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Reaching Consensus for Unified Medical Language in Fontan Care.

Brief Title: Consensus for Morbidity Definitions in Fontan

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Running Title: Fontan consensus statement

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Tweet: #Fontan terminology is confusing and imprecisely defined. This consensus statement defines key morbidities to standardize the use of language in clinical care, research and registries. Twitter: @AlsaiedTarek @rahulrathodmd @sasha_opo @wernerbudts

Abstract:

Aims:

The Fontan operation has resulted in improved survival in patients with single ventricle congenital heart disease. As a result, there is a growing population of teenagers and adults with a Fontan circulation. Many comorbidities have been increasingly recognized in this population due to the unique features of the Fontan circulation. Standardization of how Fontan co-morbid conditions are defined will help facilitate understanding, consistency, and interpretability of research and clinical experience. Unifying common language usage in Fontan is a critical precursor step for data aggregation, comparison of research findings and clinical outcomes, and ultimately accelerating improvements in management for this growing group of patients. This manuscript aimed to create unified definitions for morbidities seen after the Fontan palliation.

Methods:

In association of many congenital heart disease organizations, this work used Delphi methodology to reach a broad consensus among recognized experts regarding commonly used terms in Fontan care and research. Each definition underwent at least 3 rounds of revisions to reach a final definition through surveys sent to experts in the field of single ventricle care.

Results:

The process of reaching a consensus on multiple morbidities associated with the Fontan procedure is summarized in this manuscript. The different versions that preceded reaching the consensus are also presented in the supplemental material. Table 1 represents the final definitions according to the consensus.

Conclusions:

We propose the use of these definitions for clinical care, future research studies, registry development, and clinical trials.

Keywords: Fontan, Single ventricle, congenital heart disease, cirrhosis, portal hypertension, consensus

Reaching Consensus for Unified Medical Language in Fontan Care.

Introduction:

Since its introduction in 1969, the Fontan procedure has transformed the lives of many patients with single ventricle physiology, offering them the potential for survival and improved quality of life well into adulthood [1]. The original procedure was described by Fontan in patients with tricuspid atresia [2]. Indications for the operation have expanded over time to include all other types of single ventricle, with incremental modifications and better outcomes [2]. The procedure connects the systemic veins directly to the branch pulmonary arteries. Thus, the systemic venous blood flows passively to the lungs without a sub-pulmonary ventricle[3,4] . The procedure now is performed in almost all patients born with single ventricle congenital heart disease at an age between 2-5 years. Good Fontan candidates have good systolic ventricular function, good atrioventricular valve function and sinus rhythm. Before the procedure the patient undergoes a

hemodynamic evaluation with cardiac catheterization to ensure low ventricular filling pressure, low pulmonary vascular resistance and adequate pulmonary arteries.[3,4]

It is estimated that there are 70,000 patients alive with a Fontan circulation worldwide. The circulation is characterized by an elevated central venous pressure due to connection with the pulmonary arteries and a low cardiac output [3,4,5]. As more patients with a Fontan circulation reach adulthood, a variety of cardiac and non-cardiac complications involving almost every organ system, are increasingly common, presenting significant management challenges [3],[4]. Early recognition may be important to address potential hemodynamic causes and potentially prevent the progression of life-threatening extra-cardiac disease[5]. Many different terms have been used to describe disease states associated with the Fontan circulation, often without explicit definition which has created confusion and uncertainty. Standardization of how Fontan associated morbidities are defined will help facilitate understanding, consistency, and interpretability of research and clinical experience [6, 7]. Additionally, standardized definitions will allow direct comparison between clinical studies and aggregation of trial and registry datasets [8]. The present consensus statement proposes standardized definitions for a set of comorbid conditions commonly associated with the Fontan circulation. We present a brief summary of the available literature before each definition.

Methods and Evidence Review

In association with leading organizations and initiatives [Alliance of Adult Research in Congenital Cardiology (AARCC), the International Society for Adult Congenital Heart Disease

(ISACHD), the National Pediatric Cardiology Quality Improvement Collaborative (NPC-QIC), The Fontan Outcomes Network (FON), Fontan Outcomes Registry using CMR Examinations (FORCE) and the International Fontan Interest Group (IFIG)] we applied the University of California Los Angeles/RAND modified-Delphi methodology to arrive at definitions for a set of predetermined common Fontan-related diagnoses [9, 10].

In summary, in order for a term to make it through this entire process, each definition underwent at least 3 rounds of revisions. The initial draft of this document was circulated to the above organizations for approval and suggestions were incorporated in the document without changing the consensus definitions. The final definitions are summarized in table 1 and the percentage of agreement through the three stages of consensus is summarized in the supplement table. The process is summarized in figure 1 and the Delphi methodology is summarized in figure 2 and the supplemental document.

Terms and Definitions

Fontan Circulatory Failure (FCF)

Fontan circulatory failure (FCF) is a broad, non-specific term commonly used to indicate deteriorating clinical status [11, 12]. Published studies have variably used FCF as a composite endpoint to include death, transplantation, or listing for transplantation [11, 13]. Additionally, the development of patient-experienced exercise intolerance, inability to carry out daily life activities, or Fontan takedown have sometimes been included in the definition of FCF [2, 14-16]. Other variables included within the spectrum of FCF were heart failure symptoms, and other

comorbidities including arrhythmias, thromboembolism, protein losing enteropathy (PLE), plastic bronchitis, edema, persistent effusions, and liver dysfunction [15, 17, 18]. The causes of FCF are similarly diverse and can include systolic or diastolic ventricular dysfunction, valve disease, elevated pulmonary vascular resistance, chronic arrhythmia, Fontan associated liver disease or lymphatic insufficiency (PLE, ascites, and plastic bronchitis (PB)) [14, 19]. As the etiology of FCF is heterogenous and "heart or pump failure" is only seen in some of the cases, we avoided the term heart failure. This is similar to the term respiratory failure rather than lung failure used in pulmonary medicine as lung failure is a narrow term and capture only a portion of all cases.

