

## The Unligated Vertical Vein in Obstructive Supracardiac Totally Anomalous Pulmonary Venous Connection: Concept, Concerns and Future Directions

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### ABSTRACT

The present perspective is a synthesis of 75 published investigations in the setting of rechanneling of supracardiac totally anomalous pulmonary venous connection with or without vertical vein ligation in the literature. In this article, we review the issue of unligated/ligated vertical vein, adjustable vertical vein ligature, routine left atrial augmentation and atrial septal fenestration after rechanneling of supracardiac totally anomalous pulmonary venous connection in order to decrease perioperative pulmonary hypertensive crises, postoperative low cardiac output syndrome and mortality. Additionally, this review attempts to address the guidelines for selective vertical vein patency in patients with obstructive supracardiac totally anomalous pulmonary venous connection.

**Keywords:** Vertical vein, Totally anomalous pulmonary venous connection, Pulmonary hypertensive crises, Adjustable vertical vein ligature

### INTRODUCTION

Reports addressing the issue of not ligating the vertical vein following repair of totally anomalous pulmonary venous connection, and related postoperative hemodynamics are limited and conflicting [1-11]. Traditionally, ligation of the vertical vein at the time of rechanneling of totally anomalous pulmonary venous connection has been recommended to prevent the perceived consequences of a residual left-to-right shunt [1-11]. Some investigators have expressed concern about the occurrence of acute hepatic necrosis following ligation of the vertical vein [12]. This concept was so ingrained in the practice of rechanneling of totally anomalous pulmonary venous connection that five major anatomical and pathophysiological issues of obstructive totally anomalous pulmonary venous connection were either not well appreciated or ignored.

The first is the issue of varying reports of left heart volume characteristics in obstructive totally anomalous pulmonary venous connection from normal findings to the conclusion that the left sided chambers are smaller than normal and the left atrium lacks both normal compliance and reservoir function [13-22]. Such chamber abnormalities have been attributed to large left-to-right shunt causing reduced atrial filling and decreased left

ventricular relaxation secondary to elevated right ventricular diastolic pressure or volume [13-22]. Published literature does not address the percentage of patients with obstructive totally anomalous pulmonary venous connection who have structurally smaller left-sided chambers.

The second unresolved issue is identification of non-compliant and dysfunctional left ventricle [13-22]. The third issue is the identification and recognition of concomitant disproportionately increased pulmonary vascular medial thickness [23-30]. The fourth issue is the identification of concomitant hypoplasia of the pulmonary

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venous obstruction [24-33] and the fifth issue is the analysis of the multifactorial mechanisms causing heightened pulmonary vasoreactivity after repair of totally anomalous pulmonary venous connection and measures to decrease the prevalence and severity of pulmonary hypertensive crises [34-45].

## METHODS

With these deficiencies in mind, we have analysed the published literature to identify the described instances of repaired obstructive and non-obstructive supracardiac totally anomalous pulmonary venous connection, unligated/ligated vertical vein, left atrial augmentation, adjustable vertical vein ligation and atrial septal fenestration and evaluated all clinical studies describing the principles, indications, techniques and outcomes. The search engines employed were Medline, PubMed, Google scholar, Cochrane database and Embase. The search included literature in all languages. This strategy yielded 75 investigations that provided best answer to these topics. We have then synthesized all these features to outline the rationale, issue of concern and potential future trends of various surgical strategies of rechanneling of obstructive supracardiac totally anomalous pulmonary venous connection in general and adjustable vertical vein ligation in particular [1-75].

This review article outlines the pathophysiologic mechanisms underlying totally anomalous pulmonary venous connections and the hemodynamic consequences of leaving the vertical vein open versus occluded following rechanneling of obstructed totally anomalous pulmonary venous connection. With respect to drawing conclusions from the sum total of the peer-reviewed published literature, we have attempted to interpret the results utilizing standardized definitions of key elements as under:

Preoperative pulmonary venous drainage was considered obstructive if there was echocardiographic or angiographic data that indicated: (i) a significant gradient between the pulmonary veins and their point of drainage (flow acceleration  $>2$  m/s by echocardiography or pressure gradient  $>4$  mm Hg), (ii) monophasic and continuous Doppler flow pattern in the individual pulmonary veins, the pulmonary venous confluence or the vertical vein, or (iii) angiographically evident localized reduction in a single pulmonary vein diameter of 50% or more. Pulmonary hypertension was defined as a right-to-left ventricular systolic pressure ratio of 0.6. According to systemic pulmonary artery pressure (SPAP), as measured by cardiac catheterization or on echocardiography on the basis of the velocity of tricuspid regurgitation, pulmonary hypertension was graded as follows: none (SPAP  $<18$  mm Hg), mild (SPAP 19-30 mm Hg), moderate (SPAP 31-50 mm Hg), or severe (SPAP  $>50$  mm Hg). Isolated or simple TAPVC was diagnosed if the patient had TAPVC in association with a secundum atrial septal defect (ASD), a patent ductus arteriosus or both. An operation was classified as an

emergency if the patient was taken to the operating room within the first 24 h after arrival at the hospital for hemodynamic or ventilatory compromise.

In the published literature, the indications of preoperative cardiac catheterizations are: (1) anatomy that is unresolved by echocardiography, (2) characterization of the primary venous obstruction, or (3) exclusion of major associated cardiac anomalies that required delineation or intervention.

