Centre Hospitalier Régional Universitaire de Lille

FACULTE DE MEDECINE
UNIVERSITE DE LILLE 2
HENRI WAREMBOURG

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

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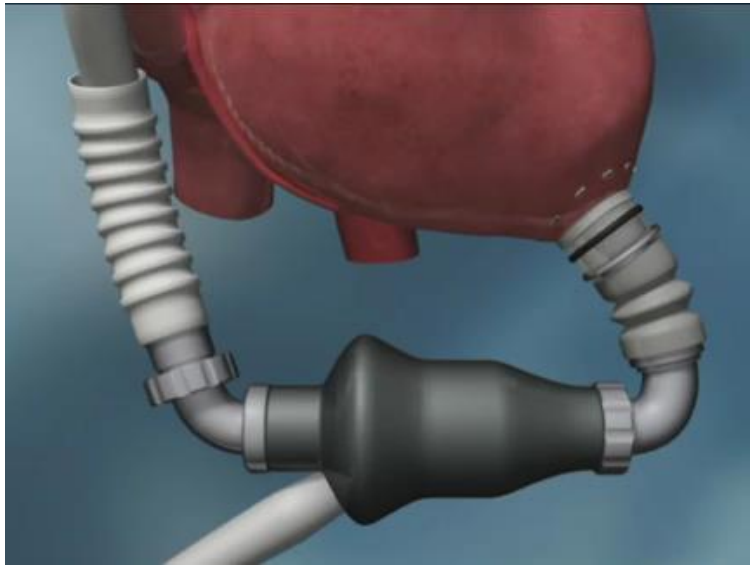
GRCI 2018

Instituts thématiques

Inserm
Institut national de la santé et de la recherche médicale

2 systems of (left ventricular) mechanical circulatory support



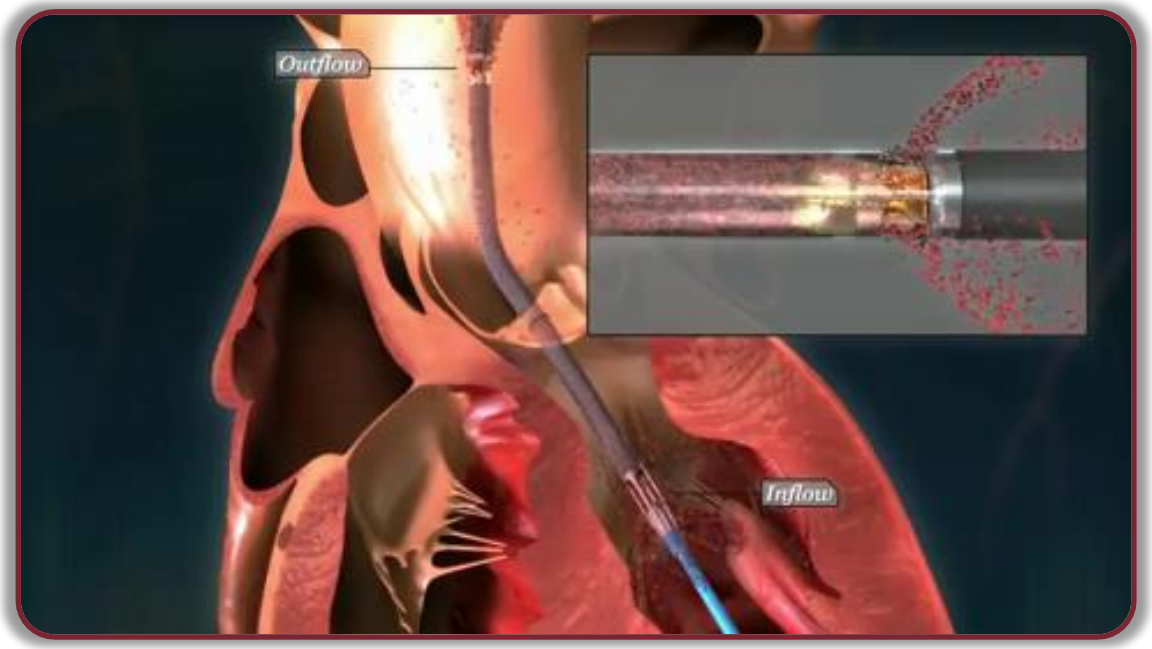
1st generation : intermittent/pulsatile devices	2nd generation: continuous/non pulsatile devices
• Intermittent ejection	• Continuous ejection
• Arterial pulsatility preserved	• Arterial pulsatility decreased
• Big, too complex	• Smaller, less complicated
• No reliable	• More reliable

Abraham WT, Smith SA. Devices in the management of advanced, chronic heart failure. Nat Rev Cardiol. févr 2013;10(2):98-110

CONTINUOUS FLOW LVAD

HIGH SHEAR STRESS LEVEL

VWF FUNCTIONAL ABNORMALITIES



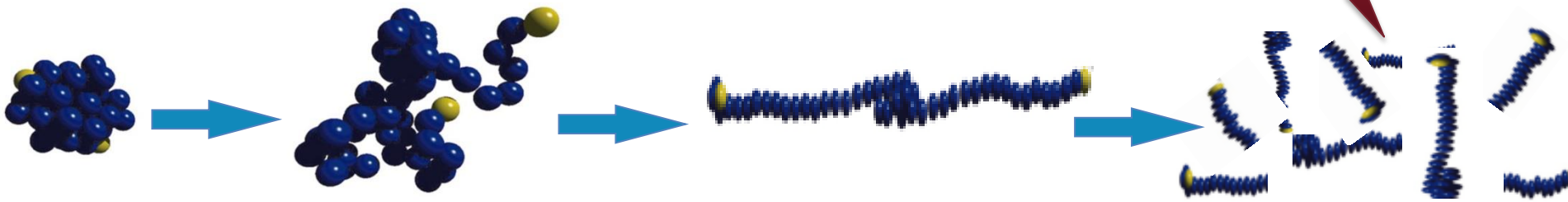
Conformation of VWF is determined by the shear stress forces

High

Low

Shear stress forces

ADAMTS 13



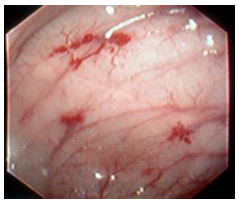
Globular → **Partially unfolded** → **Unfolded**

- Globular → Resistant to ADAMTS-13
- Unfolded → Sensitive to ADAMTS-13
- Platelet binding reduction

Acquired von Willebrand Syndrome : a feature of MCS

	During VAD Use	After HT	p Value
Decreased or absent VW multimers	100%	0%	0.001

Uriel N, et al. JACC 2010



High GI bleeding rate
But almost 50% of patients remain free of bleeding events

72 patients with CF-LVAD support (HeartMate II)

JACC Vol 56, N° 15, 2010 :1207-13

Event Site	n	Event
GI	24	
Chest	7	6 pericardial effusion, 1 hemothorax
Other	3	Dental, LE wound, postmenopausal
Epistaxis	1	
Total	35	

IN VIVO :

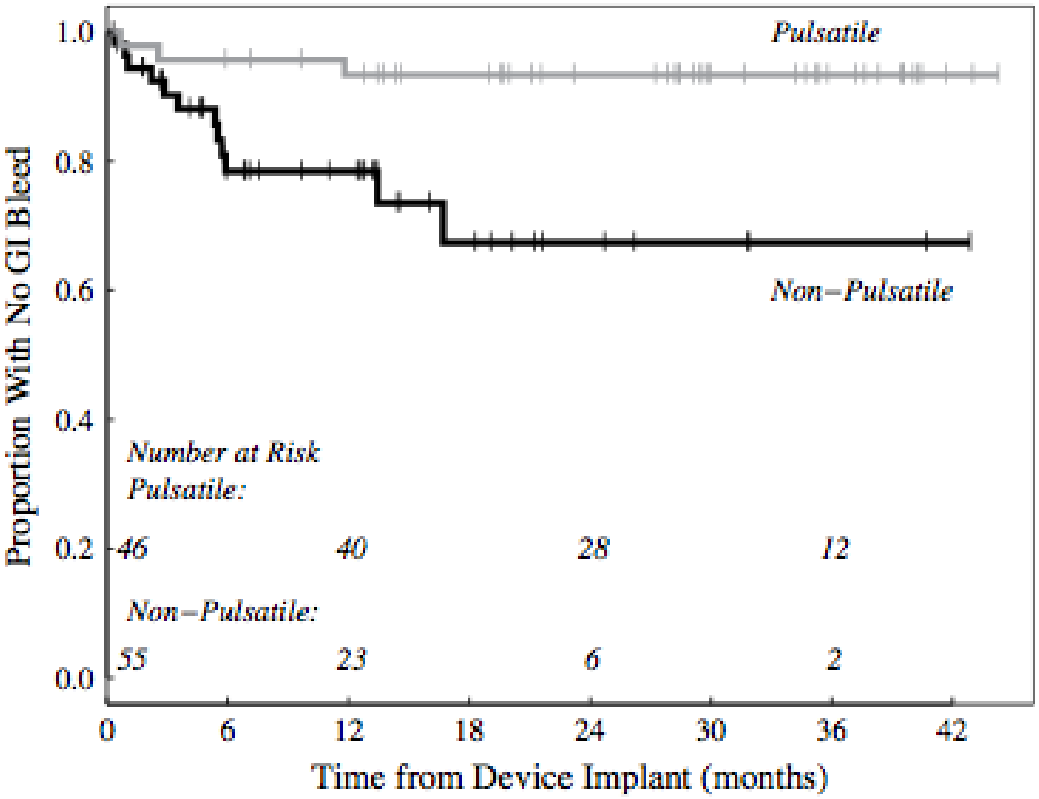
- Every CVAD recipients had loss of HMWM of VWF
- Reversible after heart transplantation

