Left Ventricular Re-training: Feasibility and Effectiveness—What Are the Limits?

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The concept of 're-training' the morphologic left ventricle (mLV) is based on the crude principle of applying a fixed afterload by means of pulmonary artery banding. The complex physiological, molecular and structural responses to banding are poorly understood, and complicated by the fact that re-training is undertaken in a variety of different morphological settings and age-groups. This article reviews the evidence for re-training in different situations with particular focus on the age at banding and on the best ways to assess suitability for subsequent repair. Particular importance is placed on the role of re-training in congenitally corrected transposition as this is the commonest current indication – looking at better ways to train the mLV, the role of combined pressure and volume loading, and more sophisticated ways of assessing the adequacy of training. Current evidence suggests that age at banding has a fundamental impact on ability to re-train and long-term mLV function with the best results being achieved in infancy and concerns at any attempt beyond 2 years of age.

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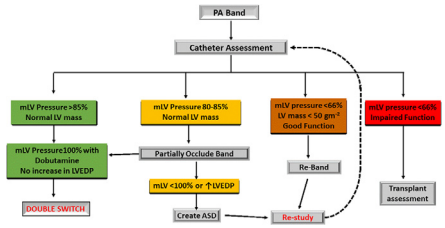

Management protocol for assessment of the left ventricle suitability for double switch.

Central Message

Re-training the left ventricle is not an exact science. Methods must be refined to extend the age limit and improve long-term function.

Nature designed the left ventricle (LV) to support the systemic circulation. The bullet shape, the length-area ratio, the arrangement and structure of the circumferential myocardium, and the design of the mitral valve provide the ideal muscular pump to work against the high afterload of the systemic circulation. Nevertheless, we encounter a variety of conditions with ventriculoarterial discordance (and its management) where the LV is found in the subpulmonary position. If untreated, the LV rapidly becomes adapted to working at a lower pressure and "involutes," losing its muscle mass.

There are many clinical situations where it is attractive to try and restore the LV to its systemic position, but this is only possible if the ventricle can somehow be "re-trained" to develop the necessary power and muscle mass. The concept of "re-training" was first described by Yacoub et al [1] in the late 1980s in the setting of infants with d-TGA. The arterial switch operation was still relatively new, but it was soon recognized (in the setting of intact ventricular septum) that the morphologic LV (mLV) would rapidly involute if the arterial switch was not performed within the first few weeks of life. Attempting the arterial switch in this situation usually failed as the mLV could not cope with suddenly being exposed to the systemic afterload. Recognition of the need to re-train these LVs was inspirational—and the concept was relatively simple: a band was placed on the pulmonary artery to place an afterload on the subpulmonary ventricle and stimulate restoration of muscle mass and function.

All "re-training"is based on this simple initial principle—yet the physiology and pathology behind this extraordinary process has been only superficially studied. The impact of age, duration, and degree of banding has been poorly understood, and most that we have learnt is from clinical experience and trial and error. The role of gradual banding or intermittent banding as well as the role of volume loading in addition to pressure loading is only now being analyzed. It is clear that not all mLVs can be successfully re-trained—not only in terms of the initial ability to work in the systemic position, but also in terms of long-term health and function of the re-trained LV. The critical impact of patient age and the technique and duration of banding is now evolving in order to establish both the limits of re-training and whether or not these limits can be stretched.

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CURRENT TECHNIQUES AND INDICATIONS

There are 3 groups of patients in which re-training can be applied:

1. Infants with d-TGA and intact septum with late presentation.
2. Cases of d-TGA initially managed with atrial switch, with late systemic RV failure.
3. Congenitally corrected transposition (ccTGA) with intact septum and systemic RV failure.

