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Blood perfusion through ventricular assist devices induces erythrocytes to interact with leukocytes

Kylie M. Foster [a], Ahmed M. El Banayosy [b], Zheila Azartash-Namin [c,1], Phillip Coghill [c,1], James W. Long [b], Edgar O'Rear [a], Hendra Setiadi [b,*]

[a] School of Sustainable Chemical, Biological and Materials Engineering, Institute for Biomedical Engineering, Science and Technology, University of Oklahoma, 100 East Boyd, Sarkeys Energy Center, Norman, OK 73019, USA
[b] INTEGRIS Advanced Cardiopulmonary Care, INTEGRIS Baptist Medical Center, 3400 NW Expressway, Ste 200, Oklahoma City, OK 73112, USA
[c] VADovations Inc., 1333 Cornell Pkwy, Oklahoma City, OK 73108, USA

A B S T R A C T

Implantations of Ventricular Assist Devices (VADs) have significantly improved quality of life and life expectancy of end-stage heart failure patients. However, despite the advancements in the VAD designs and patient management protocols, the VAD recipients remain at risk of attaining bleeding, infection, pump thrombosis, and stroke. Although blood trauma has been suggested as a critical factor in development of these adverse events, its consequences in inducing interactions between different types of blood cells are largely unknown.

Following our recent findings on erythrocyte and leukocyte trauma in VAD recipients, we decided to explore interactions between erythrocytes and leukocytes by perfusing human whole blood through two different types of VADs, HeartMate II (HMII) and HeartMate 3 (HM3), concurrently in their respective Blood Circulatory Loop (BCL). By using a flow cytometry assay, we found increasing association between erythrocytes and leukocytes as VADs propelled blood through their BCLs. This time-dependent intercellular association was shown by increasing concomitant events of stained CD235a (specifically expressed on erythrocytes) and stained CD45 (specifically expressed on leukocytes) in the $CD235a^{+}$ population. Compared to CentriMag (CM), which served as a control, VADs produced significantly higher concomitant signals. The findings described in this study have opened the need for further studies on a novel path for generation of adverse events that are commonly observed in VAD recipients, notably infection, pump thrombosis, and ischemic stroke.

1. Introduction

For end-stage heart failure patients that are refractory to medical therapy, implantation of a ventricular assist device (VAD) has now emerged as a life-defining option for them. Recent progress in VAD designs and their implantation procedures have enhanced the outcome of this therapy resulting in improved quality of life and life expectancy of VAD recipients. However, they are at risk of acquiring bleeding, infection, and stroke [1–3]. Development of thrombosis inside the device is yet another major limiting factor inhibiting this treatment from achieving its full potential [4,5]. Current literature is awash with studies attempting to delineate the underlying mechanisms of these adverse events [6–8]. As a result, several pathogenesis models have been proposed. However, most of them recognize the critical roles of blood-cell trauma following VAD implantation [9–13]. Of all potential consequences deriving from blood-cell trauma, undue interactions among different types of blood cells in circulation have not been examined. This possibility would be potentially relevant for understanding the development of the above-mentioned adverse events, particularly infection and thrombi, in VAD recipients.

Much has been reported on mechanisms regulating interactions between platelets and leukocytes [14-16] but little is known between erythrocytes and other types of blood cells. Although adhesion molecules on the erythrocyte cell surface have recently been proposed for this role [17,18], their pathophysiological significance has not been well characterized. Following our recent findings on erythrocyte [19] and leukocyte [13] trauma, we hypothesize that these two types of blood cells could indeed interact and have relevance in the development of adverse events from VAD implantation. To this end, we decided to take an initial step to address this hypothesis by performing in-vitro Blood Circulatory Loop (BCL) experimentation and examined the interactions between the two types of blood cells by flow cytometry. The initial results outlined in this study suggest erythrocytes interact with leukocytes following the perfusion of human whole blood through VADs.

* Corresponding author.
E-mail address: Hendra.Setiadi@integrishealth.org (H. Setiadi).
[1] Current addresses: Z.A.N.: Oklahoma Medical Research Foundation, 825 NE 13th St., Oklahoma City, OK 73104; P.C.: University of Central Oklahoma, 100 N. University Drive, Edmond, OK 73034.

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2. Materials and methods

2.1. Ethical statement and blood procurement

The work described in this manuscript was conducted in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki). For each experiment, de-identified human whole blood was *procured* from Our Blood Institute (OBI), a U.S. Food and Drug Administration (FDA)-licensed blood center (FEI: 1626009) in Oklahoma City, Oklahoma, USA. The whole blood samples were from random healthy volunteer donors who met FDA requirements for blood donations and had consented to whole blood donation. The blood samples were used for experiments at VADovations Inc. laboratory, which was certified by its regulatory committee to conduct hemocompatibility studies on different blood circulatory devices. All experiments were conducted within 2 h of collection and completed on the same day of blood collection.