Low cardiac output syndrome in repaired TAPVC was diagnosed if the patient required inotropic support (dopamine at 4-10  $\mu\text{g}/[\text{kg} - \text{min}]$ , dobutamine at 5-10  $\mu\text{g}/[\text{kg} - \text{min}]$ , epinephrine at 0.01-0.1  $\mu\text{g}/[\text{kg} - \text{min}]$ , milrinone at 50  $\mu\text{g}/\text{kg}$  intravenous bolus followed by 0.375-0.75  $\mu\text{g}/[\text{kg} - \text{min}]$ ), either isolated or in combination in the operating room or in the intensive care unit to maintain stable hemodynamics in the absence of residual structural lesions and mechanical external compression after correction of all electrolytes or blood gas abnormalities and after adjustment of the preload to its optimal value. Low-output syndrome was also diagnosed if there was an increasing requirement of the previously mentioned inotropes along with afterload reduction with sodium nitroprusside. Patients who received less than 4  $\mu\text{g}/(\text{kg} - \text{min})$  dopamine to increase renal perfusion were not considered to have low output syndrome.

Invasive monitoring to measure cardiac output directly (thermodilution catheter, PA pressure line and thermistors) is cumbersome and hazardous in children and generally avoided, except in complex cases. Generally, the intracardiac monitoring is limited to right atrial, left atrial and pulmonary artery pressure lines.

Accordingly, under the definition of low output syndrome after repaired TAPVC, an integration of relevant clinical, laboratory and bedside echocardiographic criteria was used. The criteria for diagnosis were as follows: cold extremities, absent pedal pulses, decreased toe temperature, reduced systolic pressure, impaired renal function and oliguria ( $<1.0$  mL/ $[\text{kg} - \text{h}]$ ), metabolic acidosis, increased serum lactate levels ( $>2$  mmol/L for  $>2$  h), low mixed venous oxygen saturation ( $<50\%$ ) and blunted sensorium in the absence of residual anastomotic or pulmonary venous obstruction.

## CONCEPT

In an attempt to address these controversial issues we have developed a conceptual framework in the context of clinical phenotypes.

### According to the age at presentation: Infants versus adults

The differences noted between infants and adults undergoing rechanneling of supracardiac totally anomalous pulmonary venous connection provide important insight into factors associated with adverse outcomes and mortality. For instance, an obstructive totally anomalous pulmonary venous connection has a greater prognostic role in pediatric patients

than in adults. Only few patients reach adulthood and they usually have non-obstructive type of totally anomalous venous connection, low pulmonary vascular resistance, normal or moderately high pulmonary artery pressure and large left-to-right shunt [46-50].

#### **According to the obstruction of pulmonary venous flow: Obstructive versus non obstructive**

The anatomical factors most important in determining the clinical status of the patient include the presence and location of a right-to-left shunt and the presence or absence of obstruction in the pulmonary venous circuit. Published literature documents seven sites of possible obstruction to the pulmonary venous flow in totally anomalous pulmonary venous connection: i) compression of the vertical vein by the left/right pulmonary artery and the left/right bronchus, ii) the vertical vein coursed between the left pulmonary artery and the ductus arteriosus and compressed by this "circulus vasculosus", iii) stenosis at the junction of pulmonary veins and the common chamber, iv) stenosis at the insertion site of the vertical vein into the superior caval vein or the brachiocephalic vein, v) compression of the vertical vein by the aortic arch, vi) small sized individual pulmonary veins, and vii) a restrictive atrial septal defect [31,45-47,53].

Subjects with obstructive totally anomalous pulmonary venous connection present early in infancy, with features of pulmonary edema. Those without obstruction, present with features of large left-to-right shunt, pulmonary plethora and congestive heart failure [31,45-47,50,53].

#### **Ligated vs. unligated vertical vein in supracardiac totally anomalous pulmonary venous connection**

Clinical studies on an unligated vertical vein in the setting of obstructive supracardiac totally anomalous pulmonary venous connection are too limited and insufficient to generate evidence-based guidelines. The vertical vein, when present is usually ligated or divided during surgical correction of totally anomalous pulmonary venous connection to prevent a residual left-to-right shunt [54]. As yet, there are no specific criteria for candidate selection to maintain a patent vertical vein and there is no consensus in the literature regarding the fate of unligated vertical vein following repair of totally anomalous pulmonary venous connection. Literature documents clear anecdotal cases of spontaneous involution of the anomalous vertical vein at one end of the spectrum and a functioning conduit with shunt induced cardiac failure at the other end [34-44].

In order to allow the left heart to adopt and maintain adequate cardiac output, various surgical techniques have been adopted to construct an unrestrictive anastomosis between the common pulmonary venous chamber and left atrium [44,49]. Historically, ligation or interruption of the vertical vein and incorporation of the vertical vein as part of the new anastomosis have been described [48]. Several investigators have developed ingenious surgical techniques

by creating a large tension-free anastomosis, maintaining precise geometric alignment of the common pulmonary venous chamber with the left atrium, thus avoiding distortion and rotation of the pulmonary veins. Innovative sutureless techniques and use of absorbable polydioxanone sutures have been described at reducing the recurrence of pulmonary vein stenosis [55-61].