Infants With d-TGA and Intact Septum With Late Presentation

This was the original use of PA banding to re-train the deconditioned LV [1], which was generally felt to be necessary after the age of 6–7 weeks. As these patients were already cyanosed, many required an additional systemic shunt to increase pulmonary bloodflow to provide adequate oxygenation (which may have had the additional benefit of volume loading the circulation). The ages of these patients were typically 2–3 months and the duration of banding necessary for re-training was found to be remarkably short, with a mean period of 8–14 days and some patients re-training in as little as 48 hours [2,3]. The criteria for assessing response to re-training were found to be a combination of LV:RV pressure ratio, increase in the indexed LV mass and the echo appearances of the LV with sustained function and commitment of the interventricular septum to the re-trained LV. The Boston experience in PA banding [3] showed that the LV mass could double in 7 days and that the LV:RV pressure ratio increased from 0.5 (±0.08) to 1.04 (±0.9) in the same time period. The mean time required for training in this group of patients who were 2–5 months of age was only 9 days.

The indications for banding are not entirely consistent across all the literature, but any patient with intact septum over 3 weeks of age should at least be considered [4], although most patients are over 6 weeks of age. More objective criteria are an LV indexed mass of $<35\ g\ m^{-2}$ and/or evidence of a collapsed, "banana-shaped" LV with septum committed to the RV.

The universal adoption of the neonatal arterial switch has meant that much of the evidence we have for PA banding in this setting is now historical. Nevertheless, particularly the developing industrial nations continue to see late presentations of d-TGA and have provided important new experiences that reinforce the earlier data [5].

Re-training Postatrial Switch in d-TGA

The Achilles' heel of the senning/mustard operations has been the unpredictable late failure of the systemic RV with more than 50% of patients having RV dysfunction within 15 years [6]. In the 1990s, the concept of re-training the mLV in these patients was introduced by Cochrane et al with the intention of then taking down the atrial switch and performing an arterial switch [7]. By definition, these were a much older age range of patients than the infants, but the principle of banding the PA to train the subpulmonary ventricle was still the same. The combined Melbourne/Cleveland Clinic experience included 39 patients with an age range of 1.2–24 years with a median of 10.8 years [8]. Banding these older patients was much more unpredictable than in infants and many patients failed banding (see below). They also required a much longer period of re-training than infants, with a median of 13 months (range 6–65 months) and used similar criteria of LV:RV pressure ratio of >80% at rest plus LV indexed mass as indicators of successful re-training.

As the routine use of the atrial switch was largely abandoned in the 1980s, this group of adolescents or young adults who may have been suitable candidates for takedown and arterial switch has now disappeared from most practices. However, there have been important lessons learnt in this group—particularly on the age limits of re-training.

Re-training in the Setting of ccTGA

This has become the most widely used indication for re-training in the current era. Over 70% of all ccTGA patients have a ventricular septal defect (VSD) and the use of PA banding in these patients is more conventional—to prevent overcirculation and protect the lungs from high flows and pressures. These patients will all have an mLV that is sustained at systemic pressures from birth and so do not require any sort of "re-training." In contrast, there are a minority of patients with ccTGA who have intact ventricular septum (or small, restrictive VSD) but who develop systemic RV dysfunction and/or tricuspid regurgitation. These patients can undergo PA banding to "re-train" the mLV with the intention of subsequently performing a double-switch procedure to restore the mLV to the systemic circulation—the so-called "anatomical repair of ccTGA." Protocols are further complicated by the fact that the PA band itself can be therapeutic: splinting the interventricular septum can help stabilize the tricuspid valve and reduce the degree of tricuspid regurgitation, which may then influence the timing or progress toward anatomic repair.

The unpredictable nature of the morphological right ventricle (mRV) has meant that these patients can present at any age, so the "re-training" techniques and protocols have to accommodate this wide age range. Most published series tend to group all "PA Band" patients together and it is important to differentiate between those that have been banded for a large VSD (the majority) and those banded to re-train the mLV. The largest of these series are listed in Table 1, highlighting the numbers who were banded for re-training [9–16].

