Association Between Tetralogy of Fallot and Tracheobronchial Branching Abnormalities: A New Clue for Pathogenesis?

Guillaume Chassagnon, MD; Bruno Lefort, MD, PhD; Mathilde Meot, MD; Elodie Carpentier, MD; Dominique Sirinelli, MD, PhD; Alain Chantepie, MD, PhD; Baptiste Morel, MD, PhD

Background—In our practice, we noticed an increased frequency of tracheobronchial branching abnormalities (TBAs) in patients with tetralogy of Fallot (ToF). This study aimed to determine whether an association exists between congenital TBAs and ToF with or without pulmonary atresia.

Methods and Results—The frequency of TBAs on chest computed tomography was assessed in 55 patients with ToF without pulmonary atresia, 34 patients with ToF with pulmonary arteria, and 100 control patients. We then looked for a possible association between TBAs and pulmonary artery branch hypoplasia, the presence of major aortopulmonary collateral arteries, and the presence of the chromosome 22q11 deletion. TBAs were significantly more frequent in patients with ToF with or without pulmonary atresia than in the control group (any TBAs, 21% versus 2% [P<0.001]; bronchial situs anomalies, 6% versus 0% [P=0.002]; right tracheal bronchus, 4% versus 0% [P=0.04]; left eparterial bronchus, 8% versus 0% [P=0.005]), and tended to be more frequent in those with ToF without pulmonary atresia than in those with ToF with pulmonary arteria (any TBAs, 27% versus 12% [P=0.11]; left eparterial bronchus, 13% versus 0% [P=0.04]). TBAs were readily multiple (8 patients of 19 with TBA) and concerned essentially the upper lobes. TBAs were not associated with pulmonary branch hypoplasia, major aortopulmonary collateral arteries, or the chromosome 22q11 deletion.

Conclusions—We demonstrated a significantly increased frequency of tracheobronchial abnormalities in patients with ToF with or without pulmonary atresia compared with a control group. These results suggest an interaction between abnormalities in conotruncal septation and tracheobronchial branching and may provide a new clue to the pathogenesis of conotruncal heart diseases. (J Am Heart Assoc. 2018;7:e006921. DOI: 10.1161/JAHA.117.006921.)

Key Words: computed tomography • congenital heart disease • pulmonary atresia • tetralogy of Fallot • tracheobronchial branching abnormalities

Tetralogy of Fallot (ToF) is the most common cyanotic congenital heart defect, with a reported birth rate of ~0.3 per 1000 live births.1,2 It belongs to the spectrum of conotruncal diseases and is attributable to an anterocephalad deviation of the outlet septum. In the most severe form of the disease, the pulmonary valve is imperforate, leading to an anatomical variant termed ToF with pulmonary arteria (ToF-PA).3 Surgical management of ToF began in the 1940s with the Blalock-Taussig shunt, and it was initially only palliative.4 Thanks to the considerable advances in pediatric anesthesiology, extracorporeal circulation, and pediatric surgery, patients with ToF without PA usually undergo a complete repair within the first months of life, with excellent short- and long-term outcomes.5 Understanding of the pathophysiological process has also expanded in the past 20 years. Although there are still gaps in our knowledge of the developmental genetics of congenital heart diseases, several chromosome anomalies have been identified. For example, a microdeletion on chromosome 22 is associated with up to one-quarter of all patients with ToF; trisomy (in 21, 18, or 13) is associated with up to one-eighth of patients with ToF.5,6 On the basis of autopsy and radiological findings, several cardiovascular defects, including anomalous origin of the coronary arteries, atrial septal defects, right-sided aortic arch, pulmonary stenosis, and aberrant subclavian artery, are also known to be associated with ToF.6,7 Some have a direct impact on surgical repair.8,9 Thus, ToF is one of the best-understood congenital heart diseases.

In our experience, we noticed an increased frequency of tracheobronchial branching abnormalities (TBAs) in patients with ToF, especially of the left eparterial bronchus, a rare TBA of the left upper lobe. Higher frequency of right-sided TBAs in

From the Radiology Department (G.C., E.C., D.S., B.M.) and Pediatric Cardiology Department (B.L., M.M., A.C.), Hôpital Clocheville, Université François Rabelais de Tours, France.

Correspondence to: Guillaume Chassagnon, MD, Service de Radiologie Pédiatrique, Hôpital Clocheville-Centre Hospitalier Regional Universitaire de Tours, 49 Blvd Béranger, 37000 Tours, France. E-mail: gchassagnon@gmail.com

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Clinical Perspective

What Is New?

