A Review of the Therapeutic Management of Multiple Ventricular Septal Defects

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Abstract

Background and Aim: We showed in our anatomical review, ventricular septal defects existing as multiple entities can be considered in terms of three major subsets. We address here the diagnostic challenges, associated anomalies, the role and techniques of surgical instead of interventional closure, and the outcomes. including reinterventions, for each subset. Methods: We reviewed 80 published investigations, noting radiographic findings, and the results of clinical imaging elucidating the location, number, size of septal defects, and associated anomalies, and the effect of severe pulmonary hypertension. Results: Overall, perioperative mortality for treatment of residual multiple defects has been cited to be between zero and 14.2%, with morbidity estimated between 6% to 13%. Perioperative mortality is twice as high for perimembranous compared to muscular defects, with need for reoperation is over four times higher. Perventricular hybrid approaches are useful for closure of high anterior or apical defects. Overall, results have been unsatisfactory. Pooled data reveals incidences between 2.8% and 45% for device-related adverse events. Currently, however, outcomes cannot be assessed on the basis of the different anatomical sub-sets. Conclusions: We have addressed the approaches, and the results, of therapeutic treatment in terms of co-existing discrete defects, the Swiss-cheese septum, and the arrangement in which a solitary apical muscular defect gives the impression of multiple defects when viewed from the right ventricular aspect. Treatment should vary according to the specific combination of defects.

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Running title: Multiple ventricular septal defects

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Methods: We reviewed 80 published investigations, noting radiographic findings, and the results of clinical imaging elucidating the location, number, size of septal defects, and associated anomalies, and the effect of severe pulmonary hypertension.

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Conclusions : We have addressed the approaches, and the results, of therapeutic treatment in terms of co-existing discrete defects, the Swiss-cheese septum, and the arrangement in which a solitary apical muscular

defect gives the impression of multiple defects when viewed from the right ventricular aspect. Treatment should vary according to the specific combination of defects.

Keywords: Congenital heart disease, Muscular ventricular septal defects, Percutaneous device closure, Perventricular hybrid device closure, Pulmonary artery banding, Swiss-cheese ventricular septal defects

Introduction

As we discussed in our anatomical review, multiple ventricular septal defects are present when there are multiple channels within the muscular septum, for example producing the arrangement well described as the Swiss-cheese septum. This arrangement is different, however, from the situation in which a muscular defect co-exists with a defect located in the perimembranous region, or when there are multiple discrete defects within the muscular septum. These combinations, furthermore, differ from the arrangement in which a solitary defect within the muscular septum can seem to be multiple when it is viewed from the right ventricle, being crossed by apical trabeculations (Figure 1). The surgical strategy for closure of isolated defects, even if the defect itself is large, is now standardized. The management of multiple defects, however, remains nebulous, the more so since as we have shown the multiple defects themselves can be considered in terms of anatomic subsets. Our review has revealed the wide variations in practice between centers reporting their approach to these various sub-sets, with some of the approaches tailored specifically to one of the sub-sets. Because of this, it is difficult to determine the ideal operative approach. This is due, in part due to the paucity of comparative reports. It also reflects a lack of long-term follow-up. In this surgical part of our review, we assess the options available for potential management of each of the sub-sets identified subsequent to our anatomical analysis.

Historical Background

In terms of surgical closure of multiple defects in general, the landmark experience was reported by Kirklin and colleagues in 1980.[1] They reported hospital mortality of 14%, and a need for reoperation to close residual defects in 28%. With regard to the Swiss-cheese septum, in an attempt hermetically to close all defects, and avoid a left ventriculotomy, Kitagawa and colleagues, in 1998, described the technique of using an oversized patch placed into the left ventricle via the right atrium.[2] As an alternative, they also described the "sandwich technique", achieved by transfixing the muscular edge of the defects to the anterior free wall of the ventricle after transecting the moderator band and right ventricular trabeculations to provide optimal exposure.[2] Subsequent to this account, again with regard to the Swiss-cheese septum, Black and colleagues, in 2000, described closure of the defects using a single large autologous pericardial patch.[3] Cetin and colleagues, in 2005, in contrast, used a composite patch of pericardium and Dacron graft. Both patches were placed using a right atrial approach.[4]Mace and colleagues then suggested placing several intermediate fixation stitches to prevent septal bulging.[5] In 2001, Yamaguchi and associates had described a "felt sandwich technique". This involved sandwiching the septum itself between two polyester felt patches placed in the left and right ventricles without need for ventriculotomy.[6,7] Brizard and associates, in 2004, reported a similar technique using intraoperative echocardiography guidelines with excellent results.[8] In 2006, Alsoufi and colleagues described transatrial re-endocardialization without dividing any trabeculations or the moderator band.[9]Much earlier, Stark and associates, in 1992, had closed the defects using a fibrin seal of human origin.[10]