Banding is performed through a median sternotomy. An introducer sheath is placed in the internal jugular vein and a pressure line then advanced across the mitral valve into the (subpulmonary) mLV. The circumference of the main PA is measured and the band initially fixed at ½ circumference. Ventricular function, mitral valve function, and septal position are carefully monitored on trans-oesophageal echocardiography (TOE) while recording mLV pressure and serially tightening or loosening the band as indicated. The aim is to achieve 60–70% systemic pressure in the mLV with preservation of

Table 1 Selected Published Series of Anatomic Repair of ccTGA

	Total	PAB	PAB for Re-training	Mean Age at PAB (y)	
Boston	103	30	10	1.6	[9]
Birmingham	113	63	23	2.3	[10]
St Augustin	63	25	14	2.0	[11]
Marie Lannelongue	20	17	3	3.0	[12]
Cleveland Clinic	46	17	6	<2.0	[13]
Melbourne	32	21	7	0.2	[14]
Tokyo	84	15	7	4.3	[15]
Stanford	48	17	8	<2.5	[16]

PAB, pulmonary artery band.
Figures in each column represent the number of patients out of the total undergoing pulmonary artery banding for any reason and those undergoing banding specifically for LV re-training.

mLV function, no mitral regurgitation and splinting of the interventricular septum. Ideally, the degree of any tricuspid regurgitation may also reduce but this is a secondary benefit and banding has to be focused on the function and pressure in the mLV. Most protocols recommend use of an inotrope such as Dobutamine to be run throughout the procedure and for the first 48 hours.

Patients need to be monitored closely for the first 24 hours as mLV function can subtly deteriorate in the early postoperative period with rising central venous pressure (CVP), liver engorgement, and fall in cardiac output. It may be necessary to return the patient to theater to loosen the band, or in some cases tighten it if the mLV pressure has decreased in the setting of good function.

Progress is assessed through serial echo and by magnetic resonance imaging that can accurately measure indexed LV mass and LV free-wall thickness. A formal cardiac catheter with stress testing is used to make the definitive assessment of suitability for double switch: most authors have suggested that the mLV should be at least 80% systemic pressure at rest, rising to systemic with Dobutamine stress and maintaining good function. Posterior free-wall thickness should reach the predicted indexed value for age and the LV mass index should be >50 g m^{-2}. The duration of banding can average from 3 to 15 months but varies considerably with age. Some patients may require a second or even third rebanding to achieve adequate training.

RESULTS

Infants With d-TGA and Intact Septum With Late Presentation

The re-training of the mLV in infants has been very successful with most series reporting 85–90% of cases responding such that arterial switch could be performed. In the larger series of the late 1980s and 1990s, patients were typically a median of 3 months of age at banding and responded within very short time periods of a mean of 8–10 days. LV:RV pressure ratios of >80% and LV indexed mass of >50 g m^{-2} (up to 80 g m^{-2}) were reliable indices of successful training [2–4,17]. Early outcomes of the switch were excellent and comparable to primary neonatal switch. However, more careful analysis of longer term outcomes in the Boston series showed that the re-trained LVs showed subtle signs of myocardial stiffness that was progressive over the 10-year follow-up, although with no clinical difference between the primary and 2-stage groups [3]. The more recent series from Beijing extended the age range of late presentation, banding 31 patients with a median age of 6 months and range up to 5 years [5]. Banding at over 3 months of age was associated with significant mLV dysfunction postoperatively and a 9.7% early mortality. Even more striking was that outcomes for patients banded at over 18 months of age were very poor with only 50% survival at 5 years. Age at banding was the only independent risk factor for survival.

Re-training Postatrial Switch in d-TGA

These are a much older group of patients with median ages of 10–16 years. There was an early realization that a proportion of patients in these age groups simply will not "re-train" and either fail immediately or are unable to mount an appropriate pressure response despite even relatively gentle banding. In the largest reported series of 39 patients (age range 13 months–24 years) [7,8], 25% of patients failed to re-train, including 80% of all patients >12 years of age . The remaining patients underwent takedown senning-arterial switch with an operative mortality of 15% and a further late mortality of 21%. Age of >12 years at banding was strongly associated with early and late mLV dysfunction. Although no definitive cut-off age could be defined (the oldest patient successfully switched was 16 years), it was noted that 63% of cases <12 years were successfully re-trained compared to only 20% of cases >12 years.

