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Twin Reversed Arterial Perfusion Sequence Associated With Decreased Fetal Cerebral Vascular Impedance

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Abstract

Objectives: Twin reversed arterial perfusion (TRAP) sequence affects 1% of monochorionic (MC) pregnancies and is caused by abnormal vascular connections between a pump twin and an acardiac mass. The effects of abnormal vascular connections on cerebral vasculature in the pump twin are unknown. We hypothesize that abnormal cerebral vascular impedance, assessed by the pulsatility index (PI), is present in pump twins and fetal intervention alters cerebral impedance.

Methods: Fetal echocardiograms performed at presentation between 2010- 2013 for TRAP pregnancies (cases, n= 19) or uncomplicated MC twins (controls, n= 36/18 pairs) were analyzed. In all subjects, the middle cerebral artery (MCA) PI, combined cardiac output (CCO) and cardiothoracic ratio (CTR) was calculated. Comparisons were made between cases and controls.

Results: The mean gestational age at echocardiogram was 20 wks in both groups. MCA PI was lower in the cases as compared to controls (1.55, 95% CI 1.47-1.64 vs. 1.74, 95% CI 1.65-1.82, $p = 0.004$). CCO in the cases was mildly elevated for gestational age (199.7 mL/min, 95% CI 138.4-261.1). In six available cases, mean MCA PI increased after intervention from 1.5 (95% CI 1.4-1.7) to 1.8 (95% CI 1.5-2.2).

Conclusion: TRAP pump twins have decreased cerebral vascular impedance as compared to controls, suggestive of a brain-sparing effect. MCA PI appears to increase in a small group of pump twins after intervention. These findings suggest a fetal cerebral autoregulatory response to a high cardiac output state that begins to change after fetal intervention. The long-term implications for neurodevelopmental outcomes warrants further study.

Introduction:

Twin-reversed arterial perfusion (TRAP) sequence, previously termed acardiac twinning, is a relatively uncommon complication of monochorionic twin pregnancy affecting 1% of all monochorionic twin gestations¹. TRAP sequence occurs when a normal or 'pump' twin perfuses an acardiac mass via placental vascular connections unique to monochorionic placentas. The pump twin perfuses the acardiac with deoxygenated blood in a retrograde manner via a placental arterio-arterial anastomosis and the acardiac returns further deoxygenated blood back to the pump twin through a direct veno-venous anastomosis^{2,3}. Historically, there is a 50% mortality rate for pump twins if the condition is left untreated, due to high output cardiac failure and subsequent development of hydrops^{1,4,5}. Fetal intervention by way of radiofrequency ablation of flow within the acardiac (cord occlusion) has improved survival of the pump twin to as high as 90% in experienced centers⁶.

Despite this improvement in survival, the effects of abnormal placental connections and a high cardiac output state on a pump twin's fetal cerebral blood flow and vasculature prior to (and following) occlusive intervention are unknown. We hypothesize that the pump twin exhibits abnormal cerebral hemodynamics in response to a high cardiac output state and that these changes are reversible with fetal intervention. Our aims were to 1) compare the cerebral vascular impedance in pump twins to healthy monochorionic twins, 2) determine if there is a correlation between cerebral vascular impedance and markers of a high cardiac output state, and 3) assess the change in cerebral vascular impedance before and after fetal intervention.

Methods:

From 2010 to 2013, the clinical and sonographic data of fetuses with TRAP evaluated by the Fetal Treatment Center at the University of California San Francisco

(UCSF) were reviewed. The inclusion criteria consisted of fetuses with a diagnosis of TRAP who underwent both an ultrasound and a fetal echocardiogram prior to any intervention. As normal controls for comparison, gestational age matched monochorionic-diamniotic twin fetuses with normal cardiovascular anatomy, normal utero-placental function and no extra-cardiac anatomic abnormalities were included. Normal monochorionic twin pregnancies comprised the control group as there are likely inherent differences in cerebral Doppler patterns in twin pregnancies as compared to singletons⁷. Twin fetuses with possible twin-twin transfusion syndrome or significant growth discordance (>20% difference in estimated fetal weights) were excluded. For the TRAP group, information obtained from the obstetric ultrasound included the weight ratio between the acardiac and pump twin (AC:PT ratio). The longitudinal, transverse and anterior-posterior dimensions (in centimeters) of the acardiac mass were measured by ultrasound. The product of these three multiplied by 0.52 yielded an estimated volume (in cubic centimeters), which was converted to an estimated weight (in grams).

