

## Long term negative pressure ventilation: Rescue for the failing fontan?

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we review the pathophysiology of failing Fontan, current therapies and propose a novel way of treating the failing Fontan by utilizing negative pressure ventilation to reverse some of the maladaptive changes. This is a hypothesis paper. We think, the ideas central to the manuscript are worth bringing out for intellectual discussion and wider testing.

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### Abstract

Current treatment strategies for single ventricle patients include non-intervention strategy, surgical palliation or primary transplantation. Surgical palliation includes a staged operative course culminating in the Fontan operation. With progress in surgical techniques, the survival has been improving. However, almost all of these Fontan patients will demonstrate pathophysiologic changes that ultimately constitute "Fontan failure physiology". This article reviews the pathophysiologic changes, current approach to management of these patients and proposes a novel way of reversing some of the pathophysiologic changes by utilization of negative pressure ventilation.

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**Key words:** Fontan; Single ventricle physiology; Negative pressure ventilation; Cardiorespiratory interactions; Congenital heart disease

**Core tip:** In the current surgical era for congenital heart disease, palliation of single ventricle patients has become standard of care. However, pathophysiologic failure after the third stage of palliation (Fontan) is commonplace, with very few therapeutic options. Failing Fontan physiology is a management challenge. Herein,

### INTRODUCTION

The Fontan pathway is a palliative pathway for single ventricle patients. This pathway allows us to utilize the single ventricle as a systemic pumping chamber and create separation between the pulmonary and systemic circuits thereby allowing sustenance of life. We have therefore dramatically altered the natural history of these congenital heart problems.

Over the last two decades, with significant improvement in the surgical and perioperative technologies, the mortality of complicated cardiac surgeries such as the Fontan procedure has been reduced<sup>[1-3]</sup>. However, as the current Fontan population becomes older, we are facing a new challenge of managing failing Fontan circulations. Currently we have very limited options for management of the failing Fontan physiology<sup>[4,5]</sup>. This paper proposes new modality for management of these complex patients and the clinico-pathologic evidence for its use.

### THE FAILING FONTAN

Fontan or total cavo-pulmonary connection is a staged surgical palliation of functional single ventricle. It allows

us to designate the single ventricle (or the dominant ventricle) as the systemic ventricle. The other essential part of this pathway, then, is to establish source of pulmonary blood flow without a designated “pulmonary” ventricle. At completion, this constitutes a staged connection of the superior vena cava to the pulmonary artery (Glenn procedure) followed by connection of the inferior vena cava to the pulmonary artery (Fontan procedure).

In the current era, this inferior vena cava to the pulmonary artery connection is made by using either an intra-atrial baffle (lateral tunnel) or by using an extracardiac conduit. After completion of this stage of repair, the systemic venous return is channeled appropriately to the pulmonary artery for oxygenation, while the pulmonary veins return to the common atrium, to be ejected out of the single systemic ventricle. Thus, circulation in series is established. This allows, in theory, for fully saturated blood to be pumped out to the systemic circulation. In practice, saturations are around 92% to 94% early postoperatively, with small arteriovenous malformations and coronary sinus blood flow contributing to the lower saturation<sup>[6]</sup>. However, as the patients get older, there is a gradual decline in the oxygen saturations due to various factors. Progressive desaturation is only one of the problems of Fontan in later years. Lack of the pulmonary ventricle eventually leads to multiple problems related to the hemodynamics of failing Fontan circuit. Main reasons for late mortality are related to arrhythmias, thromboembolism and protein losing enteropathy<sup>[7]</sup>. Other manifestations of the failing Fontan circuit include systemic venous congestion, hepatic dysfunction, coagulopathy, plastic bronchitis, progressive cardiac failure and cardiac cachexia. These are major causes of morbidity and mortality in Fontan patients<sup>[4,5,8]</sup>.

Along with the above, there is progressive decrease in the forward flow of blood to the pulmonary vascular bed, leading to progressive hypoxemia and cyanosis. Development of systemic to pulmonary venous collaterals further contributes to the development of cyanosis<sup>[6]</sup>.

