Impact of clinical follow-up and diagnostic testing on intervention for tetralogy of Fallot

Aswathy Vaikom House, David A Danford, Robert L Spicer, Shelby Kutty

ABSTRACT

Objective: Our purpose was to evaluate yield of tools commonly advocated for surveillance of tetralogy of Fallot (TOF).

Methods: All patients (pts) with TOF, seen at any time from 1/2008 to 9/2013 in an academic cardiology practice were studied. At the first and each subsequent outpatient visit, the use of tools including history and physical (H&P), ECG, Holter (HOL), echocardiogram (Echo), MR or CT (MR-CT) and stress testing (STR) were noted. Recommendations for intervention (INT) and for time to next follow-up were recorded; rationale for each INT with attribution to one or more tools was identified.

Results: There were 213 pts (mean 11.5 years, 130 male) who had 916 visits, 123 of which (13.4%) were associated with 138 INTs (47 surgical, 54 catheter-mediated, 37 other medical). Recommended follow-up interval was 9.4±6.5 months, actual mean follow-up interval was 11.7 months. All 916 (100%) patient visits had a H&P which contributed to 47.2% of INT decisions. Echo was performed in 652 (71.2%) of visits, and contributed to 53.7% of INTs. MR-CT was obtained in 129 (14.1%) of visits, and contributed to 30.1% of INTs. ECG was applied in 137 (15%) visits, and contributed to 1.6% of INTs. HOL was obtained in 188 (20.5%) visits, and contributed to 11.3% of INTs. STR was performed at 101 (11%) of visits, and contributed to 8.9% of INTs.

Conclusions: INTs are common in repaired TOF, but when visits average every 11–12 months, most visits do not result in INT. H&P, Echo and HOL were the most frequently applied screens, and all frequently yielded relevant information to guide INT decisions. STR and MR/CT were applied as targeted testing and in this limited, non-screening role had high relevance for INT. There was low utilisation of ECG and major impact on INT was not demonstrated. Risk stratification in TOF may be possible, and could result in more efficient surveillance and targeted testing.

INTRODUCTION

Tetralogy of Fallot (TOF) is the most common cyanotic congenital heart defect (CHD). Advances in surgical technique and postoperative care have dropped early surgical mortality in TOF to less than 2%, and well over 85% of patients survive into adulthood. Long-term outcomes and quality of life have also consistently improved for individuals with repaired TOF; however, several late complications are routinely observed. Chronic pulmonary regurgitation (PR) after TOF repair may result in right ventricular (RV) dilation and dysfunction, which in turn has been associated with exercise intolerance, arrhythmias and sudden death.

There is unsettled debate surrounding the ideal timing of pulmonary valve replacement and other interventions. The study identified the relative yield of frequently less frequently applied diagnostic modalities, and points to how the yield of these tools could possibly be enhanced by targeted testing and risk stratification.

The Canadian Cardiovascular Society, the European Society of Cardiology and the American College of Cardiology have published guidelines for pulmonary valve replacement (PVR) in adults with repaired TOF which are based on symptoms, severity of PR and degree of RV enlargement. However, given the lack of evidence from prospective studies proving that PVR decreases the risk of adverse events and the limited durability of PVR, the ideal timing of PVR remains an openheart-2014-000185 openheart-2014-000185


Revised 3 February 2015
Accepted 4 March 2015

Key messages
What is already known about this subject?
▸ Appropriate tools must be selected for surveillance of patients with repaired tetralogy of Fallot so as to intervene when it is in their best interest. There is unsettled debate surrounding the ideal timing of pulmonary valve replacement and other interventions.

What does this study add?
▸ The study identified the relative yield of frequently and less frequently applied diagnostic modalities, and points to how the yield of these tools could possibly be enhanced by targeted testing and risk stratification.

How might this impact on clinical practice?
▸ Increasing numbers of adults with repaired tetralogy of Fallot are undergoing clinical surveillance. With an array of diagnostic tools available, and a counterbalancing concern over healthcare costs, optimising the frequency of clinical follow-up visits and the intensity of the testing performed at each is important.
area of relative uncertainty, especially in asymptomatic patients. This has focused attention on the long-term follow-up of repaired TOF, with close surveillance of RV function forming a cornerstone of follow-up.

