717-726.
115. Gardiner EE, Karunakaran D, Shen Y, Arthur JF, Andrews RK, Berndt MC. Controlled shedding of platelet glycoprotein (GP)VI and GPIb-IX-V by ADAM family metalloproteinases. *J Thromb Haemost*. 2007;5(7):1530-1537.
116. Pasche B, Ouimet H, Francis S, Loscalzo J. Structural changes in platelet glycoprotein IIb/IIIa by plasmin: determinants and functional consequences. *Blood*. 1994;83(2):404-414.
117. Chen Z, Tran D, Li T, Arias K, Griffith BP, Wu ZJ. The role of a disintegrin and metalloproteinase proteolysis and mechanical damage in nonphysiological shear stress-induced platelet receptor shedding. *ASAIO J*. 2020;66(5):524-531.
118. Hu J, Mondal NK, Sorensen EN, et al. Platelet glycoprotein Iba/IIb ectodomain shedding and non-surgical bleeding in heart failure patients supported by continuous-flow left ventricular assist devices. *J Heart Lung Transplant*. 2014;33(1):71-79.
119. Desvages M, Rauch A, Jeanpierre E, et al. Continuous-flow mechanical circulatory support induces shedding of platelet adhesion receptors GPIIb and GPIb. *Arch Cardiovasc Dis Suppl*. 2019;11(2):193-194.
120. Kondo C, Tanaka K, Takagi K, et al. Platelet dysfunction during cardiopulmonary bypass surgery. With special reference to platelet membrane glycoproteins. *ASAIO J*. 1993;39(3):M550-M553.
121. Holada K, Simak J, Kucera V, Roznova L, Eckschlagner T. Platelet membrane receptors during short cardiopulmonary bypass—a flow cytometric study. *Perfusion*. 1996;11(5):401-406.
122. Murase M, Nakayama Y, Sessler DI, Mukai N, Ogawa S, Nakajima Y. Changes in platelet Bax levels contribute to impaired platelet response to thrombin after cardiopulmonary bypass: prospective observational clinical and laboratory investigations. *Br J Anaesth*. 2017;119(6):1118-1126.
123. Mondal NK, Pantalos GM, Chen Z, et al. Platelet activation, receptor shedding and aggregation in pediatric patients with congenital heart disease undergoing cardiopulmonary bypass. *J Heart Lung Transplant*. 2016;35(4):S399.
124. Li S, Wang Z, Liao Y, et al. The glycoprotein Iba/IIb-von Willebrand factor interaction induces platelet apoptosis. *J Thromb Haemost*. 2010;8(2):341-350.
125. Mondal NK, Li T, Chen Z, et al. Mechanistic insight of platelet apoptosis leading to non-surgical bleeding among heart failure patients supported by continuous-flow left ventricular assist devices. *Mol Cell Biochem*. 2017;433(1-2):125-137.
126. Sadler JE. Biochemistry and genetics of von Willebrand factor. *Annu Rev Biochem*. 1998;67:395-424.
127. Rauch A, Susen S, Zieger B. Acquired von Willebrand syndrome in patients with ventricular assist device. *Front Med (Lausanne)*. 2019;6:7.
128. Sadler JE. Biomedicine. Contact—how platelets touch von Willebrand factor. *Science*. 2002;297(5584):1128-1129.
129. Brinkhous KM, Sandberg H, Garris JB, et al. Purified human factor VIII procoagulant protein: comparative hemostatic response after infusions into hemophilic and von Willebrand disease dogs. *Proc Natl Acad Sci USA*. 1985;82(24):8752-8756.
130. van Schooten CJ, Shahbazi S, Groot E, et al. Macrophages contribute to the cellular uptake of von Willebrand factor and factor VIII in vivo. *Blood*. 2008;112(5):1704-1712.
131. Stockschlaeder M, Schneppenheim R, Budde U. Update on von Willebrand factor multimers: focus on high-molecular-weight multimers and their role in hemostasis. *Blood Coagul Fibrinolysis*. 2014;25(3):206-216.
132. Hassan MI, Saxena A, Ahmad F. Structure and function of von Willebrand factor. *Blood Coagul Fibrinolysis*. 2012;23(1):11-22.
133. Choi H, Aboufatova K, Pownall HJ, Cook R, Dong JF. Shear-induced disulfide bond formation regulates adhesion activity of von Willebrand factor. *J Biol Chem*. 2007;282(49):35604-35611.