Uriel N,, 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. Journal of the American College of Cardiology. oct 2010;56(15):1207-13.

Bleeding events associated with non pulsatile MCS

GASTRO-INTESTINAL BLEEDING :

- Most frequent adverse effect
- Non pulsatile : 63 per 100 patient-years
- Pulsatile : 6,8 per 100 patient-years



Crow S, et al. Gastrointestinal bleeding rates in recipients of nonpulsatile and pulsatile left ventricular assist devices. The Journal of Thoracic and Cardiovascular Surgery. janv 2009;137(1):208-15.

Interrogation

CONTINUOUS FLOW VAD

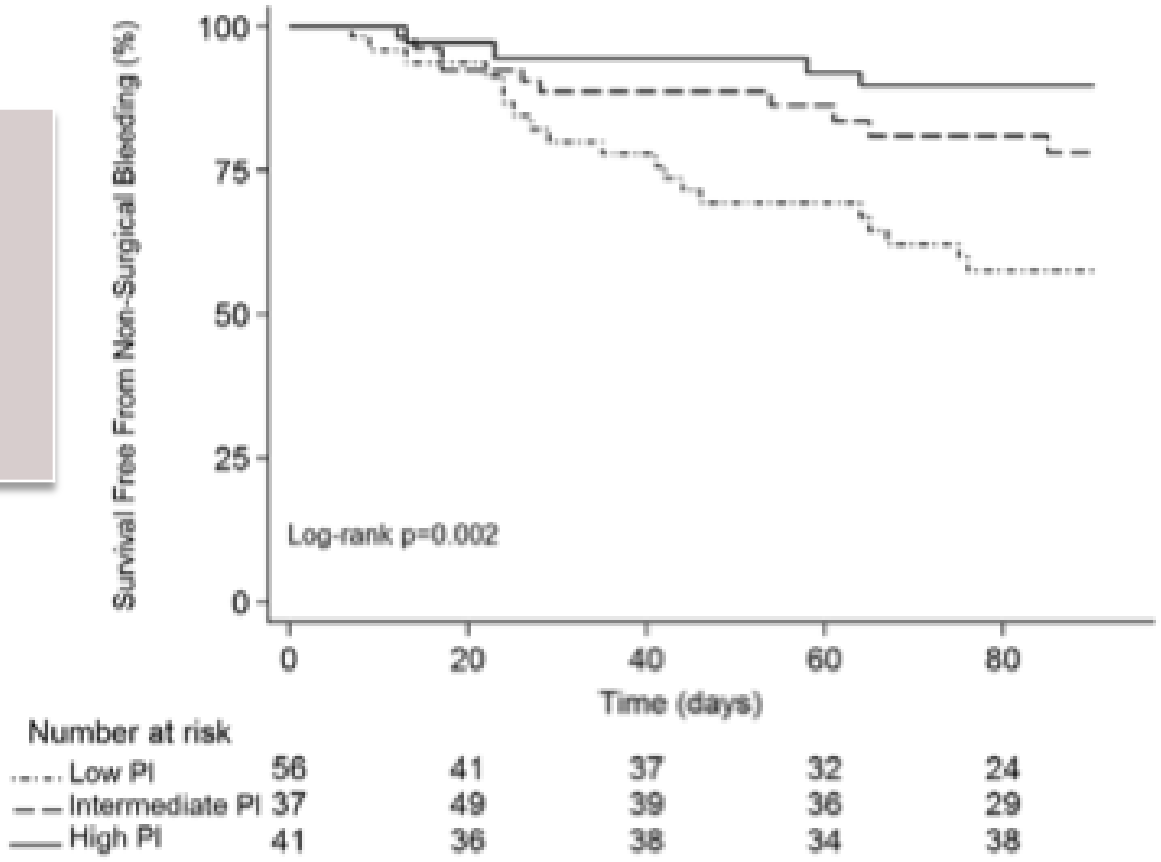
DIFFERENT SHEAR STRESS LEVEL

PULSATILITY LOSS

VWF FUNCTIONAL ABNORMALITIES ?

Pulsatility loss and bleeding risk in MCS recipients

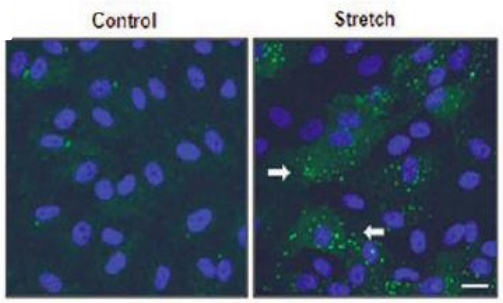
- Low pulsatility index = 4 fold increase in risk of bleeding
- No data on the multimerization of VWF



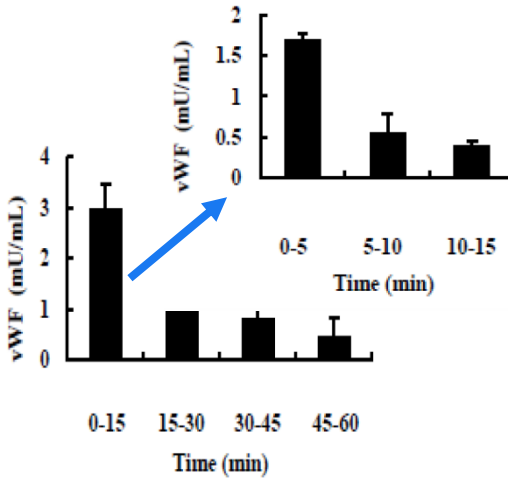
Wever-Pinzon O, et al. Pulsatility and the Risk of Nonsurgical Bleeding in Patients Supported With the Continuous-Flow Left Ventricular Assist Device HeartMate II. Circulation: Heart Failure. 1 mai 2013;6(3):517-26.

Endothelial release of VWF in response to stretch forces

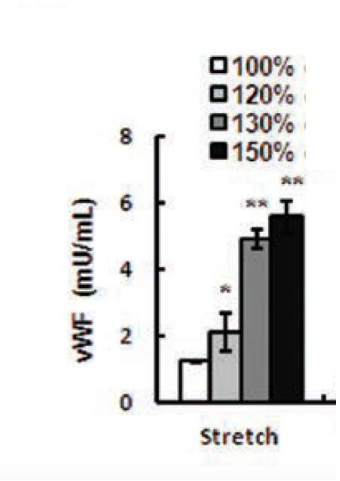
Stretch-induced release of VWF from endothelial cells occurs within minutes