Charts were reviewed to assess whether a fetal intervention was performed and, if done, the timing of the procedure. Our center offers *in utero* therapy for TRAP pregnancies in the form of intrafetal radiofrequency ablation (RFA). Indications for intervention in our center during the time period of this study included a large mass: pump ratio without compromise, clear evidence of fetal compromise, or echocardiographic findings of compromise^{6,8,9}. RFA is used to obliterate flow at the insertion site of the umbilical vessels of the acardiac mass to prevent ongoing hemodynamic burden for the pump twin. The percutaneous intervention is performed under real-time ultrasound guidance using either a 14- or 17-gauge device and the corresponding radiofrequency generator (RITA Medical Systems, Fremont CA).

Successful procedures demonstrate absence of flow by Doppler interrogation in the vessels to and from the acardiac mass. Performing post-intervention fetal echocardiograms for TRAP pregnancies became a standard protocol in our center starting in 2012 to monitor improvement in hemodynamics with intervention; therefore a subset of subjects that underwent a fetal intervention had a follow-up fetal echocardiogram to review.

Fetal Echocardiography:

All subjects (TRAP and control) underwent a complete standard-of-care fetal echocardiogram. This included multiple tomographic views of the fetal heart according to ASE guidelines¹⁰ as well as color Doppler and pulsed wave Doppler examination of the umbilical cord, venous structures and the middle cerebral artery (MCA). Studies were performed on Sequoia C512 or S2000 ultrasound systems (Siemens, Mountain View, Calif., USA). The images were stored digitally in standard DICOM format. In all fetuses, Doppler interrogation of the middle cerebral artery was performed as part of the clinical protocol. Vascular impedance was expressed as the pulsatility index [PI= (peak systolic velocity- end-diastolic velocity)/time averaged mean velocity]; three measurements were obtained and the results were averaged for analysis.

Cardiothoracic ratio (CTR) was determined by dividing the area occupied by the heart in diastole by the thoracic area in a standard axial image of the fetal thorax. Combined cardiac output (CCO) was calculated by summing the individual outputs of the right and left ventricles, derived from the equation: velocity time integral x heart rate x semilunar valve area = ventricular output. The cardiovascular profile score was calculated for every pump twin as previously described¹¹. All measurements were repeated for subjects with an available fetal echocardiogram within 48 hours after fetal intervention.

Statistical Analysis:

All continuous variables were normally distributed; therefore, for each parameter, the mean and 95% confidence intervals were calculated. For each parameter, a comparison was made between the TRAP and control group using two-sample Student t tests. To assess the relationship between MCA PI and CCO and CTR, Pearson's correlation was performed. Finally, descriptive analyses were used to compare parameters for the TRAP subjects with pre- and post- intervention echocardiography data.

Results:

There were 19 twin pregnancies with TRAP and 18 (36 fetuses) uncomplicated monochorionic, diamniotic twin pregnancies. Both TRAP and control subjects had one fetal echocardiogram for a total of 37 echocardiographic evaluations. Characteristics of the TRAP subjects are shown in Table 1. There was no difference in gestational age at the time of the fetal echocardiogram between the TRAP and control subjects. The mean estimated weight ratio between the acardiac mass and pump twin in the TRAP group was 0.87 (95% CI 0.65-1.1) and there was no evidence for hydrops or significant cardiovascular compromise (all had a cardiovascular profile score > 8). Fifteen TRAP pregnancies underwent radiofrequency ablation of the acardiac twin at a mean gestational age of 20.2 weeks (+/- 2.8). Overall survival to delivery for pump twins was 95% (n= 18) with a mean birth weight of 2722 g (+/- 723g) (Table 1).