In 2007, the authors documented their observations that acute vertical vein ligation resulted in elevated left atrial pressure and left ventricular function and cardiac output are negatively impacted suggesting that for a period of time the small, poorly compliant left ventricle of the patient with obstructive totally anomalous pulmonary venous connection was unable to maintain adequate cardiac output [34,62]. Indeed, it is routine to see elevated left atrial pressure and pulmonary artery pressure combined with systemic hypotension and decreased cardiac output after weaning from cardiopulmonary bypass in patients with obstructive totally anomalous pulmonary venous connection [34,62]. Since the pulmonary veins/capillaries do not have any valves, any rise in left atrial pressure will lead to pulmonary hypertension. The postoperative course targets management of these issues and occasionally extracorporeal membrane oxygenation is necessary while the pulmonary vascular bed recovers and left ventricular compliance improves [63,64]. The time course of this adjustment is variable. It is conjectured that there is a feedback loop whereby acute elevation of left atrial pressure results in excessive pulmonary arteriolar constriction with out-of-proportion pulmonary hypertensive response that further exacerbates the low cardiac output state caused by a poorly compliant left ventricle [65].

We postulated that a patent vertical vein may function as a temporary reservoir for pulmonary venous blood after repair of totally anomalous pulmonary venous connection, volume unloading the small, non-compliant, left-sided cardiac chambers until they grow and adopt to increased flow demands [13-20,34]. Not all investigators have accepted these findings or utilized these techniques. In order to test the above-mentioned postulates to reduce the perioperative mortality and morbidity, the authors initiated a programme of routine adjustable vertical vein ligation in patients with obstructive totally anomalous pulmonary venous connection with post bypass systemic or suprasystemic pulmonary arterial hypertension [34,62].

The unligated vertical vein served as a temporary "pop off" valve in the event of pulmonary hypertensive crises. This strategy allowed a more gradual occlusion of the vertical vein so that acute elevation of the left atrial pressure was avoided, albeit with some period of pulmonary over circulation and elevated right-sided filling pressure, thereby tiding over the postoperative phase of heightened pulmonary vasoreactivity. Such a band allowed easy tightening in increments, with gradual increase of ventricular afterload

without the need for multiple reoperations [34,62-65].

James S Tweddell in his editorial on the issue of vertical vein ligation revisited some observations during the early years of cardiology and cardiac intervention [65]. In 1916, Lutembacher [66] described the impact of an atrial septal defect on acquired mitral stenosis by trading mild elevation of right atrial pressure and pulmonary over circulation for acute elevation of left atrial pressure. In 1949, Bland and Sweet [67] anastomosed azygous vein to pulmonary vein to improve the functional status of patients with critical rheumatic mitral stenosis permitting spillover of the congested pulmonary veins into the capacious systemic venous system. Revisiting these observations of Cope et al. [2], Chowdhury [34,62], Lutembacher [66] and Bland [68] suggest that the systemic venous system and pulmonary vasculature can accommodate the excess volume and limit the impact of excessive left atrial pressure.

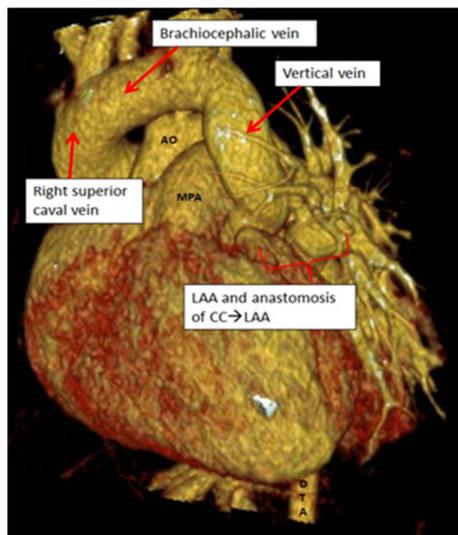
**Adjustable vertical vein ligation**

Based on the literature and reasoning cited above, the authors embarked on a programme of routine adjustable vertical vein ligation in patients with obstructive totally anomalous pulmonary venous connection with post-bypass systemic or suprasystemic pulmonary arterial hypertension and published the technical details and preliminary results in Cardiology in the Young [62]. Thus, there were seven forces driving our criteria for selection of patients whose vertical vein was kept patent after rechanneling of totally anomalous pulmonary venous connection:

- i. The desire to reduce the pulmonary artery pressure in the perioperative period after achieving an adequate-sized, unrestrictive anastomosis along with pharmacological manipulations.