At a much earlier date, Aaron and Lower, in 1975, had indicated that exposure and repair could be much easier when seemingly multipl defects were approached through the left ventricle.[11] This was because, as we showed in our anatomical review, a solitary left ventricular opening was often viewed as multiple orifices seen from the right ventricular aspect. As we also explained in our first part, however, this variant is not the same as the Swiss-cheese septum. And. although this approach can facilitate the repair, debate has continued regarding its potential sequels of a left ventriculotomy. Surgical exposure through a left ventriculotomy can also, at times, be disappointing. With the problems of a left ventriculotomy in mind, therefore, others have advocated and demonstrated the safety and effectiveness of an apical right ventriculotomy.[12-15]Still others have proposed a two-staged approach, with an initial band placed on the pulmonary trunk, but this strategy has its own inherent morbidity and mortality.[16,17]

Transcatheter closure is now well recognized as an additional therapeutic option for closure of ventricular septal defects. The option was first reported by Lock and associates from Boston using the Rashkind devices.[18] Then, in the late 1990s, a Nitinol device was added to the armamentarium of the interventionist.[19-21] The interventional approach may be particularly suitable for multiple muscular septal defects located in the mid, apical, posterior, and anterior parts of the muscular septum.[20-30] For most cardiac centers, however, devices delivered via catheters are not recommended in neonates and infants because of the need for a stiff guide wire. This can rupture the mitral valve, tear the septum, or invoke ventricular arrhythmias and cardiac arrest. In the new millennium, nonetheless, multiple groups have reported intraoperative perventricular closure, with encouraging early outcomes.[22-28]

Methods

We searched the extant literature for the described instances of the management of multiple ventricular septal defects. We then collated the demographics, the anatomical details encountered, the indications for surgery or intervention, and outcomes of management, including reinterventions. The search engines employed were PubMed, Google Scholar, Cochrane Database for Systematic Reviews, Cochrane Central Register of Controlled Trials, Ovid Medline, ACP Journal Club, Ovid EMBASE, and Database of Abstracts of Review of Effectiveness in all languages.

Analysis was based initially on the individualized review of the initial 77 investigations. These were then incorporated, as far as possible, with the results and recommendations from the Congenital Heart Surgery Database as provided by the Society of Thoracic Surgeons. The society has collated the findings from 116 participating centers. We also took note of the scientific statement of the American Heart Association, endorsed by the American Academy of Pediatrics and the Society for Cardiovascular Angiography and Intervention.[29-32] So as to unify the divergent approaches to the description and categorization of ventricular septal defects, we assessed the reports, as far as was possible, on the basis of the categorization proposed for the Eleventh Iteration of the International Classification of Disease, as produced by the International Society for Nomenclature of Pediatric and Congenital Heart Diseases.[33,34]

Due to the limited sizes of the descriptive case series reported, and the heterogeneity of clinical states at the time of surgical intervention, along with the difficulties in selection of appropriate cardiac quantifiable end points, we are unable to perform a meta-analysis. Our analysis therefore, is based on review of case reports, and small case series, along with incorporation of data from the extensive series published by the Society of Thoracic Surgeons Registry, the scientific statement of the American Heart Association, and the report from the International Society for Nomenclature of Pediatric and Congenital Heart Diseases.[28-34]

Results

Incidence

The prevalence of multiple defects in the muscular ventricular septum is low, occurring in less than one-fifth of patients in whom deficiency of the ventricular septum is the main finding, and in no more than 2% of those with co-existing lesions such as discordant ventriculo-arterial connections, tetralogy of Fallot, or atrioventricular septal defect.[35,36]

Diagnosis

Review of the cases show that, on presentation, the great majority of patients had evidence of congestive cardiac failure and pulmonary hypertension in early infancy, with these features often reported in the neonatal period when associated lesions are present. The chest roentgenogram usually reveals a moderate increase in the cardiothoracic ratio, along with pulmonary plethora. When present, multiple muscular defects are more frequently diagnosed by transesophageal color coded echocardiography, rather than transthoracic echocardiography. The identification of the morphology, and location, of the defects is important for selection of the appropriate therapeutic approach (Figures 2A, 2B).[1-32,37-78]

