Characterization of Anatomic Ventricular Tachycardia Isthmus Pathology after Surgical Repair of Tetralogy of Fallot

Running title: Moore et al.; Ventricular tachycardia substrate in TOF

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Abstract

Background - While catheter ablation has been used to target the critical isthmuses for reentrant monomorphic ventricular tachycardia (VT) in tetralogy of Fallot (TOF), the anatomy and histology of these regions have not been fully characterized. Autopsy hearts with TOF were evaluated in order to clarify the pathologic substrate.

Methods and Results - Twenty-seven hearts with the diagnosis of TOF were examined. Anatomically defined isthmuses included 1A) ventriculotomy-to-tricuspid annulus, 1B) ventriculotomy-to-VSD patch, 2) ventriculotomy-to-pulmonary annulus, 3) pulmonary annulus-to-VSD patch, and 4) VSD patch-to-tricuspid annulus. Length and wall thickness were measured for all specimens, and light microscopy was performed for those surviving surgery. For subjects ≥ 5 years at death, isthmus 1A and 1B were present in 88%, isthmus 2 in 25%, isthmus 3 in 94%, and isthmus 4 in 13%. Isthmus 1A had the greatest dimensions (mean length 3.9 ± 1.08, thickness 1.5 ± 0.3 cm), isthmus 1B intermediate (mean length 2.4 ± 0.8 and thickness 1.1 ± 0.4 cm) and isthmuses 2, 3, and 4 smallest (mean length 1.5 ± 0.5, 1.4 ± 0.8, and 0.6 ± 0.4 cm; and thickness 0.5 ± 0.2, 0.6 ± 0.2 cm, and 0.3 ± 0.04 cm respectively) Histologic examination (n=7) revealed increased fibrosis in anatomic isthmuses relative to non-isthmus controls.

Conclusions - Consistencies in isthmus dimensions and histology are found among patients with repaired TOF. Isthmus 1A is associated with the largest morphologic dimensions, while the nearby newly-described isthmus 1B is significantly smaller. Of isthmuses with the smallest dimensions, isthmus 3 is most common.

Key words: Congenital heart disease; ventricular tachycardia; catheter ablation; tetralogy of Fallot; isthmus
Introduction

Ventricular tachycardia (VT) is a major source of morbidity and mortality for patients with repaired tetralogy of Fallot (TOF). Risk factors predictive of sudden cardiac death (SCD), itself closely linked to ventricular arrhythmia in this population include symptoms,\(^1\)?\(^2\) QRS duration,\(^3\)?\(^4\) prior palliative repair,\(^2\)?\(^4\)?\(^5\) the presence of a discrete ventriculotomy,\(^4\)?\(^6\) and right ventricular (RV) dilation.\(^7\)?\(^8\) More recently, left ventricular (LV) dysfunction has also been implicated in cases of SCD.\(^4\)?\(^9\) Catheter ablation for VT has been used with increasing success but reasons for failure include non-sustained episodes of induced VT, poor hemodynamic tolerance of VT, or inadequate modification of the arrhythmia substrate. In addition, recurrences have been noted, suggesting the possibility of incomplete conduction block.\(^10\)?\(^11\)

The pathologic substrate responsible for the reentrant monomorphic VT circuit has been shown to involve discrete isthmuses between both anatomic and surgically-induced barriers that are critical to successful repair of TOF.\(^12\) Although commonly targeted for ablation, detailed pathologic and anatomic analysis of these isthmuses has not been performed. We sought to examine the morphologic characteristics of these ventricular isthmuses in a large group of archival hearts with a history of surgically-repaired (TOF), hypothesizing that significant differences in substrate pathology exist. We also considered a previously undescribed isthmus between the ventriculotomy incision and VSD patch as potential alternative for catheter ablation.