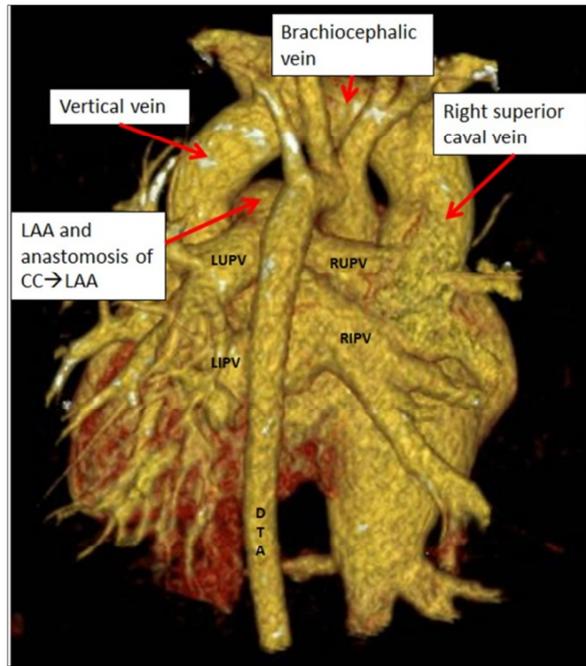
- ii. The desire to reduce pulmonary hypertensive crises, low cardiac output, and hospital mortality following repair of totally anomalous pulmonary venous connection with pulmonary hypertension.
- iii. The desire that the unligated vertical vein may function as a temporary venous reservoir for pulmonary venous blood, volume unloading the small non-compliant left-sided cardiac chambers until they are able to grow and adapt to the requisite flow demands.
- iv. The desire that the unligated vertical vein may serve as a temporary “pop-off” valve in the event of pulmonary hypertensive crises and thereafter the same may be subjected to a gradual process of occlusion.
- v. The desire to gradually tighten or loosen the ligature under optimal physiologic conditions, once the disease-related/bypass-related pulmonary vasoreactivity disappears.
- vi. The desire to gradually increase the ventricular afterload without causing unstable hemodynamics under optimal physiologic conditions, and
- vii. The desire to occlude the vertical vein in the event of a significant left-to-right shunt and right heart failure without re-sternotomy or thoracotomy [34,62].

Postoperatively, we performed computed tomographic angiography on all patients at varying time intervals during follow-up and demonstrated wide, unrestricted anastomosis between the common pulmonary venous chamber and left atrial appendage, absence of flow through the vertical vein and ruled out distortion at the left superior pulmonary vein and left brachiocephalic vein (**Figures 1-4**) [34,62].



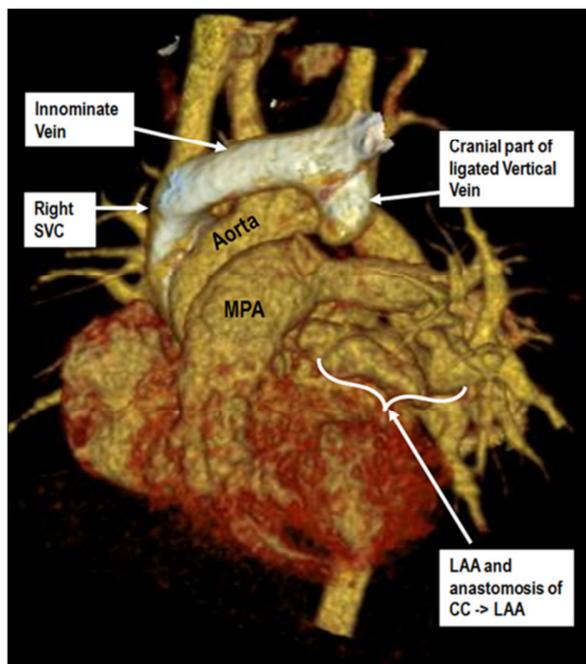
**Figure 1.** Postoperative three-dimensional oblique coronal computerized volume rendered image showing the dilated vertical vein draining into the brachiocephalic vein.

CC → LAA: Common Pulmonary Chamber → Left Atrial Appendage; DTA: Descending Thoracic Aorta



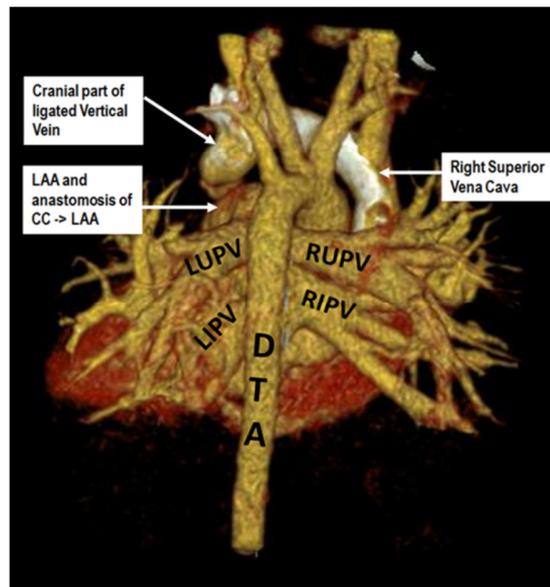
**Figure 2.** Postoperative three-dimensional coronal computerized tomographic posterior volume rendered image showing all pulmonary veins draining into the common pulmonary venous chamber, thereby draining through the vertical vein into the right superior caval vein.

*LIPV: Left Inferior Pulmonary Vein; LUPV: Left Upper Pulmonary Vein; RIPV: Right Inferior Pulmonary Vein; RUPV: Right Upper Pulmonary Vein*



**Figure 3.** Postoperative post ligation, three-dimensional volume rendered coronal computerized tomographic image showing the cranial part of the ligated vertical vein and the wide unrestricted anastomosis between the common pulmonary venous chamber and left atrial appendage.

*MPA: Main Pulmonary Artery*



**Figure 4.** Postoperative post ligation, three-dimensional volume rendered image in posterior projection showing all pulmonary veins draining into the common pulmonary venous chamber which has been anastomosed to the left atrial appendage.