Increase in P-selectin expression



Early release of VWF

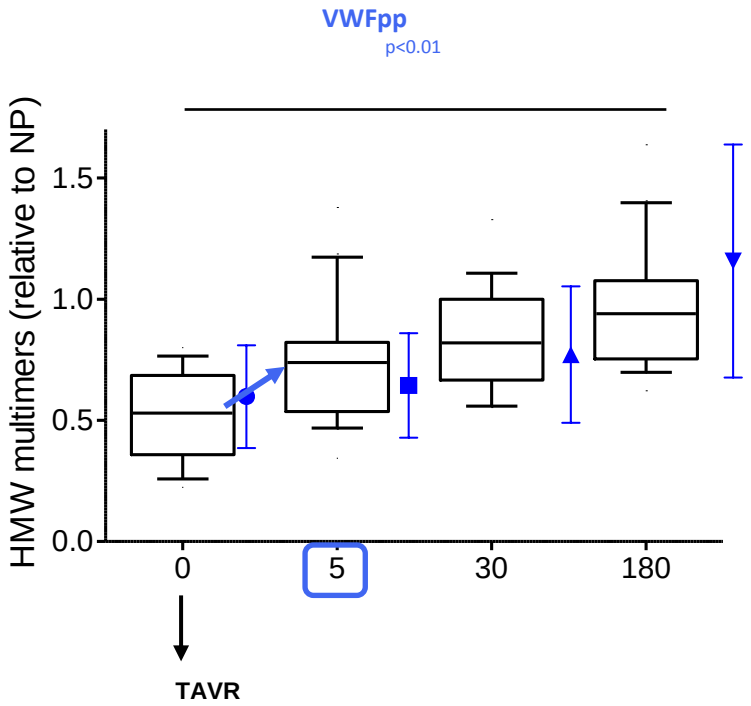


Stretch-Intensity

Xiong et al., Cell Res 2013

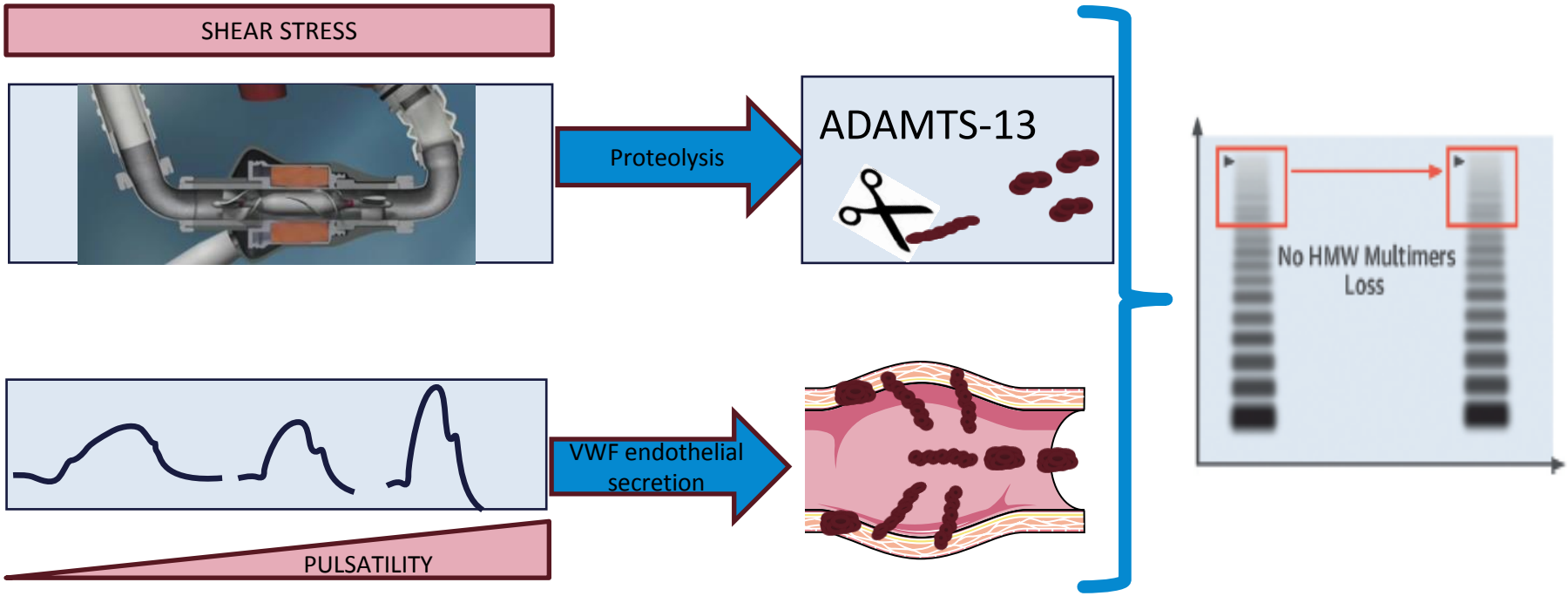
Rapid dynamic restauration of VWF multimers after TAVR

- **TAVR (n=20)**
- Significant decrease in mean transvalvular gradient
- **Increase in VWFpp**



Van Belle Rauch*, Circ Res 2015*

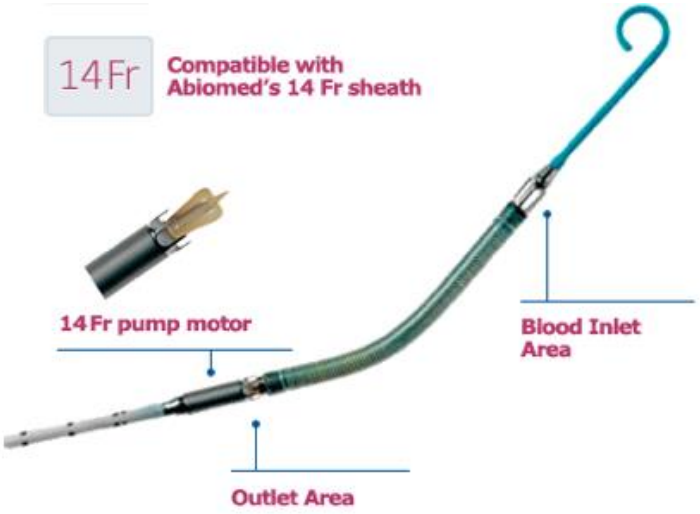
Hypothesis

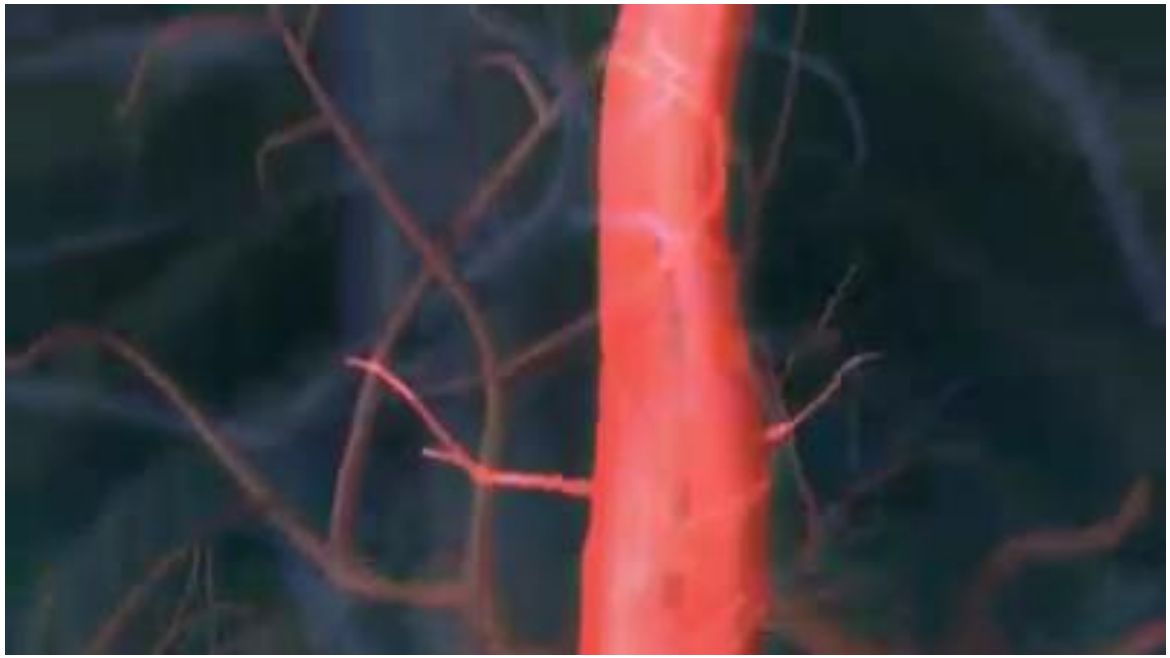

SHEAR STRESS
Proteolysis
ADAMTS-13
VWF endothelial secretion
PULSATILITY
No HMW Multimers Loss

Aim:

To investigate the effect of arterial pulsatility on the intensity of VWF defect under CF-VAD

