

Impact of atrial fibrillation on hemodynamics in a sheep model of the Fontan circulation

Megan M. McKittrick

Oregon Health & Science University

Yoshio Otaki

Oregon Health & Science University

Ashok Muralidaran

Oregon Health & Science University

Sonnet S. Jonker

Oregon Health & Science University

Samantha Louey

Oregon Health & Science University

Andrew Giustini

Oregon Health & Science University

Sarah M. Alaniz

Oregon Health & Science University

Seshadri Balaji

balajis@ohsu.edu

Oregon Health & Science University

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Abstract

Arrhythmias are a common cause of morbidity and mortality in patients who undergo the Fontan operation. The impact of atrial fibrillation (AF) on hemodynamics in the Fontan population is unclear. The aim of this study was to describe hemodynamic changes following onset of AF in a sheep model of the Fontan operation. We hypothesized that AF will negatively impact hemodynamics and Fontan pressure. Adult female non-pregnant sheep were anesthetized, intubated, had central arterial and venous lines placed, and underwent an off-bypass extracardiac Fontan operation with epicardial atrial and ventricular pacing wire placement. Data were collected in normal sinus rhythm pre- and post-operatively, and in any spontaneous dysrhythmia throughout the procedure. AF was induced using rapid atrial pacing at atrial rates of 400–600 bpm. Cardiac output was calculated using the Fick equation, with an estimated O_2 consumption of 5 mL/kg/min. Four out of 8 sheep studied developed AF: 2 spontaneously after surgery and 2 with rapid pacing. Compared with sinus rhythm, AF resulted in a significant elevation of the central venous pressure by 2mmHg ($p < 0.05$) without a change in mean arterial pressure, an increase in arteriovenous O_2 saturation difference by 30% ($p = 0.001$) and a fall in cardiac output also of 30% ($p < 0.05$). Atrial contraction contributes about 30% to the cardiac output in sheep who have undergone the Fontan. These findings have significant implications for patients those with Fontan physiology who go on to develop AF.

Introduction

The Fontan operation remains the definitive palliation for children born with single ventricle congenital heart disease, with approximately 1,100 procedures performed annually within the United States [1]. Arrhythmia development has been associated with significant morbidity and poorer survival outcomes in those with single ventricle heart disease, even when risk adjusted for a patient's baseline hemodynamics [2]. Arrhythmia remains the commonest late morbidity, with an incidence up to 65% by 25 years post-Fontan [3]. The most common tachyarrhythmia in this patient population is intra-atrial reentrant tachycardia [4]. However, as these patients age, AF is fast becoming an important problem. There are reports suggesting that AF occurs up to 30 years earlier, and with a 15-fold higher incidence, in patients with congenital heart disease versus those without [5]. Multiple studies have demonstrated a negative association between new-onset arrhythmia and ventricular function [2]. Furthermore, arrhythmia and sudden cardiac death remain the second leading cause of mortality in palliated patients, behind only Fontan failure [6].

There are few reports on the impact of AF on hemodynamics and outcomes in this patient population. We studied the acute hemodynamic impact of AF on a sheep model of the Fontan operation.

Methods

Animal details:

The study was approved by the Institutional Animal Care and Use Committee. Adult (> 1 year old) non-pregnant female sheep (53-69kg body weight) were obtained from a local vendor. Animals were acclimated to the laboratory facility for a minimum of 3 days, and fasted for 24 hours (water ad libitum) prior to surgery.