2.2. In-vitro blood circulatory loop (BCL) experiment

The HeartMate II (HMII), HeartMate 3 (HM3), or CentriMag (CM) was each connected to a BCL consisting of 3/8"x 9/16"x 35.5″ Tygon ND-100-65 hemocompatible tubing and a Medtronic R-38 Extracorporeal Membrane Oxygenation (ECMO) bladder serving as a blood reservoir. The circulatory loop (Fig. 1) was constructed based on the design originally proposed by the American Society for Testing and Materials (ASTM) for in-vitro continuous flow blood pump evaluation (ASTM Standard F1841-19) at room temperature [20]. Surface temperature of the BCL reservoir was monitored via an infrared thermometer (Fisherbrand) at the start of perfusion (time 0), and every hour thereafter to ensure temperature did not fluctuate out of range. Pumps used throughout this study were recovered post-implant from patients without history of thromboembolic complications at the time of explant and cleaned according to our established protocol [21].

The CM, a mechanical circulatory support (MCS) device commonly used in ECMO, functioned as a control for this experiment. It is widely regarded as the benchmark for hemocompatibility testing of VADs, following a report suggesting it causes low levels of damage to blood cells [22]. A total of 4 experiments were performed and, in each experiment, all three devices were examined simultaneously in individual circulatory loops each containing 145 mL human whole blood. For each experiment, one unit (~500 mL) of acid citrate dextrose-anticoagulated human whole blood was used within 2 h of collection.

Blood was perfused at 4 L/min for 6 h under constant hemodynamic conditions as recommended by ASTM Standard F1841-19 protocol [20]. Differential pressure (ΔP) across the circulatory device was set at 80 mmHg using a Hoffman clamp to apply afterload to the devices. The BCL was dismantled after each experiment and blood contacting components, including the pumps, were soaked in Tergazyme (Alconox Inc.), an anionic detergent containing a protease enzyme, enabling it to remove any protein deposits after whole-blood contact, then rinsed. They were subsequently immersed in diluted Simple Green solution (Sunshine Makers Inc. Huntington Beach, CA), a broad-spectrum disinfectant and nonabrasive surfactant, to ensure complete removal of whole blood debris. Finally, they were thoroughly rinsed with water and allowed to dry completely before reuse in subsequent experiments. Before filling with human whole blood, all blood contacting surfaces of each fully assembled BCL were rinsed extensively with phosphate buffered saline (PBS).

2.3. Flow cytometry analysis

One mL blood samples were collected into low protein retention

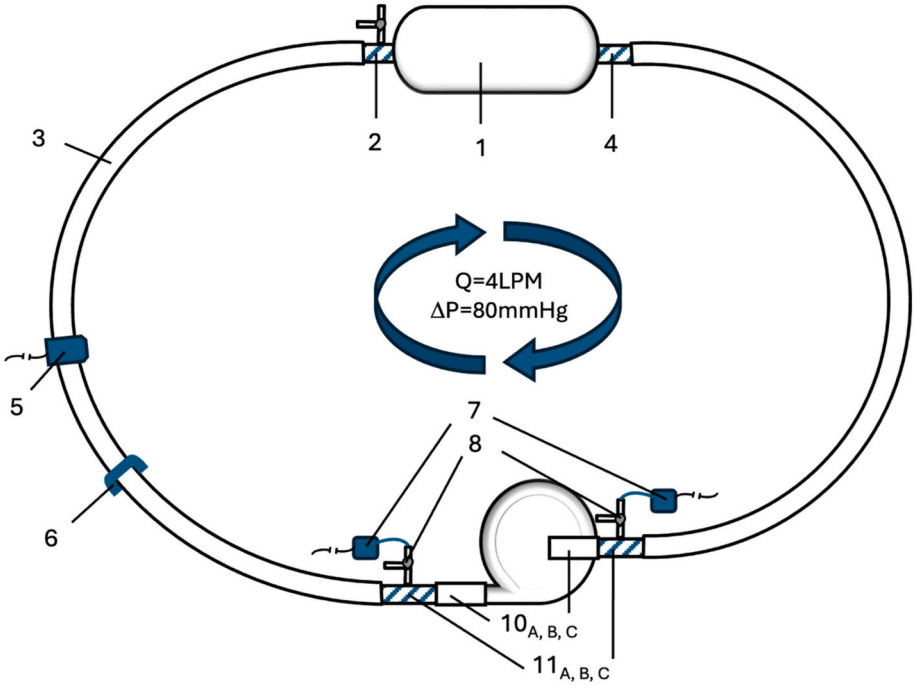

Fig. 1. Schematic diagram of In-vitro Blood Circulatory Loop (BCL). 1. R-38 ECMO Reservoir, Medtronic; 2. Sample port, 3/8″ outer diameter (OD) Luer-lock fitting with 3-way-stop-cock; 3. 3/8″ inner diameter (ID) hemocompatible Tygon tubing; 4. 3/8″ OD straight fitting; 5. 9PXL Flow Probe connected to TS410 Flow Meter, Transonic; 6. Load clamp; 7. Fluid filled (PBS) Outlet/Inlet Pressure Transducers, Medex/Smiths Medical connected to Hewlett Packard Patient monitor; 8. Pressure tap, 3-way-stop-cock connected to fluid filled (PBS) pressure transducers; 9. MCS device (CentriMag, HeartMate II, or HeartMate 3); 10A. CentriMag Inlet/Outlet: 3/8″ ID hemocompatible Tygon tubing; 10B. HeartMate II Inlet/Outlet: 1/2″ ID hemocompatible Tygon tubing; 10C. HeartMate 3 Inlet: 1/2″ ID hemocompatible Tygon tubing flared to fit pump inlet, Outlet: 3/8″ ID hemocompatible Tygon tubing; 11A. 3/8″ OD straight pressure-tap fitting; 11B. 1/2″ to 3/8″ OD pressure-tap fitting; 11C. 3/8″ OD straight pressure-tap fitting. Inlet/outlet diameters varied between MCS devices and was necessary to swap out tubing and fittings with matching diameters.