- Model 1 : in vitro
- Model 2 & 3 : in vivo with an experimental swine model



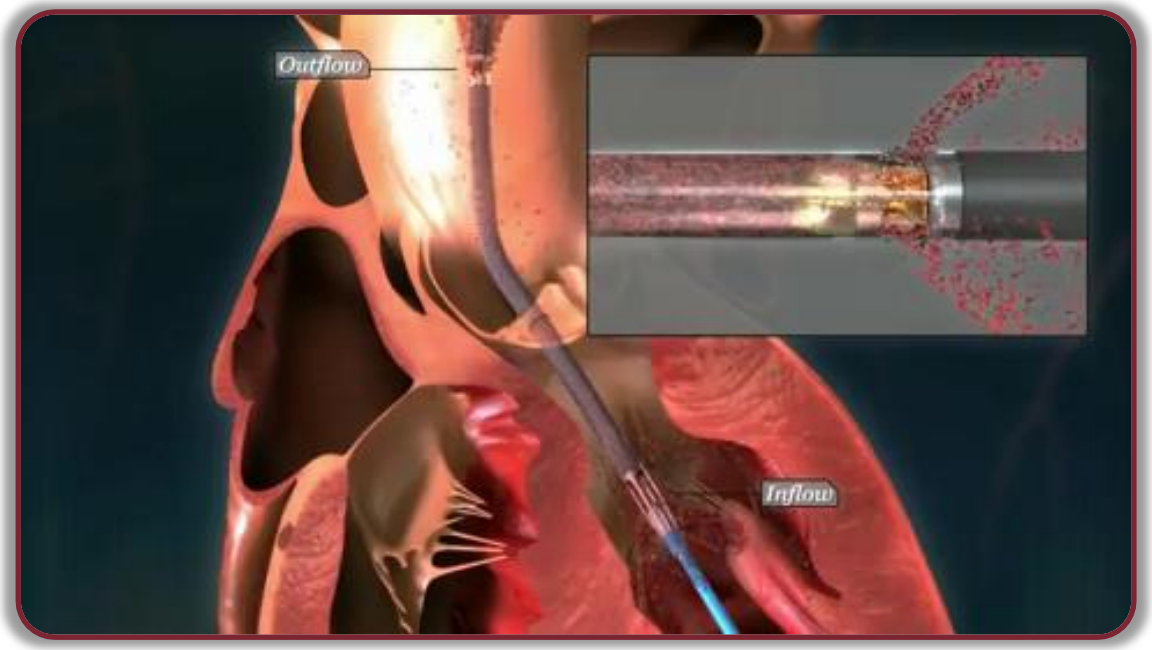


Methods

CF-MCS : IMPELLA

- Very high shear stress IMPELLA A (CP) & IMPELLA B (5.0) (>33000 rpm)
- Output : IMPELLA A : 3,5L/min vs IMPELLA B : 5,3L/min

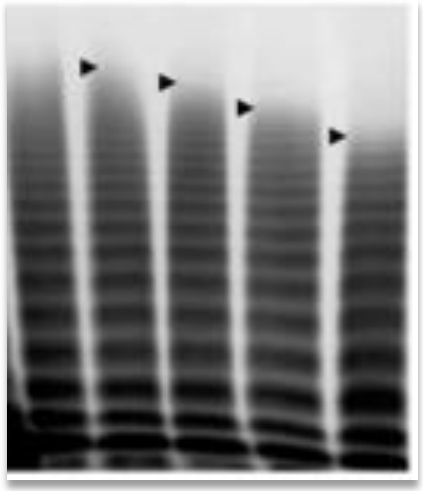
- High speed rotating impeller



Methods : experimental models

Biological endpoints :

- VWF antigen (VWF:Ag)
- VWF collagene binding capacity (VWF:CB)
- VWF multimeric structure



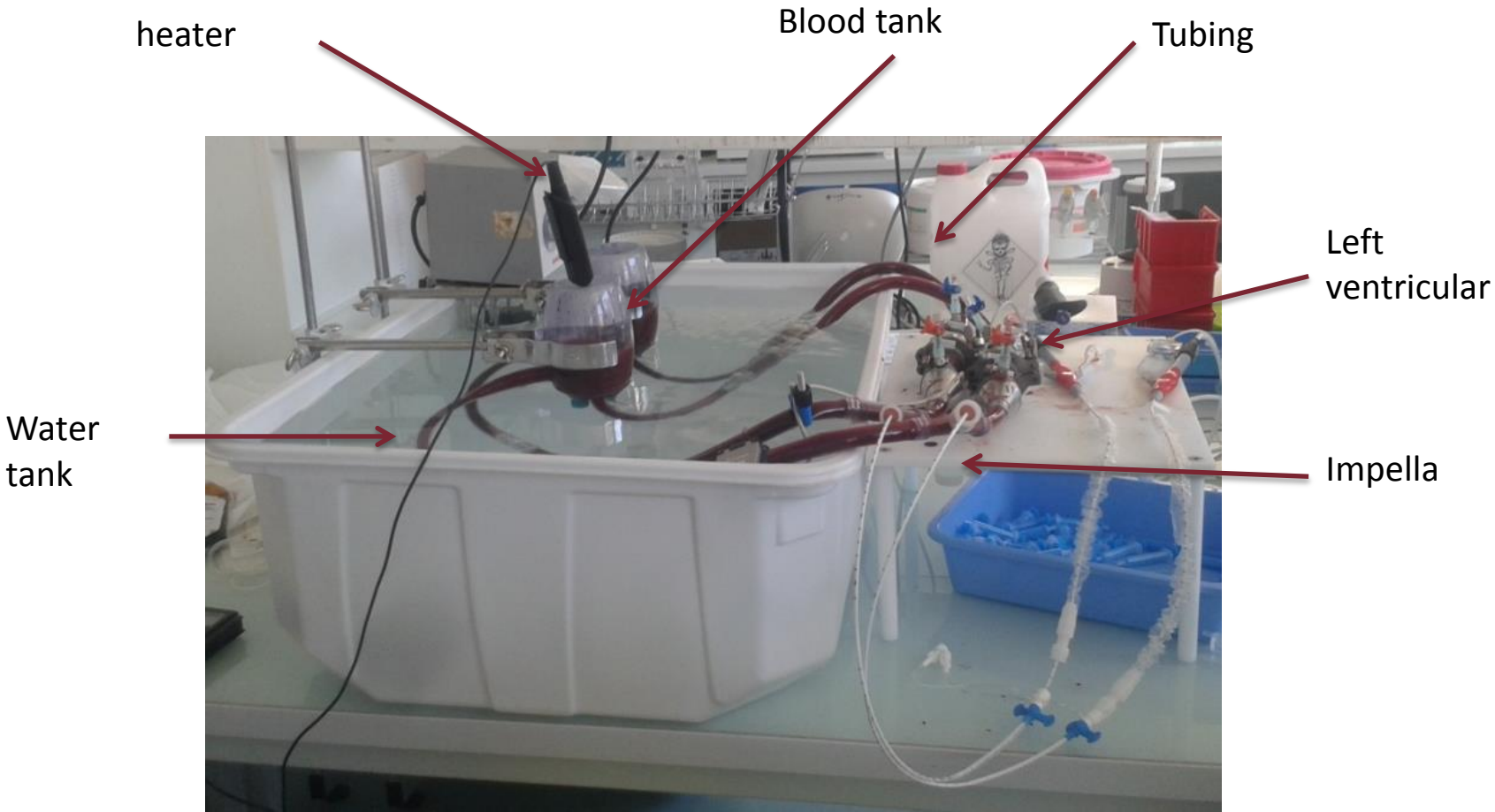
Hemodynamic endpoints :

- Carotid Pulse pressure (systolic BP – diastolic BP)

Model 1 : in vitro mock circulatory loop

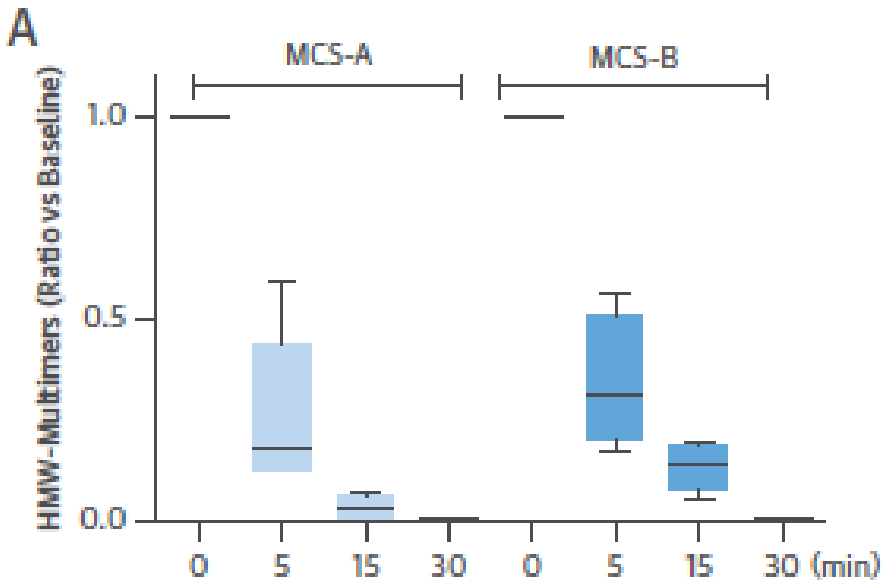
To demonstrate the pure proteolytic degradation of VWF in absence of pulsatility