Some investigators have performed “en-face” reconstruction of multiple septal defects as viewed from the

right ventricle, based on orthogonal echocardiographic views, so as to plan the surgical approach, and predict the likelihood of postoperative heart block or the occurrence of residual defects. Features noted have included the location and dimensions of the defects, the distance of separation between additional defects, the relationship to various right ventricular septal landmarks.[37] Contrast-enhanced and multidetector computed-tomographic angiocardiography in angled oblique views have also proved helpful in ascertaining the morphology and location of the septal defects, together with evaluation of the aortic arch and its branches (Figures 3A-3F, 4A-4F). Cardiac catheterization and angiocardiography may still be indicated in some circumstances for evaluation of associated cardiac anomalies. Despite echocardiography and angiocardiography, it can still be difficult to recognize the boundaries of the defect, particularly in the setting of the Swiss-cheese septum.[1-32,37-73] Indeed, we found several reports describing additional defects recognized in the intraoperative and postoperative period, as well as at necropsy.[7,13]

Associated cardiac and extracardiac anomalies were reported in one-third to three-quarters of patients. Cardiac anomalies included common atrium, Ebstein-like anomaly of the tricuspid valve with tricuspid stenosis or regurgitation, endocardial fibroelastosis of the right ventricle, pulmonary stenosis, patchy-endocardial sclerosis of the left ventricle, downward displacement of the tricuspid valve, aneurysm of the membranous septum, midline heart, juxtaposed right atrial appendages, double orifice mitral valve with mitral stenosis, double outlet right ventricle, Taussig-Bing anomaly, atrioventricular septal defect, bilateral superior caval veins, subaortic stenosis, left superior caval vein to coronary sinus, unroofed coronary sinus, tetralogy of Fallot, atretic orifice of the coronary sinus, common arterial trunk, straddling tricuspid valve, partially anomalous pulmonary venous connection, transposition, right isomerism, pulmonary atresia, divided left atrium, left isomerism, left ventricular outflow tract obstruction, interruption of inferior caval vein, hypoplastic left ventricle, hypoplastic right ventricle, congenital aortic stenosis, congenitally corrected transposition, and criss-cross ventricles. Associated extracardiac anomalies included patency of the arterial duct, hypoplasia of aortic isthmus, coarctation of aorta, interrupted aortic arch, double aortic arch, and hypoplastic aortic arch.[6-8,13-16,18,19,23,24,31,32,37]

Surgical Approaches and Management

There is currently no consensus regarding the management of multiple muscular septal defects, particularly concerning the timing and type of interventions. For those with pulmonary hypertension and congestive cardiac failure, medical management alone is ineffective. It follows that those diagnosed with multiple defects at an early age, with symptoms of congestive cardiac failure and/or pulmonary hypertension, and with volume overload of the left ventricle, should undergo surgical or hybrid intervention to prevent ventricular dilation and dysfunction, arrhythmias, aortic regurgitation, and ongoing pulmonary hypertension.[35,36] The urgency of intervention will be determined primarily by the severity of presenting symptoms, and by the associated cardiac anomalies if present. The finding of the Swiss-cheese septum, along with major associated cardiac lesions, significantly increases the risks of operation. Such patients are managed on an individual basis.[2-13]

Surgical management has evolved with time. Moderately hypothermic cardiopulmonary bypass at 32°C, with cold cardioplegia, is now the most popular technique. Several investigators have used deep hypothermic circulatory arrest for patients with low body weight, complicated anatomy, and/or associated congenital cardiac malformations.[6-8,43] The mean duration of circulation arrest was 40 minutes, with a range of 20-60 minutes.[6-8,43]

Various imaging techniques have proven their value for intraoperative identification of the defects. Either cross-sectional or three-dimensional color Doppler echocardiography, including transesophageal imaging, and echocardiographic en-face reconstruction of the right ventricular septal surface, have emerged as superior diagnostic modalities.[1-72]

While the general approach to multiple muscular septal defects is similar to that of isolated ventricular septal defects, their presence poses particular challenges for their identification and closure. As a consequence, a wide range of therapeutic approaches have been described.

When multiple defects are located in the muscular septum, oozing of blood can be demonstrated through the

defects into the right ventricle despite adequate left ventricular venting. Several maneuvers have been used to identify the defects, including intraoperative epicardial echocardiography. When using a transtricuspid approach, larger defects can easily be located via the tricuspid valve. A blunt tip right angled forceps can be placed gently through the hole, without using any force except for the weight of the angled clamp. A DeBakey forcep is then held in the left ventricle, either placed through the larger inlet muscular defect, or via an atrioseptostomy. The metallic sound of two metal tips touching each other indicates that the right angled clamp has successfully been placed through the second defect. Either a No.3 Sutupak silk suture, or a No.8 Foley catheter, can be looped through the additional septal defects to facilitate closure (Figures 5A-5F).