> ***Definition****: "A broad, non-specific term describing dysfunction of the Fontan circulation that affects a patient's ability to carry out daily life activities. Etiology may include ventricular dysfunction, atrioventricular valve failure, increased pulmonary vascular resistance, recurrent arrhythmia, Fontan pathway obstruction, lymphatic insufficiency, or end-organ dysfunction. Symptoms may be related to heart failure, Fontan pathway obstruction, hypoxemia or end-organ dysfunction including liver disease, protein-losing enteropathy, and plastic bronchitis. Severe Fontan circulatory failure is defined as a composite of mortality, listing for heart transplantation, Fontan takedown, or the decision to initiate palliative care due to lack of candidacy for heart transplantation."*

Fontan Takedown

Fontan takedown to an intermediate palliative circulation is an important treatment option for patients with FCF [16]. The majority of Fontan takedown procedures are performed in the

perioperative period after the Fontan operation to manage early FCF. Occasionally Fontan takedown has been used as a strategy for late FCF years after the initial Fontan surgery [16, 20]. In some cases creating a fenestration or enlarging an existing fenestration may provide symptomatic improvement. In more severe cases, Fontan takedown usually includes reversion to a superior cavopulmonary connection, with or without an additional aorto-pulmonary shunt [20, 21]. This procedure carries a high perioperative morbidity and mortality as the hemodynamics and clinical state of the patient at the time of undergoing surgery is usually markedly deranged [16, 20]. Despite these concerns, Fontan takedown can, in selected cases, effectively stabilize clinical status and act as a bridge to transplantation or provide time for rehabilitation and recovery prior to reattempting the Fontan procedure [20].

> ***Definition***: *"The deconstruction of one or more of the Fontan connections to partial cavo-pulmonary anastomosis and/or an aorto-pulmonary shunt due to Fontan circulatory failure."*

Systolic Ventricular Dysfunction

A progressive decrease in ventricular systolic function was recognized as an important concern after the Fontan procedure [19, 22]. The low ejection fraction can be related to altered preload without intrinsic ventricular dysfunction in some patients and that may explain the lack of response to inotropes in such cases. Accurate evaluation of ventricular systolic function in patients with Fontan circulation by echocardiography remains challenging and qualitative assessment is standard in many institutions given the heterogeneity of ventricular geometry in

these patients. Contemporary techniques, including myocardial speckle tracking strain (deformation) imaging, may prove to be a helpful adjunct in evaluating myocardial function [23, 24]. The complex 3-dimensional cardiac anatomy and the frequency of limited acoustic windows make cardiac MRI a gold standard to evaluate ventricular function in patients with a Fontan circulation[24, 25]. Many adults with a Fontan circulation have a low resting cardiac index and reduced end-systolic ventricular elastance [26]. Older age at the time of the evaluation and older age at Fontan seem to correspond to a higher risk for the development of systolic dysfunction in this patient population [27]. Once systolic dysfunction develops, and if severe enough, it may result in low cardiac output and symptoms of Fontan circulatory failure (FCF) [14].

> ***Definition***: *"The presence of single ventricle ejection fraction <50%. Severe single ventricle systolic dysfunction is defined as an ejection fraction <30%."*

Diastolic Dysfunction

While systolic function can be preserved late after the Fontan operation, diastolic dysfunction is relatively common and may play a substantial role in morbidity [28-30]. The chronic preload insufficiency may result in myocardial remodeling, increased ventricular stiffness, increased filling pressures, and eventually a progressive decline in cardiac output [31-33]. Not surprisingly, compliance and relaxation abnormalities in the single ventricle have been documented after the Fontan operation [29]. It is likely that diastolic function abnormalities start as a secondary phenomenon due to altered preload and then progresses into more advance stage with elevated filling pressures. Why only some patients develop diastolic dysfunction and elevated end-

diastolic pressures is likely multifactorial, but a genetic component may be contributory [34]. Evidence of diastolic abnormality may be detected in up to 68% of patients with a Fontan circulation at a mean age of ~ 12 years using echocardiographic criteria normally applied to biventricular hearts [35, 36]. It has yet to be confirmed, however, whether these Doppler patterns predict filling pressures of the systemic ventricle. Feature tracking deformation (strain) imaging may prove helpful in detecting diastolic dysfunction in this patient population [37, 38]. At the moment, direct measurement of ventricular end-diastolic pressure remains the gold standard for the evaluation of diastolic dysfunction [39, 40]. Various studies have suggested > 10 or 12 mmHg as defining an elevated end-diastolic pressure, with the recent emergence of the potential role for provocative testing (fluid challenge) to help identify patients with occult diastolic dysfunction [19, 40, 41]. Data on the hemodynamic definition, however, is sparse and further research is needed to provide more definitive guidance on specific cut-offs and best options for provocative testing.