The outcomes from other published series are summarized in Table 2. The Stanford group have had more success with older patients [18], although they still found that 58% of all patients >15 years failed to train. Early mortality after the arterial switch was 10%, all of whom were the oldest patients at 25, 32, and 39 years. Nevertheless, there were also 4 successful switched patients over 15 years of age, the oldest being 25 years—which is the oldest recorded patients who has been successfully re-trained.

Table 2 Published Series for d-TGA Postatrial Switch Who Underwent Re-training for Planned Takedown with Arterial Switch

Center	*n*	Median Age	% Failed to Train	Early Mortality at ASO	Number (%) of Patients >12 y Successfully Trained
Cleveland/Melbourne	39	10.8	26%	17%	3/15 (20%)
Chicago	11	12.2	45%	33%	2/9 (22%)
Birmingham	20	16.2	55%	11%	2/16 (13%)
Aachen	4	5.5	0	0	0
Stanford	25	16.0	48%	8%	5/15 (33%)

ASO, arterial switch operation.

Patients who fail to respond to banding have a very poor prognosis, with a 40–50% 5-year survival. The degree of RV failure and of coexistent arrhythmias was strongly associated with bad outcome [7].

Table 2 summarizes the difficulties in trying to re-train older patients with only 20–30% of patients >12 years of age achieving arterial switch [19–21].

Re-training in the Setting of ccTGA

These are very much the main focus of "re-training" in the current era, since indications (1) and (2) are now rarely encountered in modern practice. In general, these are a much younger age group than the historical series postsenning/mustard in d-TGA. Table 1 summaries the largest series, reinforcing the importance of separating those patients banded for VSD from the true "re-training" patients who have intact ventricular septum. The nature of presentation of this latter group is such that they are older than the VSD group of patients, typically median of 2–5 years of age at banding. However, even in the largest series, there were only 6 cases over 2 years of age in the Boston series [9], and all patients >12 years failed re-training. In the Birmingham series, there were only 4 cases over 4 years of age [10]. The Stanford series have had some success with older patients, although the median age of the whole group was still only 12 months at banding, there were 2 patients over 10 years who have successfully re-trained [18].

The Birmingham data (Fig. 1) compared the outcomes of patients banded for VSD vs those banded for re-training. Although survival was similar in both groups, a significant number of re-trained patients were found to have developed mLV dysfunction during follow-up, accounting for 14% of the whole patient group. The patients who developed late mLV dysfunction were significantly older at time of banding, at 5.2 years—compared to 2.3 years for the whole group [21].

The Ann Arbor experience attempted re-training in 11 cases, which failed in the 2 oldest patients who were 12 and 14 years. The oldest patient undergoing successful double switch was 7 years and this patient came to need a transplant for mLV dysfunction [22]. The Boston series focused on age at banding and showed that late mLV dysfunction was strongly associated with older age at banding and also with patients in whom a longer duration of banding was required to achieve systemic