• Tracheobronchial branching abnormalities are associated with tetralogy of Fallot.
• The absence of a relationship between tracheobronchial branching abnormalities and anomalies in diameter (hypoplastic pulmonary artery) or in number (major aortopulmonary collateral arteries) of pulmonary vessels goes against the hypothesis of a mechanical origin.
• Association between tracheobronchial branching abnormalities and tetralogy of Fallot suggests an interaction between abnormalities in conotruncal septation and tracheobronchial branching.

What Are the Clinical Implications?

• The presence of tracheobronchial branching abnormalities should be assessed in patients with tetralogy of Fallot undertaking computed tomography imaging.

Methods

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

Ethical Approval of the Study Protocol

The study was approved by the local ethics committee (reference number 2016-067). The need for informed consent was waived, in accordance with French rules for retrospective studies.

Patients

We conducted an observational, single-center, retrospective study. All patients with ToF or ToF-PA referred for a thoracic CT examination from January 1, 2007 to November 30, 2015 were included. All thoracic CT examinations were performed as part of standard clinical care. The control population consisted of 100 consecutive adult patients who underwent pulmonary CT angiography in our radiology department for the clinical suspicion of pulmonary embolism between January 1, and March 11, 2014.

All the CT examinations were performed with 16- to 128-slice CT scanners (Sensation 16 and Definition AS+ [Siemens Healthcare, Erlangen, Germany] and Brilliance 64 [Phillips Medical Systems, Best, The Netherlands]). Images were reconstructed with a 1- to 1.25-mm thickness using a medium-sharp algorithm; for most patients, additional 0.6- to 1.125-mm thickness images reconstructed with a sharp algorithm were also available.

Image Analysis

Examination results were retrospectively analyzed in consensus by 2 radiologists (G.C. and E.C.) with 2 and 10 years of experience in thoracic imaging, respectively. Both observers were blinded to the congenital heart disease and to clinical and genetic data. For the diagnosis of TBAs (Figure), the classification proposed by Chassagnon et al was used.12
1. Bronchial situs anomaly was defined as an unusual arrangement of the bronchial tree relative to the midline. It corresponded to an inverted bronchial situs, a left bronchial isomerism, or a right bronchial isomerism. The relationship of the upper lobe bronchus to the ipsilateral pulmonary artery was used as the main marker of bronchial situs.
2. Right tracheal bronchus was defined as an anomalous right upper lobe bronchus arising from the trachea.
3. Right preeparterial bronchus was defined as an anomalous right upper lobe bronchus, originating from the right main bronchus, higher than the level of the normal right upper lobe bronchus.
4. Right posteparterial bronchus was defined as an anomalous right upper lobe bronchus arising from the right bronchial tree at a level lower than that of the normal right upper lobe bronchus (eg, from the middle lobe bronchus).
5. Left eparterial bronchus was defined as an anomalous left upper lobe bronchus arising from the left main bronchus higher than the level where the left pulmonary artery crosses the left main bronchus. With the main differential diagnosis of left eparterial bronchus being right isomerism, the morphological characteristics of the whole left lung and the presence of associated atrial and abdominal heterotaxy were taken into account to differentiate the 2 entities.
6. Left prehyparterial bronchus was defined as an anomalous left upper lobe bronchus, originating from the left main bronchus between the level where the left pulmonary artery crosses the left main bronchus and the level of normal left upper lobe bronchus.
7. Gross upward displacement of the middle lobe bronchus was defined as a middle lobe bronchus anomaly arising at the level of or from the normal right upper lobe bronchus.
8. Suprasuperior bronchus was defined as a displaced subsegmental bronchus of the superior segment of the lower lobe, originating from the main bronchus or from the intermediate bronchus.
9. Accessory cardiac bronchus was defined as a supernumerary bronchus, originating from the medial wall of the main bronchus or intermediate bronchus and directed toward the heart.
10. Bridging bronchus was defined as an aberrant bronchus that partially or totally supplies the right lung but that originates from the left main bronchus.