Methods

The autopsy and surgical pathology database at UCLA was searched for cases of TOF and its major variants (including TOF with pulmonary atresia and/or absent pulmonary valve). Baseline demographic and clinical data were obtained from the medical record. All specimens were evaluated for the presence of naturally or surgically-related anatomic isthmuses corresponding to...
those that have been previously described. In addition, isthmus 1 was redesignated as 1A, and the previously undescribed but adjacent isthmus between the ventriculotomy incision and the ventricular septal defect (VSD) patch was classified as 1B. Using this new classification, anatomical isthmuses included: 1A) ventriculotomy-to-tricuspid annulus, 1B) ventriculotomy-to-VSD patch, 2) ventriculotomy-to-pulmonary annulus, 3) pulmonary annulus-to-VSD patch, and 4) VSD patch-to-tricuspid annulus (Figure 1). For all subjects (n=27), isthmus dimensions were recorded, and included both the shortest distance between two non-conducting barriers “isthmus length” (along the presumptive path of targeted catheter ablation lesions), and “isthmus thickness” corresponding to the minimum and maximum ventricular wall thickness in this area measured from the endocardium to the epicardium. Care was taken to exclude epicardial fat in the measurement of the latter isthmus and this was manually removed if necessary from around the coronary vessels and atroventricular groove to visualize the myocardium.

For subjects surviving surgical repair (n=7), tissue from the previously defined isthmuses were excised, processed routinely, and sectioned. Slides were stained with hematoxylin-eosin and trichrome/elastic-Van Gieson (EVG). Several sections were prepared in order to confirm whether or not a complete isthmus of myocardium was present. In some cases as many as 15 serial sections, 4 micron thick were reviewed from a single paraffin block for the evaluation. Morphologic examination included measurement of the degree of secondary endocardial fibroelastosis (EFE) as described previously, as well as a quantitative assessment of the combination of interstitial myocardial fibrosis and/or replacement myocardial fibrosis. The quantitative assessment was performed after microscopic evaluation of the entire length and depth of the ventricular isthmus, with percentage of total isthmus determined by visual inspection. Percentage of fibrosis per isthmus was evaluated by microscopic examination on the
trichrome/EVG stained slides. Fibrosis grading was by consensus of two cardiac pathologists (AS and MCF). In addition, sections were taken from the RV and LV apical free wall (1 cm from the apex) in each of these specimens to serve as non-isthmus controls.

Results are presented as mean ± SD, with the exception of non-normal distributions, where medians and interquartile range (IQR) are reported. Differences in isthmus length and wall thickness were analyzed with a linear mixed effects model after checking model assumptions of normality and homogeneity of variance. Significant outliers related to marked deviation from standard surgical technique were removed prior to analysis. In this model, isthmus category is a fixed effect and heart specimen is a random effect. The random effect component allows multiple observations on the same individual to be correlated and is an acceptable method for dealing with data that is missing at random (MAR). Tukey’s honestly significant difference (HSD) test was used for multiple comparisons after application of the model. McNemar’s test was used to evaluate differences in paired proportions between isthmus categories, using the Bonferroni-Holm method for multiplicity of tests. Adjusted p-values of less than or equal to 0.05 established statistical significance. Statistical analysis was performed with JMP software (SAS Inc., Cary, NC)

Results

Clinical data

A total of 43 hearts with the diagnosis of TOF were identified, of which 27 had a history of prior surgical repair and were included in the analysis. The diagnosis was predominantly the usual morphology of TOF (n=24), whereas TOF with pulmonary atresia (n=2) and TOF with absent pulmonary valve (n=1) were also identified. A discrete ventriculotomy or patch in the RV outflow tract (non-contiguous with the pulmonary annulus) was present in 7 specimens (26%), a transannular patch or ventriculotomy extending across the pulmonary annulus was present in 16 (59%), and a prosthetic conduit was present in 2 (7%). Two specimens had no identifiable RV incision (7%). Two patients, both with a prior transannular patch had a bioprosthetic valve in the
pulmonary position. The median age was 7.0 years (range 35 days to 66 years) with 7 subjects surviving the surgical repair, all by at least 1 year. Two subjects surviving surgical repair had a history of ICD placement with appropriate therapy for VT, and one patient died suddenly.

Baseline demographic data and details of surgical intervention are presented in Table 1.