#### Routine left atrial augmentation

As described earlier, the left sided chambers are smaller than normal and the left atrium lacks both normal compliance and reservoir function in totally anomalous pulmonary venous connection [13-22]. In order to allow the left heart to adopt and maintain adequate cardiac output, we have used a redundant Dacron patch for interatrial septum, deviating the same to the enlarged right atrium and have incorporated part of the vertical vein to achieve structural alignment and augmentation of the left atrial cavity [34,62]. The concept of enlarging the left atrium is almost similar to that described by Cooley and colleagues except that in our patients, we achieved it by excising the floor of the fossa ovalis and utilizing a Dacron patch graft to close the atrial septal defect and enlarge the left atrium [69,70]. The two-patch technique of left atrial enlargement has been popularized by Corno et al. [71]. Subsequently, several investigators have demonstrated increased incidence of supraventricular arrhythmias due to the use of a transverse right atrial incision and division of the supraventricular crest [71]. We have not used this technique.

#### Interatrial septal fenestration

Traditionally, an intentional atrial septal fenestration is created permitting the “spill-over” or “pop-off” in the setting of postoperative right ventricular dysfunction following intracardiac repair of tetralogy of Fallot, pulmonary atresia, Ebstein’s anomaly, Rastelli’s operation and one and one-half ventricular repair [34,62]. During episodes of pulmonary hypertensive crises with limited right ventricular output and an elevated central venous pressure, a fenestrated atrial

septal patch permitted right-to-left shunting; increasing left ventricular preload and cardiac output albeit with mild desaturation. A review of the literature on this topic reveals that it can be performed relatively safely and patients do reasonably well at follow-up. Since 2000, it has been the author’s practice to perform atrial septal fenestration in patients with obstructive supracardiac and infracardiac totally anomalous pulmonary venous connection [34,62].

Thus, the unligated vertical vein in conjunction with left atrial augmentation and a calibrated atrial septal fenestration, decompressed the small left atrium after repair, equalized the left atrial and central venous pressure and was the automatic choice to avoid a dismal outcome in the perioperative period [34,62].

Introduction of phenoxybenzamine in the management of pulmonary hypertensive crisis, use of ultrafiltration to remove excess lung water and delayed sternal closure are additional factors for reduced perioperative mortality in recent years [34-50].

#### CONCERNS

The technical aspects of rechanneling of supracardiac totally anomalous pulmonary venous connection, left atrial augmentation using a Dacron polyester fabric, atrial septal fenestration and adjustable vertical vein ligation along with operative pictures have previously been enumerated in detail in our earlier publication and are not repeated here [62].

An initial concern about this technique was the possibility of distortion of the left upper pulmonary vein and left brachiocephalic vein. To address these concerns, we have

performed the following maneuvers: (i) we threaded the loop ligature through a polytetrafluoroethylene felt and secured the same with the adventitia of the vertical vein to prevent its displacement, and (ii) both the arms of the silk suture were then brought out through the second left intercostal space away from the sternotomy incision, perpendicular to the vertical vein ensuring a vertical straight lie, avoiding subsequent distortion or occlusion of the left superior pulmonary and brachiocephalic veins [62].

The second concern of an unligated vertical vein is the change of the shunting pattern from the brachiocephalic vein to the left atrium via the vertical vein causing cardiac failure. In our initial investigation, 11 patients with obstructive totally anomalous pulmonary venous connection with an unligated vertical vein continued to have tachypnoea and right heart failure between 1 to 2 postoperative weeks. The vertical vein was subsequently ligated through re-sternotomy on 4 patients, left anterolateral thoracotomy in 2 patients and adjustable vertical vein ligature in 5 patients. Subsequently, all patients are managed by using an adjustable vertical vein ligature. Similar experience have been documented by other investigators [3,4].

In our previous investigation, autopsy findings on 4 patients revealed a small pulmonary venous confluence, diffuse hypoplasia, intimal hypertrophy, increased pulmonary vascular medial thickness, pulmonary lymphangiectasia and interstitial emphysema [34]. On the basis of these observations, we speculate that the medial and intimal changes seen in preoperative obstruction may predispose towards the development of intrinsic pulmonary vein

stenosis. We concur with the observations of other investigators that an unligated vertical vein in this subset of patients with co-existing pulmonary arteriopathy exerts an unfavorable effect on the morbidity and surgical outcome despite adequate pulmonary venous decompression [24-32]. Given the bleak prognosis for these patients, alternative management strategies like lung transplantation may perhaps be considered [72-74].

One important finding of our investigation, given their age at the time of surgery, is the occurrence of suprasystemic pulmonary arterial pressure in our patients subsequent to weaning from bypass. Overall, one hundred and thirteen (78.4%) patients were more than one month of age. This is in contrast to the situation in most western countries, where more than half of patients undergo surgery before one month of age. In our earlier publication, we demonstrated that late referral and late presentation lead to the development of severe pulmonary hypertension, a prolonged period of malnutrition and ultimately cardiac cohexia [34]. These factors predispose them to pulmonary infection, sepsis, postoperative pulmonary hemorrhage, and unfavorable reactions to stresses such as cardiopulmonary bypass and postoperative events [34,62].

**RESULTS**

The results of the published investigations documenting the fate of a patent vertical vein in the setting of obstructive supracardiac totally anomalous pulmonary venous connection have been summarized in **Table 1**.

**Table 1.** Summary of the published investigations documenting the fate of a patent vertical vein in the setting of obstructive supracardiac totally anomalous pulmonary venous connection (TAPVC).