Surgery:

Anesthesia was induced with ketamine (7 mg/kg, intravenous [IV]) and diazepam (0.2 mg/kg, IV). Ewes were intubated and mechanically ventilated (positive end expiratory pressure: 5cm H₂O) on 100% oxygen (2 L/min) and isoflurane (1.5%–5%) during the surgical instrumentation portion of the procedure. An IV catheter was placed in the left lateral saphenous vein (20g, Terumo, Somerset, NJ) and the left jugular vein (16g, Terumo, Somerset, NJ). A double lumen central venous access device (4fr 8cm, Teleflex, Morrisville, NC) was placed with ultrasound guidance into the right jugular vein. A single lumen arterial pressure monitoring catheter (3fr 5cm, Cook Medical, Bloomington, IN) was placed into the right carotid artery. Arterial and central venous pressures were measured using transducers (Transpac IV ICU Medical, San Clemente, CA) calibrated against a mercury manometer, and recorded digitally (Powerlab, ADInstruments, Colorado); heart rate was derived from the arterial pressure trace. Anesthesia was maintained with a fentanyl continuous infusion (5 mcg/kg bolus followed by a rate of 5–10 mcg/kg/hr, additional boluses as needed) and ketamine boluses (2 mg/kg) as needed. Blood pressure was maintained through IV fluids (Lactated Ringer Solution (LRS) with 5% Dextrose at 5 mL/kg/hr for 1 liter, then LRS alone at 5–10 mL/kg/hr) with vasopressin infusion (1.8-6.0 U/hr), and boluses of epinephrine (0.003–0.005 mg/kg) and calcium gluconate (10–30 mg/kg) as needed. Rocuronium (0.05 mg/kg) was given prior to beginning the chest incision and paralysis was monitored through a non-harmful aversive stimulus every 15 minutes.

Sheep were placed in the left lateral decubitus position and surgery was based on a previously described technique [7]. The third and fourth ribs were removed for right thoracotomy.

The pericardium was opened with an incision parallel to the phrenic nerve. The tissue between the pulmonary artery and aorta was dissected. The mobilized main pulmonary artery (MPA) was partially occluded with a curved vascular clamp at the mid-zone. We typically noticed hemodynamic perturbations at this point, necessitating vasopressor and/or inotropic support and fluid administration. The clamped segment of MPA was incised and a 16 mm Dacron graft was sutured to the arteriotomy using 4 – 0 polypropylene suture in a running fashion, creating an end-to-side anastomosis. Following this, the graft was clamped close to the MPA and the vascular clamp was removed. The inferior vena cava (IVC) was then mobilized and controlled with a partially occluding curved vascular clamp. A longitudinal incision was made and the other end of the Dacron graft was anastomosed to this incision in an end-to-side fashion using 4 – 0 polypropylene. The graft was clamped again close to this incision followed by removal of the vascular clamp. Systemic heparin (100 U/kg) was then administered.

A 24 French straight venous cannula was then inserted into the right atrial appendage via a 4 – 0 polypropylene purse-string suture controlled with a tourniquet. The superior vena cava (SVC) was

mobilized and cannulated with a 22 French right-angled cannula via a purse-string suture, with the tip of the cannula facing cephalad. The two cannulae were de-aired and connected, creating a passive superior vena cava to right atrial connection.

The SVC around the cannula was then controlled with an umbilical tape passed through a tourniquet. The SVC – right atrial junction was clamped, followed by transection of the superior vena cava and oversewing of the cardiac end using 4 – 0 polypropylene suture. The open distal end of the SVC was then anastomosed to a longitudinal incision made at a suitable location on the Dacron graft in an end-to-side fashion using 4 – 0 polypropylene. The umbilical tape around the SVC was then removed. The clamps at the proximal and distal ends of the Dacron graft were released and the graft was de-aired.

An umbilical tape was placed at the IVC – right atrial junction and passed through a tourniquet. This was synched to occlude the junction. The passive SVC-to-right atrial connection was then clamped and the cannulae removed, hence completing the Fontan circuit. Temporary epicardial atrial and ventricular pacing wires were then placed.

Experimental protocol:

The sheep remained under anesthesia as above for the duration of the experiment, with the exception that FiO_2 was adjusted by mixing medical air and oxygen to the desired range.