Uncertain as the cardiology community is regarding the ideal frequency and extent of outpatient surveillance, but armed with a wide variety of investigative tools at its disposal, there is potential for wide interinstitutional and intraintitutional variability in outpatient surveillance practices. The purpose of this study was (1) to identify practice patterns for outpatient surveillance of repaired TOF in our institution over a period of 5 years, and (2) to evaluate the yield of investigational tools on outpatient visits with regard to decision-making for interventions (INTs) in this group of patients.

METHODS
This was a single-institutional, retrospective analysis of every outpatient follow-up visit for all patients with surgically repaired TOF seen at any time from 1/2008 to 9/2013 in an academic children’s hospital-based paediatric-adult congenital cardiology group practice. The Institutional Review Board approved the study. We included TOF with pulmonary atresia, but excluded TOF with absent pulmonary valve, atrioventricular septal defect or other complex cardiac lesion.

At our institution, INT for severe PR in repaired TOF is undertaken for prevention of progressive RV dilation and dysfunction, tricuspid valve regurgitation, left ventricular dysfunction, tachyarrhythmias and diminished exercise tolerance. The potential for benefit from elimination of RV volume load is weighed against perceived surgical or transcatheter procedural risks on a case-by-case basis. Accordingly, before recommending PVR, clinical symptoms (such as exercise intolerance, other heart failure symptoms or syncope), imaging data, electrophysiological and haemodynamic factors are discussed in a multidisciplinary case conference. Volumetric and functional values which we believe warrant serious consideration for PVR include indexed RV end-diastolic volume greater than 150 mL/m², indexed RV end-systolic volume greater than 80 mL/m², RV ejection fraction less than 47% and/or left ventricular ejection fraction less than 55%. Percutaneous Melody valve implantation (Medtronic, Inc, Minneapolis, Minnesota, USA) is considered for suitable patients with moderate or severe PR or stenotic (greater than 35 mm Hg gradient) RV to pulmonary artery conduits of greater than 16 mm diameter. We utilise transcatheter balloon arterioplasty with stent implantation in patients with moderate or severe isolated residual pulmonary artery stenosis. When catheter-mediated treatment is unsuccessful or inappropriate, surgical RV outflow tract reconstruction is often recommended when RV systolic pressure is greater than two-third systemic. We recognise that some tachyarrhythmias are promoted by severe underlying haemodynamic abnormalities, and may respond to surgical or catheter-mediated treatments. For others, management is based on judgements made about the magnitude of the threats posed by the rhythm as compared with the risks of pharmacological treatment or device implantation. For aortic dilation after TOF repair, replacement of the ascending aorta is considered when the diameter exceeds 55–60 mm.

Demographics, cardiac and surgical histories obtained from the institutional cardiology database included patient gender, age at initial repair, age at follow-up and presence of genetic syndromes (trisomy 21, 22q deletions, other chromosome deletions). At each subsequent visit during the study timeframe, the use of diagnostic tools including history and physical (H&P), ECG, Holter (HOL) monitor, echocardiogram (Echo), MR or CT imaging (MR-CT) and stress testing was noted. The recommendations for time to next follow-up visit, and change in management/INT if any were noted. The nature of INT was categorised as (A) activity restriction, (B) drug therapy initiation or modification, (C) surgical INT or (D) catheter-based INT. To the extent that the narrative in the chart revealed the rationale for each INT, and the diagnostic tools that specifically contributed to the decision for INT, these were recorded.

Statistical analysis
Continuous variables were expressed as mean±SD and ranges; discrete variables were expressed as percentages. Threshold for statistical significance was p<0.05. Statistical analysis was performed using commercially available software (Minitab V.16.1, Minitab Inc, State College, Pennsylvania, USA).

RESULTS
The study population consisted of 213 patients whose 916 visits formed the database. Patient characteristics including age, gender, diagnoses, genetic syndromes and surgical history are summarised in table 1. The mean age at entry into the study was 11.5 years and the mean age at initial corrective surgery was 1.35 years. The mean age at which the most recent INT was carried out was 5.2 years. The mean recommended follow-up interval was 9.4±6.5 months (IQR 4–12 months) and the actual follow-up occurred at 11.7 months.