Clinical Data

Diagnosis of ToF without or with PA was confirmed by review of echocardiographic, angiographic, and operative reports. Patients with ToF who underwent a primary curative surgery were considered to not have hypoplastic pulmonary arteries. In patients who underwent a primary palliative approach, medical records and available preoperative imaging procedures were reviewed by pediatric cardiologists B.L. and M.M., blinded to the presence of TBA, to check the presence of hypoplastic pulmonary arteries. The presence of major aortopulmonary collateral arteries (MAPCAs) in patients with ToF and ToF-PA was also retrieved from the patient medical records. The presence of MAPCA was suspected on echocardiographic findings and confirmed by CT or angiographic findings. When available, the results of genetic analysis in patients with ToF or ToF-PA were reviewed for screening for the 22q11 deletion.

Statistical Analysis

Patient characteristics were described using frequency, median, and range. Incidences of TBAs were compared using the 2-sided Fisher exact test. Statistical significance was defined as \( P < 0.05 \). All analyses were performed with the statistical software package “R,” version 3.2.3 (R Foundation for Statistical Computing, Vienna, Austria).
Results

During the study period, 173 patients with ToF and 41 patients with ToF-PA were evaluated at our institution. Because CT examinations are not routinely performed in patients with ToF and ToF-PA, only 55 patients with ToF and 34 patients with ToF-PA underwent a thoracic CT examination and were included in the analysis. Patients’ characteristics are summarized in Table 1. CTs were performed for assessment of the congenital heart disease in 83 patients (93%) and for respiratory tract symptoms in 6 patients (7%).

A total of 30 TBAs were found in 19 patients with ToF and ToF-PA, and only 2 anomalies were diagnosed in 2 of 100 control patients (incidence, 21% versus 2%; P<0.001; Table 2). TBAs were multiple in 8 patients and concerned essentially the upper lobes (20/30 [67%]); in particular, a left eparterial bronchus was found in 7 of 19 patients. TBA tended to be more frequent in patients with ToF than in patients with ToF-PA, but without statistical significance (any TBAs: 27% versus 12%, respectively; P=0.11), whereas left eparterial bronchus was significantly more frequent in patients with ToF (13% versus 0%; P=0.04; Table 3). We then studied factors that could potentially be associated with TBAs. Surgical data were available for 52 of 55 patients with ToF. Thirty-one of them (60%) were treated with primary corrective surgery, and 21 (40%) underwent a staged approach with primary palliative surgery. Among the latter, 13 patients underwent first-step palliation for hypoplasia of at least 1 of the 2 pulmonary arteries. In the 8 remaining cases, palliative surgery was performed because of marked hypoxia attributable to severe infundibular stenosis (n=3), because of marked hypoxia associated with a left anterior descending coronary artery arising from the right coronary artery (n=1), or because a staged approach with primary palliation was the standard management in our institution at that time (n=4). Thus, 13 of 52 patients were considered to have a hypoplastic pulmonary artery, and there was no significant association with TBAs (P>0.05; Table 4). Of 82 patients with ToF or ToF-PA with available data, 29 had MAPCA. Absence of MAPCA was significantly associated with a left eparterial bronchus (P=0.04) but not with TBAs as a whole (P=0.27; Table 5). Finally, karyotype information was available for 82 of 89 patients with ToF and ToF-PA. Four patients had a 22q11 microdeletion (4/82 [5%]), and none of them had TBAs. However, the frequency of TBAs was not significantly different between patients with and without the 22q11 microdeletion (0% versus 22%; P=0.576).

Among the 6 patients (4 with ToF and 2 with ToF-PA) for whom CT was indicated for respiratory tract symptoms, 3 TBAs were found in 2 with ToF (left eparterial bronchus in 1 patient and left eparterial and right preeparterial bronchi in 1 patient). However, TBAs were not judged responsible for the respiratory tract symptoms in these 2 patients.

Discussion

To the best of our knowledge, this study is the first to demonstrate an association between TBAs and patients with ToF and ToF-PA. In this study, 21% of patients with ToF or ToF-PA had TBAs affecting the trachea, main bronchi, and intermediate bronchus. The frequency of TBAs in the control population (2%) was significantly lower and comparable to those previously reported in the literature, ranging from 0.1% to 2%.12,13 Interestingly, TBAs tended to be more frequent in patients with ToF (27%) than in patients with ToF-PA (12%).