microcentrifuge tubes (Fisher Scientific, Pittsburgh, PA) from the bulk blood control (baseline), as well as at time 0, and every hour thereafter through the sample port. Prior to sample collection from the loop, we first withdrew and discarded 1 mL blood that mostly constituted blood in the stagnant portion of the sample port. We then collected a 1 mL blood sample for the flow cytometry assay. Through the same sample port, we subsequently infused 2 mL of blood that we set aside from the experiment into the loop to keep its overall blood volume and pressure constant.

Erythrocytes in these samples were stained with mouse monoclonal antibody anti-human CD235a conjugated with phycoerythrin (PE) (ThermoFisher, MA) and leukocytes with mouse monoclonal antibody anti-human CD45 conjugated with allophycocyanin (APC) (ThermoFisher, MA). As controls, these cells were stained with appropriate isotype antibodies conjugated with respective fluorophores. The fluorescent signals of the stained cells were subsequently analyzed by flow cytometry (Accuri C6, Becton Dickenson Co, NJ). To this end, we first gated cell populations of interest based on size (forward scatter vs side scatter density plot) then quantified the fluorescent events within this gated cell population. This gating scheme is illustrated in Fig. 4. The folds increase in the fluorescent CD235a$^+$ and CD45$^+$ events were plotted at different time points. In addition to quantifying fluorescent events of each individual fluorophore, we also examined those emitted concomitantly. The percentage of the concomitant fluorescence events relative to the number of CD235a$^+$ events for each type of VAD were plotted at different time points over their respective baseline value.

2.4. Statistical analysis

Differences between data sets were assessed by Student's *t*-test, with p values ≤ 0.05 being considered significant.

3. Results

We found no change in the extent of CD235a$^+$ events at different time points during the 6-h perfusion of human whole blood through either HMII, HM3, or CM (Fig. 2A). In contrast, CD45$^+$ events gradually increased from their respective baseline values (Fig. 2B). Compared to CM, HMII and HM3 induced significant elevation in the extent of CD45$^+$ events after 2 h of perfusion and persisted largely as the perfusion continued for another 4 h.

Interestingly, we found that the percentage of concomitant CD235a$^+$ and CD45$^+$ events in the CD235a$^+$ population gradually increased as well from their respective baseline values following the perfusion of human whole blood through the three MCS devices in BCL. As shown in Fig. 3, perfusion through HMII and HM3 resulted in significantly higher concomitant events than that observed for CM after 2 h of perfusion and persisted when blood perfusion continued to 6 h.

The longitudinal profile of the concomitant CD235a$^+$ and CD45$^+$ events (Fig. 3) mimicked closely to that of CD45$^+$ events (Fig. 2B), but not CD235a$^+$ (Fig. 2A). The observed trend for concomitant events suggested increasing formation of leukocyte-erythrocyte interactions when human whole blood was perfused through HMII, HM3 and CM. This suggestion was indicated by elevated fluorescence intensity of cell-bound anti-CD45 as well as concomitant anti-CD235a and CD45 after 6-h perfusion, but not anti-CD235a (Fig. 4). Overall, these data suggest significantly higher level of leukocytes and/or potentially leukocyte fragments/microvesicles (MVs) interacted with erythrocytes in human whole blood samples upon perfusion through HMII and HM3 than those through CM.

4. Discussion

Our study showed that perfusion of human whole blood through MCS devices led erythrocytes to form association with leukocytes in a *time-dependent* manner as concomitant CD235a$^+$ and CD45$^+$ events in the CD235a$^+$ population were increasing over 6-h of perfusion. Interestingly, this association was also *device dependent* as the concomitant events increased significantly following perfusion through the two types of VADs (HMII and HM3) rather than CM.