Most investigators have performed postoperative transesophageal echocardiography and saturation determination. Large residual shunts detected intraoperatively with a pulmonary-to-systemic blood flow ratio of greater than 2, have been managed either by reinstitution of bypass and reexamination of the ventricular septum, or by hybrid device closure.[7,20-24,28-32,45]

Although catheter-based techniques appear promising, they are not yet widely used to close the entire spectrum of multiple septal defects in all age groups. For the time being at least, surgical repair remains the gold standard.[1-26]

On the basis of our initial review, we have sought, as far as possible, to assess the therapeutic options according to the specific anatomical combinations of defects. Each option, of course, may further be tailored according to the needs of the individual patient and surgeon.

Multiple discrete muscular defects

Several options have been suggested, although each option may be tailored to the individual patient, and surgeon. The decision to embark upon a one-stage repair rests with the surgeon, who must decide whether all significant defects can safely be closed. Should the repair be unsuccessful, leaving a residual shunt of greater than 1.5:1, after a prolonged pump run and potential associated myocardial ischemia, a difficult postoperative course, and death can be expected. Placement of a band on the pulmonary trunk allows for growth before attempted surgical or interventional closure. Ventricular hypertrophy, furthermore, may result in closure of smaller defects.[16,17,38-40]

Separate patch closure of multiple apical defects

Many investigators have successfully used a transatrial approach when multiple muscular defects exist cranial to the base of the anterior papillary muscle, and in the middle part of the apical muscular septum. These defects can reliably be closed by dividing the moderator band, and the body of the septomarginal trabeculation. For posteroinferior and inlet defects, the septal leaflet of the tricuspid valve may require temporary detachment for optimal exposure.[7,12,14,38,41] A transpulmonary or an approach via a right ventriculotomy have been described for anterosuperior muscular defects. Knitted Dacron, and polytetrafluoroethylene synthetic patches have been employed by various investigators, including us.[7,12,14,38,41]

Right atrial approach with a single oversized patch on the right ventricle (the septal obliteration technique)

Black and Cetin inserted a single large autologous pericardial patch and composite patch of Dacron lined with preserved heterologous pericardium respectively through the transtricuspid route without dividing the moderator band.[3,4]

Seddio and associates also described this technique using a large autologous pericardial patch after dividing the moderator band.[42] Kitagawa and associates used a polytetrafluoroethylene patch, placed on the left ventricular side of the septum after dividing the moderator band (Figures 6A, 6B).[2,41]

These techniques are useful when multiple discrete defects are present in the posterior and apical parts of the septum, caudal to the moderator band.[1-4,41,42] Intraoperative transesophageal echocardiography and cardioscopy from the left side of the septum via the aortic root have been employed for identification of the defects from the left side by these investigators.

Right atrial approach with a single large patch on the right ventricle and intermediate fixation

In 1996, Mace and associates used a right atrial approach and inserted a single large patch to cover the right side of the apical muscular septum, adding intermediate fixation stitches at the junction between the septum and anterior right ventricular free wall to prevent septal bulging (Figures 7A, 7B).[5]

Intraoperative echocardiography and double-patch device sandwiching the septum

In 2004, Brizard and associates developed a unique technique in which the discrete defects were located with intraoperative epicardial echocardiography and transfixed with a guide wire inserted directly through the right ventricular free wall.[8] The multiple ventricular septal defects were then sandwiched with custom made multilayered double patches from both sides of the ventricular septum under cardioplegic arrest via a right atriotomy. Multiple patches were used for distantly located ventricular septal defects. For closely related ventricular septal defects, oversized patches were used for collective closure of the septal defects.[8]

Device closure of multiple midmuscular septal defects

In cases of multiple septal defects separated by a moderate margin, double and triple devices have been inserted, either by a hybrid approach or percutaneously. in select institutions.[21-28,52-55]

Combined perimembranous and inlet muscular septal defects

Black and associates used a standard patch to close the perimembranous defect, and inserted a pericardial patch to obliterate the associated muscular ventricular septal defect.[3] Serraf and associates also used a patch to close the perimembraneous defect, but used pledget-reinforced mattress sutures for the smaller muscular defect.[43] Alsoufi and associates used separate patches to close combined perimembranous and muscular defects, but used Dacron patches to close large apical defects located underneath the moderator band.[9] These latter authors employed a strategy of re-endocardialization for associated smaller septal defects without dividing any major trabeculations. using double-layered suturing of the septal trabeculations with fine, superficial, subendocardial running sutures.[9] Yashimura and associates closed the perimembranous defects using a Dacron polyester patch. Like Serraf and colleagues, they used pledget reinforced mattress sutures for the muscular defects, or re-endocardialisation using 6-0 prolene.[44] Closure of these ventricular septal defects using separate patches, however, entails the risks of surgical complete heart block, since the conduction axis runs in between two ventricular septal defects.[38,43] Because of this, closure has been recommended and practiced using a single patch. Another option is to temporize by banding the pulmonary trunk, as described above, anticipating that growth will facilitate the placement of separate patches (see below).

