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## Preliminary Study to the Development of a Right Ventricular Assist Device for the Patients with Univentricular Heart: An Animal Model

**Background:** Children with univentricular pathologies in whom a biventricular repair is impossible can survive with a palliative repair. Thereafter, only a Fontan correction or a heart-lung transplantation can be proposed. But, we believe that an implantable VAD could palliate the lack of organ for transplantation. We decided to explore the possibility of a definitive RVAD in the pulmonary circulation in the situation of univentricular heart. The aim of the present study was to test in this situation if a pulsatile or non-pulsatile device had different effects on pulmonary vascular reactivity.

**Methods:** A univentricular circulation was created into five pigs and their circulation was maintained with either or continuous flow by means of a roller pump or a pulsatile flow with a pneumatically driven assist device (Medos®). Insufflation pressure in the device was set at 150 mmHg or 300 mmHg. Adaptation of the pulmonary vasculature was evaluated by continuous pulmonary artery pressure (PAP) monitoring and its response to non-pharmacologic stimuli after 120 minutes support.

**Results:** The PAP is more than 35 mm Hg when the insufflation pressure is 300 mm Hg but with 150 mm Hg, the PAP is 20 mm Hg. The continuous flow assistance shows the same results. Non-pulsatile or pulsatile VAD with a low driving pressure in the right circulation don't change the pulmonary reactivity to hypoxia and hypercapnia.

**Conclusion:** A pulsatile right assistance with an insufflation pressure of 300 mm Hg must be avoided because of the risk of creating pulmonary hypertension. Assistance with 150 mm Hg or with a continuous flow doesn't create short-term threatening effect. The pulmonary arterial reactions during hypoxia and hypercapnia before and during mechanical support are not altered.

### Key words:

univentricular hearts, Fontan operation, right ventricular assist device, pulmonary vascular reactivity

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## **Vorläufige Studie zur Entwicklung eines RVAD (Right Ventricular Assist Device) für Patienten mit univentrikulärem Herzen: ein Tiermodell**

**Hintergrund:** Kinder mit univentrikulären Pathologien, bei denen keine biventrikuläre Reparatur möglich ist, können mit einer palliativen Reparatur überleben. Danach kann nur eine Fontan-Korrektur oder eine Herz-Lungen-Transplantation vorgeschlagen werden. Wir glauben jedoch, dass mit einem implantierbaren VAD der Mangel an Organtransplantaten gelindert werden kann. Wir beschließen, die Möglichkeit eines definitiven RVAD im Lungenkreislauf bei Vorliegen eines univentrikulären Herzens zu untersuchen. Ziel der Studie war abzuklären, ob in dieser Situation ein pulsatile oder ein nicht-pulsatile Gerät eine unterschiedlichen Einfluss auf die pulmonale Gefäßreaktivität ausübt.

**Methoden:** Es wurde bei fünf Schweinen ein univentrikulärer Kreislauf erzeugt, der jeweils entweder mit einem kontinuierlichen Fluss mittels Rollenpumpe oder mit einem pulsatilem Fluss über ein pneumatisch betriebenes Assist Device (Medos®) aufrechterhalten wurde. Der Einblasdruck im Gerät wurde auf 150 mmHg oder 300 mmHg eingestellt. Die Anpassung des Lungengefäßsystems wurde durch kontinuierliches Monitoring des pulmonalarteriellen Druckes (PAP) sowie durch die Reaktion auf nicht-pharmakologische Stimuli nach 120 Minuten Support untersucht.

**Ergebnisse:** Der PAP liegt über 35 mmHg, wenn der Einblasdruck 300 mmHg beträgt, bei 150 mmHg liegt der PAP jedoch bei 20 mmHg. Die kontinuierliche Fluss-Unterstützung zeigt die gleichen Ergebnisse. Nicht-pulsatile oder pulsatile VAD mit einem niedrigen Antriebsdruck im rechten Kreislauf bewirken keine Veränderungen der pulmonalen Reaktivität auf Hypoxie und Hyperkapnie.

**Schlussfolgerungen:** Eine pulsatile Unterstützung im rechten Kreislauf mit einem Einblasdruck von 300 mmHg muss vermieden werden, da hier das Risiko besteht, dass eine pulmonale Hypertension erzeugt wird. Eine Unterstützung mit 150 mmHg oder mit einem kontinuierlichen Fluss führt nicht zu kurzfristigen Gefahren. Die pulmonal-arteriellen Reaktionen während Hypoxie und Hyperkapnie vor und während mechanischem Support bleiben unverändert.