**Gross examination**

The presence of various isthmuses differed significantly among categories. Isthmus 1A, 1B, and 3 were encountered more frequently than isthmuses 2 and 4 (p<0.001). Isthmus 1A and 1B were both present in 25 cases (93%). Isthmus 2 was present in 7 cases (26%) and was related to a discrete ventriculotomy or patch in all specimens. Isthmus 3 was present in 24 cases (89%), being absent in the single case of TOF with absent pulmonary valve as well as the two cases with bioprosthetic pulmonary valves that had been sewn to region of the VSD patch in the RV outflow tract. Isthmus 4 was least commonly seen (19%) and was identified in 3 subjects who had died in the immediate perioperative period and in only 2 surgical survivors.

Isthmus dimensions also varied significantly by category. Isthmus 1A length was greater than isthmus 1B, isthmus 3, and isthmus 4 (p<0.05). Maximum ventricular wall thickness also varied among categories, whereas there was no significant difference in minimum wall thickness. Mean maximum thickness was greatest for isthmus 1A relative to isthmuses 1B, isthmus 2, and isthmus 3 (p<0.05).

There were 2 outliers related to substantial deviation in standard surgical technique. The first was a 61-year old female who underwent intracardiac repair in 1965. Gross evaluation revealed a circular ventriculotomy in the inferolateral RV free wall remote from both the pulmonary and tricuspid annuli. The second was an 11 year old female who had undergone repair in 1972 and whose cardiac evaluation demonstrated an unusual ventriculotomy measuring...
11.5 cm that extended inferiorly from the pulmonary annulus to the midportion of the RV free wall and then transversely to within 0.15 cm of the tricuspid annulus. Isthmus 1A and 2 dimensions for these subjects were significant outliers and were therefore not used in the statistical analysis.

Subgroup analysis

Subjects ≥ 5 years at the time of death (n=16) were analyzed separately. The frequency of ventricular isthmuses again varied by category, with isthmus 1A and 1B both present in 13 cases (88%), isthmus 2 in 3 cases (25%), isthmus 3 in 14 cases (94%), and isthmus 4 in 2 cases (13%). Isthmus 1A, 1B, and 3 were more common than isthmuses 2 and 4 (p<0.05), similar to that of the overall population. Isthmus dimensions were likewise dissimilar among categories, with greater length for isthmus 1A compared to all other isthmus categories, including isthmus 1B (Figure 2A). Likewise, maximum ventricular wall thickness varied by category with greater thickness for isthmus 1A versus all other isthmus categories, and greater thickness for isthmus 1B versus all other categories with the exception of 1A. No significant differences in length or wall thickness were apparent among isthmuses 2, 3, and 4 (Figure 2A and 2B). Subgroup characteristics are summarized in Table 2.

Gross evaluation of hearts revealed consistent anatomic findings pertinent to the ventricular wall thickness. For isthmus 1A, minimum wall thickness was typically related to surgical thinning near the site of the prior ventriculotomy or patch. This thinning extended for a variable distance toward the tricuspid annulus, where wall thickness tended to increase substantially (Figure 3). Wall thickness for isthmus 1B was more uniform than that of 1A, with the exception of occasional specimens in which a prominent parietal band coursed superiorly and laterally to the VSD patch. Isthmus 2 showed little variation in thickness dimension, and was
thin-walled in those specimens in which it was present. Isthmus 3 was also notable for minimal wall thickness that was related to surgical resection of the anteriorly malaligned conal septum. For isthmus 4, ventricular wall thickness was minimal for all specimens in which it was observed.

**Histologic examination**

Histologic examination for all cases surviving surgical repair (n=7) revealed maximum EFE that was particularly prominent at sites of prior surgery, including the VSD patch and the RV free wall incision. The median maximal EFE for all isthmuses was 1.03 mm, ranging from 0.12 mm to 4.0 mm. The degree of interstitial fibrosis and/or replacement fibrosis was significantly greater than the non-isthmus apical control sections for isthmuses 1A, 1B, and 3 (p<0.05 Figure 4). The mean ratio of maximal EFE-to-wall thickness was 48% for isthmus 2, 35% for isthmus 4, 29% for isthmus 3, 19% for isthmus 1B, and 8% isthmus 1A (p=ns). For case 5, surviving myocyte bundles were encountered at an initial section of isthmus 4 but not in remaining sections, indicating the absence of a true isthmus for this case (Figure 3G). In addition, clinical correlation for case 7 revealed presence of isthmus 4 in a prior surgical report (VSD patch closure), whereas no evidence of this isthmus was present at microscopic analysis. Details of the histologic examination for the 7 surgical survivor cases are given in Table 3.