> ***Definition****: "A state of decreased single ventricle compliance leading to increased filling pressures. An end-diastolic pressure or pulmonary capillary wedge pressure ≥ 12 mm Hg at rest or ≥ 15 mmHg after rapid volume expansion is suggestive of diastolic dysfunction."*

Fontan Pathway Obstruction

An unobstructed Fontan pathway is essential for optimal Fontan hemodynamics [42, 43]. Obstruction in the Fontan pathway can happen at any level from the vena cavae to the branch pulmonary arteries [42]. Some common locations include the inferior limb of the Fontan baffle, the

lateral tunnel or extra-cardiac conduit, and the branch pulmonary arteries. The left pulmonary artery (LPA) can become compressed by the aortic root or ascending aorta, especially in patients with hypoplastic left heart syndrome (HLHS) [44]. Right pulmonary artery (RPA) torsion may be associated with the use of an extra-cardiac conduit for Fontan completion [45]. Fontan baffle obstruction and branch pulmonary artery stenosis or compression may result in elevated Fontan baffle pressures and are associated with worse exercise capacity [46]. Obstruction in the Fontan circuit may be associated with significant power loss and may expose the abdominal viscera, especially the liver, to a greater congestive burden. Previous elegant work using computational flow dynamics showed that power loss correlates with the minimum cross-sectional area of the pulmonary arteries in Fontan circulations [47, 48]. Stent implantation in the Fontan conduit and lateral tunnel baffle to eliminate obstruction has been reported to optimize hemodynamics with few side effects [42, 49].

> ***Definition:*** *"An anatomical or functional narrowing detected by catheterization or cross-sectional imaging anywhere in the cavo-pulmonary pathways. This may or may not manifest with flow discrepancy on cardiac MRI or hemodynamic perturbation with a gradient as low as 1 mmHg at cardiac catheterization."*

Elevated Pulmonary Vascular Resistance

Growth, development, and regulation of the pulmonary vasculature are inherently abnormal in patients with single ventricle physiology. Reduced pulmonary blood flow can start in fetal life and continues after Glenn and Fontan palliation [31, 32]. Pulsatile flow is often absent after

completion of the superior cavopulmonary connection [31, 50]. However, even before the loss of pulsatility, significant regional maldistribution of pulmonary blood flow may occur due to abnormal connections, ductal constriction, external compression, or local alterations in small vessels resulting in heterogeneous vascular resistance [51]. Further, the normal vasodilatory mechanisms may be suppressed due to the absence of pulsatile blood flow and the effect of gravity on venous return to the lungs which may only become evident during exertion [52, 53]. The resultant physiology, the relatively low flow and low pressure system, presence of multiple sources of pulmonary blood flow, and high prevalence of arteriovenous malformations, together make it challenging to assess pulmonary resistance. Further larger-scale data is needed to define expected findings in resting pulmonary vascular resistance and pressure-flow relationships in the pulmonary circulation in the absence of a right ventricle, and to define the relationship between pulmonary vascular resistance and clinical outcomes [50, 51].

The existing small retrospective and prospective published series have consistently reported worse outcomes when resting pulmonary vascular resistance exceeded 2 indexed Wood units [13, 54, 55]. There are currently no published data using non-indexed PVR in patients with a Fontan circulation.

> ***Definition**: "Pulmonary vascular resistance (PVR) above 2 indexed Wood units (Wood units * m^2 body surface area) in individuals with normal or near normal body surface area (BSA). In individuals with extremes of BSA, no data currently exist for the Fontan*

circulation, but the clinically applied cut-off is > 2.3WU, a value which has been considered to indicate poor outcomes in the context of biventricular circulations."

Lymphatic Insufficiency

The pathophysiology of PLE and PB is intricately related to lymphatic system abnormalities [56, 57] (Figure 3). Elevated venous pressure at the micro-circulation level results in increased lymphatic production. Chronic severe lymphatic overload may cause pathologic dilation and consequent dysfunction of the lymphangion, the functional unit of the lymphatic system. Proximal drainage from the lymphatic system into the venous circulation may become impaired due to high central venous pressures, physical obstruction due to stenosis at the lympho-venous connections causing exit block from the lymphatic circulation, or from impaired contractile function of the lymphangion [58]. This leads to focal sites of abnormal lymphatic drainage and lymphatic proliferation due to increased lymphangiogenesis signaling [59]. Lympho-venous channels abound in the lymphatic circulation and anatomic variation of such lympho-venous connections together with lymphatic rupture to lower pressure compartments determine specific clinical phenotypes of lymphatic insufficiency. Lymph effluent usually drains proximally at the level of the innominate vein into the central venous circulation. However, a considerable variation of these proximal connections has been documented, and prior cardiac surgical intervention has been associated with impaired or obstructed lymphatic drainage to the venous system [56, 60, 61]. Decompressing lymph drainage into the pleural cavity results in chylous pleural effusion, drainage into the peritoneal cavity causes ascites, into the bronchial tree (PB), into the bowels (PLE), and into a

specific limb, lymphedema praecox [62]. Importantly, there are many causes of ascites or pleural effusion in the Fontan circulation, and the presence of these findings does not necessarily indicate that lymphatic insufficiency is the primary cause.

