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Arterial Pulsatility and Circulating von Willebrand Factor in Patients on Mechanical Circulatory Support

Flavien Vincent, MD,[a,b,c,*] Antoine Rauch, MD, PhD,[b,c,d,*] Valentin Loobuyck, MD,[b,c,e] Emmanuel Robin, MD, PhD,[b,c,f] Christoph Nix, MSc,[g] André Vincentelli, MD, PhD,[b,c,e] David M. Smadja, PharmD, PhD,[h,i] Pascal Leprince, MD, PhD,[j] Julien Amour, MD, PhD,[k] Gilles Lemesle, MD, PhD,[a,b,c] Hugues Spillemaeker, MD,[a,b,c] Nicolas Debry, MD,[a] Christian Latremouille, MD, PhD,[l] Piet Jansen, MD, PhD,[m] Antoine Capel, PhD,[m] Mouhamed Moussa, MD,[b,c,f] Natacha Rousse, MD,[e] Guillaume Schurtz, MD,[a] Cédric Delhaye, MD,[a] Camille Paris, MD,[d] Emmanuelle Jeanpierre, PharmD,[d] Annabelle Dupont, PharmD, PhD,[b,c,d] Delphine Corseaux, PhD,[b,c] Mickaël Rosa, PhD,[b,c] Yoann Sottejeau, PhD,[b,c] Svenja Barth, MSc,[g] Claudia Mourran, PhD,[g] Valérie Gomane, BSc,[d] Augustin Coisne, MD,[a,b,c] Marjorie Richardson, MD,[a] Claudine Caron, MD, PhD,[d] Cristian Preda, PhD,[n] Alexandre Ung, BSc,[b,c,d] Alain Carpentier, MD,[l,m] Thomas Hubert, DVM, PhD,[o] Cécile Denis, PhD,[p] Bart Staels, PhD,[b,c] Peter J. Lenting, PhD,[p] Eric Van Belle, MD, PhD,[a,b,c,*] Sophie Susen, MD, PhD[b,c,d,*]

ABSTRACT

BACKGROUND The main risk factor for bleeding in patients with continuous-flow mechanical circulatory support (CF-MCS) is the acquired von Willebrand factor (VWF) defect related to the high shear-stress forces developed by these devices. Although a higher bleeding rate has been reported in CF-MCS recipients who had reduced pulsatility, the relation between pulsatility and the VWF defect has never been studied.

OBJECTIVES The purpose of this study was to investigate the relation between pulsatility and VWF under CF-MCS.

METHODS We assessed the effect of 2 CF-MCS on VWF multimer degradation in a mock circulatory loop (model 1). Using these devices, we investigated in a dose-effect model (model 2) 3 levels of pulsatility in 3 groups of swine. In a cross-over model (model 3), we studied the effects of sequential changes of pulsatility on VWF. We reported the evolution of VWF multimerization in a patient undergoing serial CF-MCS and/or pulsatile-MCS.

RESULTS We demonstrated the proteolytic degradation of VWF multimers by high shear CF-MCS in a circulatory loop without pulsatility. We observed both in swine models and in a patient that the magnitude of the VWF degradation is modulated by the pulsatility level in the high shear-stress level condition, and that the restoration of pulsatility is a trigger for the endothelial release of VWF.

CONCLUSIONS We demonstrated that the VWF defect reflects the balance between degradation induced by the shear stress and the endothelial release of new VWF triggered by the pulsatility. This modulation of VWF levels could explain the relationship between pulsatility and bleeding observed in CF-MCS recipients. Preservation of pulsatility may be a new target to improve clinical outcomes of patients. (J Am Coll Cardiol 2018;71:2106–18) © 2018 by the American College of Cardiology Foundation.

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From the [a]CHU Lille, Cardiology, Lille, France; [b]University of Lille, INSERM U1011-EGID, Lille, France; [c]Institut Pasteur de Lille, Lille, France; [d]CHU Lille, Hematology Transfusion, Lille, France; [e]CHU Lille, Cardiac Surgery, Lille, France; [f]CHU Lille, Department of Anesthesia and Intensive Care, Lille, France; [g]Abiomed Europe GmbH, Aachen, Germany; [h]Hematology Department, Hôpital Européen Georges Pompidou, Assistance Publique-Hôpitaux de Paris, University Paris Descartes, Sorbonne Paris Cité, Paris, France; [i]Inserm UMR-S1140, Paris, France; [j]Sorbonne Université, UMR INSERM 1166, IHU ICAN, Assistance Publique-Hôpitaux de Paris (AP-HP), Department of Thoracic and Cardiovascular Surgery, Pitié-Salpêtrière Hospital, Paris, France; [k]Sorbonne Université, UMR INSERM 1166, IHU ICAN, Assistance Publique-Hôpitaux de Paris (AP-HP), Department of Anesthesiology and Critical Care Medicine, Pitié-Salpêtrière Hospital, Paris, France; [l]Department of Cardiovascular Surgery, Hôpital Européen Georges Pompidou, Assistance Publique-Hôpitaux de Paris, University Paris Descartes-Sorbonne Paris Cité, Paris, France; [m]Carmat SA, Vélizy-Villacoublay, France; [n]Laboratoire de Mathématiques, Paul Painlévé, UMR CNRS 8524, Université de Sciences et Technologies de Lille, Lille, France; [o]INSERM U1190-EGID, Lille, France; and the [p]INSERM U1176, University Paris-Sud, University Paris-Saclay, Le Kremlin-Bicêtre, France. *Drs. Vincent, Rauch, Van Belle, and Susen contributed equally to the study. This work was supported by Lille-II University and