There are limited medical and surgical options for management of these patients<sup>[4,9,10]</sup>. For some patients who meet the eligibility criteria including a low pulmonary vascular resistance, heart transplantation is an option. The early outcomes of heart transplantations in patients with failed Fontan are slightly worse compared to patients with cardiomyopathies or other congenital heart diseases<sup>[11,12]</sup>. Heart transplantation is therefore a reasonable option in selected group of patients, with organ supply being a significant limiting factor. Patients with classic atriopulmonary connection and incessant arrhythmias or flow obstruction may need conversion to an extracardiac cavo-pulmonary connection<sup>[9]</sup>. Other surgical interventions focus on relieving obstructive causes of Fontan failure (*e.g.*, conduit obstruction) or systemic atrioventricular valve replacement for significant regurgitation. As a palliation for high Fontan pressures, creation of a fenestration from the Fontan to the atrium is considered<sup>[13]</sup>.

Medical management of failing Fontan focuses on treating individual issues<sup>[4,5]</sup>. Systemic venous congestion

and volume overload is treated with diuretics. Aggressive diuresis however, can be counterproductive. Anticoagulation, either with anti-platelet agents or coumadin is used in the presence of thrombosis. Myocardial dysfunction manifests itself as both systolic and diastolic dysfunction. Severe myocardial dysfunction may warrant intravenous milrinone therapy. There is limited data to suggest significant benefits occur from using ACE inhibitors or beta-blockers in failing Fontan<sup>[14,15]</sup>. Similarly, newer agents such as endothelin receptors antagonists have failed to show impact in Fontan patients. Medical therapy for other complications such as protein losing enteropathy has only had modest success<sup>[16]</sup>.

As mentioned above, all of these constitute piecemeal approach and none of these strategies address the one of the primary problems, which is, decreased antegrade flow across the Fontan circuit to the pulmonary vascular bed causing the pathophysiology of failure.

## HEMODYNAMIC EFFECTS OF NEGATIVE PRESSURE VENTILATION

Negative pressure ventilators were one of the first ventilators developed and served a vital role during the Polio epidemics in the twentieth century. Overtime, positive pressure ventilators have completely replaced them as conventional modes of ventilation. As a result, there are very limited circumstances in contemporary medicine under which negative pressure ventilation negative pressure ventilation (NPV) is being considered<sup>[17,18]</sup>. An example would be patients with neuromuscular disorders for long term respiratory support<sup>[17]</sup>.

Currently, there are some commercially available devices for delivering NPV. Porta- Lung<sup>TM</sup> is a modern version of the iron lung. It is a closed chamber system that delivers effective negative pressure ventilation and has been used for long term ventilatory support. Cuiras<sup>®</sup> ventilator is a shell that is applied over the chest and delivers NPV. This mode applies negative pressure locally over the thorax only and allows for better patient mobility and ease of access. The ventilators that drive these units have also undergone significant improvements over the years, including ability to synchronize breaths with patient initiated breaths as well as with cardiac cycle<sup>[19]</sup>.

From cardiac and hemodynamic standpoint, NPV has significantly different effects as compared to positive pressure ventilation (PPV). These cardiopulmonary interactions are much more physiologic than those of PPV.

In a normal heart, NPV and by extension, negative intrathoracic pressure leads to reduction in the right ventricular afterload thus augmenting right ventricular function and right ventricular cardiac output. NPV helps maintain lung volumes close to functional residual capacity, which reduces the pulmonary vascular resistance and improves pulmonary blood flow<sup>[20]</sup>. In physiologic states as well as in patients after simple cardiac surgery, NPV has been shown to augment cardiac output<sup>[21]</sup>. In patients with Glenn or Fontan physiology, where there is depen-

dence on passive diastolic blood flow, NPV directly augments passive blood flow to the lungs by creating a negative thoracic gradient<sup>[22,23]</sup>. As a downstream consequence, there is an increase in the pulmonary venous return and cardiac output.

In experimental models and small studies, benefits of NPV in immediate post-operative period have been documented<sup>[24]</sup>. Shekerdemian *et al.*<sup>[25,26]</sup> have shown hemodynamic benefits of NPV in patients with right ventricular dysfunction in post-operative period<sup>[25,26]</sup>. Similarly, augmentation of cardiac output by using NPV, in the immediate post operative period for patients undergoing Fontan procedure has also been documented<sup>[23]</sup>.