Patch closure of perimembranous defect and device closure of muscular defects

A combination of hybrid transcatheter closure of the muscular defect, followed by surgical closure of the perimembranous defect, has been described in cases of locations deemed surgically inaccessible, this avoiding ventriculotomy, reducing the need for extensive septal suturing, and decreasing the bypass time.[29-32,45]

Device closure of perimembranous and outlet septal defects

Although not approved by Food, Drug and Administration, USA, several institutions have performed interventional closure of associated perimembranous and outlet septal defects using perimembranous Amplatzer device in anatomically suitable patients weighing more than 8 kilograms.[54,55,66,67,73-78]

Staged approach with an initial banding of the pulmonary trunk

As suggested above, in small infants with combined perimembranous and inlet muscular defects separated by a thin muscle bundle, some investigators have preferred initial banding of the pulmonary trunk, thus promoting growth of the muscle bar containing the conduction axis which separates the defects.[14,16,17,43] The hope is that the passage of time will permit growth of the muscle bar interposing between perimembranous and muscular defects, thus allowing placement of sutures to secure separate patches at the time of second-stage surgery.[16,17,38-40] This strategy is helpful in preventing iatrogenic heart block.

Apical ventricular septal defects

The "Felt Sandwich Technique"

Several authors have described this technique, approaching the septum through the transtricuspid route for multiple muscular defects located just underneath the moderator band or at the apex of the heart, where it is difficult to place sutures, and hence making the defects unsuitable for direct closure.[7,44,79] A 3F Nelaton catheter (Bard, Haverhill, Mass) was railroaded through the septal defect. The Nelaton catheter led an oversized circular polyester felt patch mounted on a 4-0 braided polyester suture. The suture ends were then passed through a slightly smaller polyester felt patch on the right ventricular side of the septum. The braided polyester suture was then tied, thereby sandwiching the septum between two polyester felt patches (Figure 8).[7,44,79]

Modified Sandwich technique

Kitagawa and associates modified the "sandwich" technique for multiple small anterior muscular septal defects. Using the transtricuspid route, they passed mattress sutures through the septum, continuing through the anterior wall of the ventricle away from the anterior interventricular coronary artery, and finally through a felt buttress effectively to close the defects by "sandwiching" them against the anterior wall of the heart (Figure 9).[2,41]

Apical right ventriculotomy approach

This approach has been described when multiple ventricular septal defects are located between the left and right ventricular apex, antero-inferior to the moderator band. Surgical closure has been accomplished through a small right ventricular incision of approximately 2 cm using a sandwich technique under bypass and hypothermic cardioplegic arrest (Figures 10A-10C).[12-15]

Device closure

Apical multiple septal defects have been closed using a Clampshell device via percutaneous and hybrid perventricular approaches.[21-28,51-55]

Spurious multiple ventricular septal defects

Limited apical left ventriculotomy approach

This approach has been employed for multiple apical muscular defects inaccessible through the transtricuspid route. When viewed from the left side of the septum, of course, a single discrete defect is observed.[11,46-49] A short "fish-mouth" incision about 1 cm long is made at the apex of the left ventricle away from, and parallel to the interventricular coronary arteries on a non-vented heart filled with cardioplegia solution, avoiding injury to the anterior papillary muscles of the mitral valve. The recommended incision is usually smaller than the size of the defect. The ventriculotomy is closed by a double layer of continuous polypropylene suture, sandwiching a portion of the patch used to close the septal defect without injuring the coronary arteries (Figure 11).[2,11,41,43,46-50]

Apical right ventriculotomy

This approach has also been employed in diagnosed cases of the large muscular defects that seem to be multiple because of the overlying right ventricular apical septal trabculations.[12-15]When a large acute marginal branch is present, a small right ventriculotomy of approximately 2 cm is performed 4 mm lateral to the left anterior interventricular coronary artery. When the acute marginal branch is less prominent, a transverse incision is made above the acute margin of the heart. Trabeculations overlying the margins of the septal defect were taken down sharply to expose the edge of the defect. 5-0 polypropylene sutures are placed full thickness at the superior margin of the defect, maintaining pledgets on the left ventricular side. The ventricular septal defect was closed with a Dacron patch (Figures 10A-10C).[12-15]

Device closure

For defects with multiple right ventricular openings, and a single left ventricular opening, the Amplatzer delivery system should be positioned through the largest right ventricular opening to avoid compression of the device. For those defects with so-called "wind sock type" morphology, with a large left ventricular orifice and smaller right ventricular sites of exit, the device should be placed within the wind sock to avoid interference with the conduction system and/or aortic valve. Since patients with previous banding of the pulmonary trunk may not exhibit shunting across the multiple defects, it is crucial to deband prior to any attempted hybrid closure. It is always desirable to cross the largest defect first and subsequently cross the smaller defects.[21-28,51-55]