**Discussion**

We report the first detailed analysis of the gross anatomic and histologic characteristics of the known potential VT isthmuses in patients with surgically-repaired TOF. The 3 major findings in this study are 1) the various ventricular isthmus categories are significantly different in terms of their overall geometric size with isthmus 1A larger than the remaining isthmuses, 2) the presence of the various VT isthmuses is highly variable (in particular, isthmuses 1A, 1B, and 3 are most frequently observed), and 3) a substantial amount of fibrosis is observed in all of these anatomic
regions after surgical repair when compared to non-isthmus sites, with implications for their role in arrhythmogenesis.

This first finding has potential implications for catheter ablation for interruption of reentrant VT after repair of TOF, since inadequate modification of the isthmus substrate may be more likely to occur in regions of lengthier or thicker ventricular tissue. Longer isthmus targets may yield unsatisfactory results because gaps in linear ablation and recurrences are typically more common as the length of the targeted isthmus increases. In addition, the creation of lesions with deep tissue penetration appears to be a requirement for transection of the ventricular isthmus in the setting of TOF similar to the situation for other ventricular tachycardia circuits. Although the now mainstream use of irrigated catheter technology can increase the size of lesions produced by radiofrequency energy, maximum tissue depths of only ~1 cm are observed when both catheter tip cooling and contact pressure are optimized. While creation of bidirectional block is the optimal endpoint after linear ablation, the inability to achieve this goal with ablation of lengthier and/or thicker isthmuses such as IA may account for clinical recurrences. The present study suggests that prominent myocardial hypertrophy commonly exists near the tricuspid annulus and this may create difficulty for effective catheter ablation of this isthmus. Knowledge of the typical morphology derived from this study may be useful when considering catheter ablation for VT in the setting of TOF.

Interestingly, the previously undescribed isthmus between the RV outflow tract incision and the VSD patch (“isthmus IB”) was evaluated in this study, and may serve as an alternate strategy for creation of conduction block between the ventriculotomy incision and the tricuspid annulus in many cases. This isthmus is adjacent to isthmus IA, but traverses an area that is typically excised to a greater extent by the surgeon at the time of repair (i.e. RV infundibulum),
resulting in shorter length and reduced wall thickness along its path. These observations suggest that isthmus 1B can serve as a superior target for catheter ablation when electrophysiologic evaluation suggests that the region between the ventriculotomy and tricuspid annulus is a critical part of the reentrant circuit. Overall, the combination of block in isthmus 1B and isthmus 4 can produce the same electrical sequelae as block across isthmus 1A. In the absence of a muscular connection between the VSD patch and the tricuspid annulus therefore, transection of isthmus 1B can be a useful and technically more straightforward alternative to ablation of 1A. Since there is a very low prevalence of muscular tissue in the region of isthmus 4, conduction through this site may rarely pose a problem. However, if myocardial tissue at this site is encountered, ablation of this additional isthmus can be performed to completely interrupt conduction through the entire region (Figure 1). Since the VSD patch in tetralogy of Fallot may extend to the superior aspect of the TA in many cases after repair, it is possible that catheter ablation intended to target isthmus 1A may even inadvertently create conduction block between the RV incision and the VSD patch at times (isthmus 1B). This may in part explain reports of successful ablation of the classically described isthmus 1A despite seemingly unfavorable characteristics in this region.12

Although not specifically addressed in the present study, AV conduction tissue is known to run along the posteroinferior border of the VSD in the setting of TOF, so that lesions placed as laterally as possible in isthmus 4 will be most remote from the conduction system and are expected to be of greatest safety. Nevertheless, given its inherent proximity to the conduction system, we believe that ablation of isthmus 4 should always be conducted with great care.