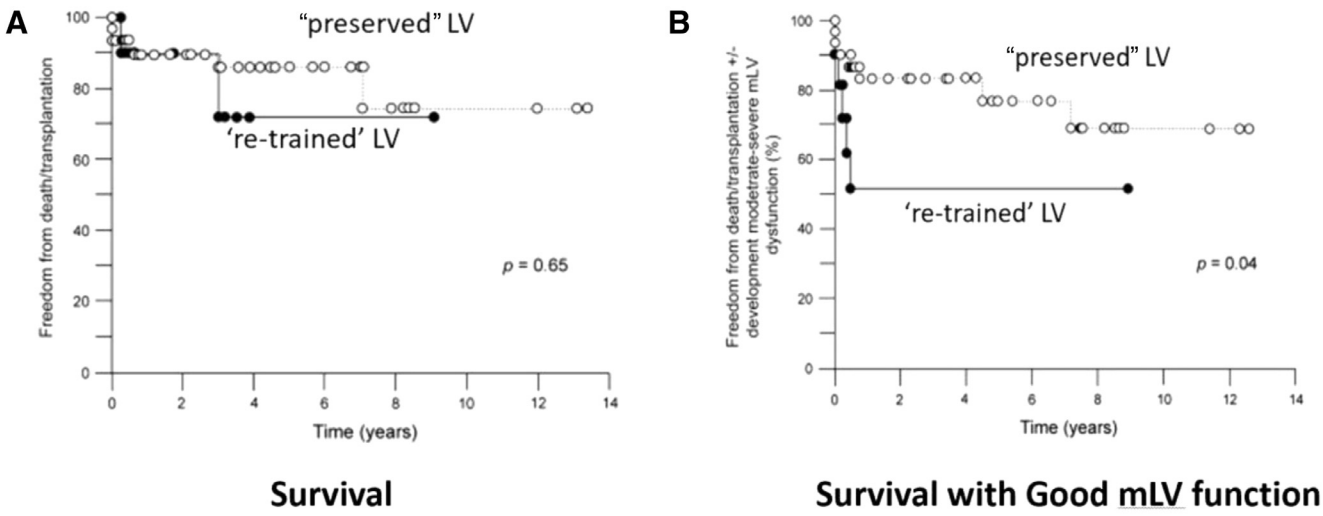

Figure 1 Actuarial survival of patients with ccTGA who have undergone PA banding prior to double switch. Patients are divided into those who had "preserved" mLV pressure (ie, PA band due to VSD) and those who required PA band for "re-training" (ie, no VSD). Panel (A) shows actuarial freedom from death or transplantation. Panel (B) shows actuarial freedom from death, transplantation, or impaired mLV function. mLV, morphologic left ventricle; PA, pulmonary artery; VSD, ventricular septal defect. (Adapted with permission from Winlaw DS et al [21].)

levels. A group of 20% of the banded patients developed late mLV dysfunction, which was associated with any banding at over 2 years of age and any repair performed after 10 years of age [9].

The immediate response to banding is also a predictor of long-term mLV function. Cases who developed late dysfunction only achieved a band gradient of 60 ± 32 mm Hg at initial banding compared to 85 ± 23 mm Hg in those who had sustained good mLV function [23]. Several studies have shown that the need to perform serial PA banding and the need for prolonged duration of banding are surrogate markers of late mLV function following double switch [8,18,21].

DISCUSSION

The simple concept of re-training through placement of a fixed afterload on the ventricle is an intriguing prospect. When successful, it has transformed the prognosis and outcomes for patients living with a failing systemic RV and has been rewarding justification for the premise that "anatomical repair" will be a valid solution for these challenging clinical situations.

The broad experience across the 3 different applications of this concept tells us that this is anything but a "simple" process—the variable and unpredictable response to banding suggests that not all patients can be "re-trained" and that age clearly plays a key role in this process. Equally, the rather crude process of placing a fixed band, the methods of assessment and the definition of suitability to progress to anatomic repair are mostly based on empirical judgments and clinical experience.

The issue of age is at the core of this problem. There is considerable evidence that the young and immature myocardium retains the capability to adapt to changes in afterload much more effectively than at older ages. It has been shown in animal models that the neonatal heart responds to afterload with myocardial hyperplasia and a balanced microvascular response, whereas in adolescents the response is predominantly hypertrophy with an irregular and inadequate microvascular response [24]. Nevertheless, a lesser degree of hyperplasia is still seen in this age group. When hypertrophy is the predominant response, the capillary density does not increase adequately within the myocardium with less flow reserve and a subsequent degree of ischemia and fibrosis [25]—but the infant myocardium retains an ability to mount a more appropriate and proportionate neovascular response. These findings would support the clinical evidence that patients banded at a much younger age show a much more predictable and faster response to banding with sustained normal function of the mLV at follow-up. Even in the setting of late presentation of d-TGA, re-training beyond just 3 months of age showed a risk of late mLV dysfunction with a more marked increase in the risk to patients who were >18 months of age.

Thus, it should not be surprising that attempting to re-train the mLV in older patients would be less successful. The oldest patients have tended to be in the studies of d-TGA postatrial switch, some even attempted in young adults. The failure rates in these series of older patients are striking, with the majority (usually 70−80%) of patients over 12 years of age failing to re-train at all or being at risk of subsequent mLV dysfunction after anatomic repair. Nevertheless, it is intriguing that occasional older patients have responded well, and it remains unclear as to why these cases have retained this ability. The oldest patient to respond with good outcome has been 25 years of age [18] but it is notable to record that successful re-training and sustained good mLV function has only ever been recorded in less than 10 patients >12 years of age in the entire world literature. It is possible that some of these older patients may have been "physiologically" sustained at higher pressures for many years, possibly due to chronic mRV failure and tricuspid regurgitation or a degree of baffle obstruction in the senning/mustard, which can be a potent stimulant of pulmonary hypertension.