### **Schlüsselwörter:**

Univentrikuläre Herzen, Fontan-Operation, rechtsventrikuläres Unterstützungssystem, pulmonale Gefäßreaktivität

## **Introduction**

Patients born with univentricular hearts that cannot undergo a biventricular repair have to survive with a palliative procedure. A little more than 50% will die following various complications: ar-

rhythmias, pulmonary insufficiency, etc. (1-2). In the years following surgical palliation, a paediatric cardiac transplantation or a Fontan type correction can provide long-term survival. But, if pulmonary resistances are a little too elevated, the procedure is vowed to

failure (3-6). Moreover, a part of these patients will progressively endure a loss of their physical capacity and will die from progressive cyanosis and cardiac failure. The only possible alternative for these patients is a heart-lung transplantation with a life expectancy of 55% at 3 years (7).

Different studies have suggested that implantable devices for cardiac assistance could replace the organ for the patients with terminal cardiac failure that are not candidates for cardiac transplantation (8-17).

However all the experiments have been performed in animals or patients where the right ventricular assist device was implanted in parallel to the native circulation, the ejection from the native ventricle masking therefore the lack of pulsatility of the device. We have developed an animal model of univentricular heart where the whole pulmonary circulation is exclusively assured by the assist device. This model seemed the ideal setting to study the pulmonary vascular reactivity of the assisted pulmonary circulation.

## **Methods**

### *Animals and animal care*

Five landrace piglets (36,8-48kg, mean 42,75kg) were used for this research. All experimental protocols were approved by the ethic comity of the medical sciences for the animal experimentation. The study complied with the Principals of Laboratory Animal Care developed by the National Society for Medical Research and the Guide for the Care and Use of Laboratory Animals written by the National Institutes of Animal Resources and published by the NIH.

### *Preparation*

The animals were anesthetised following the same protocol than previously described (18). The measurements are taken at baseline, at the 15<sup>th</sup> minute, the 30<sup>th</sup> minute, 60<sup>th</sup> minute and finally at the 120<sup>th</sup> minute. The data are not instantaneous but expressed as a mean during one minute with the range.

Left atrial and pulmonary artery pressures are measured by direct puncture

of the left auricular appendix and the main pulmonary artery with a 23 G needle connected to a pressure transducer (Baxter®) and a bedside monitor (Standard Monitoring).

A Swan-Ganz catheter allows the measurement of the cardiac output by the thermodilution before surgery.

To measure  $p_aO_2$ ,  $p_aCO_2$  and pH, we have used the i-STAT (Birmingham, UK).

Finally, vascular resistances are calculated by the pressure difference divided by the flow ( $R = \Delta P/Q$ ).

### Pumps

To create a pulsatile flow, a pneumatic driven ventricular assist device was used, the MEDOS®. For the experiment, we used a 57 millilitres pump. The driving pressure was experimentally selected and the rate was adapted to get an output near the baseline native heart output.

To create a continuous flow, we used a roller pump. The technique of canulation of the ventricle and the canulas we used were identical, only the pump and the length of tubing were different. Flow was regulated to obtain the baseline cardiac output of the pig.

### Surgical Technique

The pulmonary artery (PA) is then clamped to insert the inlet canula from the VAD. The canula is placed 1 cm below the PA separation and is connected to the pump with a 30 cm long tubing. The main PA is tied with a thread of silk to avoid any blood return to the right ventricle.

Then, the pump is activated at a fixed rate. Blood recovered by the suction canula is reinjected to the pig to avoid hypovolemia. Blood unfit for reinjection is compensated by blood (pig donors) or a colloidal solution.

Coagulation time is checked every 30 min by use of the Hemotec Medi-bridge® to have an ACT above 200. At the same time, blood gases were analysed by use of the i-STAT®. Animal ventilation was adapted if needed to keep the  $pCO_2$  between 35-40 mm Hg and a pH of 7,35-7,45. The  $FiO_2$  is kept constant (0,3-0,5). Blood is transfused if haemoglobin values are less than 6 g/100ml.