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Continuous flow (CF) mechanical circulatory support (MCS) devices have been developed to treat end-stage heart failure in patients waiting for heart transplant or as a destination therapy. Bleeding is currently the most frequent adverse event observed in patients with CF-MCS and represent a major source of morbidity. Gastrointestinal bleeding occurs in ≤50% of patients and impact their management, quality of life, and ultimately survival (1–3).

The acquired von Willebrand factor (VWF)-defect related to the high shear-stress forces developed by these devices has been shown to be 1 of the main risk factors of bleeding (4–6). VWF is a multimeric glycoprotein synthesized and released by the endothelial cells involved in hemostasis and angiogenesis. The supra-physiological shear stress induced by CF-MCS promotes the proteolytic degradation of the high molecular weight (HMW) multimers of VWF into smaller protein complexes with less hemostatic potential (7).

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CF-MCS also decreases arterial pulsatility to a various extent depending on the balance between the residual native left ventricle (LV) contractility and the flow rate of the device. Several studies have reported a higher bleeding rate in CF-MCS-supported patients who had reduced pulsatility (8–10). However, the direct relationship between pulsatility and multimeric profile of VWF has never been studied. This question is of major clinical importance to understand whether preservation of pulsatility under CF-MCS could reduce the incidence of bleeding and affect patient management (11,12).

We hypothesized that the defect of VWF observed under MCS could be modulated by the endothelial response to the level of pulsatility. One in vitro endothelial-free mock circulatory loop model and 2 experimental swine models with CF-MCS were used to investigate the relationship between pulsatility and VWF multimerization. We further investigated the evolution of VWF parameters in a patient with cardiogenic shock requiring MCS with successively 3 serial pulsatile and CF devices.

METHODS

STUDY DESIGN. To assess the effect of changes of pulsatility as a modulator of VWF defect under CF-MCS, we developed 3 experimental models and we investigated a patient undergoing sequential changes of pulsatility. The results obtained in this patient are part of the "first clinical use of a bioprosthetic total artificial heart" CARMAT study (**Figure 1,** Online Table 1).

For the experimental part, we used 2 percutaneous micro-axial catheter-mounted high shear rotary pumps adapted from Impella-CP (MCS-A) and Impella-5.0 (MCS-B) and using a dedicated cannula adapted to pig anatomy constraints (Abiomed Europe-GmbH, Aachen, Germany). The 2 pumps were designed to induce very similar shear with a tip velocity of 9.5 and 10.0 m · s^{-1} for MCS-A and -B, respectively. During all of the experiments, the pumps were used at a constant and maximal speed with a maximum flow of 3.2 l/min (MCS-A) and 4.5 l/min (MCS-B).

For the in vitro model, we used an endothelial-free mock circulatory loop (without pulsatility) to investigate the intrinsic capacity of these 2 high-shear CF-MCS to induce a loss of HMW multimers after proteolytic degradation of VWF (**Figure 1A**). For the in vivo experimental part, we developed 2 swine models with normal heart function to study the relationship between pulsatility and the intensity of VWF defect (**Figures 1B and 1C**).

We further investigated the evolution of multimeric profile in a patient with cardiogenic shock requiring MCS with successively 3 serial pulsatile and CF devices: 1) CF-MCS with venoarterial

ABBREVIATIONS AND ACRONYMS

ADAMTS13 = A disintegrin and metalloprotease with thrombospondin type I repeats-13

CF = continuous flow

ECMO = extracorporeal membrane oxygenation

FVIIIc = Factor VIII coagulant activity

HMW = high molecular weight

LDH = lactate dehydrogenase

LV = left ventricle/ventricular

MCS = mechanical circulatory support

PF = pulsatile flow

PP = pulse pressure

VWF = von Willebrand factor

VWF:Ag = von Willebrand factor antigen

VWF:CB = von Willebrand factor collagen-binding activity

WPB = Weibel Palade body

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