We have recently documented the dramatic application of a NPV in the rescue of a failing Kawashima patient, resulting in successful recovery after failure of all conventional therapies<sup>[27]</sup>.

All of these applications of NPV in Fontan patients have been for a very short term ; either in the immediate post-operative state or during hemodynamic studies. There has not been an application for long-term use of NPV in cardiac patients as a rescue measure or mode of palliation for these single ventricle patients. We propose such a novel application, based on strong hemodynamic reasoning as outlined above as well as the aforementioned short term application studies.

## HYPOTHESIS

Our hypothesis is that long-term use of negative pressure ventilation is an effective mode of rescue for patients with failing Fontan physiology. Our hypothesis extends to suggest that long term use of NPV will: (1) improve antegrade flow to the pulmonary bed across the Fontan circuit (by creating intrathoracic negative pressure). This in turn would lead to: decrease Fontan pressures; decrease hepatic vein wedge pressure thereby decreasing hepatic congestion and improving hepatic function; decrease formation of ascites; and decrease peripheral edema; (2) stabilize and even improve oxygen saturation (better Fontan flow and improved oxygenation); (3) improve cardiac output (based on 21-23); and (4) provide symptomatic improvement as measured by exercise capacity and patient self-assessment scores.

## CLINICAL APPLICATION

The proposed method of practical application of this management strategy is as follows. The initial step is appropriate patient selection. Patients who have undergone Fontan procedure and have been classified as failing Fontan patients will be candidates for this therapy. Patients with fixed obstruction that is reversible (such as stenosis of branch pulmonary artery) should be intervened on prior to selection. All patients should get a comprehensive imaging workup, either with echocardiography or an MRI where echocardiography is inadequate.

The recommended method of delivery of NPV is by using a synchronized biphasic cuirass ventilator. Initiation

of NPV should be in hospital setting. This will provide closer monitoring during initiation as well as allow adjustments on ventilator setting, assessment of patient comfort and patient education. A baseline complete metabolic assessment including electrolytes, liver function tests and brain natriuretic peptide (BNP) should be obtained. More invasive monitoring including blood gases (arterial and mixed venous) as well as pulmonary artery pressure should not be mandated, but may be beneficial during initial experience.

Settings on the NPV to be optimized as tolerated. After this short stay, patients should be able to use the NPV at home. Home NPV therapy may be designed with various levels of intensity. The proposed level is about 10 to 12 h of NPV during evening and night hours , thus allowing patients to continue with there daily activities during the day time. For younger patients as much as 16 h of NPV time would be recommended. Recommendations for follow-up include telephone call follow-up every week to address any concerns as well as maintain compliance. Patients will be asked to check weights at home every week.

Follow-up as outpatient should be in two weeks initially, followed by monthly until the care-giver deems appropriate. A repeat complete metabolic panel and BNP should be obtained in 3 mo. Functional status assessment as well as exercise capacity testing should be performed at 6 mo. Continued follow-up to assess improvement in hemodynamics and symptomatology as deemed appropriate by the primary cardiologists should be maintained.

Possible problems related to long-term use of NPV are very minimal and have been described in other settings. Main issues are related to obtaining a good comfortable fit so as to minimize skin contact injury. Patients with upper airway obstruction or significant tracheomalacia are not suitable candidates for NPV and should be excluded<sup>[17,18]</sup>.

## CONCLUSION

Palliation of single ventricle patients has led to increase in long term survival for these complex patients. Current staged surgical palliation concludes with Fontan surgery. However, there are multitudes of problems related to the Fontan circulation that result in significant morbidity and mortality, ultimately resulting in a state of Fontan failure.

As described above, there are limited options for management of a failed Fontan. Here in we propose an innovative use of NPV to augment the Fontan flow and improve the underpinnings of the pathophysiology of Fontan failure.

There is strong experimental and clinical data to suggest that NPV augments the hemodynamics in patients with single ventricle physiology<sup>[21-25]</sup>. The ability of the modern negative pressure ventilators to be portable, accessible and effective has provided the opportunity of unique application of these ventilators as a long term therapy for failing Fontan patients.

The authors propose that this strategy will provide a

novel therapy to address a growing problem and provide improved quality of life to this group of patients.

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