Author	Year of study	Diagnosis	Number of patients	Age/Weight	Unligated vertical vein (Number)	Follow-up	Results	Recommendations
Cope et al. [2]	1974-1995	Supracardiac TAPVC obstructive (n=4)	4	1 day-5 years	4	1 day-106 months	All had patent vertical vein on follow-up. All survived.	No residual left to right shunt. Vertical vein should be left unligated in obstructive TAPVC.
Zhao et al. [6]	1982-2008	Supracardiac (n=77)	20 unligated	8.5 ± 7.0 years 27 days-	20	1 day-5 years	Spontaneous closure (n=8).	Recommended patent vertical vein obstructive

				44 years			Remained patient (n=12).	TAPVC.
Kelle et al. [8]	1990-2008	Supracardiac (n=39) obstructive (n=22)	39 ligated	0-1.7 years (range) 14.6 days (median) 1.3-10 kg (range) 3.5 kg (median)	39 (used nitric oxide in addition)	4.21 ± 5.2 years (1 month-18.6 years)	Vertical vein ligated in all patients + nitric oxide 12 died (30.7%).	Should be closed in all.
Caspi et al [3]	1993-2000	Supracardiac TAPVC Unobstructive (n=9), obstructive (n=3)	3 unligated snared	21 ± 8 days Weight 3 ± 0.2 kg	3	(8-71 months) 38 ± 6 months	Closed in ICU in all patients, tightened on snare.	Patent vertical vein has favourable effects on the morbidity and postoperative outcome.
Kumar et al. [9]	1995-1999	Supracardiac TAPVC obstruction	10	5-80 days Weight 3-4.5 kg	3	6 months-2 years	All patients at follow-up. No spontaneous closure.	Do not support elective non-ligation.
Saritas et al. [10]	1996-2010	Supracardiac TAPVC obstruction	14	3.8 ± 2.1 months Weight 4.4 ± 1.1 kg	14	48 ± 36 months	Spontaneous closure (n=1). Surgical closure (n=2).	Shunt through vertical vein does not cause any negative hemodynamic. Contributes to left ventricular functions long term. Should be left open in obstructive TAPVC.
Shah et al.	2000	Supracardiac	2	2.5	2	5	Both	Recommended

[4]		c TAPVC obstructive (n=2)		months/3. 5 kg 2 months/4. 0 kg		months and 7 months	survived. Vertical vein ligated in both patients.	unligated vertical vein obstructive TAPVC. Significant left to right shunt.
Chowdhury et al. [34]	1997-2006	Supracardiac obstructive TAPVC	30	1 day-8 months (range) Mean 1.49 ± 1.63 months Median 1 month Weight: 3.75 ± 1.08 kg	30	1 month-104 months (range) Mean 33.34 ± 29.88 months Median 30 months	Vertical vein was ligated in all patients- approaches re-sternotomy, left anterolateral thoracotomy, adjustable vertical vein ligation.	Recommended unligated vertical vein obstructive TAPVC.
Chowdhury et al. [62]	2007	Supracardiac obstructive	5	2, 4, 3, 4 and 3 months Weight: 3.2, 4.0, 3.6, 4.2 and 3.4 kg	5	2-107 months Mean: 55.4 ± 45.5 months	Adjustable vertical vein ligation. Gradually tightened over 24-96 h	Routine use of percutaneously adjustable ligature allows gradual tightening of loosening under optimal physiologic conditions without re-sternotomy.

Cope et al. [2] in 1997 reported 4 patients of repaired obstructive supracardiac totally anomalous pulmonary venous connection and unligated vertical vein, aged between 1 day to 5 years. At a range of 1 day to 106 months after operation, echocardiography failed to reveal flow in any of the unligated vertical vein. They concluded that vertical vein

should be left unligated in obstructive totally anomalous pulmonary venous connection [2].

Caspi et al. [3] in 2001 reported 12 patients with a mean age at operation of 21 days and standard deviation of 8 days, weighing between 3 and 4 kg with supracardiac totally

anomalous pulmonary venous connection. Nine patients had obstructive and 3 patients had unobstructive drainage. Three patients with obstructive totally anomalous pulmonary venous connection had an unligated vertical vein. All patients had a 5-0 polypropylene purse string suture around the vertical vein at the junction with the brachiocephalic vein. All patients underwent closure of the vertical vein in intensive care unit by tightening the snare. They concluded that a patent vertical vein has favorable effects on the morbidity and postoperative outcome [3].

Shah et al. [4] in 2000 reported 2 patients aged 2.5 months and 2 months, weighing 3.5 kilogram and 4.0 kg respectively with repaired obstructive supracardiac totally anomalous pulmonary venous connection with post bypass suprasystemic pulmonary artery pressure and unligated vertical vein. Both patients survived the operation. Both the patients developed symptoms of left-to-right shunt and cardiac catheterisation demonstrated widely patent vertical vein. Both underwent delayed successful vertical vein ligation and the author recommended non-ligation in obstructive totally anomalous pulmonary venous connection [4].

Kumar et al. [9] in 2001 documented four patients aged between 5 and 80 days, weighing between 3.0 and 4.5 kg undergoing rechanneling of obstructive totally anomalous pulmonary venous connection. Three patients with repaired supracardiac and one patient with infracardiac drainage had an unligated vertical vein. Cardiac catheterization between 6 months to 2 years after surgery demonstrated widely patent vertical vein in all of them and these investigators did not support elective non-ligation of the vertical vein at the time of initial surgery [9].