Hemodynamics (arterial and central venous pressures, heart rate) were recorded throughout the duration of the experiment, as described above. A three lead ECG was recorded. Baseline recordings were commenced at completion of the Fontan, as described above. Data were collected in normal sinus rhythm pre- and post-operatively, and in any spontaneous dysrhythmia throughout the procedure. AF was induced using rapid atrial pacing at atrial rates of 400–600 bpm for 60–120 seconds. Paired blood samples were obtained from the central arterial and venous canulae at baseline and after the animal had been in AF for five minutes. Blood gases were run on a Radiometer 825 (Radiometer America, OH). Cardiac output was calculated using the Fick equation, with an estimated O_2 consumption of 5 mL/kg/min.

At the end of the experiment, the animal was euthanized via venous injection of 10ml lb^{-1} of pentobarbital sodium and phenytoin sodium.

Statistics:

Paired-samples t-tests were used to compare means. A p-value of ≤ 0.05 (2-sided alpha) was used to determine statistical significance. Data are reported as mean $\pm$ SD and shown as raw data in the figures.

Results

Given the aim of the study was to determine hemodynamic changes following onset of AF, data are only included for sheep that developed AF. Four of eight total sheep studied developed AF and were included

in this study. Two (ewes #1 and #2) developed spontaneous AF immediately post-operatively, while AF was induced in two sheep following rapid atrial pacing (ewes #3 and #4). Two sheep (ewes #1 and #3) had ventricular rates approximating normal sinus rates (100 – 120 bpm) while the remaining two (ewes #2 and #4) had rapid ventricular response with ventricular rates 200 – 250 bpm. Figure 1 shows a representative ECG tracing of AF.

Although there was not a significant effect on mean arterial pressure (51.8 ± 4.4 vs 42.8 ± 9.3 mmHg, $p > 0.05$, Figure 2A), AF led to a 2.1 mmHg increase in Fontan (central venous) pressure vs normal sinus rhythm (19.8 ± 2.8 vs 21.9 ± 3.1 mmHg, $p < 0.05$, Figure 2B). AF resulted in a significant increase in arteriovenous oxygen difference (ΔAVO_2) as compared to normal sinus rhythm, with ΔAVO_2 increasing from 46 ± 10 % to 66 ± 11 %, $p = 0.001$, Figure 2C). Cardiac output decreased by approximately 30%, 6.9 ± 2.0 to 4.8 ± 1.4 L/min, $p < 0.05$, Figure 2D).

Discussion

Our study showed that AF led to significant hemodynamic changes including a 2.1 mmHg increase in Fontan pressure and a 30% reduction in cardiac output in a sheep model of the Fontan operation. Thus, AF appears to have an immediate negative effect on hemodynamics in the Fontan circulation.

The hallmarks of Fontan physiology include chronically elevated systemic venous pressures which supply the pressure-head for the passive, non-pumped flow into the pulmonary circulation. Any perturbation which elevates this pressure has been shown to result in adverse outcomes [2]. In the Fontan circulation, the pulmonary vasculature and its resistance become the limiting step which determines the preload available to the systemic ventricle. This, in turn, prevents the circulation from augmenting cardiac output as needed during periods of increased demand. Thus, the Fontan circulation is an inherently fragile one, which does not tolerate any additional impediments to cardiac output [2].

The hemodynamic impact of AF in otherwise structurally normal hearts remains poorly described. Newer studies utilizing advanced imaging suggest a decrease in hemodynamic efficiency with decreased myocardial perfusion, increased myocardial oxygen extraction, and decreased cardiac power during AF [8]. These perturbations are exacerbated in those with univentricular hearts who have undergone the Fontan palliation. Fontan and Baudet originally described the hemodynamic foundation of the univentricular circulation in 1971, with its preload limitations and sensitivity to atrioventricular synchrony [9]. Choussat and colleagues subsequently emphasized the importance of sinus rhythm in maintaining cardiac output [10]. Dysrhythmias, especially tachyarrhythmias, cause significant perturbations in pulmonary and systemic circulation in patients with a Fontan circulation [11]. Rapid atrial rates lead to increased atrial pressures, which are directly transmitted to the Fontan circuit, impairing passive pulmonary flow. This leads to decreased pulmonary venous return and diastolic filling time, increased diastolic filling pressures, and ultimately, a decrease in cardiac output. In such a preload-dependent system, maintenance of sinus rhythm and effective and synchronized atrial contraction is crucial in optimizing cardiac output and preventing hemodynamic deterioration.

