Hémodynamique

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Systemic Hemodynamic, cardiac mechanics and cellular signaling pathways induced by ExtraCorporeal Life Support in a sheep cardiogenic shock model

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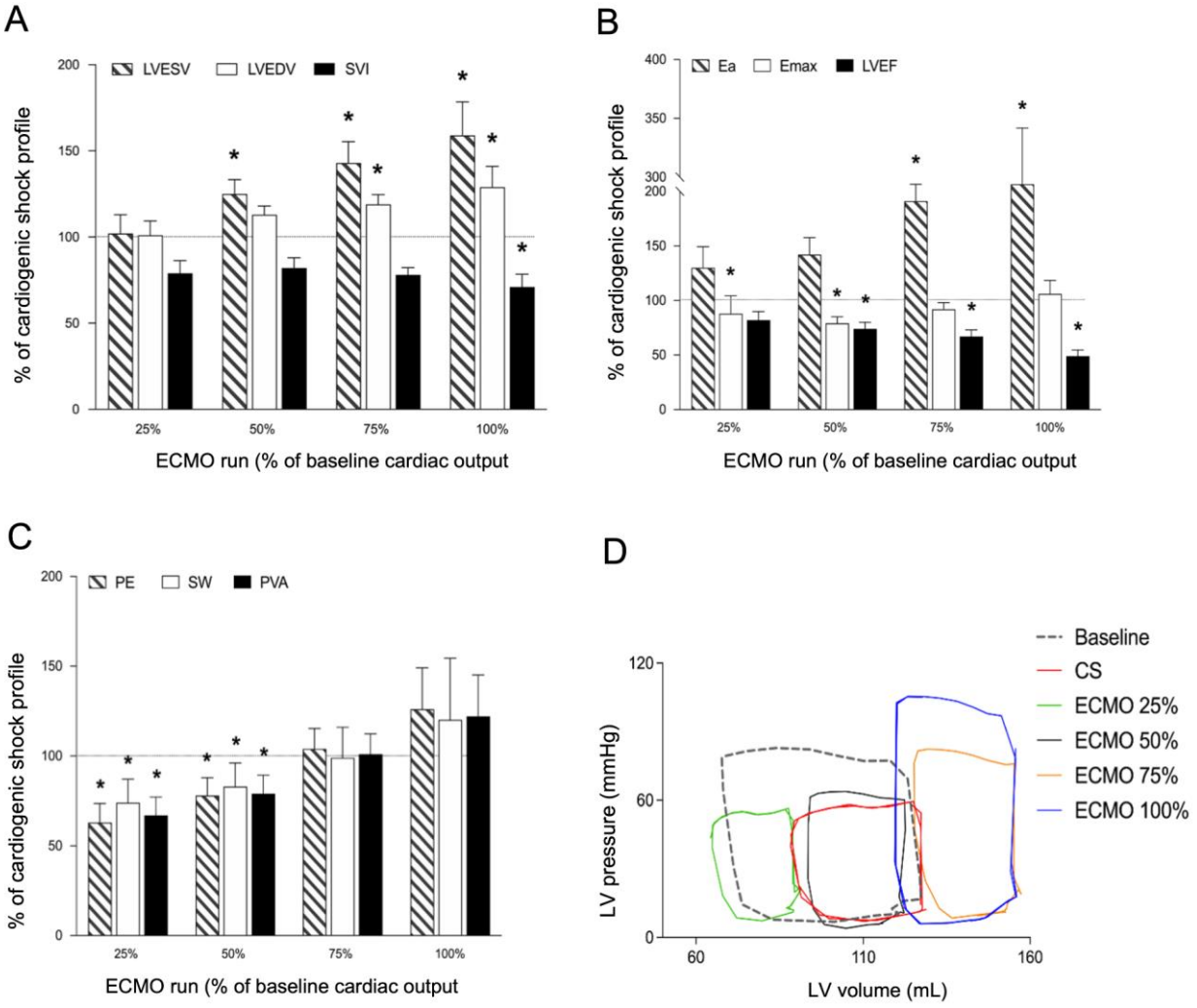
Position du problème et objectif(s) de l'étude:
A subset of patients surviving cardiogenic shock (CS) may develop chronic heart failure after ventricular remodelling. Cardiac overload appears to play a key role, through cell signaling pathways. For refractory CS, a peripheral venoarterial ECMO device can be implanted. This study was performed to confirm the presence of pVA-ECMO-induced overload, then examine its impacts on infarct size and signaling pathways involved in apoptosis and associated with cardiac remodeling.

Matériel et méthodes:
CS was induced in sheep by coronary injection of ethanol. Then, a pVA-ECMO device was implanted, and blood flow was increased from 25% to 100% of baseline cardiac output at 30-min intervals. At the end of the experiment, sheep hearts were removed for assessment of infarct size, histology, and apoptosis.
Sections were bathed in triphenyltetrazolium chloride solution to distinguish infarct, border, and remote zones. We then conducted immunoblotting analysis to examine the ERK-MAPK and reperfusion injury salvage kinase (RISK) cellular signaling pathways; the RISK pathway consists of a combination of twoparallel cascades: p38-MAPK and PI3K-Akt-mTOR pathways. Data are expressed as means ± standard errors of the mean. Shapiro–Wilk test was used for testing normality. Comparisons of two means were performed using paired or unpaired forms of Student's t-test, or the Wilcoxon test, as appropriate.
One-way analysis of variance was used for comparisons of ≥ 3 groups.

Résultats & Discussion:
A pVA-ECMO device was implanted in 17 female Dorset sheep (age, 20 ± 3 months). The hemodynamicprofile of CS was characterized by significant decreases in mean arterial pressure (−32% ± 3%), cardiacindex (−44% ± 4%). A significant increase in the arterial lactate level was observed from 1.5 ± 0.1 to 3.5 ± 0.2 mmol·L−1 ($P<0.01$). pVA-ECMO induced significant and blood flow-dependent increases in LV afterload (arterial elastance, Ea) and preload (LV end-diastolic volume and pressure) (fig 1 A and B). Pressure–volume area decreased up to pVA-ECMO blood flow at 50% of baseline, then returned to baseline values with higher blood flow (fig 1C and D). pVA-ECMO did not affect infarct size while a significant decrease in p38-MAPK phosphorylation and cardiac myocyte apoptosis were observed in border zone. pVA-ECMO was also associated with increased phospho-Akt levels while phospho-ERK1/2 levels were decreased in remote zone.

Conclusion:
The principles findings of our preclinical study are that pVA-ECMO : 1) induces a significant and flow-dependent increase in left ventricular loading conditions, 2) decreases contractility and energy indices correlated with lower energy consumption at low blood flow (<50% of baseline cardiac output); 3) does not affect infarct size, although it reduces pro-apoptotic p38-MAPK cellular signaling pathway andthe extent of apoptosis in the vulnerable border zone and 4) induces opposite changes in PI3K-Akt-mTOR

and ERK-MAPK cellular signaling pathways in remote zone.



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