Saritas et al. [10] in 2011 reported 14 patients with obstructive totally anomalous pulmonary venous connection with a mean age of  $3.8 \pm 2.1$  months and mean body weight of  $4.4 \pm 1.1$  kg. All patients had an unligated vertical vein at operation. At a mean follow up of  $48 \pm 36$  months, the vertical vein in two patients was closed surgically and in one patient with high pulmonary artery pressure and pulmonary vascular resistance, it closed spontaneously. These authors concluded that patients with obstructive totally anomalous pulmonary venous connection benefit from intact vertical vein in the postoperative period. Since they have left chambers with poor compliance [10].

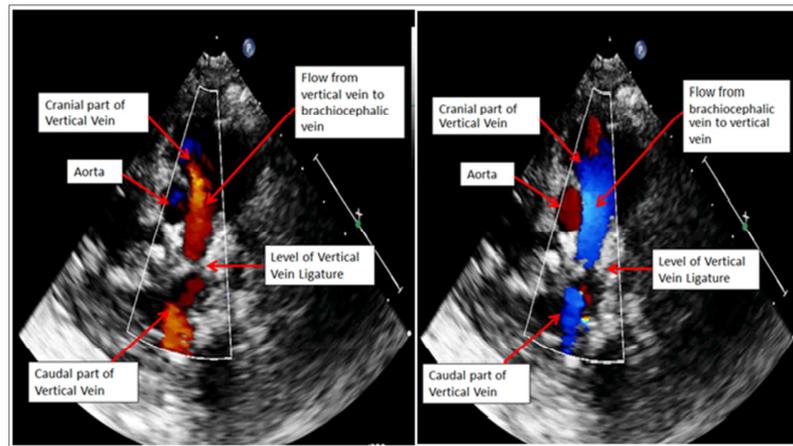
Zhao et al. [6] in 2015 reported 77 patients of supracardiac totally anomalous pulmonary venous connection with age ranging from 27 days to 44 years, with a mean of 8.5 and standard deviation of 7 years. Twenty patients with an unligated vertical vein were followed up from day one to five years. Eight patients had spontaneous closure and in 12 patients, the vertical vein remained patent. They recommended patent vertical vein in obstructive totally

anomalous pulmonary venous connection [6].

On the other hand in the study reported by Kelle et al. [8] in 2010 on 39 patients of obstructive supracardiac totally anomalous pulmonary venous connection with age ranging from 0 to 1.7 years and a median age of 14.6 days. Their weight was ranging between 1.3 and 10 kg with a median weight of 3.5 kg. 22 patients had obstructive supracardiac totally anomalous pulmonary venous connection. The vertical vein was ligated in all patients and postoperative pulmonary hypertension was managed by nitric oxide therapy and conventional ventilator management strategies with a mortality rate of 30.7%. These authors advised ligation of vertical vein in all patients of obstructive and non-obstructive supracardiac totally anomalous pulmonary venous connection [8].

In our initial investigations on 48 patients undergoing rechanneling of totally anomalous pulmonary venous connection between 1997 and 2006, 27 (46.5%) patients did not undergo vertical vein ligation [34]. Contrary to the report by Cope et al. [2,34], in which patent venous pathway atrophied, 11 of 23 survivors of obstructive supracardiac totally anomalous pulmonary venous connection allowed symptoms of a large left-to-right shunt through the unligated vertical vein requiring delayed closure of the vertical vein in all cases. Although delayed closure of the vertical vein was successful in all cases, with concomitant elevation of pulmonary artery pressure, it was attended by extremely high left atrial pressure in six patients and proved a difficult postoperative challenge. These findings were suggestive of a relatively small, non-compliant, dysfunctional left-sided chamber [34].

Subsequently, in 2007 we introduced the concept of adjustable vertical vein ligation in the setting of obstructive supracardiac totally anomalous pulmonary venous connection with the aims and objectives as narrated above [62]. We demonstrated that the unligated vertical vein during repair of obstructive totally anomalous pulmonary venous connection is associated with decreased episodes of pulmonary hypertensive crisis, postoperative low cardiac output syndrome, lessened duration of ventilation and inotropic support, provided early normalization of hemodynamic and decreased in hospital mortality. There were no late deaths. At a mean follow-up of  $33.34 \pm 29.88$  months, median, 30 months, the actuarial survivals were  $92.6\% \pm 0.05\%$  in the unligated category and  $71\% \pm 0.08\%$  for the ligated category ( $p=0.03$ ) [34,62]. All patients underwent serial cross-sectional and Doppler echocardiographic evaluation in the postoperative period and gradual process of vertical vein ligation at varying time intervals between 5 and 25 days, as soon as right-to-left shunting through the vertical vein disappeared (**Figures 5A and 5B**). None required anti-failure cardiac medications [34,62].



**Figure 5. A)** Postoperative transthoracic two-dimensional echocardiogram (day 1 postoperative) with color flow patterns of venous flow in the unligated vertical vein showing left-to-right shunting from the left atrium to the brachiocephalic vein via the patent vertical vein. **B)** Demonstration of change of the shunting patterns on the 7<sup>th</sup> postoperative day on the same patient from the brachiocephalic vein to the left atrium via the vertical vein.