The aim was to test three settings for the RVAD: pulsatile flow with the Medos at a driving pressure of 300 mmHg, pulsatile flow with the Medos at a driving pressure of 150 mmHg and non pulsatile flow with a roller pump at a flow set near the baseline cardiac output of the pig.

So that we finally had one pig with two hours at 300 mmHg, two pigs with two hours at 150 mmHg, one pig at continuous flow driving two hours and one pig with changing driving pressure.

Beside hemodynamic and biological measurements during support, after two hours the reactivity of the pulmonary circulation to pathophysiological stimuli was tested by inducing hypoxia (by decreasing  $FiO_2$ ) and hypercapnia (by decreasing minute ventilation).

## Results

### Pulmonary Pressures and Pulmonary Vascular Resistances

As described in table 1 reporting pulmonary pressures and table 2 reporting pulmonary vascular resistances, a significant increase of pulmonary pressures and resistances is observed after starting right ventricular support at 300

mmHg. Whereas in the first pig, both pressure and resistances decreased over time and returned towards baseline values, the second pig didn't tolerate this support and, even though driving pressure was decreased after 20 minutes, pulmonary bleeding remained untractable. On the contrary, with a pulsatile support and a driving pressure of 150 mmHg as well as with a continuous flow set at the baseline cardiac output of the pig, only small variations of pulmonary pressure and resistances were observed throughout the experimental period.

### Hypoxia and Hypercapnia

To evaluate the pulmonary vasoreactivity after two hours of support, we first measured baseline changes in pulmonary pressure and resistances during hypoxia and hypercapnia when the pig was anaesthetized, equipped with the lines and with the chest opened (same conditions as measurement with mechanical support).

As shown in table 3, hypercapnia in this situation slightly increased pulmonary pressure (+20%) but more the calculated vascular resistances (+79%)

Tab. 1: Pulmonary Artery Pressure (mmHg)

|                 | Baseline | 15 minutes | 60 minutes | 120 minutes |
|-----------------|----------|------------|------------|-------------|
| Medos RVAD 300  |          |            |            |             |
| Pig 1           | 21±1,2   | 28±1,4     | 25±1,2     | 28±0,9      |
| Pig 2           | 16±1,2   | 37±2,3     | -          | -           |
| Medos RVAD 150  |          |            |            |             |
| Pig 3           | 14±1,0   | 15±1,1     | 15±0,9     | 15±0,8      |
| Pig 4           | 9±1,2    | 10±1,3     | 12±1,1     | 12±0,9      |
| Continuous Flow |          |            |            |             |
| Pig 5           | 14±1,3   | 15±1,2     | 17±1,1     | 19±0,9      |

RVAD: Right Ventricular Assist Device

Tab. 2: Pulmonary Vascular Resistances (dyne.s.cm<sup>-5</sup>)

|                 | Baseline | 15 minutes | 60 minutes | 120 minutes |
|-----------------|----------|------------|------------|-------------|
| Medos RVAD 300  |          |            |            |             |
| Pig 1           | 328      | 408        | 160        | 220         |
| Pig 2           | 160      | 212        | -          | -           |
| Medos RVAD 150  |          |            |            |             |
| Pig 3           | 136      | 144        | 88         | 160         |
| Pig 4           | 168      | 128        | 144        | 168         |
| Continuous Flow |          |            |            |             |
| Pig 5           | 240      | 296        | 144        | 168         |

RVAD: Right Ventricular Assist Device

Tab. 3: Basal Test of Pulmonary Vascular Reactivity

|             | p <sub>a</sub> O <sub>2</sub><br>(mmHg) | p <sub>a</sub> CO <sub>2</sub><br>(mmHg) | pH   | PAP<br>(mmHg) | PVR<br>(dynes.s.cm <sup>-5</sup> ) |
|-------------|---|--|------|---------------|------------------------------------|
| Baseline    | 140                                     | 51                                       | 7,41 | 15±1,2        | 93                                 |
| Hypercapnia | 140                                     | 88                                       | 7,15 | 18±1,5        | 167                                |
| Baseline    | 150                                     | 52                                       | 7,37 | 16±1,1        | 111                                |
| Hypoxia     | 52                                      | 49                                       | 7,43 | 24±2,4        | 204                                |