The cerebral vascular impedance in TRAP pregnancies as measured by PI was lower than in controls ($p < 0.01$), indicating increased cerebral vasodilation and lower impedance (Table 2). Furthermore, MCA Doppler patterns in TRAP pump twins exhibited a lower peak systolic velocity and more diastolic flow as compared to controls. The mean CCO among TRAP subjects was elevated at 199.7 (95% CI 138.4-

261.1), which is at the 95th percentile for gestational age and was higher as compared to controls ($p = .022$). Similarly, the mean CTR among TRAP subjects was larger than controls ($p < 0.01$), although still within normal range (0.31, 95% CI .30-.33). Correlation statistics did not demonstrate a relationship between MCA PI and CCO indexed to fetal weight or with CTR (Figure 1).

A subset of TRAP subjects ($n = 6$) had a post-intervention fetal echocardiogram within 48 hours of RF ablation. There was no change in CTR from the pre- to post-intervention echocardiogram (mean CTR pre-intervention 0.31, 95% CI 0.29-0.32, mean CTR post-intervention 0.31, 95% CI .29-.35). However, the mean MCA PI increased after the intervention from 1.5 (95% CI 1.3-1.7) to 1.8 (95% CI 1.4-2.2) (Figure 2).

Discussion:

Our study demonstrates that TRAP pump twins in a high output state have lower cerebral vascular impedance as compared to control twins in uncomplicated monochorionic pregnancies. However, there appears to be no significant correlation between cerebral vascular impedance and fetal hemodynamic markers of a high output state. Finally, in a small subset of pump twins with post-intervention fetal echocardiograms, there appears to be a trend towards an increased MCA PI after fetal intervention.

Our findings highlight a number of physiological considerations. Due to abnormal placental vascular connections and the presence of the acardiac mass, TRAP pump twins exist in a high cardiac output state. The mean CCO in the TRAP pump fetuses was significantly higher as compared to unaffected monochorionic twin controls. In many untreated cases, the pump twin can progress to developing high-output cardiac failure and subsequent hydrops, which has been associated with poor

outcomes^{1,3,12}. In fact, studies have demonstrated that an elevated CCO and CTR predicts those at high risk of cardiovascular compromise and/or poor outcomes even prior to the onset of hydrops^{9,13}. The TRAP subjects in our series did not demonstrate frank cardiovascular compromise despite having an elevated CCO (all had a cardiovascular profile score of greater than 8 with no evidence of hydrops), suggesting that the cerebral vascular findings can develop before significant heart failure and overt cardiac compromise. Interestingly, our findings demonstrate that there is no significant correlation between cerebral vascular impedance and hemodynamic markers of a high cardiac output state (CCO and CTR). This may be secondary to our small sample size, or could be suggestive of an alternate etiology for the lower cerebral vascular impedance seen in pump twins.

The cerebral vasodilation seen in the pump twins may be secondary to unique and abnormal placental vascular connections, particularly arterio-arterial and veno-venous connections. Specifically, relatively deoxygenated blood is sent by the pump twin via its umbilical artery toward the shared placenta. Some blood does not perfuse a placental cotyledon but rather is diverted via an arterio-arterial anastomosis and supplies, via retrograde flow in the umbilical artery, the acardiac mass. That blood is then further deoxygenated as it perfuses the acardiac. This blood then returns via retrograde flow in the acardiac's umbilical vein, passes through a veno-venous anastomosis and enters the umbilical vein returning blood to the pump twin's circulation. This circuit results in decreasing total oxygen delivery to the one potentially viable fetus. This may trigger the autoregulatory capacities of the cerebral vasculature in the pump twin leading to cerebral vasodilation in an attempt to increase total oxygen delivery to the brain.