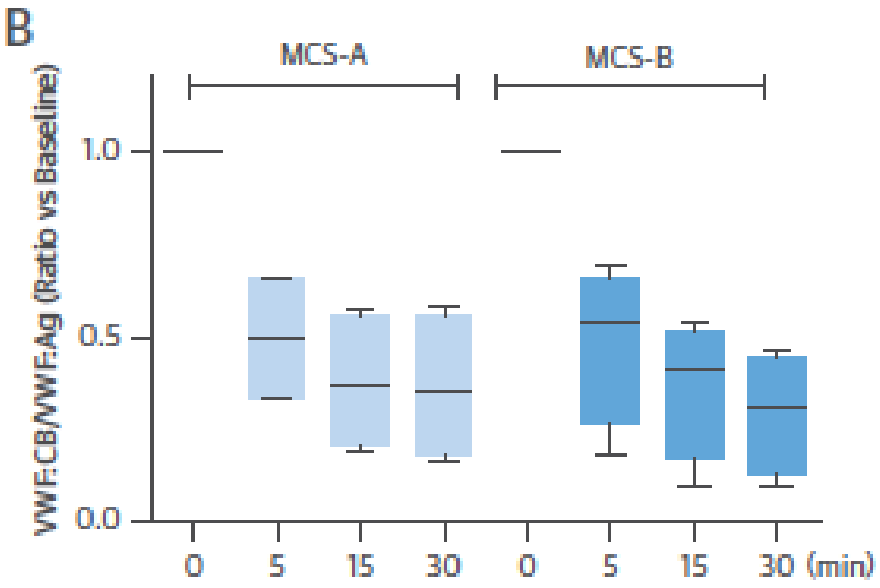
- Human whole blood
- Impella running at maximal speed during 30 min
- Two pump with different maximal flow (impella A & Impella B)
- +/- enzymatic inhibitor (EDTA)



Model 1 : in vitro mock circulatory loop

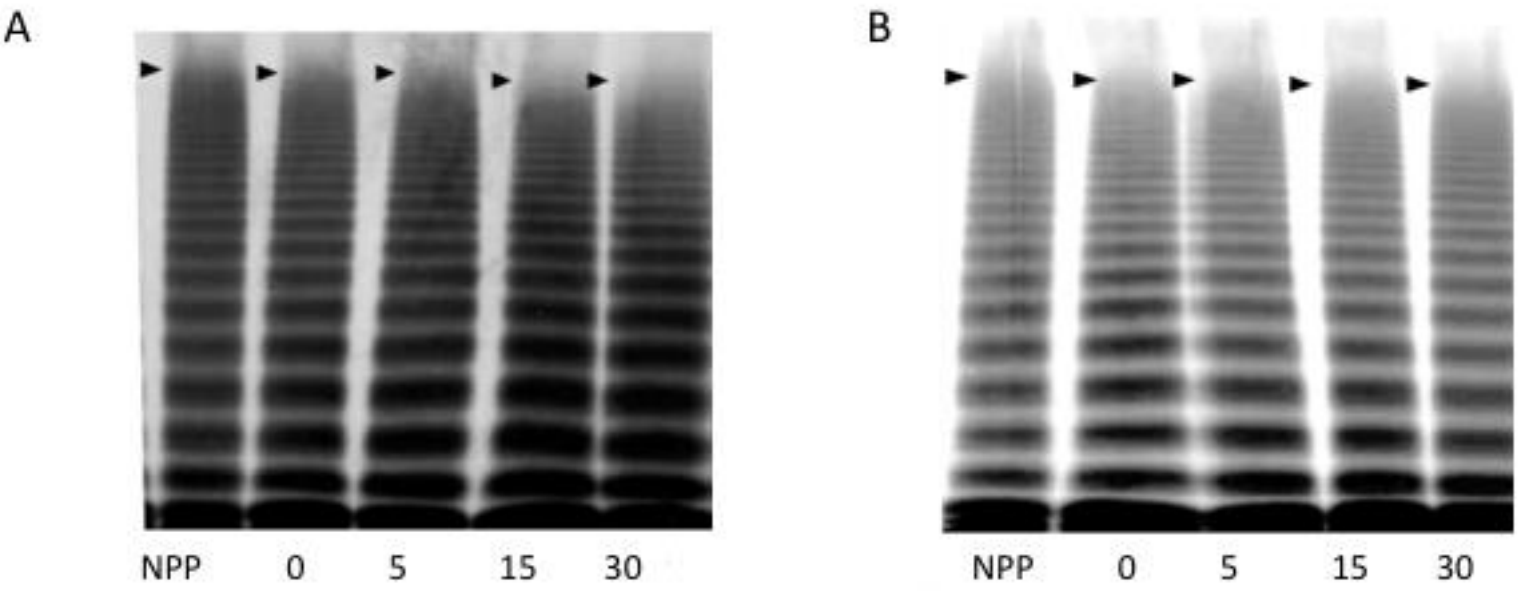
- Both Impella were associated with rapid and complete VWF degradation in 30 min





Results Model 1: *in vitro* mock circulatory loop

- Both Impella were associated with rapid and complete VWF degradation in 30 min
- Enzymatic degradation (fully prevented by EDTA)



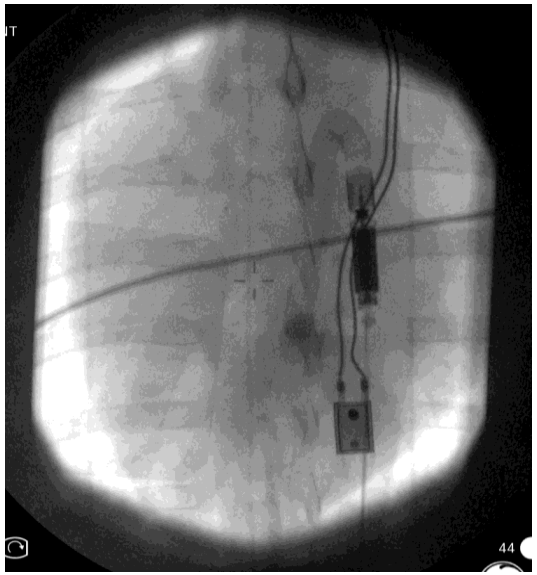
VWF multimeric profile after EDTA spiking with Impella A (left) and Impella B (right)