The setting of ccTGA is the most common indication for re-training in modern practice and remains a controversial topic. In general, these are much younger patients than the historical series of re-training d-TGA after the atrial switch, yet some series do include much older patients. The increasing evidence on re-training in this setting has not only focused on the ability of the mLV to tolerate double switch, but also on the mid- and long-term performance of the mLV in the systemic position. Most larger series have identified a consistent finding of a group of 13−20% of patients who develop late mLV failure and the strongest association in all these series has been an older age at banding and longer duration of banding required prior to double switch [9,10,16]. Although a small number of older patients have been reported, it is remarkable how few patients beyond 12 years have ever been successfully re-trained and that actually patients >6 years are very unusual in most centers.

These findings have led to the discussion as to whether there is a true age limit at which re-training can be attempted. The Boston data [9] suggesting the ideal age may be as low as 2 years and it is certainly true that consistently good results have been reported by many centers for the double switch in these younger age groups. However, the undeniable (but less predictable) successes in older ages have prevented most authors from stating an absolute age cut-off. This rationale is entirely understandable since many ccTGA patients with intact septum may not present until older childhood. The dismal natural history for these patients (once that mRV dysfunction is established) has to be compared to the substantially better survival offered by re-training and anatomic repair, even in these older age groups. Thus, it seems reasonable to at least attempt re-training in these patients up to 12 years of age, accepting that it may not be successful. Beyond 12 years the evidence for successful re-training is extremely poor and we feel that other options should be considered (optimization of medical therapy, multisite pacing if indicated, possible tricuspid valve replacement if mRV function is still maintained, and, ultimately, transplant assessment).

The favorable response to banding in young children may also be related to the trajectory of somatic growth, which is steep in children of 0–5 years. A fixed band in this age group will steadily but gently become progressively tighter as the child grows—generating a naturally increasing increment that may be a better mechanism to re-train. Compare this to a 10-year-old child where the somatic growth is (relatively) much slower and so the band remains at a similar relative size over the critical 6–12 months of the postbanding period.

The other important part of understanding this problem is whether we can get better or smarter at the re-training process. The first component of this is the banding process itself, with most authors aiming to achieve 60–70% systemic pressures at the initial procedure but with no increase in end-diastolic pressure. The work of Zartner et al [26] has emphasized the importance of volume loading the mLV as well as pressure loading. Creating an atrial septal defect (ASD) at the same time as banding will increase the preload on the mLV and the results in a small group of patients showed favorable responses with both rapid and effective re-training in all (median age at double switch 3.8 years). A small ASD will also provide increased preload during exercise and so may help to incrementally train the mLV. More gradual or intermittent banding may be a kinder approach to re-training that may avoid undue strain on the mLV and reduce the risk of ischemia and fibrosis. Animal studies using devices that can be inflated or deflated to provide intermittent banding have been effective [27]. The ideal device could be the "FloWatch" band that utilizes a pusher-plate design that can be transcutaneously altered by induction—however, clinical use has been very limited and not usually in the setting of ccTGA [28].

The duration of banding and the assessment of preparedness also need to be optimized. Resting pressures of 80% systemic in the mLV were often accepted as adequate in the past, but more recent publications have suggested that resting pressures of up to 90% systemic and LV mass index >50 g m^{-2} may be better evidence of completed training [18].

Better ways of banding and monitoring the mLV could not only improve the outcomes of double switch but could also extend the limits at which banding can be attempted.