Vasodilation of the cerebral vasculature has been identified in other fetal disease states, including growth restriction^{14,15} and congenital heart disease¹⁶. Fetuses with placental insufficiency and growth restriction demonstrate decreased cerebral vascular impedance as assessed by the MCA pulsatility index, which may represent an effective protective mechanism for significant neurologic injury^{17,18}. However this compensation may be inadequate, as some studies suggest that growth restricted fetuses with lower MCA Doppler-derived cerebral vascular impedance born prematurely have a higher degree of neurobehavioral abnormalities later in life¹⁹. Similarly, fetuses with hypoplastic left heart syndrome (HLHS) have been shown to have lower MCA Doppler-derived cerebral vascular impedance as compared to normal fetuses^{16,20-22} with evidence of abnormal neurodevelopmental outcomes²³. In HLHS, these findings are thought to be due to decreased total blood flow to the brain and therefore decreased total oxygen delivery^{24,25}. Although very different disease states in the fetus, all present with brain-sparing suggesting some degree of overlap in etiology as well as in ultimate neurodevelopmental outcomes.

Fetal intervention for TRAP sequence at our center has increased the survival rate of the pump twin to as high as 90%⁶. This success has been replicated in larger multi-center studies establishing the benefit of fetal intervention, particularly for cases with a large acardiac mass (greater than 50% weight ratio between the acardiac and pump twin)⁸. Studies have also demonstrated no difference in survival of the pump twin with expectant management for cases with an AC:PT ratio of less than 50%²⁶; therefore, most centers (including ours) currently only offer intervention for cases with an AC:PT ratio of greater than 50%. Additionally, the optimal timing of intervention has not been established with certainty. A large multi-center study demonstrated less intrauterine fetal demise when intervention was performed greater than 19 weeks gestation as

compared to less than 18 weeks gestation⁸. However, a recent study demonstrated that survival is not different when prophylactic intervention is performed earlier in gestation and the rates of premature delivery are lower²⁷. Our study demonstrates that mean MCA PI increased in a small subset of pump twins after intervention, suggesting an improvement in cerebral hemodynamics. However, this finding deserves further study in a larger group of subjects. It remains to be seen whether timing of intervention can impact other parameters, such as neurodevelopmental outcomes, given the possible changes in cerebral hemodynamics with intervention. Similarly, although survival is not impacted with expectant management for those cases with an AC:PT ratio of less than 50%, neurodevelopmental outcomes both in the short- and long-term in this cohort of largely untreated patients is unknown.

Our study is limited by its retrospective nature and small sample size. In addition, the TRAP cases included in this study were likely on the severe end of the spectrum as our institution is a referral center for fetal intervention. Furthermore, post-intervention fetal echocardiograms were performed only in a subset of subjects after it became part of the standard protocol, thus our conclusions regarding post-intervention cerebral hemodynamics are limited.

In conclusion, our study shows that cerebral vascular impedance is decreased in pump twins, indicating a brain-sparing effect in these fetuses. Larger, multi-center studies correlating fetal cerebral hemodynamics in TRAP pump twins to ultimate neurodevelopmental outcomes are necessary to add to current criteria for ideal candidates and optimal timing for fetal intervention. This information will be useful not only for management strategies, but also in counseling the family with an affected pregnancy.

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Figure 1 Caption:

Scatterplot demonstrating the relationship between middle cerebral artery pulsatility index (MCA PI) and combined cardiac output (CCO) and cardiothoracic ratio (CTR) in TRAP subjects. There appears to be no significant correlation between MCA PI and hemodynamic markers of a high cardiac output state (CCO and CTR).

Figure 2 Caption:

Graphical display of pre- and post-intervention middle cerebral artery pulsatility indices (MCA PI) for six TRAP pump twin subjects. Mean MCA PI was higher after intervention (pre- mean 1.5 95% CI 1.3-1.7; post- mean 1.8, 95% CI 1.4-2.2).

Table 1. Demographics of TRAP subjects

	TRAP (n= 19)
AC:PT ratio Mean (SD)	0.87 (.45)
Fetal Intervention N (%)	15 (79%)
GA at Intervention (weeks) mean (SD)	20.2 (2.8)
Pump twin survival N (%)	18 (95%)
Pump twin birth weight (g) mean (SD)	2722 (723)

*AC:PT Ratio: sonographic estimated weight ratio between the acardiac and pump twin

TRAP= twin reversed arterial perfusion; SD= standard deviation; GA= gestational age

Table 2. Mean and 95% confidence intervals for measured parameters in monochorionic (MC) twin controls and TRAP pump twins