Swiss-cheese defects

The "septal obliteration technique" using a single oversized patch on the right ventricle

In patients with the true Swiss-cheese septum, adequate closure of the multiple defects essentially requires ventricular septation. An oversized composite patch of Dacron lined with preserved heterologous pericardium with multiple points of intermediate fixation was used by Cetin and other investigators with satisfactory short-term results.[4] Their outcome may be complicated by abnormal ventricular function, and may require cardiac transplantation.[4,8,42,48,49,56-61] This technique has also been described for multiple discrete muscular defects located in the posterior, and apical part of the septum caudal to the moderator band.

Conventional, absorbable, and telemetric adjustable FloWatch banding techniques

Conventional, absorbable, or telemetrically adjustable bands placed on the pulmonary trunk have been employed in several institutions as initial palliation in premature infants with low body weight having either multiple muscular defects, or alternatively the true Swiss-cheese septum. This protocol has also been employed in cases of multiple septal defects having anatomical peculiarities predisposing to postoperative heart block, and residual defects in a small infant.[14,16,17,43]

Two-patch and right ventricle apex exclusion technique

Wu and Perez-Negueruela developed this technique of closing either multiple large apical muscular or the Swiss-cheese septum using a procedure that involved exclusion of the right ventricular apex through the tricuspid route. Associated septal defects were closed separately.[50,62] A 10-Fr Foley catheter was railroaded through a defect to facilitate visualization of the overall arrangement by applying gentle traction. Two patches of bovine pericardium were used to close the defects, excluding the apex of the right ventricle (Figure 12).[62] The first bovine pericardial patch was sutured at the upper edge of the deficient septum and moderator band using a 6-0 polypropylene suture. A second pericardial patch was used to close the defects present between the moderator band and anterior free wall of the right ventricle. Some investigators have used a 5-0 polypropylene purse string suture to exclude the apical portion of the right ventricle, thereby occluding multiple defects between the trabeculations of the right ventricle.[50,62]

Repair of the Swiss-cheese septum using biologic glue

In 1992, Stark and associates developed this technique using fibrin seal of human origin (Tissucal, Immuno-France, Orly, France). Fibrin seal consists of concentrated lyophilized fibrinogen enriched with factor XIII and fibronectin. An aprotinin solution warmed to 37°C was added to the fibrinogen.[10] After closing any larger defects either using a pericardial or composite Dacron fabric lined with pericardium, and direct pledget supported sutures, the fibrin seal was injected into a dry operating field. Precautions were taken to avoid too deep an insertion into the left ventricle. Other authors subsequently reported good results with fibrin glue.[10,63]

Transcatheter closure

Percutaneous closure of such defects with catheter-delivered devices has been extensively explored in select institutions.[19-21]Delivery in the catheterization laboratory by percutaneous femoral exposure is generally limited to older children weighing more than 5-10 kg, to minimize femoral vessel injury. The size of the Amplatzer muscular defect occlude ranges in size from 4-18 mm.[19-28] Depending on the location, number,

and size of the muscular defects, several technical details need to be taken into account. The proximity of the tricuspid valve for defects located below the moderator band may cause entrapment of the sheath in the chordal apparatus.

Hybrid closure of multiple apical muscular septal defects

Hybrid, perventricular delivery of the device involves direct access to the right ventricle via a surgical incision, which may be median sternotomy, or a limited subxiphoid, parasternal or infra-axillary incision.[23-25,51-55,69] The procedure is performed on a beating heart without fluoroscopy using continuous transesophageal or epicardial echocardiographic guidance. The approach to device delivery include direct puncture into the right ventricle, direct transthoracic puncture, and placement with the heart open under cardiopulmonary bypass.[55,68] In some institutions, device closure is the treatment of choice if the defect is difficult to access, such as in the apical or anterior muscular septum, and in the setting of the Swiss-cheese septum.[19-28,51-55]

Orthotopic cardiac transplantation

Cardiac transplantation has been recommended for extremely large apical septal defects with severe biventricular dysplasia, and persistent ventricular dysfunction following closure of Swiss-cheese septal defects through apical left ventriculotomy.[6,8,29-32,41,42,47,56-60]