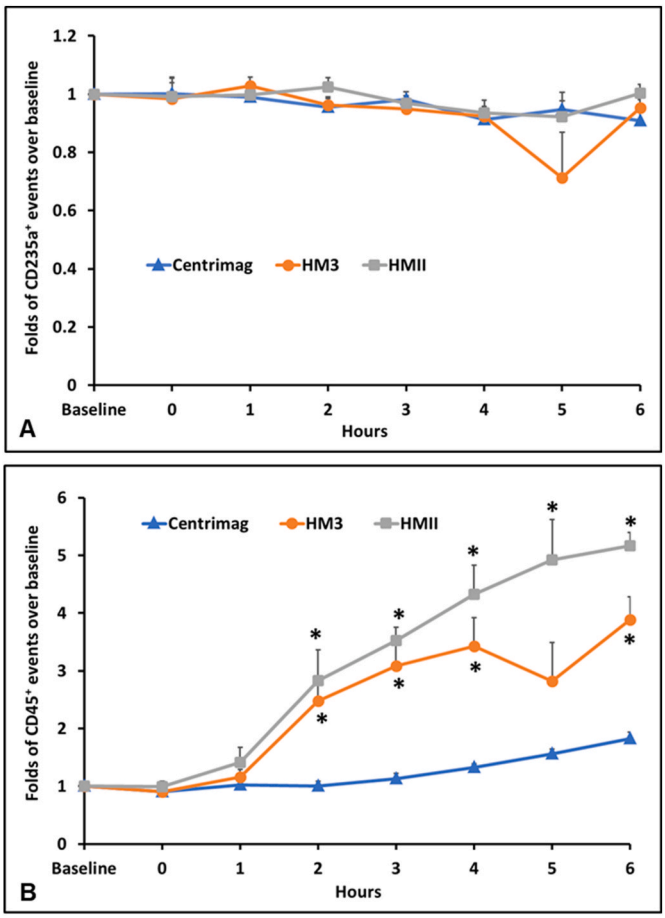

Fig. 2. Longitudinal profile of folds increase of CD235a$^+$ (A) and CD45$^+$ (B) events in human whole blood perfused in BCL through different MCS devices. Following blood sample collection from the flow loop as described in the *Materials and methods* section, CD235a on erythrocytes was stained with mouse monoclonal antibody anti-human CD235a conjugated with phycoerythrin (PE). CD45 on leukocytes was stained with mouse monoclonal antibody anti-human CD45 conjugated with allophycocyanin (APC). After defining a gate in the forward-vs side-scatter density plot that included both CD235a$^+$ and CD45$^+$ events, folds increase with perfusion time of the individual CD235a$^+$ or CD45$^+$ events in this gate were quantified. The data at each hour of perfusion were plotted as mean ± SEM. The statistical difference of the HMII or HM3 data to those of CM was analyzed with Student *t*-test. *$p \leq 0.05$.

Although HMII seemingly resulted in higher concomitant events than HM3 at multiple time points, the difference between the two was found insignificant. This was despite the difference in their pump design as HMII functions as a continuous axial-flow pump, whereas HM3 as a magnetically levitated continuous and pulsatile centrifugal-flow pump [4,6]. In contrast, the concomitant events were largely unchanged in CM samples over the 6-h perfusion, confirming its suitability as a credible benchmark for in-vitro testing of hemocompatibility of VADs [22].

Examining the longitudinal pattern of the concomitant CD235a$^+$ and CD45$^+$ events in the CD235a$^+$ population (Fig. 3) we found it closely mimicked to that of CD45$^+$ (Fig. 2B) while CD235a$^+$ events remained the same during the 6-h perfusion through all MCS devices (Fig. 2A). Together with the data presented in Fig. 4, we hypothesized that the dominant factor of increasing concomitant CD235a$^+$ and CD45$^+$ events was due to increasing leukocyte association with erythrocytes, in form of MVs and/or whole cells. Formation of leukocyte MVs has indeed been

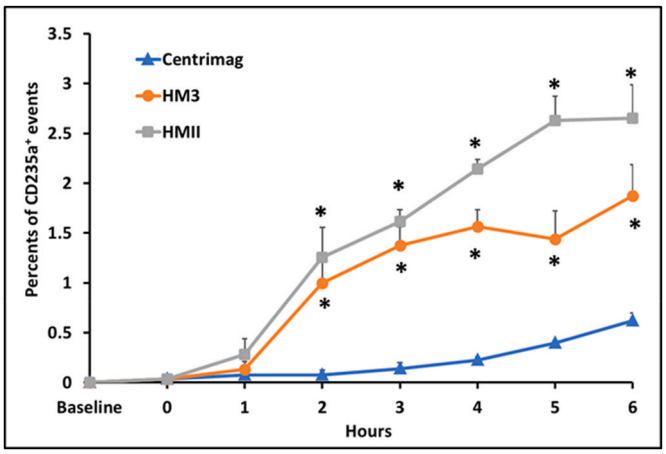

Fig. 3. Longitudinal profile of the percent increase of concomitant CD235a$^+$ and CD45$^+$ events in human whole blood perfused in BCL through different MCS devices. A gate in forward-vs side-scatter density plot that included both CD235a$^+$ and CD45$^+$ events was first defined. Concomitant CD235a$^+$ and CD45$^+$ events in this were then quantified. As outlined in the *Materials and Methods* section, the percentage of the concomitant fluorescence events in the CD235a$^+$ population at different time points for each type of VAD were plotted after being normalized with its respective baseline value. These data at each hour of perfusion were plotted as mean ± SEM. The statistical difference of the HMII or HM3 data to those of CM was analyzed with Student *t*-test. $^*p \leq 0.05$.

reported in VAD recipients and in-vitro experimentations [23,24], although their roles in the erythrocyte-leukocyte interactions reported here require further studies. Nevertheless, this hypothesis of erythrocyte-leukocyte interaction is in agreement with a recently reported association between elevated activation status of neutrophils in VAD patients and their increased risk of infection [27].