Imaging the lymphatic system remains challenging, but T2-weighted MRI techniques are promising [63, 64]. An improved understanding of lymphatic anatomy and the development of catheter-based lymphatic interventions to embolize abnormal channels may result in significant improvement in the management of PB and some cases of PLE [64, 65]. Additionally, diverting the lymphatic drainage of the thoracic duct to a lower pressure compartment (e.g. the systemic atrium) may alleviate symptoms of PLE and PB [57, 66-68].

> ***Definition***: *"Any abnormality in the form or function of the lymphatic system resulting in a clinical disease state. Depending on the location of the lymphatic vessel decompression, lymphatic insufficiency may manifest variably as protein-losing enteropathy, plastic bronchitis, ascites or pleural effusion."*

Plastic Bronchitis

PB is a serious complication of the Fontan circulation, occurring in 1-4% of patients [69-71]. Risk factors include post-operative prolonged pleural effusions or ascites[72]. The pathophysiology is thought to be related to abnormal lymphatic drainage around the airways [61]. The disease may manifest as episodic expectoration of bronchial-shaped casts or visualization of these on

bronchoscopy; this can cause wheezing and respiratory distress. Acute airway obstruction can be life-threatening and may lead to suffocation, hypoxemia, and death.

> ***Definition***: *"A pulmonary lymphatic disorder characterized by the leakage of proteinaceous material into the airways, resulting in episodic expectoration or bronchoscopic visualization of bronchial shaped casts that can be associated with respiratory distress, wheezing or significant airway obstruction."*

Protein-Losing Enteropathy

PLE is a major cause of morbidity and mortality after the Fontan operation [61, 73, 74]. The prevalence is thought to be between 3-18 % and can occur at any point after the Fontan operation [61, 75]. The causes are poorly understood but likely include a combination of high venous pressure, abnormal mesenteric circulation, gut inflammation, and abnormal lymphatic flow [60, 76]. Though PLE is often progressive, some patients have a waxing-and-waning course. Many patients exhibit a preclinical phase with protein loss, but without any symptoms or hypoalbuminemia. Remission can occur, with the only manifestation of prior PLE being either hypoalbuminemia or abnormally high enteric protein loss.

> ***Definition***: *"The state of increased enteric protein loss [as measured by fecal α1 antitrypsin (spot > 54 mg/dl, α1 antitrypsin clearance > 27 ml /24 hours without diarrhea and > 56 ml/24 hours with diarrhea) or by nuclear scintigraphy using technetium-99m labeled albumin]. It can be subclinical or associated with 1)*

hypoalbuminemia < 3.5 g /dl, and total protein < 6 g/dl and 2) any of the following clinical symptoms: edema, abdominal distention or discomfort, diarrhea, or effusions (ascites, pleural or pericardial effusions).”

Low Exercise Performance

Although Fontan completion may result in improved exercise capacity, as measured by peak oxygen consumption (VO_2), patients with Fontan circulation generally have markedly reduced exercise capacity [77]. Most studies report a mean peak VO_2 of 48 to 65 percent of what would be predicted for age, sex, and weight [78-81]. Decreased exercise capacity in patients with Fontan circulation is attributed to a blunted increase in stroke volume with exercise due to limited venous return, presumably due to a bottleneck in the pulmonary circulation [82]. Other factors include the inability to appropriately increase heart rate and systemic arterial desaturation. Further, the Fontan circulation is associated with decreased muscle mass which may affect exercise capacity as it may decrease the ability to augment preload during exercise or to use oxygen during exercise [83, 84]. Decreased exercise capacity is associated with increased mortality in patients with a Fontan circulation [79, 81, 85, 86]. Extremely low peak VO_2 in patients with a Fontan circulation (peak VO_2 below 16.6 mL/kg/min) is an important mortality predictor [85, 87]. Additionally, a decline in peak VO_2 over time is also an important predictor of death and transplantation [88, 89]. Peak heart rate and heart rate reserve may also provide prognostic information [85, 86].

***Definition**: "Peak VO_2 below 50% of the predicted value for the general non-affected population of equivalent age, sex, and body size on a symptom-limited maximal exercise test. High performance is considered present when peak VO_2 is above 80% of predicted values."*

Fontan-Associated Liver Disease

Fontan-associated liver disease (FALD) is a major non-cardiac complication of the Fontan circulation, which may lead to substantial morbidity and early mortality [4]. The etiology of FALD remains unclear, with elevated central venous pressure and possibly abnormal liver lymphatic drainage as important contributors [90]. Liver fibrosis is ubiquitous in adult patients with a Fontan circulation and about two-thirds have severe fibrosis [91]. Some risk factors recognized in previous studies included older age, longer time since the Fontan completion, and peri-operative insults [4, 12, 91, 92]. Weight control to prevent steatohepatitis, avoiding alcohol, and hepatotoxic medication avoidance and vaccination against hepatitis may help slow progression of FALD. Recent expert guidance includes screening for liver disease every 3-5 years in childhood and every 1-2 years in adolescents using laboratory screening [4], though there have been no empirical studies evaluating the benefit of any particular approach to liver evaluation. Abdominal ultrasound is reasonable at baseline and referral to hepatology should be considered in patients with abnormal screening results [4, 90, 93]. In addition, abdominal cross-sectional imaging using magnetic resonance imaging and computerized tomography (CT) scan is an important tool to screen for liver lesions [94].

***Definition**: "The broad spectrum of liver disease and its consequences, attributable to Fontan hemodynamics. FALD includes varying degrees of hepatic fibrosis, compensated and decompensated cirrhosis, focal nodular hyperplasia, laboratory evidence of hepatic injury or impaired synthetic function, and hepatocellular neoplastic lesions."*

Please refer to the supplement for the complete list of definitions and the steps taken to reach consensus on each definition. A complete list of references are also presented.