Swine experimental model

Transcatheter approach via surgical aortic access

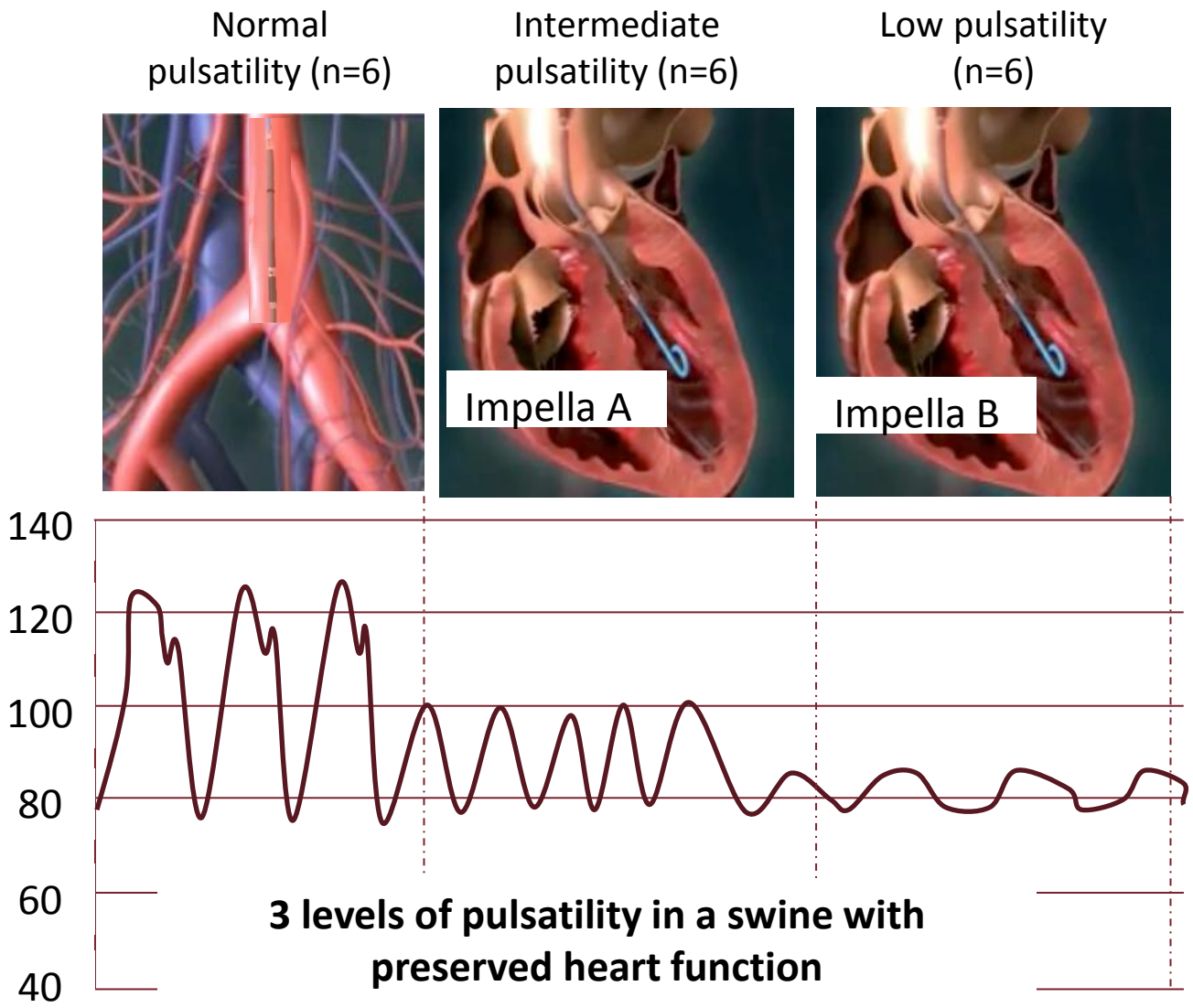
- Median laparotomy
- Abdominal aorta puncture
- Insertion via 22 Fr introducer
- Fluoroscopic guidance
- Pulse pressure monitoring via carotid catheter