Current literature offers limited information on molecular and cellular mechanisms regulating erythrocyte-leukocyte interactions, although phagocytosis of senescent erythrocytes by leukocyte-derived macrophages has been extensively examined [17,25,26]. Interactions between the two cell types have also been reported in pathological conditions, such as in thrombus formation [15,27] and in sickle cell anemia [28]. In these processes, platelets could associate with erythrocyte-leukocyte aggregates when adhesion molecule, P-selectin, on activated platelets binds to its ligand, PSGL-1, on leukocytes [15,27]. Concurrent binding of adhesion molecules, GP1α on platelets to αMβ2 on leukocytes, could lend further support to leukocyte-platelet interactions [29]. Eichhorn et al. reported 16.5 % of platelet extracellular vesicles were CD45$^+$ in COVID-19 patients [30]. The possibility of platelet association to erythrocyte-leukocyte aggregates would undoubtfully accelerate thrombus formation in VAD recipients.

Despite their pathological relevance, molecular mechanisms regulating direct interactions between erythrocytes and leukocytes, remain largely unknown. However, recent studies have reported that subjecting erythrocytes to supraphysiological flow conditions in VADs would result in trauma as evidenced by their enhanced ability to release MVs [19,23,24]. Furthermore, these erythrocytes exhibited characteristics like those observed in senescent erythrocytes which include conformational change of Band 3 and subsequent binding of plasmatic IgG on the erythrocyte surface [31]. These observations offer a possible path for opsonized erythrocytes to interact with leukocytes when surface-bound IgGs bind to Fc receptors on leukocytes [17,18,25,26].

The clinical relevance of our findings would become apparent when erythrocyte-leukocyte interactions lead to the formation of blood cell

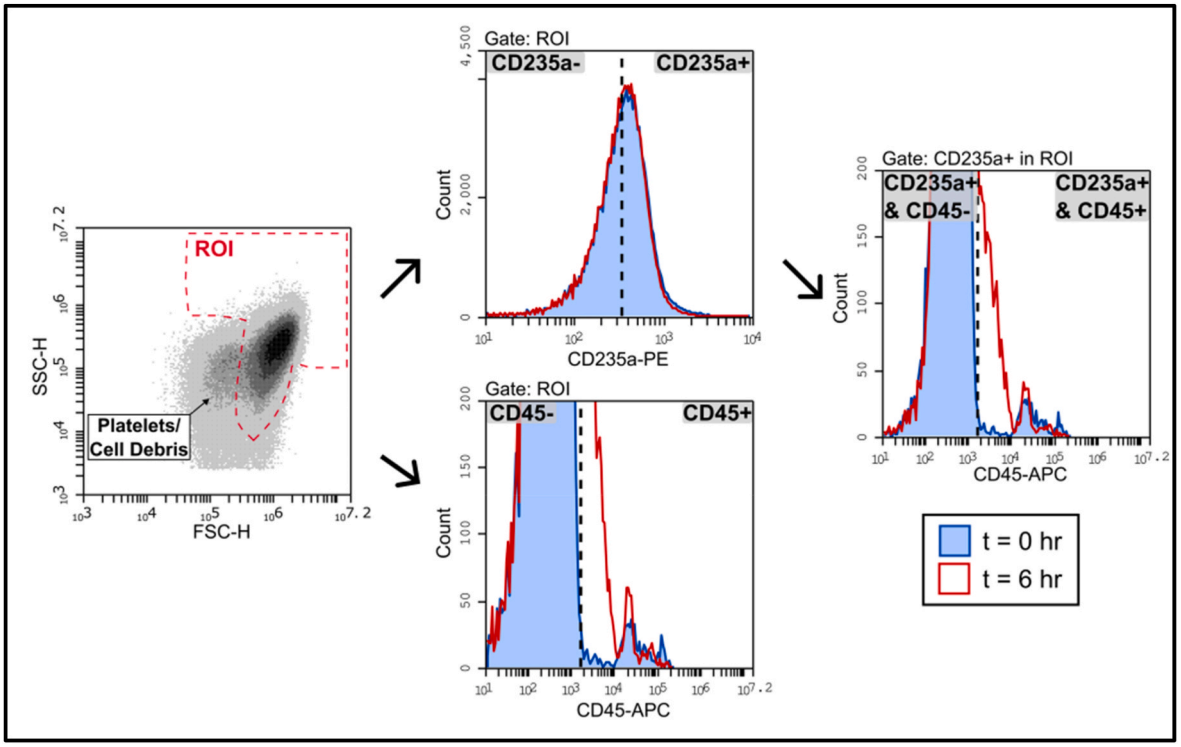

Fig. 4. Representative flow cytometric data of CD235a$^+$, CD45$^+$, and concomitant CD235a$^+$ and CD45$^+$ expression in human whole blood samples at start of perfusion (t=0 h) and after 6-h perfusion (t=6 h) through HMII. Collected events were first gated based on size (ROI, region of interest) in a forward-vs side-scatter density plot, after which they were gated on positive CD235a, CD45, and concomitant signals, indicated by the arrows. The number of events positive for each fluorescent signal (to the right of the black dashed line in each fluorescence plot) was examined for the ROI population. As seen for both the CD45 and concomitant signal, there was an increase in the number of positive events after 6 h of perfusion with a shift in the fluorescent intensity of the main peak to the right of the fluorescent gate. This indicates an increase in leukocyte-erythrocyte association.