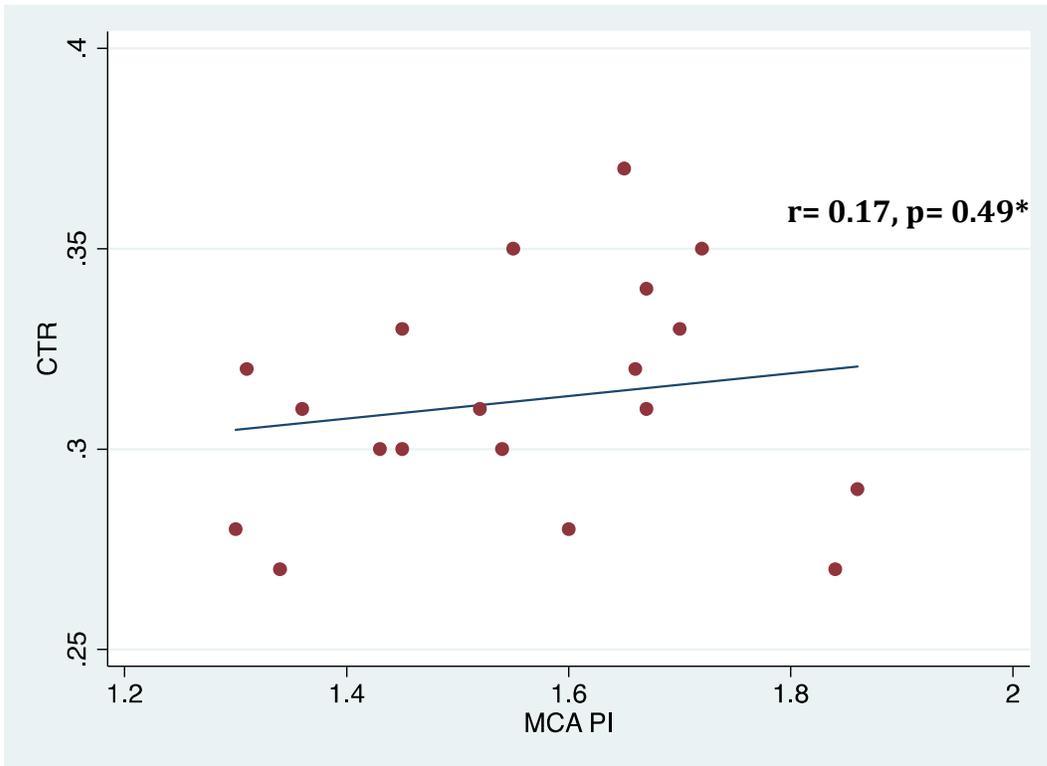
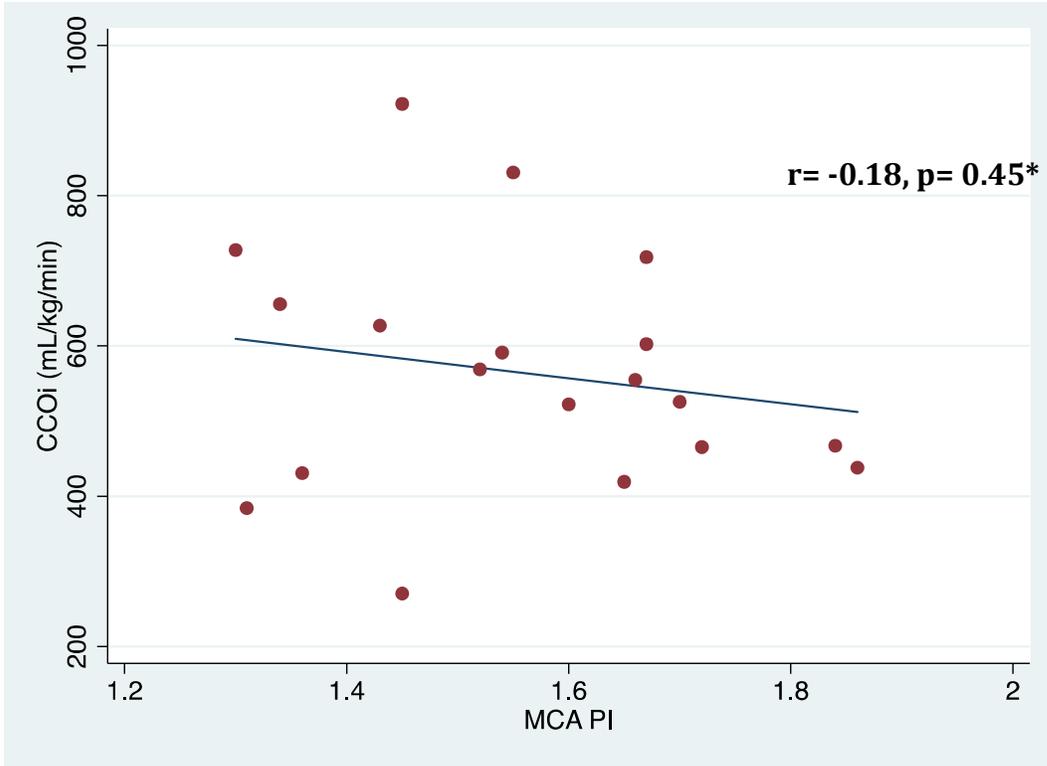
	Control MC twins (n= 36)	TRAP pump twins (n= 19)	P-value**
Gestational age*	20.3 (19.4-21.2)	19.9 (18.7-21.2)	0.63
MCA PI	1.7 (1.6-1.8)	1.5 (1.5-1.6)	0.004
CCO (mL/min)	131.4 (102.2-160.7)	199.7 (138.4-261.1)	0.022
CTR	0.28 (0.28-0.29)	0.31 (0.30-0.33)	<0.001