134. Muller JP, Mielke S, Lof A, et al. Force sensing by the vascular protein von Willebrand factor is tuned by a strong intermonomer interaction. *Proc Natl Acad Sci U S A*. 2016;113(5):1208-1213.
135. Wang Y, Morabito M, Zhang XF, Webb E III, Oztekin A, Cheng X. Shear-induced extensional response behaviors of tethered von Willebrand factor. *Biophys J*. 2019;116(11):2092-2102.

136. Tsai HM, Sussman II, Nagel RL. Shear stress enhances the proteolysis of von Willebrand factor in normal plasma. *Blood*. 1994; 83(8):2171-2179.
137. Meyer AL, Malehsa D, Bara C, et al. Acquired von Willebrand syndrome in patients with an axial flow left ventricular assist device. *Circ Heart Fail*. 2010;3(6):675-681.
138. Wu T, Lin J, Cruz MA, Dong JF, Zhu C. Force-induced cleavage of single VWFA1A2A3 tridomains by ADAMTS-13. *Blood*. 2010;115(2):370-378.
139. Shim K, Anderson PJ, Tuley EA, Wiswall E, Sadler JE. Platelet-VWF complexes are preferred substrates of ADAMTS13 under fluid shear stress. *Blood*. 2008;111(2):651-657.
140. Warkentin T. Aortic stenosis and bleeding gastrointestinal angiodysplasia: is acquired von Willebrand's disease the link? *Lancet*. 1992;340(8810):35-37.
141. Vincentelli A, Susen S, Le Tourneau T, et al. Acquired von Willebrand syndrome in aortic stenosis. *N Engl J Med*. 2003; 349(4):343-349.
142. Hasan F, O'Brien CS, Sanyal A, Dalton HR. Aortic stenosis and gastrointestinal bleeding. *J R Soc Med*. 2004;97(2):81-82.
143. Netuka I, Kvasnicka T, Kvasnicka J, et al. Evaluation of von Willebrand factor with a fully magnetically levitated centrifugal continuous-flow left ventricular assist device in advanced heart failure. *J Heart Lung Transplant*. 2016;35(7):860-867.
144. Heilmann C, Geisen U, Beyersdorf F, et al. Acquired von Willebrand syndrome is an early-onset problem in ventricular assist device patients. *Eur J Cardiothorac Surg*. 2011;40(6): 1328-1333; discussion 1233.
145. Meyer AL, Malehsa D, Budde U, Bara C, Haverich A, Strueber M. Acquired von Willebrand syndrome in patients with a centrifugal or axial continuous flow left ventricular assist device. *JACC Heart Fail*. 2014;2(2):141-145.
146. Uriel N, Pak SW, Jorde UP, et al. Acquired von Willebrand syndrome after continuous-flow mechanical device support contributes to a high prevalence of bleeding during long-term support and at the time of transplantation. *J Am Coll Cardiol*. 2010; 56(15):1207-1213.
147. Geisen U, Heilmann C, Beyersdorf F, et al. Non-surgical bleeding in patients with ventricular assist devices could be explained by acquired von Willebrand disease. *Eur J Cardiothorac Surg*. 2008;33(4):679-684.
148. Heilmann C, Trummer G, Beyersdorf F, et al. Acquired von Willebrand syndrome in patients on long-term support with HeartMate II. *Eur J Cardiothorac Surg*. 2017;51(3):587-590.
149. Letsou GV, Shah N, Gregoric ID, Myers TJ, Delgado R, Frazier OH. Gastrointestinal bleeding from arteriovenous malformations in patients supported by the Jarvik 2000 axial-flow left ventricular assist device. *J Heart Lung Transplant*. 2005;24(1): 105-109.
150. Kalbhenn J, Schmidt R, Nakamura L, Schelling J, Rosenfelder S, Zieger B. Early diagnosis of acquired von Willebrand Syndrome (AVWS) is elementary for clinical practice in patients treated with ECMO therapy. *J Atheroscler Thromb*. 2015;22(3):265-271.
151. Heilmann C, Geisen U, Beyersdorf F, et al. Acquired von Willebrand syndrome in patients with extracorporeal life support (ECLS). *Intensive Care Med*. 2012;38(1):62-68.