Interventions
Of 916 visits, 123 (13.43%) visits resulted in at least one INT. Of 138 INTs (table 2), catheter-based INT was most frequent (n=54), followed by surgical management (n=47) and medical therapy (n=32). Activity restriction was the least common INT (n=5).

Table 3 lists the exact type of INTs separately for the paediatric and adult visits.

Table 4 summarises each category of INT and how they were attributed to each diagnostic tool. Table 5 summarises all visits in which INT followed, and lists the number of tool applications per patient year of
observation, and the number of INTs attributable, at least in part, to the application of each tool. The most frequently applied tool was H&P, followed by Echo, HOL, ECG, MR-CT and stress test (table 5).

Reasons for INT in adults that were attributed to change in symptoms or physical examination were: subjective fatigue, shortness of breath and exercise intolerance (n=23), fast or irregular heart rate (n=12), and pharmacological INT for pregnancy (n=2) or hypertension (n=2). Among paediatric INT, reasons were subjective fatigue, shortness of breath and exercise intolerance (n=25), fast or irregular heart rate (n=2), hypertension (n=1) or cyanosis (n=1). Eighteen INTs (10 paediatric and 8 adults) were attributed to objective changes in exercise capacity measured by the stress test. Forty INTs (11 adult, 29 paediatric) were attributed to valvular dysfunction; 44 INTs (21 adults, 23 paediatric) for RV dilation on MRI and 14 INTs (4 adults, 10 paediatric) for cardiac chamber dysfunction. INTs were attributed to branch PA stenosis noted on Echo/MRI in 16 patients (all paediatric).

## Diagnostic tools and their yield

### History and physical examination

All 916 (100%) patient visits had a H&P examination; 123 (13.4%) visits resulted in an INT. The H&P contributed to the decision to intervene in 58 (47.2%) of the visits where such a decision was made.

### Imaging tests

Six hundred and fifty-two (71.2%) of the total visits involved Echo as an investigational tool, of which 90 visits (13.8%) resulted in an INT. The Echo findings contributed to the INT in 66 (53.7%) of all the visits where such a decision was made. MR-CT was obtained in 129 (14.1%) of visits, 42 (32.6%) visits resulted in an INT and MR-CT contributed to the INT in 37 (30.1%) visits.

### ECG, HOL and stress test

ECG was applied in 137 (15%) visits, of which 22 visits (16.1%) resulted in an INT. The ECG findings contributed to the INT in 2 (1.6%) visits where such a decision was made. HOL was obtained in 188 (20.5%) of the total patient visits. Of these 188 visits, 36 (19.1%) resulted in INTs. The HOL contributed to the decision to intervene in 14 (11.3%) of all visits where such a decision was made. Stress test was utilised as an investigational tool in 101 (11%) of the total patient visits, and of those visits, 31 (30.7%) resulted in a change in management. The stress test contributed to the INT in 11 (8.9%) of all the visits where such a decision was made.

### Discussion

Residual haemodynamic burden is common after TOF repair, and may include PR, tricuspid regurgitation, RV dilatation or dysfunction, residual shunts, or obstruction of the RV outflow tract or pulmonary artery branches.13 14 The threat of atrial and ventricular tachyarrhythmias is also significant.11 12 15 Long-standing PR has been an active recent research focus as it is considered a reversible cause of RV dilatation. With mounting evidence that PVR is most useful prior to the onset of frank RV dysfunction, there is unsettled debate surrounding the ideal timing. In this relatively ambiguous clinical landscape, cardiologists must select the appropriate tools and schedule for surveillance of these patients so as to intervene when it is in their best interest. With an array of diagnostic tools available, and a counterbalancing concern over healthcare costs,16 17 the question of optimal frequency of clinical follow-up visits and the intensity of the testing performed at each is very relevant.