aggregates in blood circulation. This event might be associated with heightened incidence of thrombosis and ischemic stroke, which are commonly observed adverse events of post-VAD implantations [1–9]. Although we did not observe a significant difference between HMII and HM3 for concomitant $CD235a^+$ and $CD45^+$ events over the 6-h perfusion, the tendency of higher events in HMII samples was in line with reported observations on higher incidence of pump thrombosis development in HMII than in HM3 [4]. Nevertheless, our finding on 1–2 % of the concomitant $CD235a^+$ and $CD45^+$ events among the $CD235a^+$ cells (Fig. 3) mirrors the reported levels of MVs previously in VAD recipients [23]. In addition, it also supports our earlier report on elevated activation status of leukocytes and its association with heightened risk of infection in VAD recipients [27]. Moreover, our findings could potentially address a longstanding question on the relationship between the development of infection and thrombosis in these patients. This relationship has been proposed in many clinical studies, including our own [31,32], although its underlying causes remain unclear. Future studies should not only validate this interesting initial observation, but also delineate the basic molecular and cellular mechanisms regulating erythrocyte-leukocyte interactions in VAD recipients. These studies should include possibilities for other blood cell types and MVs of different blood cell origins in these interactions.

4.1. Study limitations

The time lapse of erythrocyte-leukocyte interactions described in this report was limited to in-vitro conditions, whereas its interpolation to VAD recipients awaits further studies. Using residence time calculations, we estimated that blood cells recirculate approximately 34 times more frequently in the BCL circuit, making the 6-h experimental period equivalent to approximately 8 days in VAD recipients. However, this estimate may vary depending on individual patient-specific pathophysiological factors, which may lead to the wide variability in the onset of adverse events such as thrombosis and/or infection in clinical practice.

5. Conclusion

This initial study suggested that perfusion of human whole blood through ventricular assist devices (VADs) in a blood circulatory loop (BCL) would lead to the formation of erythrocyte-leukocyte association in a time-dependent manner. This observation potentially opens a new path for future research to examine the development of adverse events in VAD recipients. Moreover, it proposed an additional measure for testing hemocompatibility of VADs.

CRediT authorship contribution statement

Kylie M. Foster: Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Investigation, Formal analysis, Data curation. **Ahmed M. El Banayosy:** Writing – review & editing, Writing – original draft, Visualization, Validation, Project administration, Methodology, Data curation. **Zheila Azartash-Namin:** Writing – review & editing, Visualization, Validation, Formal analysis, Data curation. **Phillip Coghill:** Validation, Supervision, Methodology, Formal analysis, Data curation. **James W. Long:** Writing – review & editing, Resources. **Edgar O'Rear:** Writing – review & editing, Visualization, Validation, Supervision, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation. **Hendra Setiadi:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: James W. Long reports a relationship with BrioHealth Solutions that includes: consulting or advisory. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

[1] Y. Sanaiha, P. Downey, R. Lyons, A. Nsair, R.J. Shemin, P. Benharash, Trends in utilization, mortality, and resource use after implantation of left ventricular assist devices in the United States, J. Thorac. Cardiovasc. Surg. 161 (2021) 2083–2091, https://doi.org/10.1016/j.jtcvs.2019.12.121.

[2] C. Lindvall, B. Udelsman, D. Malhotra, E.Y. Brovman, R.D. Urman, D. A. D'Alessandro, J.A. Tulsky, In-hospital mortality in older patients after ventricular assist device implantation: a national cohort study, J. Thorac. Cardiovasc. Surg. 157 (2019) 1168–1177, https://doi.org/10.1016/j.jtcvs.2018.10.142.

[3] A. Iyengar, J. Feinman, J. Jiang, C. Song, S. Kim, A. Mathew, S. Golec, A. Rao, A. Radakrishnan, M. Asher, D. Rekhtman, J. DePaolo, N. Moss, S. Itagaki, A. Anyanwu, J. Wald, M. Cevasco, A. Parikh, Epidemiology and impact of deice-specific infections on patients receiving left ventricular assist devices, JHLT Open 8 (2025) 100208, https://doi.org/10.1016/j.jhlto.2025.100208.

[4] M.R. Mehra, D.J. Goldstein, J.C. Cleveland, J.A. Cowger, S. Hall, C.T. Salerno, Y. Naka, D. Horstmanshof, J. Chuang, A. Wang, N. Uriel, Five-Year outcomes in patients with fully magnetically levitated vs axial-flow left ventricular assist devices in the MOMENTUM 3 Randomized Trial, JAMA 12 (2022) 1233–1242, https://doi.org/10.1001/jama.2022.16197.