Conclusion

The above terms and definitions represent the consensus of a large panel of experts in single ventricle physiology and selected-non-cardiac specialties. We propose utilizing these definitions for clinical care, future research studies, registries, and clinical trials. Unifying common language usage in Fontan is a critical precursor step for data aggregation, comparison of research findings and clinical outcomes, and ultimately accelerating improvements in management for this growing group of patients.

Term	Definition
Fontan Circulatory Failure	A broad, non-specific term describing dysfunction of the Fontan circulation that affects a patient's ability to carry out daily life activities. Etiology may include ventricular dysfunction, atrioventricular valve failure, increased pulmonary vascular resistance, recurrent arrhythmia, Fontan pathway obstruction, lymphatic insufficiency, or end-organ dysfunction. Symptoms may be related to heart failure, hypoxemia or end-organ dysfunction including liver disease, protein losing enteropathy, and plastic bronchitis. Severe Fontan circulatory failure is defined as a composite of mortality, listing for heart transplantation, Fontan takedown, or the decision to initiate palliative care due to lack of candidacy for heart transplantation.
Fontan Takedown	The deconstruction of one or more of the Fontan connections to partial cavo-pulmonary anastomosis and/or an aorto-pulmonary shunt due to Fontan circulatory failure.
Systolic Dysfunction	The presence of single ventricle ejection fraction <50%. Severe single ventricle systolic dysfunction is defined as an ejection fraction <30%.
Diastolic Dysfunction	A state of decreased single ventricle compliance leading to increased filling pressures. An end-diastolic pressure or pulmonary capillary wedge pressure ≥ 12 mm Hg at rest or ≥ 15 mmHg after rapid volume expansion is suggestive of diastolic dysfunction.
Fontan Pathway Obstruction	An anatomical or functional narrowing detected by catheterization or cross-sectional imaging anywhere in the cavo-pulmonary pathways. This may or may not manifest with flow discrepancy on cardiac MRI or hemodynamic perturbation with a gradient as low as 1 mmHg at cardiac catheterization.
Elevated Pulmonary Vascular Resistance	Pulmonary vascular resistance (PVR) above 2 indexed Wood units (Wood units * m2 body surface area) in individuals with normal or near normal body surface area (BSA). In individuals with extremes of BSA, no data currently exist for the Fontan circulation, but the clinically applied cut-off is > 2.3 Wood Units, a value which has been considered to indicate poor outcomes in the context of biventricular circulations..
Sustained Atrial or Ventricular Tachycardia	An atrial or ventricular rate of more than 100 beats per minute in adults, or two standard deviations above the mean in children, lasting for more than 30 seconds, or <30 seconds if associated with hemodynamic instability, or of any duration, if arrhythmia therapy is used. This definition excludes sinus tachycardia. Atrial and ventricular tachycardia should be categorized separately.
Bradycardia	Heart rate below 50 beats per minute in adults or below the 5th percentile for age in children.
Lymphatic Insufficiency	Any abnormality in the form or function of the lymphatic system resulting in a clinical disease state. Depending on the location of the lymphatic vessel decompression, lymphatic insufficiency may manifest variably as protein-losing enteropathy, plastic bronchitis, ascites or pleural effusion.
Plastic Bronchitis	A pulmonary lymphatic disorder characterized by the leakage of proteinaceous material into the airways, resulting in episodic expectoration or bronchoscopic visualization of bronchial shaped casts that can be associated with respiratory distress, wheezing or significant airway obstruction.
Protein-Losing Enteropathy	The state of increased enteric protein loss [as measured by fecal α1 antitrypsin (spot > 54 mg/dl, α1 antitrypsin clearance > 27 ml /24 hours without diarrhea and > 56 ml/24 hours with diarrhea) or by nuclear scintigraphy using technetium-99m labeled albumin]. It can be subclinical or associated with 1) hypoalbuminemia < 3.5 g /dl, and total protein < 6 g/dl and 2) any of the following clinical symptoms: edema, abdominal distention or discomfort, diarrhea, or effusions (ascites, pleural or pericardial effusions).
Low Exercise Performance	Peak VO_2 below 50% of the predicted value for the general non-affected population of equivalent age, sex, and body size on a symptom-limited maximal exercise test. High performance is considered present when peak VO_2 is above 80% of predicted values.
Fontan-Associated Liver Disease (FALD)	The broad spectrum of liver disease and its consequences, attributable to Fontan hemodynamics. FALD includes varying degrees of hepatic fibrosis, compensated and decompensated cirrhosis, focal nodular hyperplasia, laboratory evidence of hepatic injury or impaired synthetic function and hepatocellular neoplastic lesions.
Cirrhosis	A histologic diagnosis defined by bridging fibrosis and nodular regeneration. While defined by histology, the diagnosis can be strongly suggested by radiological assessment (e.g., nodular liver contour, features of portal hypertension such as splenomegaly, collateral vessels, ascites, and significantly elevated liver stiffness using ultrasound or magnetic resonance).