In Birmingham, we have tried to incorporate the lessons that have been learnt on re-training and use the protocol shown in Figure 2. We do not routinely create an ASD, but if the initial response to banding is suboptimal, we will then create an ASD in the cath lab and reassess after 6 months. All patients undergo formal assessment with cardiac catheter and magnetic resonance imaging. A resting pressure of >85% systemic minimum and this should come up to systemic or more during Dobutamine stress with no significant change in left ventricular end-diastolic pressure (LVEDP) (Fig. 3). If there is any concern then a balloon is partially inflated in the banded PA to further increase the afterload to explore whether or not the mLV can generate systemic pressures without rise in LVEDP or any loss of function.

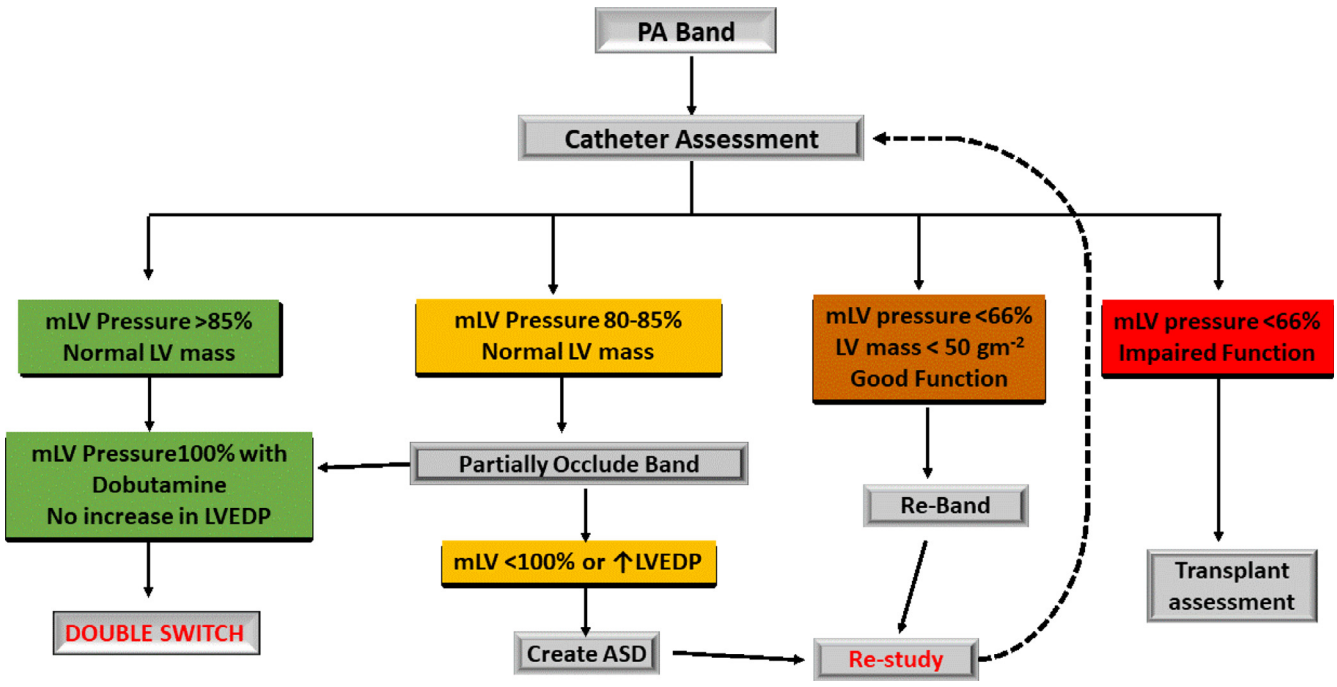

Figure 2 Management protocol for assessment of the mLV after PA banding prior to double switch. mLV, morphologic left ventricle; PA, pulmonary artery.