Experimental setup

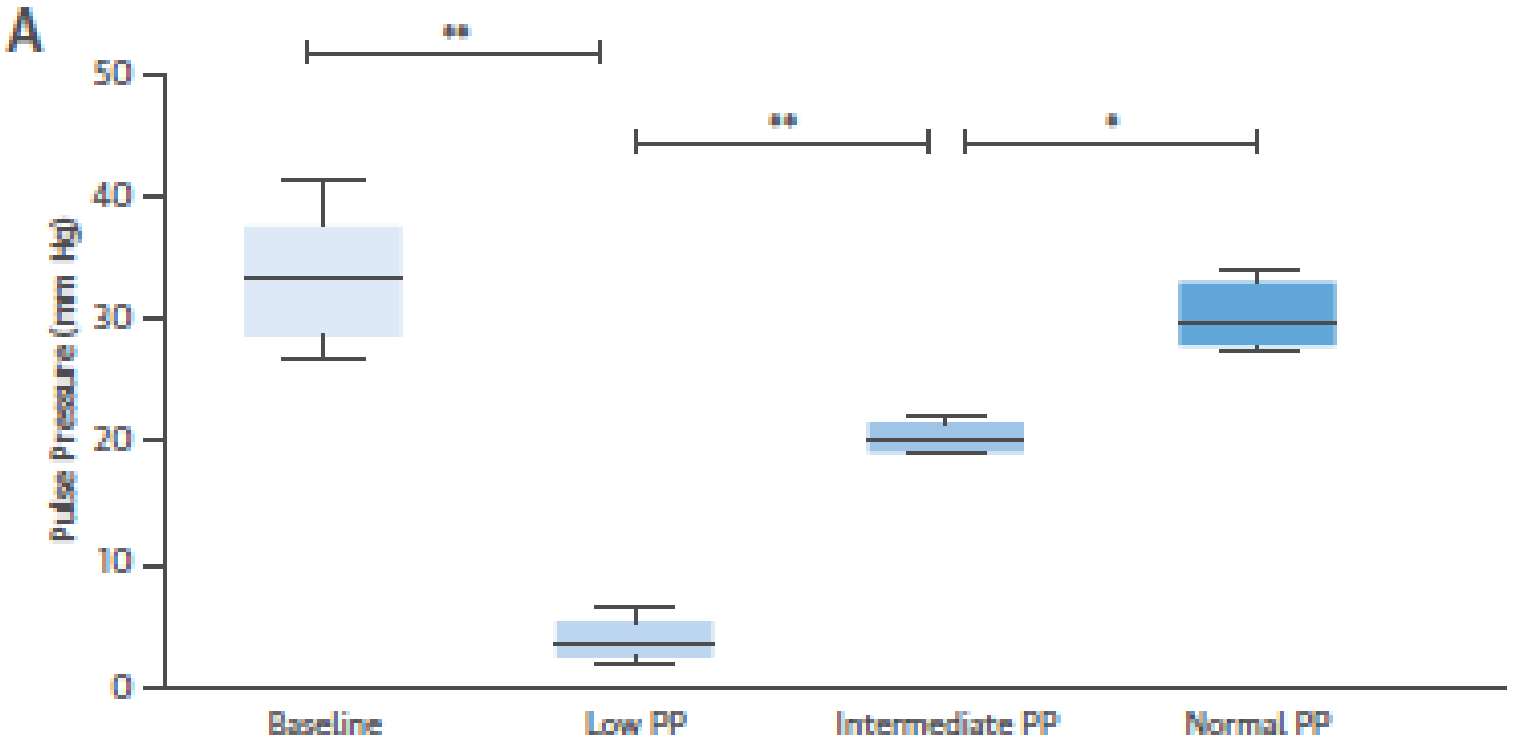


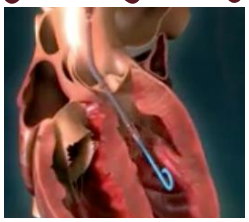
Impella inside LV

Results : Model 2 in vivo : Dose effect model of pulsatility on VWF degradation



Results : Model 2 in vivo : Dose effect model of pulsatility on VWF degradation

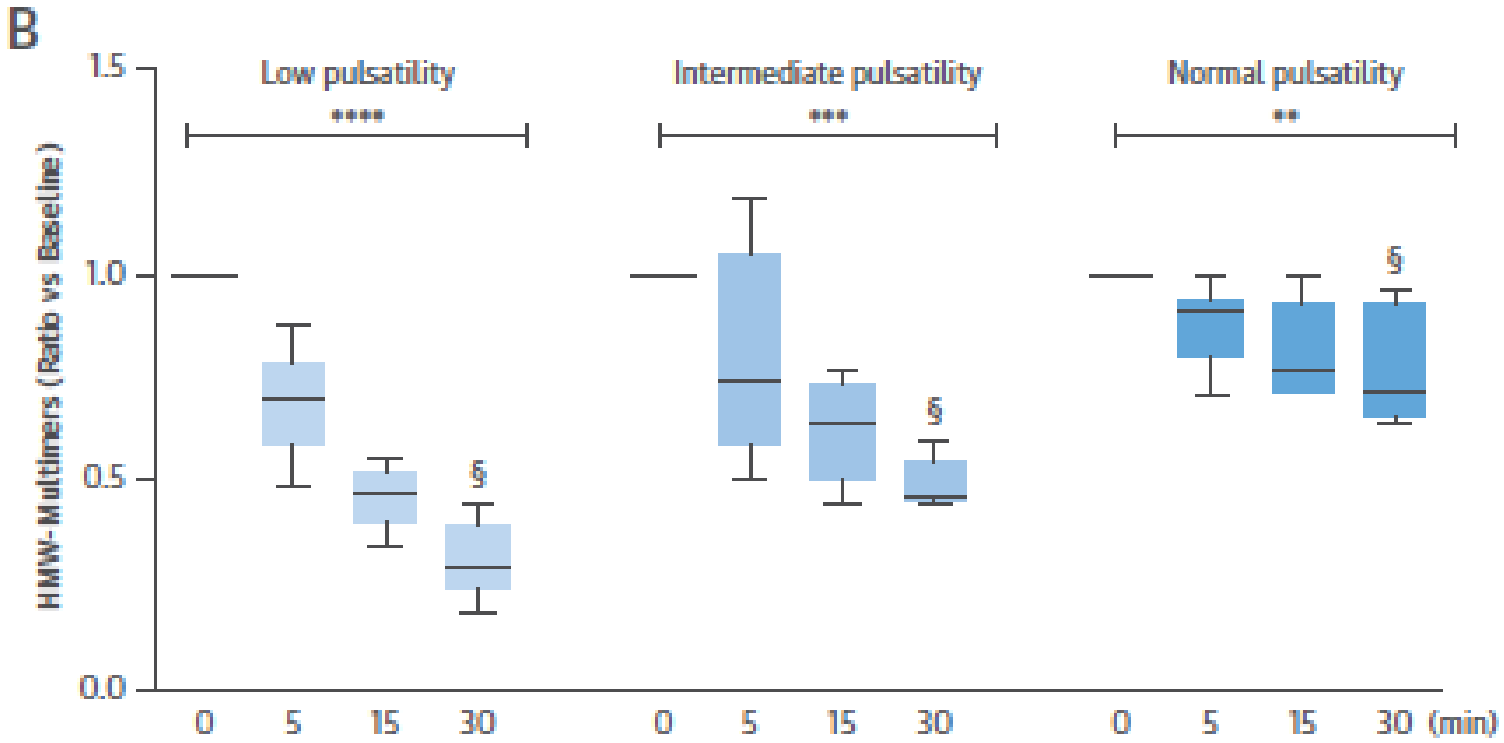




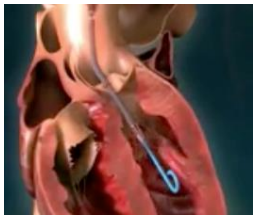
Impella B

Impella A

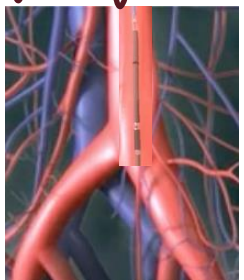
Results : Model 2 in vivo : Dose effect model of pulsatility on VWF degradation



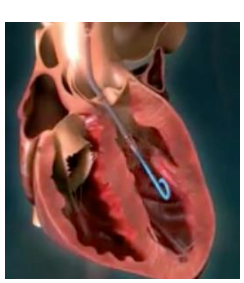
Impella B

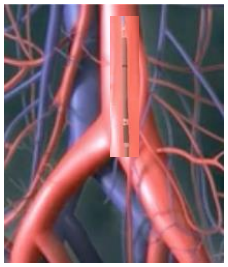


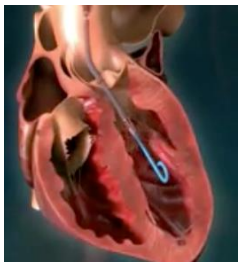
Impella A



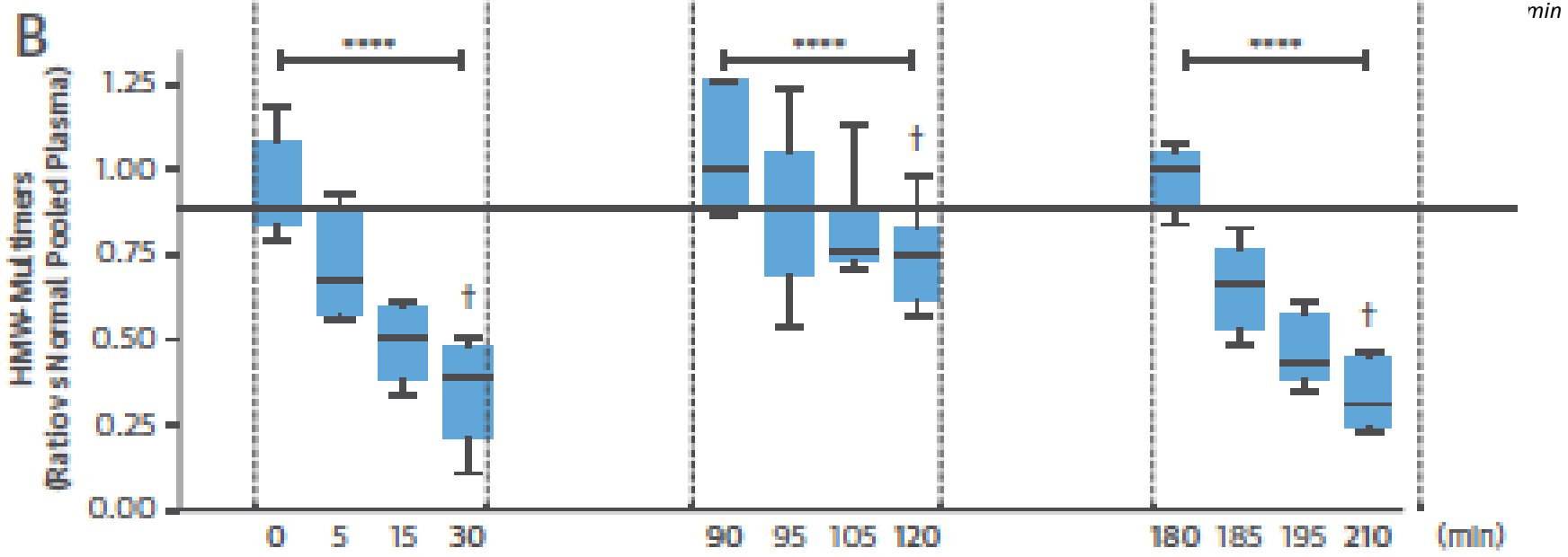
Results : Model 3 in vivo : Cross over study sequential change in pulsatility and shear in a same animal







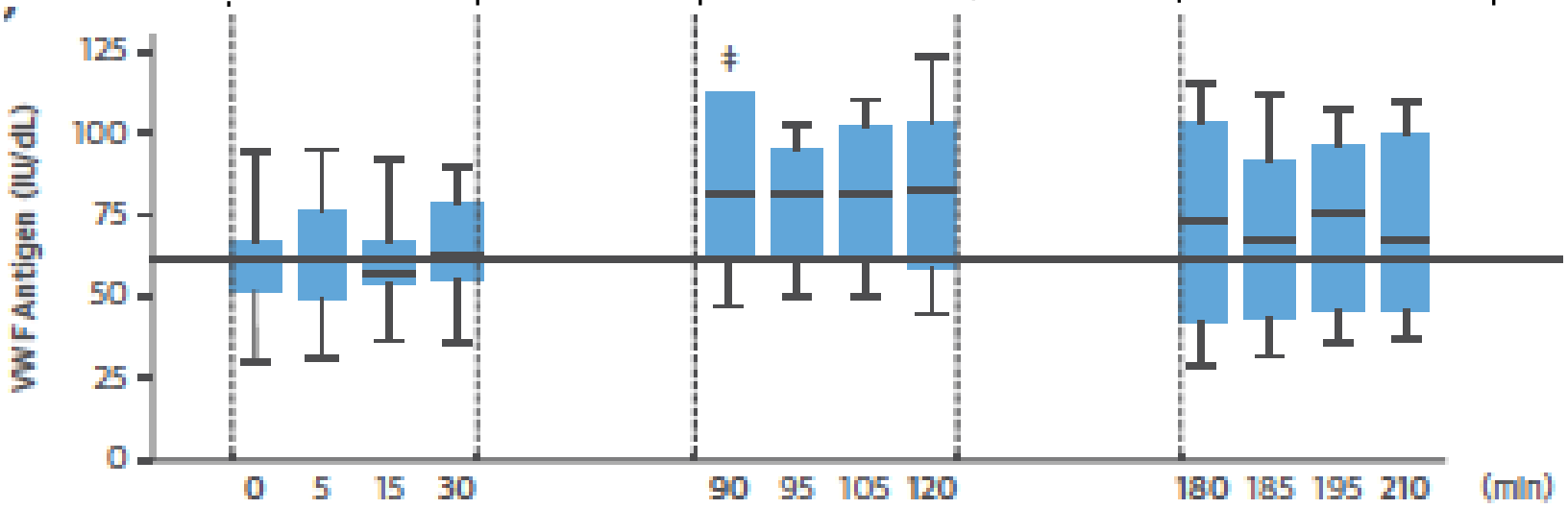
	Impella in LV	Stop Impella Native Heart only	Impella in Aorta	Stop Impella Native Heart only	Impella in LV
Shear	High	Low	High	Low	High
Pulsatility	Low	Normal	Normal	Normal	Low