	Clinical features supporting the presence of cirrhosis include signs of 1) vasodilation: spider naevi, palmar erythema, and 2) portal hypertension: varices bleeding, ascites or portosystemic shunting including encephalopathy. Laboratory findings often observed with cirrhosis include elevated liver enzymes, bilirubin and prothrombin time, with low platelet count and albumin, in the absence of protein losing enteropathy.
Portal Hypertension	Portal hypertension is intrinsic to the Fontan circulation, as portal pressure is inherently elevated due to the high suprahepatic central venous pressures. Though rare, in some cases, it can have an intrahepatic component. Portal hypertension can be clinically silent or present as any combination of splenomegaly, ascites, varices, and thrombocytopenia.

Table 1 and Central Figure: Terms and definitions for patients with a Fontan circulation.

VO_2: Oxygen consumption, MRI: Magnetic resonance imaging.

Figure 1: Steps in the process to reach consensus on standardized definitions

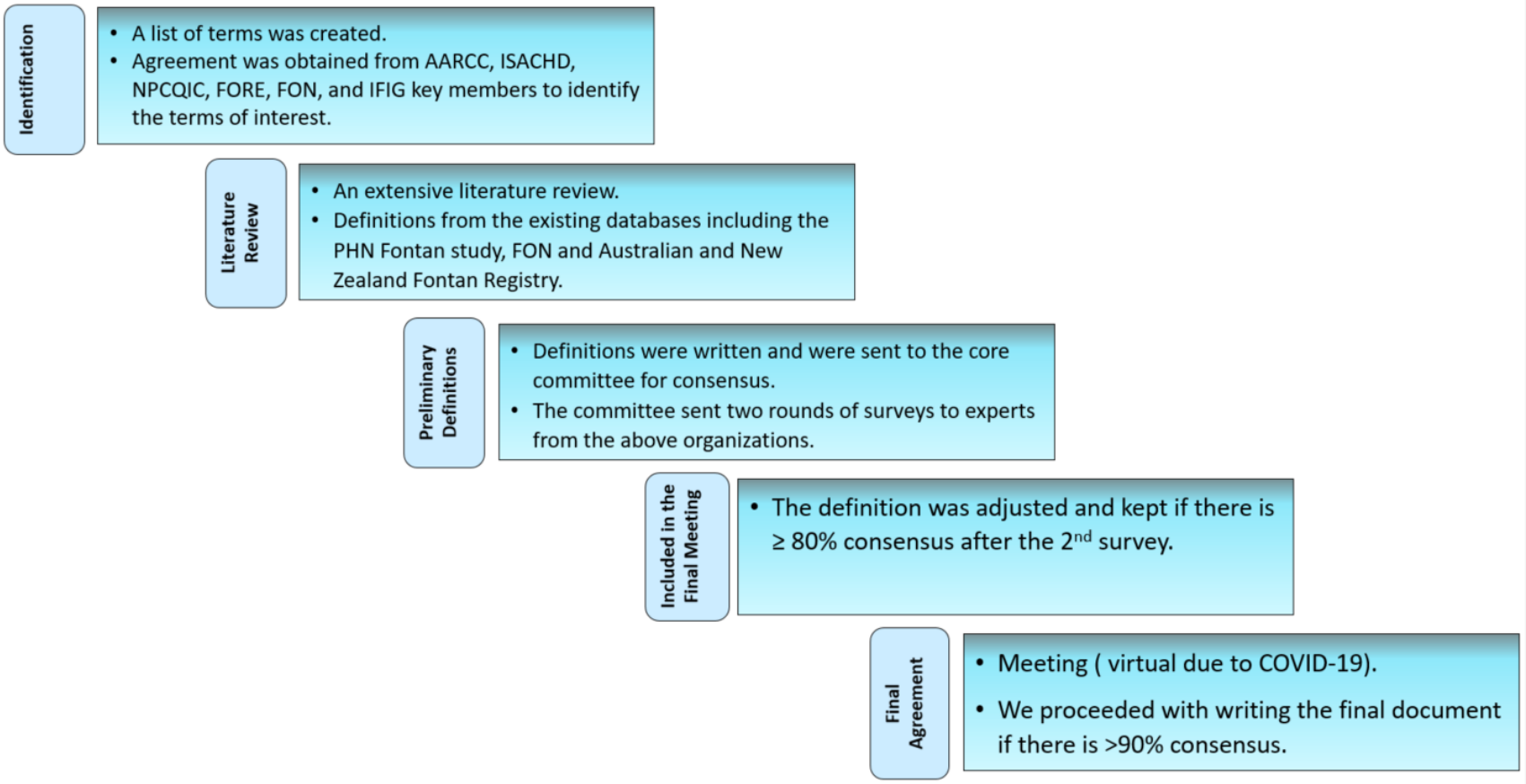


Figure 2: Steps in Delphi Methodology.