There are few published studies on the impact of AF on the Fontan circulation. Sugimoto and colleagues reported the impact of AF on cardiac output using a computational model of the Fontan circulation [12]. They found that AF reduced the cardiac output by approximately 25%; a number similar to our findings.

One arrhythmia which could be considered somewhat similar in some respects to AF, is junctional rhythm. Junctional rhythm secondary to sinus node dysfunction is common in patients who have had the Fontan operation [13]. Acute studies have demonstrated a decrease in cardiac output by up to 28% in those with junctional rhythm with Fontan circulation [14-15]; this is on par with our calculated reduction in cardiac output even in only 4 animals. However, the impact of AF is likely more substantial than that of junctional rhythm given the irregularity of the rhythm and the potential for increased ventricular rate, which may pose an additional negative impact on cardiac output secondary to limited ventricular filling time.

Studies have shown the significantly higher incidence, and earlier occurrence of AF in patients with complex congenital heart disease. Advances in surgery are now allowing more patients with complex congenital heart disease to survive and the cohort of adults with congenital heart disease is increasing in number and age [2]. This implies that we could witness a huge wave of adults with Fontan who develop AF in the coming decades. One conclusion to draw from our study is that we need to develop techniques to prevent the development of AF, to recognize it as soon as it occurs and to treat it effectively so that it does not become persistent and impact long term outcomes in this patient cohort.

Limitations:

While sheep offer the advantage of a similar body size and cardiac structure to human patients, there are some noteworthy limitations to the present study. Unlike the staged approach used in humans, sheep models (including those included in this analysis) utilize a single stage approach, converting directly from baseline normal biventricular circulation to Fontan physiology in otherwise healthy animals. Given the staged timing of interventions in human palliation, it is reasonable to expect some different hemodynamic responses to arrhythmia following Fontan completion.

Although we studied 8 sheep, AF only developed in only four of them, two of which developed AF spontaneously. The remaining four did not develop AF despite rapid atrial pacing. It has been noted that responses can be highly variable with anywhere from 29% to 77% of sheep developing AF depending on the pacing duration [16]. Given the small number of sheep that developed AF, we are unable to make any broad conclusions.

Additionally, our findings reflect the impact of AF immediately post-Fontan. This limits our ability to make any conclusions regarding the chronic impact of persistent AF. Patients experience a wider range of arrhythmia than those described here, and many develop arrhythmia over the longer term. As such, the data described here represents a small subset of the hemodynamic perturbations likely experienced by

those with Fontan circulations. These findings highlight the need for further research into the hemodynamic impacts of AF in human patients with Fontan physiology.

Conclusion

Sustained AF leads to significantly impaired cardiac output and elevation of central venous pressure in sheep with a newly-created Fontan circulation. Our study implies that prevention of AF and prompt recognition and management of AF will be important in the management of patients who have had a Fontan operation.

Declarations

Competing Interests

Non-financial interests: AG acted as site PI for a research grant funded by Purdue Pharma through April 2025. Financial interests: SB acts as a consultant to Milestone pharmaceuticals. The remaining authors have no relevant financial or non-financial interests to disclose.

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Disclosures, declarations

If you have any, list them next to your name, otherwise write “none”.

McKittrick – none

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Author Contribution

S.B, S.J, and S.L. conceived and designed the study, all authors contributed to model creation and data collection, M.M. and S.B. analyzed the data, M.M. drafted the manuscript and all authors edited the manuscript.

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Data Availability

Restrictions apply to the availability of these data, which were generated and used under licence for the current study and are not publicly available. The data are, however, available upon request and with the permission of the Knight Cardiovascular Institute.