[5] I.B. Hollis, D.L. Jennings, S. Krim, V.K. Ton, A. Ducharme, J. Cowger, M. Looby, J. J. Eulert-Green, N. Bansal, E. Horn, M. Byku, J. Katz, C.J. Michaud, I. Rajapreyar, P. Campbell, C. Vale, R. Cosgrove, J. Hernandez-Montfort, J. Otero, A. Ingemi, S. Raj, P. Weeks, R. Agarwal, E.S. Martinez, L.F. Tops, M.M. Ahmed, A. Kiskaddon, J. Kremer, M. Keebler, R.K. Ratnagiri, An ISHLT consensus statement on strategies to prevent and manage hemocompatibility related adverse events in patients with a durable, continuous-flow ventricular assist device, J. Heart Lung Transplant. 8 (2024) 1199–1234, https://doi.org/10.1016/j.healun.2024.04.065.

[6] M. Yuzefpolskaya, S.E. Schroeder, B.A. Houston, M.R. Robinson, I. Gosev, A. Reyentovich, D. Koehl, R. Cantor, U.P. Jorde, J.K. Kirklin, F.D. Pagani, D. A. D'Alessandro, The society of thoracic surgeons intermacs 2022 annual report: focus on the 2018 heart transplant allocation system, Ann. Thorac. Surg. 115 (2023) 1282–1288.

[7] C.B. Patel, L. Blue, B. Cagliostro, S.H. Bailey, J.W. Entwistle, R. John, V. Thohan, J. C. Cleveland Jr., D.J. Goldstein, N. Uriel, X. Su, S.I. Somo, P. Sood, M.R. Mehra, Left ventricular assist systems and infection-related outcomes: a comprehensive analysis of the MOMENTUM 3 trial, J. Heart Lung Transplant. 39 (2020) 774–781, https://doi.org/10.1016/j.healun.2020.03.002.

[8] P. Shah, M. Yuzefpolskaya, G.W. Hickey, K. Breathett, O. Wever-Pinzon, V.-K. Ton, W. Hiesinger, D. Koehl, J.K. Kirklin, R.S. Cantor, J.P. Jacobs, R.H. Habib, F. D. Pagani, D.J. Goldstein, Twelfth interagency registry for mechanically assisted circulatory support report: readmissions after left ventricular assist device, Ann. Thorac. Surg. 113 (2022) 722–737, https://doi.org/10.1016/j.athoracsur.2021.12.011.

[9] L. Grosman-Rimon, F. Billia, A. Fuks, I. Jacobs, M.A. McDonald, D.Z. Cherney Dz, V. Rao, New therapy, new challenges: the effects of long-term continuous flow left ventricular assist device on inflammation, Int. J. Cardiol. 215 (2016) 424–430, https://doi.org/10.1016/j.ijcard.2016.04.133.

[10] R. Zayat, A. Moza, O. Grottke, T. Grzanna, T. Fechter, T. Motomura, C. Schmidt-Mewes, T. Breuer, R. Autschbach, R. Rossaint, A. Goetzenich, C. Bleilevens, In vitro comparison of the hemocompatibility of two centrifugal left ventricular assist devices, J. Thorac. Cardiovasc. Surg. 157 (2019) 591–599.e4, https://doi.org/10.1016/j.jtcvs.2018.07.085.

[11] A. Nascimbene, S. Neelamegham, O.H. Frazier, J.L. Moake, J.F. Dong, Acquired von Willebrand syndrome associated with left ventricular assist device, Blood 127 (2016) 3133–3141, https://doi.org/10.1182/blood-2015-10-636480.