The second major finding in this study was that the ventricular isthmuses exist with variable frequency after surgical repair. Certain isthmuses, such as 1A, 1B, and 3 were commonly present in this study whereas others, such as 2 and 4 were more often absent. Isthmus
2, between the ventriculotomy and pulmonary annulus, is frequently described in the literature as a target for catheter ablation.\textsuperscript{21-24} However, this isthmus was often absent secondary to a transannular incision or avoidance of RVOT incision altogether, and it is likely that with changes in surgical technique this isthmus will be encountered even less frequently with time.\textsuperscript{4,6} Likewise, isthmus 4 was seen only occasionally and was noticeably uncommon in the older surgical survivors in the present series. Since isthmus 4 is congenitally absent in most patients with TOF (existing \textit{a priori} in only \textasciitilde20\%), this finding is not surprising.\textsuperscript{25} The results of the present study also suggest that the small rim of myocardium between the VSD patch and the tricuspid annulus may be easily disrupted at the time of surgical manipulation due to inflammatory and reparative processes. This finding was evident in at least one subject from the present series in whom a prior surgical report described this isthmus, whereas it was not detectable by our histologic examination. The same phenomenon was possible in a second case with a few surviving myocyte bundles in one segment but not an intact isthmus, suggesting that loss of myocardium had occurred with progressive fibrosis after surgery.

The third finding in this study was the abundant evidence of fibrosis among the previously reported VT isthmuses.\textsuperscript{12} Post-repair VT in the setting of TOF was originally classified as arising from both the outflow tract and from the septal-inflow area of the RV where fractionated electrograms were commonly observed with their induction.\textsuperscript{21,26-27} Follow-up studies based on excision of ventricular tissue at the time of arrhythmia surgery also demonstrated prominent fibrosis with subendocardial islets of surviving myocytes in the region of the RVOT.\textsuperscript{21} The inclusion of a group of cases surviving surgical repair in the present analysis afforded an opportunity to evaluate these findings and confirm their consistent presence in the ventricular conduction isthmuses that have been more recently described in TOF.\textsuperscript{12} Histologic examination
of these more recently described isthmuses revealed increased levels of both interstitial as well as replacement fibrosis in these regions, supporting their pathogenic role in the maintenance of reentrant VT after repair of TOF.

Limitations
In addition to the aforementioned limited number of surgical survivors in the present study, the major limitation was the absence of clinical VT in the majority of the cases examined. Patients presenting with sustained monomorphic VT may possess a dissimilar ventricular substrate than the general population of patients with TOF in whom VT has not previously occurred. In particular, isthmus 1A has been reported to be successfully targeted for catheter ablation in TOF patients with recurrent VT,\textsuperscript{12,16} suggesting that this isthmus may possess alternate characteristics in such patients, possibly related to progressive RV volume overload and/or aneurysmal dilation over time. Alternatively, regional differences in surgical technique may have resulted in a different anatomical substrate in our series relative to that of other centers, contributing to the findings.

Conclusions
There is significant variation both in the frequency and anatomic characteristics of VT isthmuses in patients with surgically-repaired TOF. In general, isthmus 1A is of the greatest overall dimensions in terms of length and wall thickness, whereas the adjacent and previously undescribed isthmus 1B (from the ventriculotomy to the VSD patch) is significantly smaller and may serve as a superior ablation site. Although isthmuses 2, 3 and 4 are all of generally small morphologic dimensions, isthmuses 2 and 4 are uncommon while isthmus number 3 is much more frequently observed. Knowledge of these differences may be useful when contemplating catheter ablation for treatment of monomorphic VT in the surgically-repaired TOF population.
Conflict of Interest Disclosures: None.

References:


Table 1. Population characteristics

<table>
<thead>
<tr>
<th>Subject characteristic</th>
<th>All subjects, n=27</th>
<th>Subjects ≥ 5 yrs, n=16</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs</td>
<td>7 (2.5-12)</td>
<td>10 (7.3-40)</td>
</tr>
<tr>
<td>Age category, n</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>1-5</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>6-10</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>11-20</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>21-30</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>&gt;30</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Gender, male (%)</td>
<td>12 (44)</td>
<td>6 (38)</td>
</tr>
<tr>
<td>Heart weight, gms</td>
<td>135 (78-240)</td>
<td>217 (127-585)</td>
</tr>
<tr>
<td>LV length, cm</td>
<td>5.4 (4.6-6.6)</td>
<td>6.0 (5.3-8.5)</td>
</tr>
<tr>
<td>Diagnosis (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TOF</td>
<td>24 (89)</td>
<td>16 (100)</td>
</tr>
<tr>
<td>TOF/PA</td>
<td>2 (7)</td>
<td>0</td>
</tr>
<tr>
<td>TOF/Absent PV</td>
<td>1 (4)</td>
<td>0</td>
</tr>
<tr>
<td>Type of RVOT surgery (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ventriculotomy</td>
<td>7 (26)</td>
<td>4 (25)</td>
</tr>
<tr>
<td>Isolated conduit</td>
<td>2 (7)</td>
<td>0</td>
</tr>
<tr>
<td>Transannular incision/patch*</td>
<td>16 (59)</td>
<td>11 (69)</td>
</tr>
<tr>
<td>None</td>
<td>2 (7)</td>
<td>2 (13)</td>
</tr>
<tr>
<td>Postsurgical survival, yrs</td>
<td>0.003 (0.001-1.08)</td>
<td>0.006 (0.001-11.0)</td>
</tr>
<tr>
<td>Postsurgical survival &gt; 1 yr (%)</td>
<td>7 (26)</td>
<td>6 (38)</td>
</tr>
</tbody>
</table>

*Group includes subjects with a bioprosthetic pulmonary valve (n=2). Values in parenthesis represent IQR unless specified otherwise.
LV = left ventricle; PA = pulmonary atresia; PV = pulmonary valve; RVOT = right ventricular outflow tract ; TOF = tetralogy of Fallot.
Table 2. Summary of anatomic ventricular isthmus characteristics in the subgroups of patients ≥ 5 years and surgical survivors

<table>
<thead>
<tr>
<th>Isthmus No.</th>
<th>Overall frequency (%)</th>
<th>Mean length, cm</th>
<th>Mean wall thickness, cm†</th>
<th>Median fibrosis (%)</th>
<th>Median EFE, mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>1A</td>
<td>88</td>
<td>3.9 (1.08)</td>
<td>1.5 (0.29)</td>
<td>20 (10 – 40)</td>
<td>1.0 (0.9 – 1.0)</td>
</tr>
<tr>
<td>1B</td>
<td>88</td>
<td>2.4 (0.75)</td>
<td>1.1 (0.43)</td>
<td>35 (35 – 65)</td>
<td>2.2 (1.0 – 2.25)</td>
</tr>
<tr>
<td>2</td>
<td>25</td>
<td>1.5 (0.47)</td>
<td>0.5 (0.15)</td>
<td>60 (55 – 65)</td>
<td>1.8 (1.4 – 2.2)</td>
</tr>
<tr>
<td>3</td>
<td>94</td>
<td>1.4 (0.77)</td>
<td>0.6 (0.25)</td>
<td>50 (35 – 75)</td>
<td>1.4 (1.3 – 1.6)</td>
</tr>
<tr>
<td>4</td>
<td>13</td>
<td>0.6 (0.35)</td>
<td>0.3 (0.04)</td>
<td></td>
<td>0.9 (0.5 – 1.2)</td>
</tr>
</tbody>
</table>

Mean (SD) is reported for subgroup ≥ 5 years of age (n=16) and median (IQR) for those surviving surgery that were evaluated histologically (n=7). EFE, endocardial fibroelastosis. †Wall thickness values are the maximum values observed across the isthmus.