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Figures

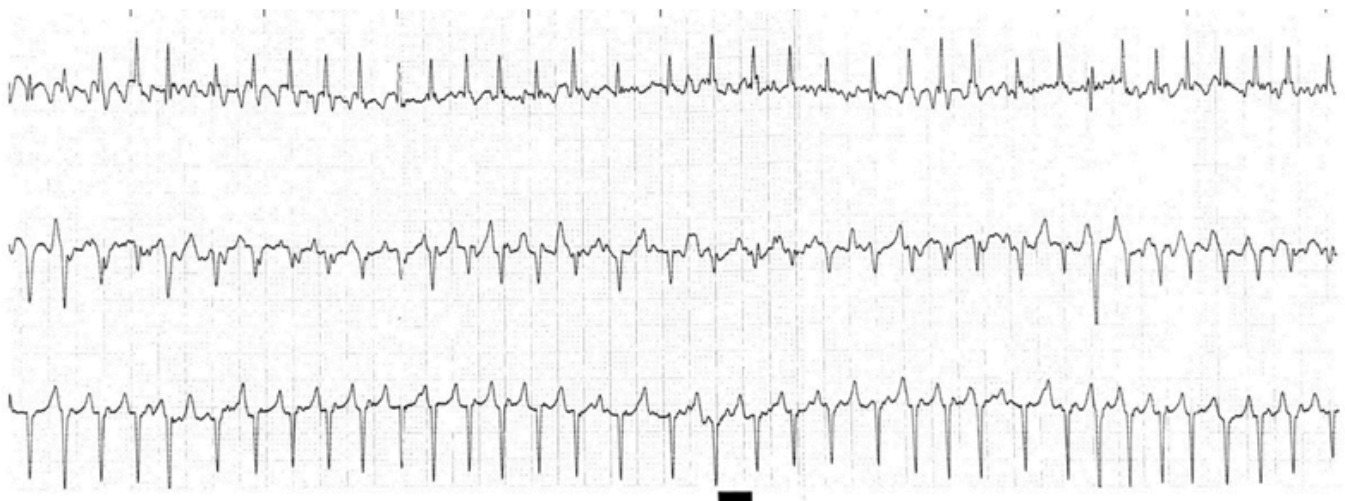


Figure 1

Representative ECG tracings (paper speed 25 mm/s) of AF.

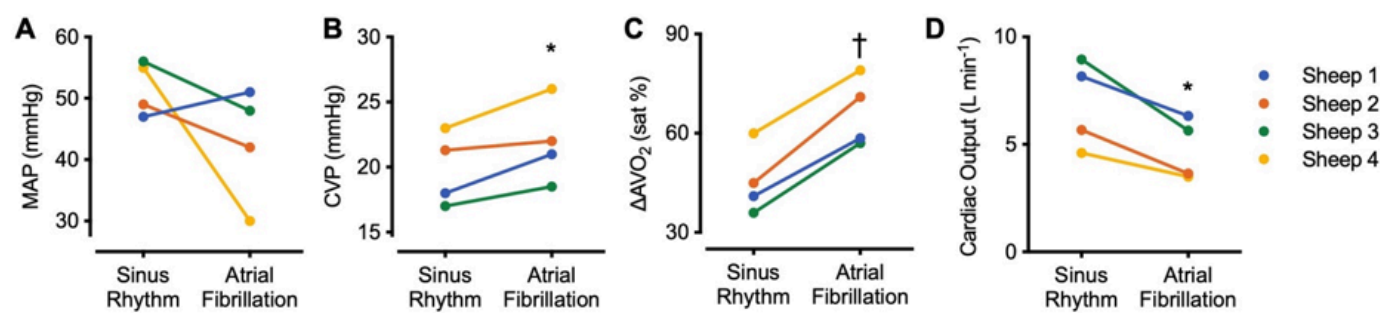


Figure 2

Hemodynamic changes between sinus rhythm and AF. (A) Mean arterial pressure and (B) central venous pressure averaged over a period of three seconds in normal sinus rhythm and after five minutes of AF. (C) Arteriovenous oxygen difference (saturation %) and (D) cardiac output (via Fick equation) were calculated after five minutes of AF. Data are shown for individual animals; * $p<0.05$, † $p=0.001$.