So far, there is insufficient data to allow a cardiologist to balance the costs and benefits of the means of clinical surveillance of the patient with surgically modified TOF. Guidance for how frequently these patients should be seen and what tests should be ordered is therefore largely derived from expert consensus. The American College of Cardiology/American Heart Association guidelines for management of adults with congenital heart disease (CHD) state that all patients with repaired TOF should have regular follow-up with a cardiologist with expertise in adult CHD.7 While the frequency of follow-up is typically annual, this may be modified based on severity and type of residua. Other recommendations include annual surveillance with ECG, assessment of RV function and periodic exercise testing for patients with...
pacemakers or automatic implantable cardiac defibrillators. Periodic HOL monitoring is believed to be helpful, and is also recommended in routine follow-up, but its frequency should be individualised depending on the haemodynamics and level of clinical suspicion of arrhythmia.

Current European and Canadian guidelines have similar recommendations for annual clinical and echocardiographic follow-up for the majority of patients with TOF (less frequently for those with less severe, stable disease) and also recommend MR evaluation at intervals guided by severity and nature of the individual patient’s pathology.4 9 Helpful as these guidelines might be, they are not nearly so strong or specific as the circumstances in general adult cardiology for which appropriate use criteria have been published for both Echo and cardiac CT.18 19 Guidelines written by experts who recognise the clinical heterogeneity of the surgically modified TOF population are broad enough to leave latitude for rather broad variability in practice patterns, which could lead

<table>
<thead>
<tr>
<th>Type of INT</th>
<th>INT</th>
</tr>
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<tbody>
<tr>
<td>Surgery</td>
<td></td>
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<tr>
<td>Adult n=12</td>
<td>10 surgical PVR</td>
</tr>
<tr>
<td>Ped n=35</td>
<td>1 tricuspid valve repair with right atrial reduction</td>
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<tr>
<td></td>
<td>1 implantable cardioverter defibrillator placement</td>
</tr>
<tr>
<td></td>
<td>20 surgical PVR</td>
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<tr>
<td></td>
<td>1 aortic valve repair</td>
</tr>
<tr>
<td></td>
<td>14 right ventricular outflow tract reconstructions</td>
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<tr>
<td>Catheter-based</td>
<td></td>
</tr>
<tr>
<td>Adult n=13</td>
<td>4 transcatheter PVR</td>
</tr>
<tr>
<td>Ped n=41</td>
<td>4 electrophysiological studies</td>
</tr>
<tr>
<td></td>
<td>5 diagnostic catheterisations</td>
</tr>
<tr>
<td></td>
<td>3 transcatheter PVR</td>
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<tr>
<td></td>
<td>15 diagnostic catheterisations</td>
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<td></td>
<td>4 electrophysiological studies</td>
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<tr>
<td></td>
<td>18 pulmonary arterioplasty procedures</td>
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<tr>
<td></td>
<td>1 endomyocardial biopsy for unexplained LV dysfunction</td>
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<tr>
<td>Medical therapy</td>
<td></td>
</tr>
<tr>
<td>Adult n=18</td>
<td>1 anticoagulation regimen change</td>
</tr>
<tr>
<td>Ped n=14</td>
<td>2 bronchodilator therapy</td>
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<td></td>
<td>6 antihypertensive therapy</td>
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<tr>
<td></td>
<td>8 antiarrhythmic therapy</td>
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<tr>
<td></td>
<td>1 diuretic regimen adjustments</td>
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<tr>
<td></td>
<td>1 medication change for frequent premature ventricular complexes</td>
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<td></td>
<td>2 antiarrhythmic medication changes</td>
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<tr>
<td></td>
<td>4 diuretic regimen adjustments</td>
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<tr>
<td></td>
<td>1 pulmonary vasodilator therapy</td>
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<tr>
<td></td>
<td>6 ACE inhibitor therapy for worsening LV dysfunction</td>
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<tr>
<td>Activity restriction</td>
<td></td>
</tr>
<tr>
<td>Adult n=2</td>
<td>2 activity restrictions pending exercise stress test for palpitation</td>
</tr>
<tr>
<td>Ped n=3</td>
<td>Work up</td>
</tr>
<tr>
<td></td>
<td>2 for frequent ectopy on Holter</td>
</tr>
<tr>
<td></td>
<td>1 patient with moderate ventricular hypertrophy</td>
</tr>
</tbody>
</table>