*Gestational age (in weeks) at the time of first echocardiogram

**Two sample t-test

MCA PI= middle cerebral artery pulsatility index; CCO= combined cardiac output; CTR= cardiothoracic ratio

Figure 1.



*Pearson's Correlation

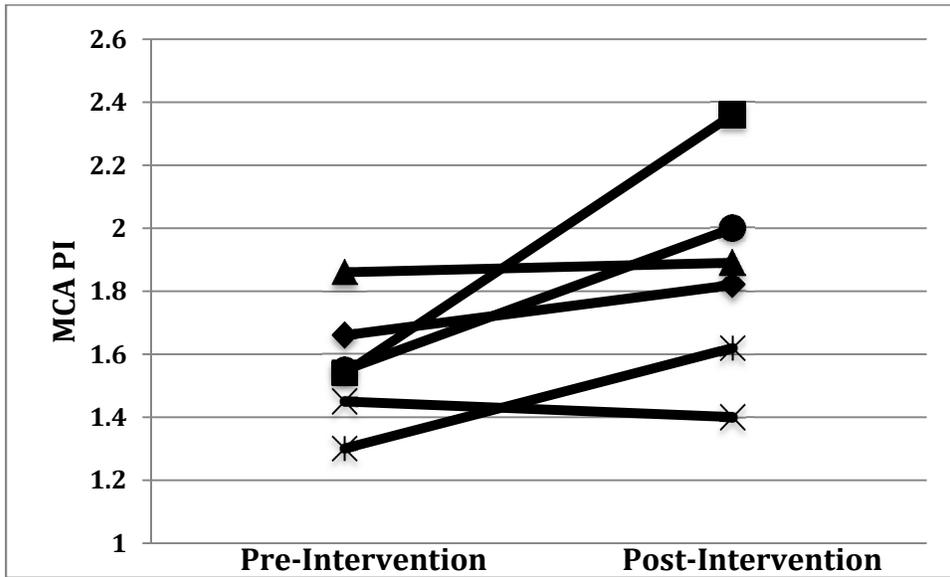
CCOi= combined cardiac output indexed to estimated fetal weight (mL/kg/min)

CTR= cardiothoracic ratio

MCA PI= middle cerebral artery pulsatility index

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Figure 2.



MCA PI= middle cerebral artery pulsatility index