Short- and long-term outcomes

The overall reported perioperative mortality for patients undergoing conventional repair of multiple septal defects, including the Swiss-cheese variety, has been cited to be between zero and 14.2%.[1-15,29-62] The causes of death were due to intractable pulmonary hypertensive crises, residual defects, and congestive cardiac failure. The requirement of reoperation for residual defects has been between 6 and13%, with a reoperative mortality of around 33%.[1-15,29-62] The STS Congenital Heart Surgery Spring 2017 Database provides results from 116 participating centers on 7322 operations for ventricular septal defects over 4 years with a mean operative mortality of 0.6%, mean cardiopulmonary bypass time of 77 minutes and cross-clamp time of 49 minutes.[29-32] Repair for multiple defects, their "category 2", accounted for 4.5% of operations, with an operative mortality of 2.6%, requirement of mechanical circulatory support in 2.6%, and the need for a permanent pacemaker in 3.4% of cases. When compared with isolated perimembranous defects, the rate of mortality was thrice as high with multiple defects, the rate of reoperation was over 4 times higher with muscular defects, and the rate of heart block was 3 times higher with muscular and multiple septal defects.[1,29-32] It is not possible, however, to interrogate the registry according to outcomes for the different anatomical subsets.

Opinion is divided on the recommendation of limited apical left ventriculotomy for closure of apical defects. Although favorable short- and long-term results have been reported by some investigators, others have reported left ventricular dysfunction apical aneurysm formation, and ventricular arrhythmia in long-term survivors undergoing left ventriculotomy.[2,41,43,46,47,57-60,61,65]

Recent results of use of devices inserted percutaneously to close multiple septal defects have allegedly been encouraging.[19-28,54,55,66,75,76] In terms of outcomes, nonetheless, in some of these small series rates of mortality have been between 14 and 24%, with rates of failure between 20 and 40%.[53,75,76] In a combined series, Holzer and associates reported the results of a multicentric trial involving 14 tertiary referral centers in the United States of America. They collected outcomes from 75 treated patients, finding a total of 59 (45%) adverse events, and 10.7% major procedure-related complications, including device embolization, cardiac perforation, stroke. There were two deaths (2.7%).[20-28,60,66-70,75]

Discussion

Although the diagnostic procedures, surgical techniques, and results are standardized for patients with isolated ventricular septal defects, diagnosis is less secure, surgical techniques are more varied, and published incidence of perioperative mortality, ventricular dysfunction, and complete heart block are higher in those with multiple defects, including the Swiss-cheese septum,. Major associated cardiac lesions add to the complexity of repair.[1-72]

Analysis of the STS Congenital Heart Surgery Database analysis over a period of 4 years revealed that, when defects are multiple, it takes longer to close them. When compared with the more common isolated perimembranous defects, the rate of heart block is three times higher with multiple defects. The rate of unplanned reoperation is over four times higher even with isolated muscular septal defects, and almost twice as high with multiple septal defects. Before discharge from the hospital, the mortality rate is over twice as high with muscular septal defects, and over three times as high with multiple septal defects.[29-32] As already discussed, however, it did not prove possible to analyse the outcomes in terms of the outcomes for the anatomical combinations of multiple defects as suggested in our reviews. This is something that might be achieved in the future, since the anatomical differences are striking, and certainly impact on the optimal therapeutic approach.

The key to closure of multiple defects is accurate identification, edge detection, and proper cavitary entry. Guidance for closure have been described by multiple investigators using three dimensional color-coded echocardiography, echocardiographic en-face reconstruction of the right ventricular septal surface, contrast enhanced and multidetector computed tomography, fast gradient magnetic resonance cardiac imaging, angiocardiography, and perventricular wire placement, or by cardioscopy.[1-9,14,22-28,71]

Taken together, these investigations collectively provide comprehensive assessment of anatomical information to obtain an accurate preoperative diagnosis, yet it remains difficult to ascertain whether all defects are recognised, particularly when one large defect is non-restrictive.[1-28,59,64,71] Our review revealed several instances of diagnosis of additional defects intraoperatively, postoperatively, or at necropsy.[1,7,13]

The optimal surgical repair involves complete closure of the multiple defects. Ideally the moderator band and septomarginal trabeculation should remain intact, without a need for ventriculotomy, without compromising the size of the ventricular cavities, without producing ventricular dysfunction, surgical complete heart block, aortic and tricuspid regurgitation, and without compromising the coronary arterial flow. That this ideal has yet to be achieved is evident from the numerous surgical and interventional techniques described, along with short-term follow-up studies that report an undesirable incidence of perioperative mortality and morbidity.[1-72] Residual defects, and postoperative myocardial dysfunction, are still the Achille's heel of poor surgical results. They are related mainly to the uncertainty of location of the defects, and the difficulty in obtaining complete closure without right and/or left ventriculotomy.[1-17,19-27,29-32,41,43,46-53,59,61,65]

With the evolving knowledge of the complex variable anatomy, individualized surgical techniques have been described to suit the different anatomical variants. Some approaches, furthermore, are suitable for several variants. All surgeons acknowledge, nonetheless, that these defects, when multiple, are difficult to close, particularly in small infants presenting with congestive cardiac failure.[1-17,19-27,29-32,41,43,46-53,59,61,65]