Table 3. Detailed characteristics of subjects surviving intracardiac repair

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age, yrs</th>
<th>Cause of death</th>
<th>Isthmus 1A</th>
<th>Isthmus 1B</th>
<th>Isthmus 2</th>
<th>Isthmus 3</th>
<th>Isthmus 4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Post-surgical survival, yrs</td>
<td>Length</td>
<td>Wall thick</td>
<td>% IF/RF</td>
<td>Length</td>
</tr>
<tr>
<td>1</td>
<td>9</td>
<td>Intra-op**</td>
<td>1.1</td>
<td>4.4</td>
<td>2</td>
<td>35</td>
<td>2.7</td>
</tr>
<tr>
<td>2</td>
<td>19</td>
<td>Sepsis</td>
<td>5.0</td>
<td>2.7</td>
<td>0.6</td>
<td>70</td>
<td>1.3</td>
</tr>
<tr>
<td>3</td>
<td>66</td>
<td>OHT*</td>
<td>11.0</td>
<td>5.5</td>
<td>1.2</td>
<td>20</td>
<td>2.5</td>
</tr>
<tr>
<td>4</td>
<td>42</td>
<td>OHT</td>
<td>35.0</td>
<td>4.5</td>
<td>1.2</td>
<td>10</td>
<td>2.7</td>
</tr>
<tr>
<td>5</td>
<td>61</td>
<td>SCD</td>
<td>43.0</td>
<td>3.3</td>
<td>1.8</td>
<td>40</td>
<td>3.1</td>
</tr>
<tr>
<td>6</td>
<td>1.1</td>
<td>Peri-op**</td>
<td>1.0</td>
<td>2.2</td>
<td>1.3</td>
<td>10</td>
<td>1.9</td>
</tr>
<tr>
<td>7</td>
<td>34</td>
<td>OHT*</td>
<td>31.0</td>
<td>4.2</td>
<td>1.9</td>
<td>15</td>
<td>1.8</td>
</tr>
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</table>

*Two subjects with prior ICD placement had appropriate therapy for VT prior to transplantation. **Two subjects died peri-operatively during surgical revision, greater than 1 year after initial intracardiac repair. †Significant outlier. §Surviving myocytes were found in isthmus 4, but were non-contiguous by serial section. §Surgical report described a muscular rim around the VSD, but this was not found during histologic section. OHT orthotopic heart transplant, IF intersitital fibrosis, RF replacement fibrosis, SCD sudden cardiac death.
Figure Legends:

**Figure 1.** (A) Diagram of the ventricular isthmuses in modified LAO view and (B) representative gross specimen displayed in an identical view. 1A) ventriculotomy (V, dotted line)-to-tricuspid annulus, 1B) ventriculotomy-to-VSD patch, 2) ventriculotomy-to-pulmonary annulus (solid black line), 3) pulmonary annulus-to-VSD patch, and 4) VSD patch-to-tricuspid annulus. PV = pulmonary valve; RV = right ventricle; Sep = septum, TV = tricuspid valve.

**Figure 2.** Scatterplots of length (Figure 2A) and ventricular wall thickness (Figure 2B) by isthmus category. The isthmus mean (center circle) and SEM (vertical bars) are displayed to the right of each sample population. Ventricular isthmus length and wall thickness both varied significantly by isthmus category.

**Figure 3.** Representative macroscopic and microscopic anatomic isthmuses for case 3 (isthmuses 1 to 3) and case 5 (isthmus 4) who had a history of appropriate ICD therapy for VT and who died suddenly, respectively (equivalent magnification for all gross specimens). Panel A, isthmus 1A is both longer and associated with a greater wall thickness than other isthmuses. The maximum wall thickness (yellow arrowhead) is shown in panel B, where microscopic evaluation with trichrome/EVG stain shows minimal replacement/interstitial fibrosis. Panel C, isthmus 1B is of a shorter dimension and lesser wall thickness, as well as noticeable fibrosis (Panel D). Panel E, isthmuses 2 and 3 are shown. These isthmuses were shorter and thinner, and associated with a greater degree of fibrosis (Panel F, panel H). Isthmus 4 (Panel G) was least frequently observed, but was associated with the smallest dimensions and most prominent fibrosis. Red circle (Panel
I) highlights surviving myocyte bundles in isthmus 4 from case 5, although serial microscopic sections revealed that the isthmus was not continuous.

AV = aortic valve; E = endocardial fibroelastosis; IF = interstitial myocardial fibrosis; p = VSD patch; PV = pulmonary valve; RF = replacement myocardial fibrosis; TV = tricuspid valve; V = outflow tract patch.

**Figure 4.** Box-plots of percentage of fibrosis by isthmus category. Upper and lower margin of boxes correspond to the IQR, while center horizontal line corresponds to the median for each group. The box width is proportional to the number of observations in each isthmus category. *Isthmuses 1A, 1B, and 3 contained significantly greater degrees of fibrosis than the control sections taken from the RV apex (RV) and LV apex (LV).*
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