Whether an adjustable vertical vein ligature with concomitant rechanneling of supracardiac totally anomalous pulmonary venous connection is advantageous over the traditional concept of routine vertical vein ligation is a subject of debate [34,62]. Since all investigators and surgeons have not accepted these findings or utilized these techniques, the answer to the above postulates and observations is forthcoming.

It is pertinent to state that a persistent left-to-right shunt and right heart failure through an unligated vertical vein does not necessarily relegate a patient to a second stage operation and does not warrant modification of our selection criteria for the unligated vertical vein. They may be candidates for adjustable vertical vein ligature or percutaneous angiographic vertical vein embolization [75].

The mechanisms causing heightened pulmonary vasoreactivity following repair of totally anomalous pulmonary venous connection are multifactorial, and may reflect release of platelet-activating factors, endothelin and arachidonic acid metabolites from pulmonary endothelial cells, decreased ratio of prostacyclin to thromboxane and a decline or absence of acetylcholine responsiveness [34-50]. Many agents have been advanced as being optimal on the grounds that they selectively reduce pulmonary vascular resistance, but few do so, and no clearly superior one has been identified. Therefore, in the authors' centre, a varying combination of fentanyl, hyperventilation, correction of acidosis, inhaled nitric oxide, sodium nitroprusside and phenoxybenzamine were used to manage pulmonary hypertensive crises [34,62].

#### EXPLORING THE UNKNOWN: FUTURE DIRECTIONS

This short communication is not meant in any way to

convince those surgeons satisfied with their own methods of rechanneling of totally anomalous pulmonary venous connection. Rather it hopes to point out that a patent vertical vein is beneficial in the setting of totally anomalous pulmonary venous connection with more than moderate pulmonary arterial hypertension.

A careful quantitative evaluation of the preoperative morphologic and physiologic characteristics of both left and right-sided chambers for all patients with obstructive totally anomalous pulmonary venous connection could then be used to determine whether and under what left heart conditions, leaving vertical vein patent is beneficial. Such information would be welcome and noteworthy. Nothing in the literature even remotely addresses the issue of making a quantitative assessment of the left side of the heart that can be used to objectively decide between the surgical options. Indeed, when one examines the underlying concepts, it is clear that there are new concerns and basic questions that await resolution by careful investigation only after its basic physiology is better understood will its potential benefit be realized.

In our study, the occurrence of systemic or suprasystemic pulmonary artery pressure on snaring the vertical vein was the determining factor for leaving the vertical vein open [34,62]. To properly test the hypothesis that "vertical vein ligation results in inferior outcome and non-ligation in selected subsets of totally anomalous pulmonary venous connection results in superior outcome", a multi-institutional, prospective randomized trial of ligation vs. non-ligation would be necessary and would be the last refuge for those who cannot accept the conflicting complex findings of the anatomy and pathophysiology of obstructive totally anomalous pulmonary venous connection.

These types of trials are challenging due to small sample

sizes, heterogeneity of the underlying congenital heart disease and exclusion of sicker patients. Perhaps one of the greatest challenges in designing such trials is the selection of appropriate end points. End points must include not only cardiac quantifiable end points (such as pulmonary vein sizes, pulmonary venous chamber and left heart dimensions) but also specific pulmonary vascular obstructive changes such as indexed pulmonary vascular disease and neurocognitive assessments.

We have known for a while that creation of a large, tension-free anastomosis, precise geometric alignment of the pulmonary venous chamber with the body of left atrial avoiding torsion and rotation of pulmonary veins, introduction of phenoxybenzamine in the management of pulmonary hypertensive crisis and delayed sternal closure are the factors for reduction of perioperative mortality after repair of totally anomalous pulmonary venous connection in recent years [34-44]. Future publications auditing the above-mentioned issues will add nothing to our understanding of the problem of postoperative low cardiac output syndrome. Now, we need to identify the anatomic and physiologic issues involved in a subset of patients with obstructive totally anomalous pulmonary venous connection. The issues to be resolved are: a) identification of the structurally smaller left sided chambers, b) identification of non-compliant and dysfunctional left ventricle, c) identification of concomitant disproportionately increased pulmonary vascular medial thickness, and finally, d) identification of concomitant hypoplasia of the pulmonary venous system.

## CONCLUSION

On the basis of the published literature including ours enunciated in this manuscript, we conclude that a patent, unligated vertical vein in patients with obstructive and non-obstructive totally anomalous pulmonary venous connection with more than moderate post cardiopulmonary bypass pulmonary arterial hypertension facilitates reduction of pulmonary arterial pressures, thus avoiding pulmonary hypertensive crisis and postoperative low cardiac output syndrome and contributes to a favorable outcome. Patients who have undergone this approach should be followed closely for a significant, persistent left-to-right shunt and right heart failure.

The technique of adjustable vertical vein ligature is simple, safe, effective and allows easy tightening in increments with gradual increase of ventricular afterload without the need for multiple operations. We submit that an increased appreciation of an adjustable vertical vein ligature, left atrial augmentation and atrial septal fenestration in patients with supracardiac totally anomalous pulmonary venous connection with more than moderate pulmonary hypertension may well contribute to improved future surgical management.

## COMPLIANCE WITH ETHICAL STANDARDS

## Statement of human rights/ethical approval

The authors assert that all procedures contributing to this study comply with the ethical standards of the relevant national guidelines on human experimentation and with the Helsinki declaration of 1975, as revised in 2008 and has been approved by the Institutional Research Committee.

## Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship and/or publication of the article.

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