PAP: Pulmonary Artery Pressure; PVR: Pulmonary Vascular Resistances

Tab. 4: Test of Pulmonary Vascular Reactivity after two hours RV support at 150 mmHg

|             | p <sub>a</sub> O <sub>2</sub><br>(mmHg) | p <sub>a</sub> CO <sub>2</sub><br>(mmHg) | pH   | PAP<br>(mmHg) | PVR<br>(dynes.s.cm <sup>-5</sup> ) |
|-------------|---|--|------|---------------|------------------------------------|
| Baseline    | 210                                     | 49                                       | 7,43 | 14,3±1,2      | 176                                |
| Hypercapnia | 172                                     | 104                                      | 7,12 | 15,3±1,4      | 164                                |
| Hypoxia     | 13                                      | 44                                       | 7,49 | 20±2,3        | 280                                |

PAP: Pulmonary Artery Pressure; PVR: Pulmonary Vascular Resistances; RV: Right Ventricular

Tab. 5: Test of Pulmonary Vascular Reactivity after two hours RV support at continuous flow

|             | p <sub>a</sub> O <sub>2</sub><br>(mmHg) | p <sub>a</sub> CO <sub>2</sub><br>(mmHg) | pH   | PAP<br>(mmHg) | PVR<br>(dynes.s.cm <sup>-5</sup> ) |
|-------------|---|--|------|---------------|------------------------------------|
| Baseline    | 237                                     | 30,9                                     | 7,42 | 18,3±1,4      | 160                                |
| Hypercapnia | 46                                      | 67,9                                     | 7,12 | 28±2,3        | 560                                |
| Hypoxia     | 27                                      | 51,5                                     | 7,45 | 40±5,6        | 737                                |

PAP: Pulmonary Artery Pressure; PVR: Pulmonary Vascular Resistances; RV: Right Ventricular

Tab. 6: Pressure Measurement at different sites of the circuit

|        | Medos<br>D.P. :<br>300 mmHg<br>Output:<br>3,6 L/min | Medos<br>D.P. :<br>150 mmHg<br>Output:<br>2,7 L/min | Roller Pump<br>Output:<br>3,6 L/min | Roller Pump<br>Output:<br>2,7 L/min |
|--------|---|---|-------------------------------------|-------------------------------------|
| Site 1 | 260±40  | 180±32  | 136±27                              | 104±11                              |
| Site 2 | 187±35,6  | 114±13,5  | 58±6,8                              | 36±7                                |
| Site 3 | 64±7,2  | 29±3,1  | 33±3,4                              | 29±3                                |
| PAP    | 40±8,2  | 24±3,2  | 28±2,3                              | 19±1,3                              |

D.P.: Driving Pressure; PAP: Pulmonary Artery Pressure

whereas hypoxia significantly increased both pressure (+50%) and resistance (+80%). After two hours right ventricular support with the Medos and a driving pressure of 150 mmHg (Table 4) and with a continuous flow (Table 5), the same pattern is observed: a moderate increase of pressure and resistances during hypercapnia and much bigger increase during hypoxia.

#### Pressure in the circuit

Finally, we were interested in measuring the pressure drop along the circuits and therefore a small needle was inserted at various sites and connected to the pressure transducer. Site 1 was just at the outlet of the pump, site 2 was at the connection between the circuit and the pulmonary artery cannulae and site 3 was 3 centimetres, before the end of the pulmonary artery canula (Figure 1 and Figure 2).