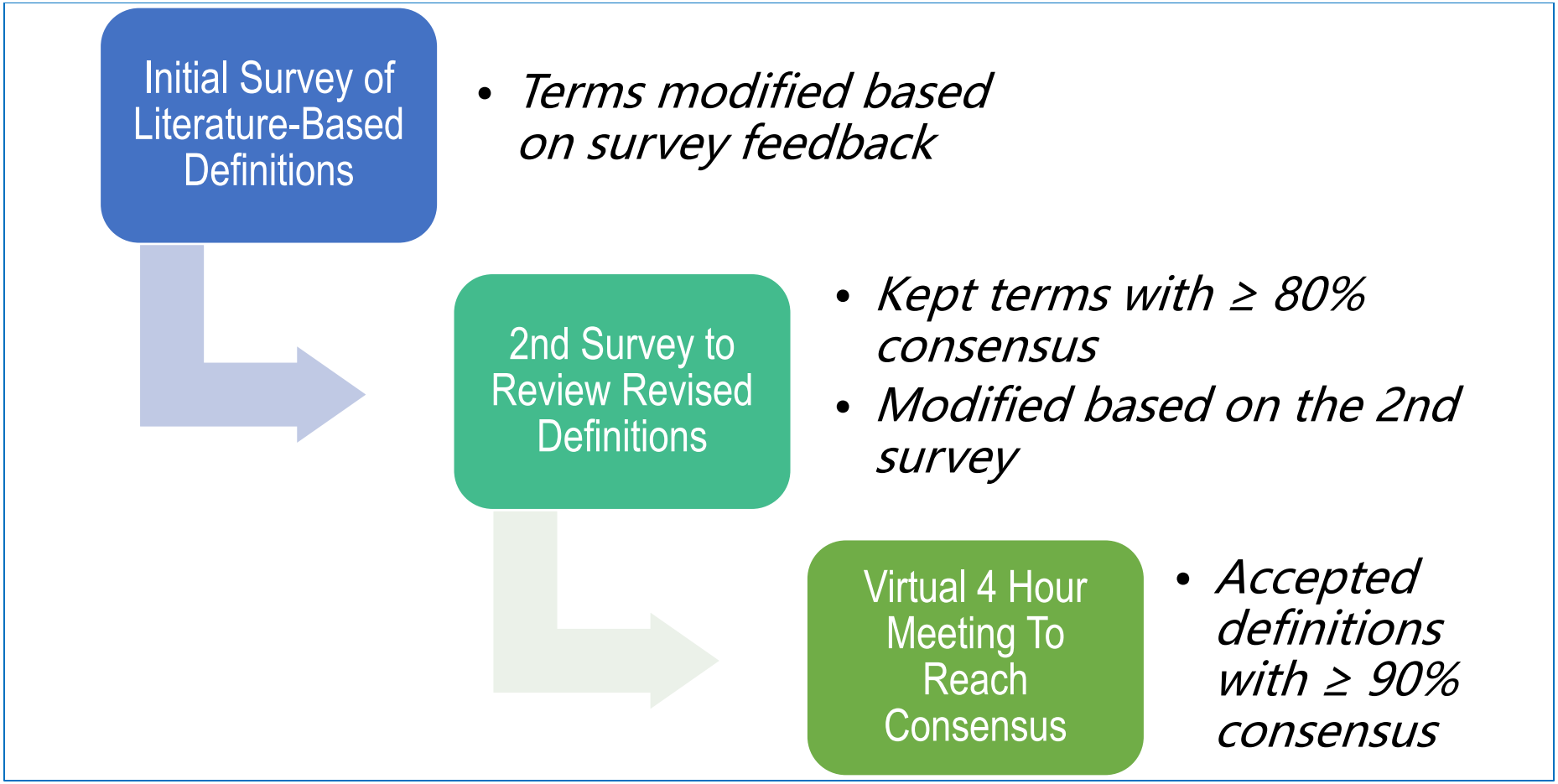


Figure 3: Lymphatic Insufficiency in Fontan. The pathophysiology of the lymphatic insufficiency (black font) is increased central venous pressure (CVP) leading to increased lymphatic production from the liver and impaired lymphatic drainage. This leads to dilation and dysfunction of the lymphangion. Depending on the location for lymphatic decompression a disease state may occur (red color). The green dots represent the lymphatic drainage.