152. Linneweber J, Dohmen PM, Kertzsch U, Affeld K, Nose Y, Konertz W. The effect of surface roughness on activation of the coagulation system and platelet adhesion in rotary blood pumps. *Artif Organs*. 2007;31(5):345-351.
153. Kang J, Zhang DM, Restle DJ, et al. Reduced continuous-flow left ventricular assist device speed does not decrease von Willebrand factor degradation. *J Thorac Cardiovasc Surg*. 2016; 151(6):1747-1754 e1.
154. Michiels JJ, van Vliet HH, Berneman Z, et al. Intravenous DDAVP and factor VIII-von Willebrand factor concentrate for the treatment and prophylaxis of bleedings in patients With von Willebrand disease type 1, 2 and 3. *Clin Appl Thromb Hemost*. 2007;13(1):14-34.
155. Borasino S, Kalra Y, Elam AR, et al. Impact of hemolysis on acute kidney injury and mortality in children supported with cardiac extracorporeal membrane oxygenation. *J Extra Corpor Technol*. 2018;50(4):217-224.
156. Tchanchaleishvili V, Sagebin F, Ross RE, Hallinan W, Schwarz KQ, Massey HT. Evaluation and treatment of pump thrombosis and hemolysis. *Ann Cardiothorac Surg*. 2014;3(5):490-495.
157. Ye T, Phan-Thien N, Lim CT, Li Y. Red blood cell motion and deformation in a curved microvessel. *J Biomech*. 2017;65:12-22.
158. Nakamura M, Bessho S, Wada S. Analysis of red blood cell deformation under fast shear flow for better estimation of hemolysis. *Int J Numer Method Biomed Eng*. 2014;30(1):42-54.
159. Da Q, Teruya M, Guchhait P, Teruya J, Olson JS, Cruz MA. Free hemoglobin increases von Willebrand factor-mediated platelet adhesion in vitro: implications for circulatory devices. *Blood*. 2015;126(20):2338-2341.
160. Zhou Z, Han H, Cruz MA, Lopez JA, Dong JF, Guchhait P. Haemoglobin blocks von Willebrand factor proteolysis by ADAMTS-13: a mechanism associated with sickle cell disease. *Thromb Haemost*. 2009;101(6):1070-1077.
161. Zhou Y, Qin S, Hilton T, et al. Quantification of Von Willebrand factor cleavage by adamts-13 in patients supported by left ventricular assist devices. *ASAIO J*. 2017;63(6):849-853.
162. Helms CC, Marvel M, Zhao W, et al. Mechanisms of hemolysis-associated platelet activation. *J Thromb Haemost*. 2013;11(12): 2148-2154.
163. Iuliano L, Violi F, Pedersen JZ, Pratico D, Rotilio G, Balsano F. Free radical-mediated platelet activation by hemoglobin released from red blood cells. *Arch Biochem Biophys*. 1992; 299(2):220-224.
164. Rother RP, Bell L, Hillmen P, Gladwin MT. The clinical sequelae of intravascular hemolysis and extracellular plasma hemoglobin: a novel mechanism of human disease. *JAMA*. 2005; 293(13):1653-1662.
165. Kato GJ, Taylor JG. Pleiotropic effects of intravascular haemolysis on vascular homeostasis. *Br J Haematol*. 2010;148(5):690-701.
166. Schafer A, Wiesmann F, Neubauer S, Eigenthaler M, Bauersachs J, Channon KM. Rapid regulation of platelet activation in vivo by nitric oxide. *Circulation*. 2004;109(15):1819-1822.
167. Nieuwland R, Berckmans RJ, Rotteveel-Eijkman RC, et al. Cell-derived microparticles generated in patients during cardiopulmonary bypass are highly procoagulant. *Circulation*. 1997; 96(10):3534-3541.

168. Meyer AD, Gelfond JA, Wiles AA, Freishtat RJ, Rais-Bahrami K. Platelet-derived microparticles generated by neonatal extracorporeal membrane oxygenation systems. *ASAIO J.* 2015; 61(1):37-42.
169. Diehl P, Aleker M, Helbing T, et al. Enhanced microparticles in ventricular assist device patients predict platelet, leukocyte and endothelial cell activation. *Interact Cardiovasc Thorac Surg.* 2010;11(2):133-137.
170. Nascimbene A, Hernandez R, George JK, et al. Association between cell-derived microparticles and adverse events in patients with nonpulsatile left ventricular assist devices. *J Heart Lung Transplant.* 2014;33(5):470-477.