INT, intervention; LV, left ventricular; PVR, pulmonary valve replacement.

| Table 4 Categories of intervention with attribution to each diagnostic tool |
|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
|                            | Surgery (N=47)              | Catheter-based (N=54)       | Medical therapy (N=32)      | Activity restriction (N=5)  |
| INT attributable to H&P, n  | 20                          | 32                          | 12                          | 3                           |
| INT attributable to ECG     | 2                           | 0                           | 0                           | 0                           |
| INT attributable to Echo    | 37                          | 43                          | 9                           | 3                           |
| INT attributable to stress test | 5                         | 10                          | 3                           | 0                           |
| INT attributable to CT-MR   | 13                          | 33                          | 4                           | 0                           |
| INT attributable to Holter   | 5                           | 6                           | 8                           | 0                           |

Echo, echocardiogram; H&P, history and physical; INT, intervention.
than did Echo. These differences probably re
ttributed to a decision to change clinical management
year of observation. Per test it more often con-
muted approximately 10% of the times it was obtained.
change management overall, and yielded such a contri-
sion in this series is in remarkable agreement with
Table 5
Tool Number of times tool applied N. (% of total number of visits) Tool applications per patient-year of observation Number of times tool contributed to INT decision N. (% of contributions per tool application)* Percentage of total INT decisions to which tool contributed
H&P 916 (100) 1.02 58 (6.3) 42.0
Echo 652 (71.2) 0.73 66 (10.1) 47.8
Holter 188 (20.5) 0.21 14 (7.4) 10.1
ECG 137 (15) 0.15 2 (1.5) 1.4
MR-CT 129 (14.1) 0.14 37 (28.7) 26.8
Stress test 101 (11) 0.11 11 (10.9) 8.0
*More than one tool may contribute to a decision. Some visits are associated with more than one INT.
Echo, echocardiogram; H&P, history and physical; INT, intervention.
to either overutilisation or underutilisation of healthcare
services in this population.

The 1.02 follow-up visits per patient-year of observa-
tion in this series is in remarkable agreement with
published guidelines, but only 15% of these encoun-
ters resulted in a change in therapy. These INTs were
most commonly surgical or catheter-mediated, but a
significant minority were changes in medical manage-
ment. It is beyond the scope of this report to judge
whether the ratio of roughly seven visits to one INT is
too high or low, but it might be deemed appropriate
since it is the result of general adherence to the
expert consensus of how often these patients should
be seen.

Echo was utilised at the majority of the visits in this
series (there were 0.73 Echos per patient-year of deci-
sion), it contributed to close to half the decisions
to change management overall, and yielded such a contri-
bution approximately 10% of the times it was obtained.
MR or CT imaging was arranged far less frequently than
Echo in this series, 0.14 MR or CT examinations per
patient year of observation. Per test it more often con-
tributed to a decision to change clinical management
than did Echo. These differences probably reflect the
ease with which Echo can be arranged, which lends itself
to be applied more broadly as a screen in this
population. MR or CT can be cumbersome to arrange,
but provide more precise RV volumetrics, so these
are apparently reserved for a targeted group of patients
for whom INT to relieve RV volume overload is more
likely.

HOL monitor was carried out at a rate of 0.21 recordings
per patient-year of observation, but only contributed to
decisions for management change about 7% of the times
it was done. This suggests that it was primarily used as a
periodic screen for the known electrophysiological complica-
tions of surgically modified TOF. Stress test, on the other
hand, was less frequently obtained, but resulted in a higher
rate of contribution to INT, which would fit with a pattern
of targeted testing, done ‘for cause’ in selected patients
perceived to be more likely in need of INT.

Contrary to published guidelines, the standard ECG
was not frequently obtained in this series. Seldom could
the case be made, retrospectively at least, that the ECG
contributed to decisions to intervene. These data should
be interpreted with caution, as the results of the ECG
(eg, exceptionally wide QRS) could trigger further inves-
tigation (like MR) which might, in turn, prompt an INT.
The indirect role of the ECG in a decision to intervene,
therefore, might not be explicit enough to be recogni-
ised in a chart review such as this, leading to an under-
estimate of its value.