In patients with ToF, the frequency of TBA was comparable to the usually cited frequency of right aortic arch (18%–25%)3,9,14,15 and higher than the frequency of anomalous distribution of the coronary arteries (6%–13%).15,16 These malformations are also known to be associated with ToF. Oswal et al recently reported that the presence of an aberrant subclavian artery origin in ToF with pulmonary stenosis was significantly associated with a higher risk of chromosomal or genetic anomaly, including the 22q11.2 deletion and trisomy 21.9 In our study, none of the 4 patients with the 22q11 deletion had a TBA. This finding may appear counterintuitive because many patients with the 22q11 deletion experience respiratory tract insufficiency or failure,16 but it is in accordance with data from the literature. Indeed, DiGeorge syndrome is often associated with tracheobronchial abnormalities, and the 22q11 deletion is considered a critical region for the development of the respiratory tract. Therefore, the absence of TBAs in our patients with the 22q11 deletion may suggest that the presence of these malformations is not a prerequisite for the 22q11 deletion or may reflect differences in the genetic background of the patients included in the study.

Table 1. Patient Characteristics

| Characteristics                   | Patients With ToF (n=55) | Patients With ToF-PA (n=34) | Control Group (n=100) |
|----------------------------------|-------------------------|-----------------------------|-----------------------|
| Age, median (range), y           | 1 (0–49)                | 4 (0–44)                    | 65 (20–94)            |
| Female sex                       | 27 (49)                 | 20 (59)                     | 57 (57)               |
| 22q11 Microdeletion              | 2/50 (4)                | 2/32 (6)                    | NA                    |
| Presence of pulmonary artery branch hypoplasia | 13/52 (25)         | ...                         | ...                   |
| Presence of MAPCA                | 6/49 (12)               | 23/33 (70)                  | 0                     |

Values are number (percentage) or number/total (percentage) unless otherwise indicated. MAPCA indicates major aortopulmonary collateral artery; NA, not applicable; PA, pulmonary atresia; and ToF, tetralogy of Fallot.
syndrome can be associated with structural airway anomalies, such as bronchomalacia, but TBAs are rare.\textsuperscript{16} The frequency of right tracheal bronchus in patients with ToF (5%) and patients with ToF-PA (3%) was similar to that reported by Ming and Lin in children with congenital heart disease (3.64%).\textsuperscript{11} However, in patients with ToF and ToF-PA, we observed TBAs of the left upper lobe to be as frequent as those of the right upper lobe. Usually, TBAs of the left upper lobe are rare. In the general population, they have been reported to be 3 to 6 times less frequent than TBAs of the right upper lobe.\textsuperscript{13,17} But strikingly, in patients with ToF, left eparterial bronchus was the most frequent TBA. The 7 cases reported in our study were all found in patients with ToF, and they form the second largest series of left eparterial bronchi after the 10 cases reported in the multicenter study of Oshiro et al.\textsuperscript{18}

Interestingly, TBAs were not associated with the presence of pulmonary artery branch hypoplasia in patients with ToF, nor with the presence of MAPCA in patients with ToF or ToF-PA. Thus, the absence of a relationship between TBAs and anomalies in diameter (PA) or in number (MAPCA) of pulmonary vessels goes against the hypothesis of a mechanical origin. Our findings should suggest the existence of common pathways between conotruncal septation and tracheobronchial branching. Cardiac organogenesis begins during the third week of development and originates from the mesoderm.\textsuperscript{19,20} Development of the tracheobronchial tree also begins early in fetal life, but the tracheobronchial

| Table 2. Comparison of the Frequencies of TBAs Between Patients With ToF or ToF-PA and Control Patients |
|-------------------------------------------------|------------------|------------------|------------------|
| Abnormality                                      | Patients With ToF or ToF-PA (n=89) | Control Group (n=100) | P Value |
| Any abnormality                                  | 19 (21)           | 2 (2)            | <0.001          |
| Multiple abnormalities                           | 8 (9)             | 0                | 0.002           |
| Bronchial situs anomalies                        | 5 (6)             | 0                | 0.02            |
| Abnormalities of the upper lobes                 |                   |                  |                 |
| Right tracheal bronchus                          | 4 (4)             | 0                | 0.04            |
| Right preeparterial bronchus                     | 4 (4)             | 1 (1)            | 0.19            |
| Right posteparterial bronchus                    | 2 (2)             | 0                | 0.22            |
| Left eparterial bronchus                         | 7 (8)             | 0                | 0.005           |
| Left prehyparterial bronchus                     | 3 (3)             | 0                | 0.10            |
| Abnormality of the middle lobe                   |                   |                  |                 |
| Gross upward displacement of the middle lobe bronchus | 1 (1)         | 0                | 0.47            |
| Abnormality of the inferior lobes                |                   |                  |                 |
| Suprasuperior bronchus                           | 1 (1)             | 1 (1)            | 1               |
| Other abnormalities                              |                   |                  |                 |
| Bridging bronchus                                | 2 (2)             | 0                | 0.22            |
| Accessory cardiac bronchus                       | 1 (1)             | 0                | 0.47            |