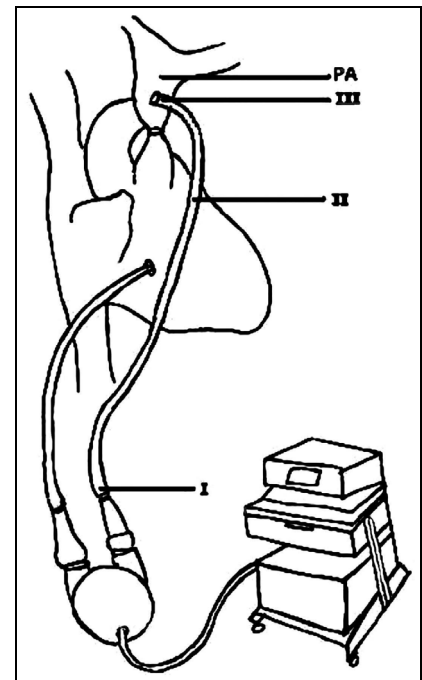


Fig. 1: Implantation of the Medos® system

PA: pulmonary artery  
I, II, III: site I, II and III

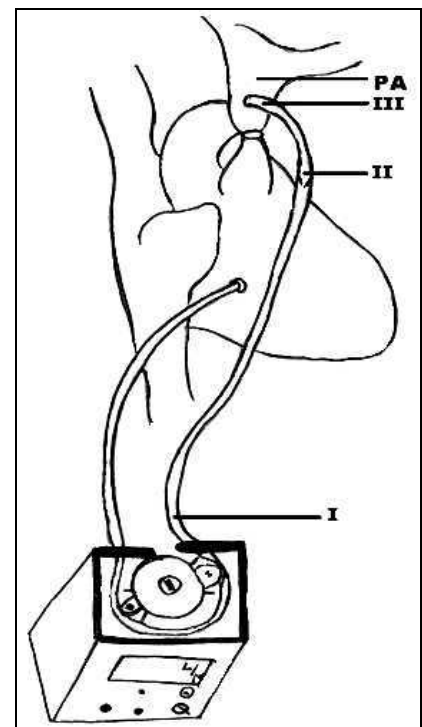


Fig. 2: Implantation of the roller pump

PA: pulmonary artery  
I, II, III: site I, II and III

The material between the sites 1 and 2 is the extension tube made of silicone, between the sites 2 and 3 is the arterial canula in PVC and between the sites 2

and 3 it's the insertion of this canula in the pulmonary artery.

As shown in table 6, with the Medos, the largest pressure drop occurred between site 2 at site 3 (in the pulmonary artery canula) whereas the pressure drop between these 2 points was much lower with the roller pump.

## Discussion

These experiments were conducted in order to test what should be the best choice for a prolonged right ventricular assistance in an animal model of univentricular heart.

We tested if a continuous flow that would in theory be less physiological than a pulsatile flow would change pulmonary vascular reactivity to non pharmacological stimuli.

Continuous flow was provided by means of a roller-pump. Even though this pump is not suited for prolonged support, for a relatively short period of time, it is producing a flow that is similar to other continuous flow producing pumps like centrifugal or axial pumps.

Pulsatile flow was produced with a pneumatically driven paracorporeal pump connected to the right ventricle and the pulmonary artery. This pump has been chosen because it is relatively cheap as compared to other pulsatile devices and its transparency allows visual inspection of the pump. Parameters that are to be set by the operator are pump rate, driving pressure, negative pressure and duration of systole. From our experiments, using a high driving pressure (300 mmHg) was clearly deleterious; even though in some animals, this was well tolerated, in two animals this resulted in high pulmonary artery pressure leading to pulmonary haemorrhage in one pig.

Staged pressure measurement indicated that, with the material we used, the pressure at the tip of the pulmonary artery canula was largely above a normal pulmonary artery pressure.

On the opposite, with a driving pressure of 150 mmHg, the pressure at the tip of the canula was near the normal range of pulmonary artery pressure and was well tolerated by all animals.

Both continuous flow or pulsatile flow with a driving pressure of 150 mmHg were well supported by the animals after more of 2 hours of support, the re-

sponse to vasoconstricting stimuli (hypoxemia and hypercapnia) was similar to the response to the same stimuli before RVAD implantation, that is a slight increase of the PAP in hypercapnia and much higher increase during hypoxia.

From the staged pressure measurements in the circuit, it appears that the major pressure drop was observed in the return canula because of its stiffness and diameter. Of an efficiency point of view, to avoid such loss of power other cannulas with different diameters and materials should be used. Due to the size of the pigs, it is however difficult to decrease the size of the canula so that probably only other materials could be tested. The driving pressure should be set accordingly so that the pressure at the end of the circuit should be in the range of normal pulmonary pressure.

For the different variations in pressures or in resistances during the tests "Hypercapnia" and "Hypoxia", the reactivity of the pulmonary artery is preserved because changes observed during mechanical support are in the same range as without support.

Thus our experiments let us conclude that a longer period of mechanical RV support seems possible without altering pulmonary vascular reactivity, with continuous or pulsatile flow provided pressure at the end of the circuit remains in the normal range of pulmonary pressure.

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