Results : Model 3 in vivo : Cross over study sequential change in pulsatility and shear in a same animal

	Impella in LV	Stop Impella Native Heart only	Impella in Aorta	Stop Impella Native Heart only	Impella in LV
Shear	High	Low	High	Low	High
Pulsatility	Low	Normal	Normal	Normal	Low

0 min | 30 min | 90 min | 120 min | 180 min | 210 min



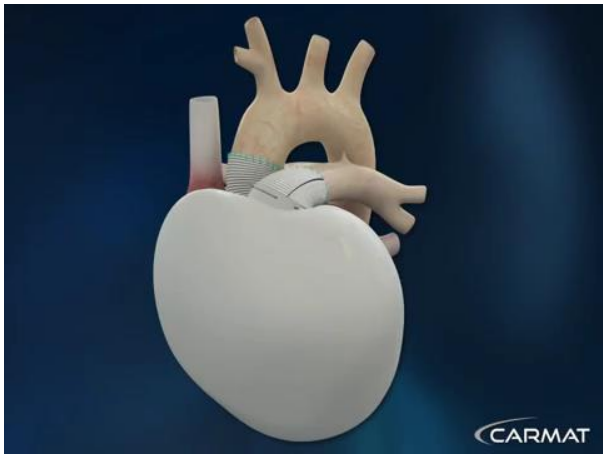
Sequential change of pulsatility and shear in a patient with cardiogenic shock requiring MCS

Clinical history

- 58 year old man
- Severe dilated cardiomyopathy, cardiogenic shock

Underwent 3 successively phases of MCS with different hemodynamic and shear pattern

- Phase 1: Peripheral ECMO : high shear and low pulsatility
- Phase 2: CARMAT Total artificial heart : low shear and normal pulsatility
- Phase 3: Peripheral ECMO + CARMAT: high shear and low pulsatility



Clinical report : 3 phases of MCS with different shear/pulsatility

Continuous-flow MCS

- Marked decrease of HMW-multimers

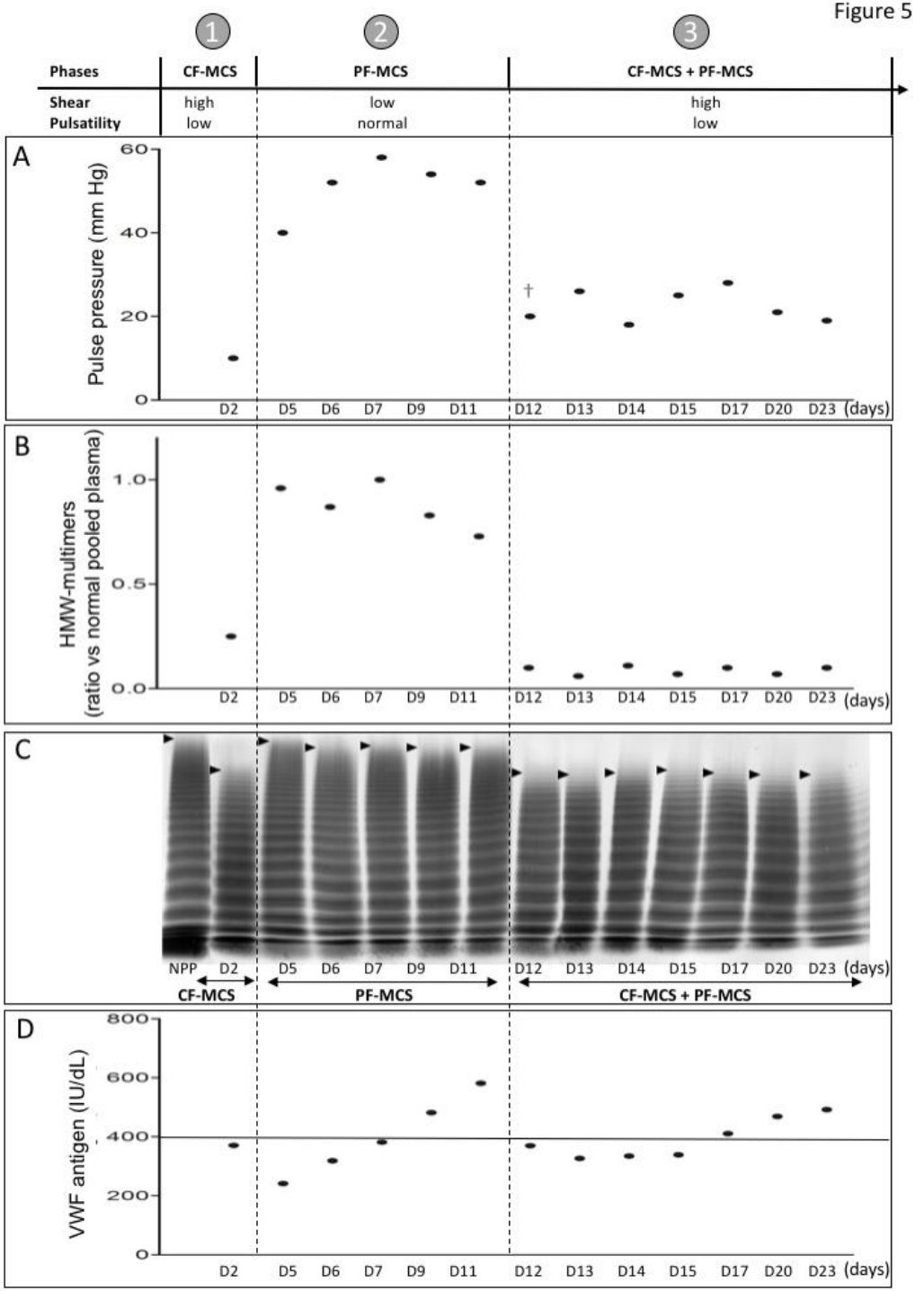
Pulsatile-flow MCS

- Rapid restoration of HMW-multimers
- Rapid increse in VWF Antigen

CF-MCS + PF-MCS

- Rapid loss of HMW-multimers

Figure 5

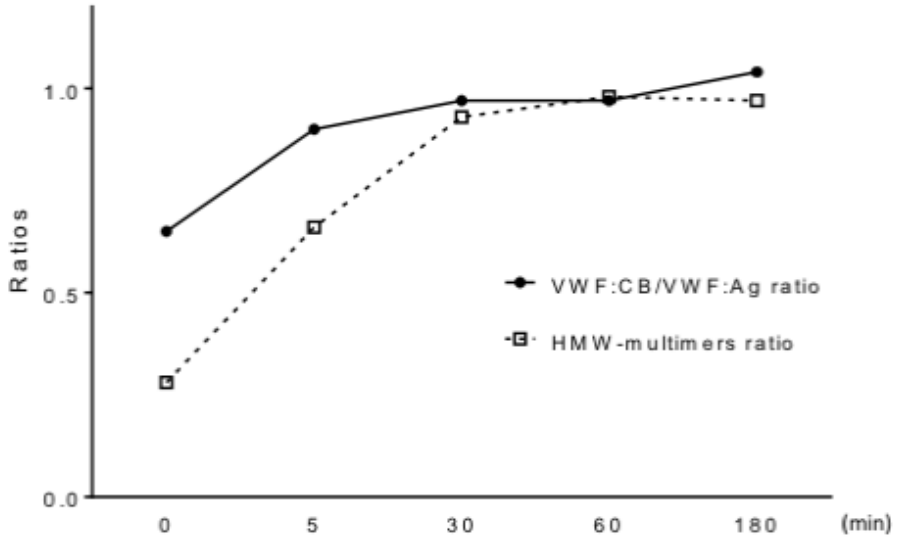


Clinical report : 3 phases of MCS with different shear/pulsatility

Pulsatile phase

- Rapid restoration of HMW-multimers
- Rapid increse in VWF Antigen

Online Figure 3



Conclusion

First animal model with variable pulsatility and constant shear stress forces

- Degree of pulsatility is a strong modulator of VWF multimerization

Endothelium response to restoration of pulsatility

- Not only the inhibition of VWF shear-induced proteolysis
- Acute recovery of VWF defect triggered by pulsatility

Clinically relevant : toward a better prevention of acquired VWF defect ?

- VWF defect not only dependent of device's geometry (shear stress)
- Nature of the flow matters !
- Concept of developing new mechanical circulatory devices with optimal balance between pulsatility properties and shear

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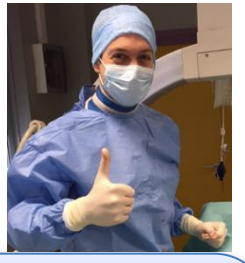

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