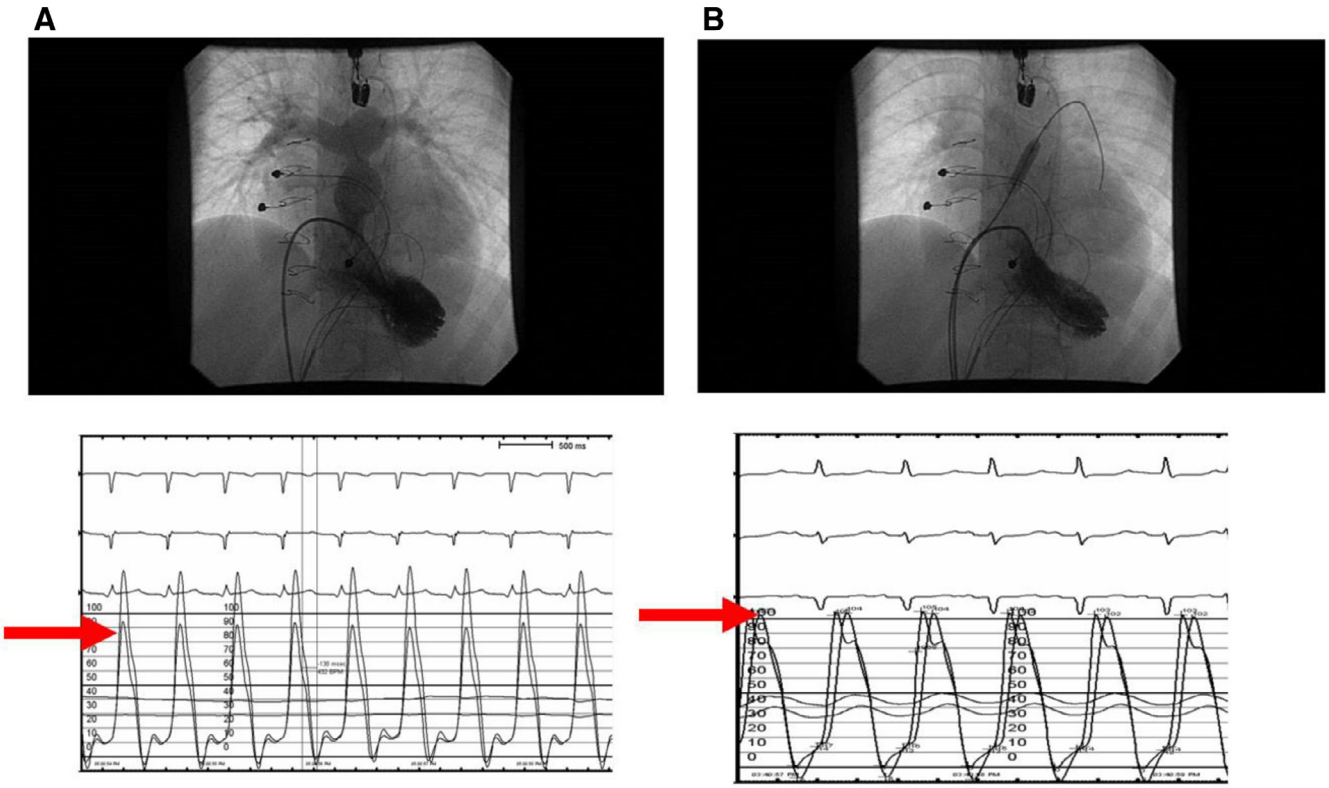

Figure 3 Assessment of preparedness for double switch. Panel (A) shows an angiogram still image of a pressure catheter in the mLV of a patient with ccTGA who has undergone previous PA banding. The lower image is the pressure traces for the left and right ventricle showing that the mLV is at 80% systemic pressure (marked with the arrow). Panel (B) shows the same patient but now with a balloon partially inflated across the PA band site to increase the afterload. The pressure traces show the mLV pressure is no systemic (arrow) with no increase in the end-diastolic pressure. mLV, morphologic left ventricle; PA, pulmonary artery.

CONCLUSION

Re-training the LV is a complex process that has been over-simplified in the past. There is a strong relationship between age and the ability of the mLV to mount an appropriate physiological response, which is undoubtedly at its best during infancy and possibly up to 2 years of age. Successful re-training is still possible up to 12 years of age, but has a greater risk of failure or of late mLV dysfunction that increases with age. Beyond 12 years the chances of successful training are very poor and unpredictable. Better methods of training and assessing the mLV prior to double switch may help improve long-term results and push the age limits for banding.

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