Values are number (percentage) unless otherwise indicated. PA indicates pulmonary atresia; TBA, tracheobronchial branching abnormality; and ToF, tetralogy of Fallot.

| Table 3. Comparison of the Frequencies of TBAs Between Patients With ToF and ToF-PA |
|-------------------------------------------------|------------------|------------------|------------------|
| Abnormality                                      | Patients With ToF (n=55) | Patients With ToF-PA (n=34) | P Value |
| Any abnormality                                  | 15 (27)           | 4 (12)           | 0.11            |
| Multiple abnormalities                           | 7 (13)            | 1 (3)            | 0.15            |
| Bronchial situs anomalies                        | 3 (5)             | 2 (6)            | 1               |
| Abnormalities of the upper lobes                 |                   |                  |                 |
| Right tracheal bronchus                          | 3 (5)             | 1 (3)            | 1               |
| Right preeparterial bronchus                     | 4 (7)             | 0                | 0.29            |
| Right posteparterial bronchus                    | 2 (4)             | 0                | 0.52            |
| Left eparterial bronchus                         | 7 (13)            | 0                | 0.04            |
| Left prehyparterial bronchus                     | 2 (4)             | 1 (3)            | 1               |
| Abnormality of the middle lobe                   |                   |                  |                 |
| Gross upward displacement of the middle lobe bronchus | 1 (2)         | 0                | 1               |
| Abnormality of the inferior lobes                |                   |                  |                 |
| Suprasuperior bronchus                           | 1 (2)             | 0                | 1               |
| Other abnormalities                              |                   |                  |                 |
| Bridging bronchus                                | 1 (2)             | 1 (3)            | 1               |
| Accessory cardiac bronchus                       | 1 (2)             | 0                | 1               |

Values are number (percentage) unless otherwise indicated. PA indicates pulmonary atresia; TBA, tracheobronchial branching abnormality; and ToF, tetralogy of Fallot.

| Table 4. Frequency of Hypoplastic Pulmonary Artery in Patients With ToF, Depending on the Presence of TBAs |
|-------------------------------------------------|------------------|------------------|------------------|
| Variable                                        | ToF With Hypoplastic Pulmonary Artery (n=13) | ToF Without Hypoplastic Pulmonary Artery (n=39) | P Value |
| Any TBA                                         |                   |                  |                 |
| Yes                                             | 4 (31)            | 10 (26)          |                 |
| No                                              | 9 (69)            | 29 (74)          | 0.73            |
| Multiple TBAs                                   |                   |                  |                 |
| Yes                                             | 3 (23)            | 4 (10)           | 0.35            |
| No                                              | 10 (77)           | 35 (90)          |                 |
| Left eparterial bronchus                        |                   |                  |                 |
| Yes                                             | 2 (15)            | 5 (13)           |                 |
| No                                              | 11 (85)           | 34 (77)          | 1               |

Values are number (percentage) unless otherwise indicated. TBA indicates tracheobronchial branching abnormality; and ToF, tetralogy of Fallot.
epithelium originates from the endoderm. On gestational day 24, lung development begins as a ventral wall diverticulum of the foregut and then the endoderm undergoes a series of dichotomous and lateral branching to produce the conducting airways.\textsuperscript{10,21} These events occur during the embryonic (weeks 5–7) and pseudoglandular (weeks 5–17) phases. At day 36, segmental buds are already present.\textsuperscript{10,21} Thereafter, at the end of the sixth week, the branching pattern of lobar and segmental portions of the airway tree is established.\textsuperscript{21} The development of the tracheobronchial tree is accompanied by the parallel development of the pulmonary vasculature that originates from the sixth pair of aortic arches. Conotruncal septation occurs at almost the same time, around the 16th Carnegie stage (day 39).\textsuperscript{22} Although arising from endoderm, tracheobronchial epithelium development is induced by epitheliomesenchymal interactions that require close proximity of the epithelium and the mesenchyme.\textsuperscript{21,23}

The association between conotruncal heart defects and TBAs possibly involves signaling pathways, such as sonic hedgehog, bone morphogenetic protein 4, and Noggin, which are known to be involved in both conotruncal septation and regulation of bronchial branching morphogenesis in mice.\textsuperscript{23–25} For example, sonic hedgehog–null mice develop a phenocopy of ToF-PA, but they are also known to have bilateral hypoplastic lungs attributable to an absence of branching morphogenesis.\textsuperscript{23–25} Our observation suggests the need for further experiments to better understand these potential interactions. The high frequency of left-sided TBAs in patients with ToF and ToF-PA is a plausible clue to the involved mechanism. Indeed, some genes, such as sonic hedgehog, are supposed to have a left-right effect on the secondary heart field.\textsuperscript{26} Last, the lower frequency of TBAs in ToF-PA, which is considered to be the most severe form of ToF, should support differences in the signaling pathway between these 2 diseases on the same spectrum.