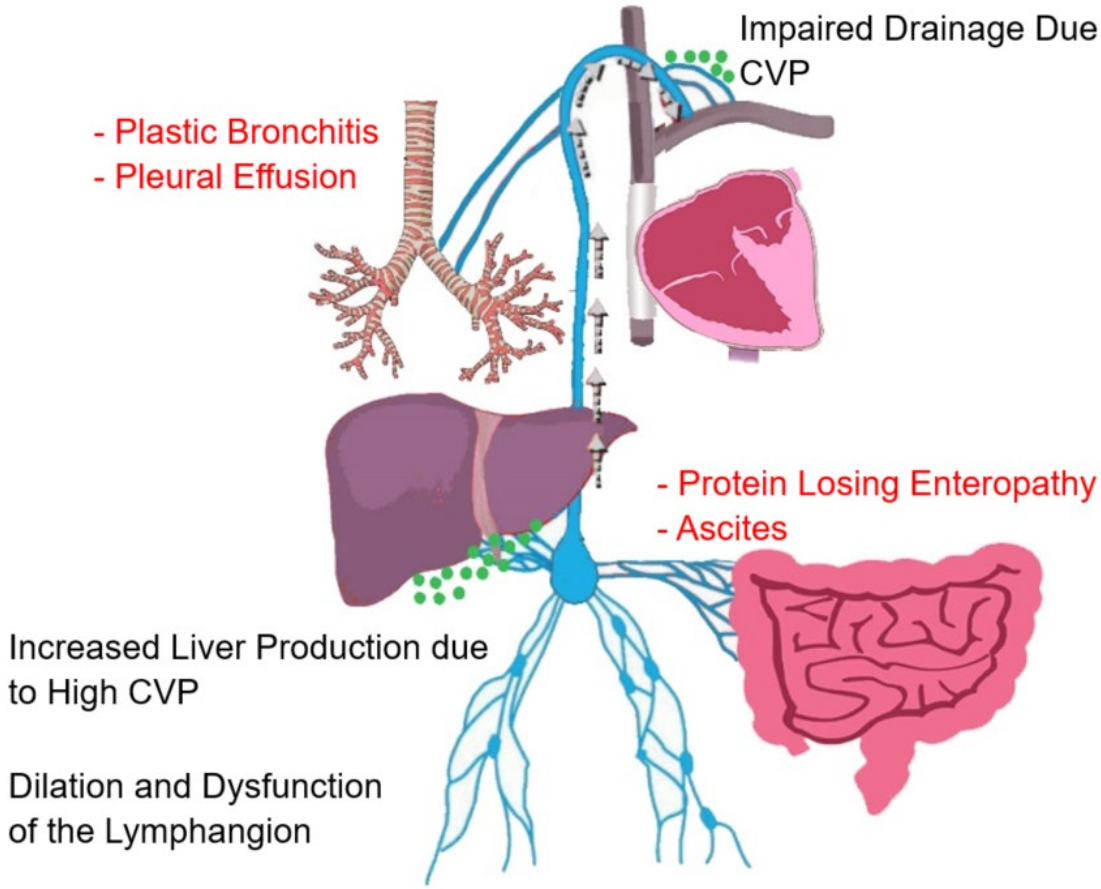
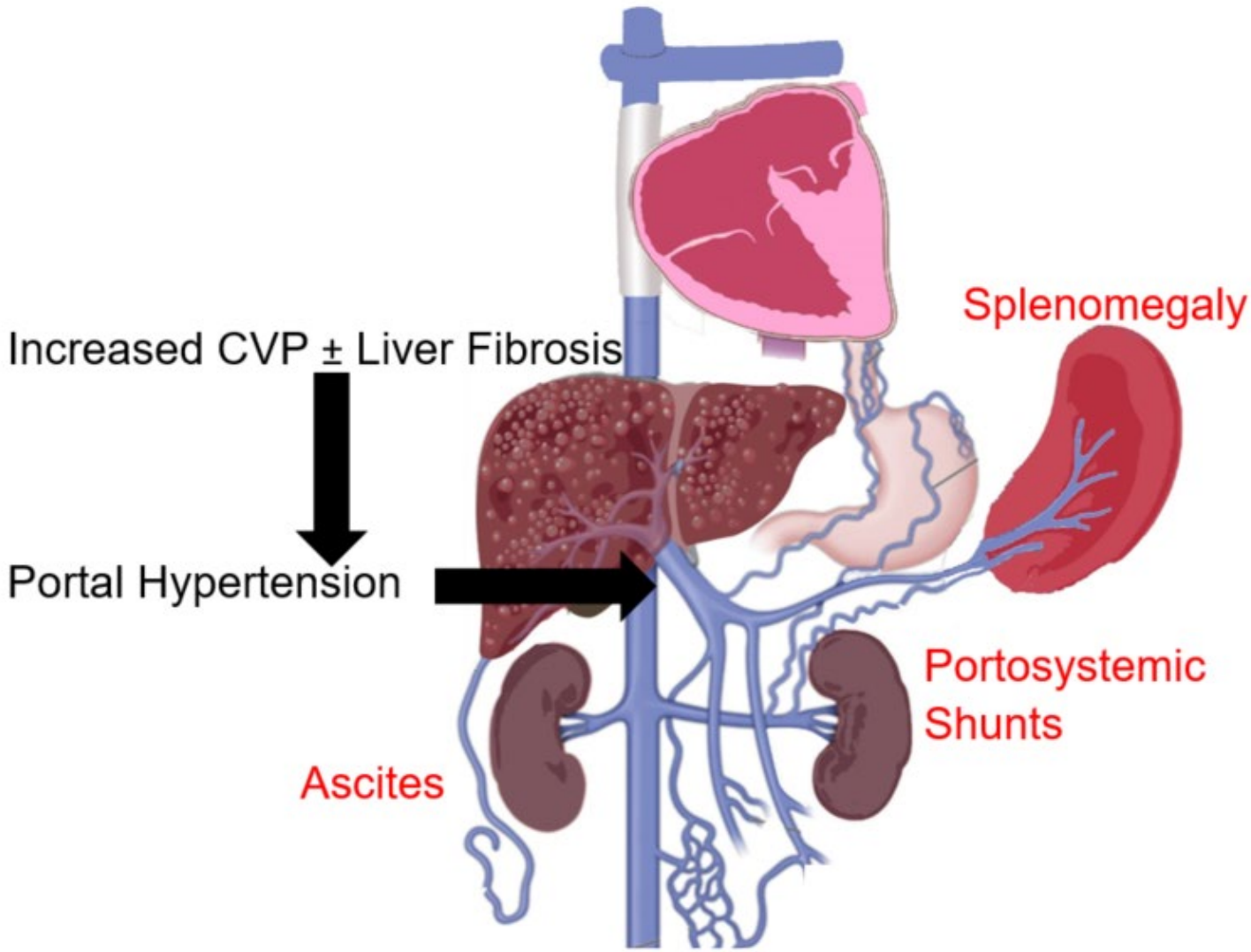


Figure 4: Portal hypertension in Fontan results from increased central venous pressure (CVP) with or without hepatic fibrosis (black font). Portal hypertension leads to splenomegaly, varices "portosystemic shunts" and ascites.



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