[12] W. Wagner, J. Woolley, J. Teuteberg, C. Bermudez, J. Bhama, K. Lockard, R. Kormos, Temporal leukocyte numbers and granulocyte activation in pulsatile and rotary ventricular assist device patients, Artif. Organs 38 (2014) 447–455, https://doi.org/10.1111/aor.12200.
[13] H. Setiadi, A.M. El-Banayosy, S. George, D.W. Schmidtke, A. El-Banayosy, D. A. Horstmanshof, J.L. Long, Oncostatin M: a potential biomarker to predict infection in patients with left ventricular assist devices, ASAIO J. 68 (2022) 1036–1043, https://doi.org/10.1097/MAT.0000000000001608.
[14] L.J. Mereweather, A. Constantinescu-Bercu, J.T.B. Crawley, I.I. Salles-Crawley, Platelet–Neutrophil crosstalk in thrombosis, Int. J. Mol. Sci. 24 (2023) 1266, https://doi.org/10.3390/ijms24021266.
[15] R.D. Cummings, E. Chiffoleau, Y. van Kooyk, R.P. McEver, C-type lectins, in: A. Varki, R.D. Cummings, J.D. Esko, P. Stanley, G.W. Hart, M. Aebi, D. Mohnen, T. Kinoshita, N.H. Packer, J.H. Prestegard, R.L. Schnaar, P.H. Seeberger (Eds.), Essentials of Glycobiology [Internet], fourth ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor (NY), 2022. Chapter 34.
[16] G. Nash, The rheology of interactions between leukocytes, platelets and the vessel wall in thrombo-inflammation, Biorheology (Oxf.) 59 (2024) 63–80, https://doi.org/10.3233/BIR-230040.
[17] V. Pretini, M.H. Koenen, L. Kaestner, M.H.A.M. Fens, R.M. Schiffelers, M. Bartels, R. Van, Wijk Red blood cells: chasing interactions, Front. Physiol. 10 (2019) 945, https://doi.org/10.3389/fphys.2019.00945.
[18] M.J. Telen, Red blood cell surface adhesion molecules: their possible roles in normal human physiology and disease, Sem. Hematol. 37 (2000) 130–142, https://doi.org/10.1016/s0037-1963(00)90038-6.
[19] J.P. Buerck, D.K. Burke, D.W. Schmidtke, T.A. Snyder, D.V. Papavassiliou, R. A. O'Rear, Production of erythrocyte microparticles in a sub-hemolytic environment, J. Artif. Organs 24 (2021) 135–145, https://doi.org/10.1007/s10047-020-01231-7.
[20] Designation, F1841-19: Standard practice for assessment of hemolysis in continuous flow blood pumps. http://www.astm.org/f1841-19e01.html.
[21] P.A. Coghill, S. Kanchi, Z.J. Azartash-Namin, J.W. Long, T.A. Snyder, Benchtop von Willebrand Factor Testing: Comparison of commercially available ventricular assist devices and evaluation of variables for a standardized test method, ASAIO J. 65 (2019) 481–488, https://doi.org/10.1097/MAT.0000000000000849.
[22] C.H. Chan, I.L. Pieper, R. Hambly, G. Radley, A. Jones, Y. Friedmann, K. M. Hawkins, S. Westaby, G. Foster, C.A. Thornton, The CentriMag centrifugal blood pump as a benchmark for in vitro testing of hemocompatibility in implantable ventricular assist devices, Artif. Organs 39 (2015) 93–101, https://doi.org/10.1111/aor.12351.
[23] P. Diehl, M. Aleker, T. Helbing, V. Sossong, F. Beyersdorf, M. Olschewski, C. Bode, M. Moser, Enhanced microparticles in ventricular assist device patients predict platelet, leukocyte and endothelial cell activation, Interact. Cardiovasc. Thorac. Surg. 11 (2010) 133–137, https://doi.org/10.1510/icvts.2010.232603.
[24] R. Sansone, B. Stanske, S. Keymel, D. Schuler, P. Horn, D. Saeed, U. Boeken, R. Westenfeld, A. Lichtenberg, M. Kelm, C. Heiss, Macrovascular and microvascular function after implantation of left ventricular assist devices in end-stage heart failure: role of microparticles, J. Heart Lung Transplant. 34 (2015) 921–932, https://doi.org/10.1016/j.healun.2015.03.004.
[25] S. Gordon, An immunologic process, Immunity (Camb., Mass.) 44 (2016) 463–475, https://doi.org/10.1016/j.immuni.2016.02.026.
[26] U. Lendeckel, S. Venz, C. Wolke, Macrophages: shape and functions, Chem.Texts. 8 (2022) 12, https://doi.org/10.1007/s40828-022-00163-4.
[27] H. Setiadi, T. Yago, Z. Liu, R.P. McEver, Endothelial signaling by neutrophil-released oncostatin M enhances P-selectin-dependent inflammation and thrombosis, Blood Adv. 3 (2019) 168–183, https://doi.org/10.1182/bloodadvances.2018026294.
[28] H. Shi, B. Shao, L. Gao, T. Venkatesan, J.M. McDaniel, M. Zhou, S. McGee, P. Yu, J. Ahamed, J. Journeycake, J.N. George, L. Xia, Endothelial VWF is critical for the pathogenesis of vaso-occlusive episode in a mouse model of sickle cell disease, Proc. Natl. Acad. Sci. U S A. 119 (2022) e2207592119, https://doi.org/10.1073/pnas.2207592119.
[29] D.I. Simon, Z. Chen, H. Xu, C.Q. Li, Jf Dong, L.V. McIntire, C.M. Ballantyne, L. Zhang, M.I. Furman, M.C. Berndt, J.A. López, Platelet glycoprotein ibalpha is a counterreceptor for the leukocyte integrin Mac-1 (CD11b/CD18), J. Exp. Med. 192 (2000) 193–204, https://doi.org/10.1084/jem.192.2.193.
[30] J.P. Buerck, D.K. Burke, D.W. Schmidtke, T.A. Snyder, D. Papavassiliou, E. A. O'Rear, A flow induced autoimmune response and accelerated senescence of red blood cells in cardiovascular devices, Sci. Rep. 9 (2019) 19443, https://doi.org/10.1038/s41598-019-55924-y.
[31] T. Eichhorn, R. Weiss, S. Huber, M. Ebeyer-Masotta, M. Mostageer, R. Emprechtinger, L. Knabl Sr., L. Knabl, R. Wurzner, V. Weber, Expression of Tissue Factor and platelet/leukocyte markers on extracellular vesicles reflect platelet-leukocyte interaction in severe COVId-19, Int. J. Mol. Sci. 24 (2023) 16886, https://doi.org/10.3390/ijms242316886.
[32] A.M. El Banayosy, S. George, D.W. Vanhooser, H. Setiadi, D.R. Freno, M.T. Bell, C. C. Elkins, M.R. Mihu, D.A. Horstmanshof, A. El Banayosy, J.W. Long, Omentoplasty for ventricular assist device infections: encouraging outcomes, JHLT Open 8 (2025) 100264, https://doi.org/10.1016/j.jhlto.2025.100264.