Most patients with TBAs remain asymptomatic; however, some of them could experience dyspnea, recurrent pneumonia, or hemoptysis.\textsuperscript{12} Consequences of these abnormalities in patients with ToF and ToF-PA, especially during the perioperative period, are unknown and need to be assessed in further research.

This study has several limitations. Because of the observational and retrospective design, the study may have had missing data and selection bias. Indeed, CT examinations are not routinely performed in patients with ToF and ToF-PA; and because patients with ToF-PA are more likely to undergo CT to evaluate the anatomical features of the pulmonary arterial tree, the much rarer ToF-PA is highly represented in our cohort. Only 89 of 214 patients with ToF and ToF-PA evaluated at our institution during the study period underwent a thoracic CT examination, which could introduce a selection bias of the patients included in our cohort. However, even if none of the remaining patients with ToF- and ToF-PA had TBA, the prevalence of TBA would have remained significantly higher than in the control group (19/214 versus 2/100; \(P=0.02\)). Furthermore, we did not look for TBAs in the other, but rarer, conotruncal heart defects, such as truncus arteriosus or interruption of the aortic arch, because the number of patients with these congenital heart diseases was too low to perform statistical analyses. Looking for TBAs in these heart diseases could be of great interest because they have the same embryological origin as ToF or ToF-PA. Another limitation was the definition we used for hypoplastic pulmonary arteries. Patients were considered to have hypoplastic pulmonary arteries if they underwent a primary palliative approach because of hypoplastic pulmonary arteries, according to preoperative data. Because of the retrospective design, heterogeneity of anatomical preoperative evaluation of the pulmonary arteries and missing data and objective assessment of pulmonary artery diameter (eg, McGoon ratio or Z score) could not be calculated. Another limitation was the small size of the cohort; therefore, the lack of significance for the association between TBA and pulmonary branch hypoplasia, MAPCA, or 22q11 deletion does not necessarily indicate the absence of a relationship. Results from larger cohorts are required to confirm our findings. Finally, because of the retrospective design, we were not able to assess the relationship between TBA and clinical respiratory symptoms, especially during the postoperative period. TBAs were not judged responsible for the respiratory tract symptoms in the 2 patients with TBAs who underwent CT indicated for respiratory tract symptoms, but this does not rule out the possibility of clinical respiratory tract symptoms attributable to TBAs. Further investigations are needed to evaluate the consequences of TBA on respiratory tract function.

**Table 5.** Frequency of MAPCAs in Patients With ToF or ToF-PA, Depending on the Presence of TBAs

| Variable                  | Presence of MAPCA (n=29) | No MAPCA (n=53) | \(P\) Value |
|---------------------------|--------------------------|------------------|-------------|
| Any TBA                   |                          |                  |             |
| Yes                       | 4 (14)                   | 14 (26)          |             |
| No                        | 25 (86)                  | 39 (74)          | 0.27        |
| Multiple TBAs             |                          |                  |             |
| Yes                       | 2 (7)                    | 6 (11)           | 0.71        |
| No                        | 27 (93)                  | 47 (89)          |             |
| Left eparterial bronchus  |                          |                  |             |
| Yes                       | 0 (0)                    | 7 (13)           | 0.04        |
| No                        | 29 (100)                 | 46 (87)          |             |

Values are number (percentage) unless otherwise indicated. MAPCA indicates major aortopulmonary collateral artery; PA, pulmonary atresia; TBA, tracheobronchial branching abnormality; and ToF, tetralogy of Fallot.
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In conclusion, we demonstrated a significantly increased frequency of TBAs in patients with ToF or ToF-PA. In particular, we observed a high frequency of left-sided TBAs. Our results suggest an interaction between abnormalities in conotruncal septation and tracheobronchial branching and may provide a new clue for pathogenesis. Further studies are needed to clarify the precise pathophysiological process involved.

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None.

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