In summary, this survey of care for surgically modified
TOF reveals that a simple list of recommended surveil-
ance modalities, and the frequency with which they
ought to be obtained is an oversimplification, which
perhaps with good reason, would not reflect current
practice. There are frequently applied modalities that
can be thought of as screens, some of which (Echo and
HOL) are higher yield than others (H&P). Other less
frequently applied modalities are best thought of as tar-
geted testing, with MR/CT having very high yield, and
stress testing more moderate yield.

The yield of targeted testing could, in theory, be
enhanced by risk stratification to limit the portion of the
patient population in which tests are applied. There
has been substantial work to identify risk factors for
major adverse events such as death, ventricular tachycar-
dia and heart failure in surgically modified TOF.
A number of predictors have emerged, including older
age at repair, prolonged QRS duration, sustained ven-
tricular tachycardia, and the haemodynamic conse-
quences of severe PR leading to RV dilatation, ventricular
dysfunction, and regional wall motion abnormalities.
Risk stratification in repaired TOF is presently based on
retrospective studies and remains a work in progress. How-
ever, it may be possible to develop risk stratification into an
integrated model capable of refining outpatient practices to enhance surveillance of
those at higher risk, and limit testing among lower risk
patients who would have minimal potential to benefit.
The result would be an increased efficiency of use of
diagnostic modalities and more effective resource
utilisation.

Development and implementation of a standardised
Clinical Assessment and Management Plan (SCAMP)
for outpatient follow-up of repaired TOF would be one method to explore this further. SCAMPs are innovative quality improvement initiatives that actively collect data on deviations from the standardised algorithms that occur in actual practice. A standardised algorithm for follow-up of repaired TOF could be established, and then periodic analysis of patterns of deviation from the algorithm could help identify subgroups of patients for targeted testing. Ultimately, by iterative incorporation of the systematically productive deviations into the algorithm, a more comprehensive algorithm is produced, from which there will be fewer practice variations, and by which patient care will be enhanced.

LIMITATIONS
This is a retrospective study. The only outcome studied was active management change, whereas clinically important decisions not to change management were not accounted for in this design. The patient population was heterogeneous, and included many potential confounders, ranging from a variety of insurance types and financial circumstances, to other non-cardiac medical conditions, chromosomal anomalies, diverse ages at intracardiac repair and at entry into the study, inconsistent history of prior palliative shunts and inconsistent history of subsequent surgical and catheter-mediated cardiac procedures. While this heterogeneity is an advantage in the sense that it reflects the clinical realities of surgically modified TOF, the influences of the many clinical factors on the frequency of clinical follow-up and the application of diagnostic modalities could not be effectively addressed. Attribution of the decision to the information gathered by one or more of the diagnostic tools was done with care, but when derived from record review, is recognised to be imperfect. Finally, there are no safeguards to assure that the clinical INTs in this series were always appropriate. While we believe that most times they were, and therefore the tests on which they are based were of positive value to the patient, we acknowledge that it is a leap to conclude that a diagnostic modality is good just because it leads to an INT.

CONCLUSIONS
Although the results of this study must be understood in light of the limitations, it does contain several valuable observations. (1) Clinical follow-up of surgically modified TOF at approximately yearly intervals resulted in management changes at about 15% of the visits. (2) Echo and HOL monitoring served primarily in a screening capacity, and although they were not utilised as frequently as clinical H&P in this series, they more often yielded relevant information to guide decisions to intervene. (3) Stress testing and MR/CT were applied as targeted testing and in this limited, non-screening role had high yield in the decision to intervene. (4) There was low utilisation of ECG in this series and major impact on INT yield could not be demonstrated.

Acknowledgements The authors appreciate the assistance of Carolyn Chamberlain, RN BSN MPH. SK receives support from the American Heart Association and the Children’s Hospital Foundation.

Contributors AV/H and SK designed the study protocol, analysed the data and drafted the manuscript. DAD participated in the study design and helped with the statistical analysis. RLS helped to draft the manuscript. All authors read and approved the final manuscript.

Competing interests None declared.

Ethics approval University of Nebraska.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement No additional data are available.

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*Open Heart* 2015 2:
doi: 10.1136/openhrt-2014-000185

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