It may be hard to recognize the boundaries of defects because the moderator band and multiple trabeculations hide apical defects, while Swiss-cheese defects may remain misdiagnosed.[1-72]Visualization and closure of most muscular defects is usually possible via a right atriotomy. Exposure of apical defects from the right side, however, has been plagued by poor visualization, and the uncertainties of identifying the true margins of the defects when approaching through the coarse trabeculations of right ventricular apex.[1-72] These problems are then still further exacerbated in the setting of the Swiss-cheese septum. It is because of the limited exposure, and difficulties in exploring Swiss-cheese defects, that banding of the pulmonary trunk is still being performed in premature infants with low body weight to protect the pulmonary vascular bed and to relieve symptoms of congestive heart failure to delay definitive repair.[14-17,30-32]

As we have discussed, such banding can also have its place in treatment of individuals with other combinations of multiple defects. Presently, banding as an initial palliative procedure is being performed in select institutions under specific circumstances. These include the proximity of margins of the defect to the atrioventricular conduction axis, which predisposes to atrioventricular block in small infants when constraints exist in terms of space for placing a permanent pacemaker. Other indications include multiple apical defects, particularly the Swiss-cheese septum, selected patients with large trabeculations traversing the defects that could interfere with complete closure, co-existing perimembranous and muscular inlet defects, an associations

with coarctation in infants aged less than 2 months, association with lesions such as twisted atrioventricular connections and those selected individuals deemed generally to be at high-risk.[13,14,16,17,30-32,37] The staged approach, furthermore, is known to promote spontaneous closure of some of the smaller defects. Against these potential advantages must be weighed the deleterious effects of biventricular muscular and fibrous hypertrophy and long-lasting hypoxia leading to arrhythmic events, increased mortality, and chronic heart failure.[22-24,30,32,41,42,48]

Since the pulmonary vascular bed is both pressure and volume overloaded, there is difficulty in determining the optimal tightness of the band. Hence the need for frequent reoperations for adjustment. The added complexity of the second stage includes pericardial adhesions, need for pulmonary arterioplasty, damage to the potential neoaortic valve and right ventricular hypertrophy, further contributing to difficult exposure of septal defects.[16,17,29-32] To address these concerns, Corno and associates introduced the telemetrically adjustable FloWatch pulmonary artery band (FloWatch-PAB®). Use of this approach not only eliminates the requirement of reoperation to adjust the band, but also allows for precise and progressive tightening over days or weeks.[16,17] The non-circular shape of FloWatch, furthermore, maintains the pliability of pulmonary arterial wall and avoids pulmonary arterioplasty.

The approach through the left ventricle still retains its advocates. Thus, when using this technique, Aaron and Hanna demonstrated that exposure and repair of apical defects was much easier.[11] It is particularly appropriate for those cases with a solitary defect seemingly having multiple channels when assessed from the right ventricle. Its use has been advocated by multiple surgeons producing small series with excellent short- and long-term results. Recently, a limited apical left ventriculotomy approach has been introduced.[2,57,61,65] Debate continues, nonetheless, with regard to its potential risks. The exposure gained can also be disappointing at times. Because of all these considerations, some argue that the risks, in the long-term, are unacceptable, since they include apical dyskinesia, aneurysm formation, left ventricular dysfunction, ventricular arrhythmia, and the need for cardiac transplantation.[2,30-32,57-61,65,66] The mechanisms identified that result in left ventricular dysfunction and aneurysm formation have included damage to epicardial coronary arteries, the myocardium, and the left ventricular conduction system.[11,58,60,61] It is also the case that the precise anatomic location and orientation of the ventriculotomy has great impact on the results. Waldhausen and DiBernardo, for example, demonstrated that a longitudinal left ventriculotomy causes less disruption to coronary vasculature, less injury to papillary muscles, better preservation of ventricular function, and smaller areas of ischemia when compared to transverse lesions.[2,58]

The advocates of an apical right ventriculotomy have demonstrated the safety and effectiveness of this approach for large solitary apical defects with multiple overlying trabeculations, and for apical and anterior defects.[12-15] The technical features include a limited right ventricular incision that is close to left anterior interventricular coronary artery without endangering the vessel. As described by Tsang and associates, a ventriculotomy in this area allows entry to the space between the papillary muscles and the septum.[15]

All surgeons acknowledge that the Swiss-cheese septum is particularly difficult to close, particularly when encountered in neonates and premature infants with low body weight presenting with congestive cardiac failure.[1-72] The true Swiss-cheese septum emdodies all the morphologic features of so-called "non-compaction". Repair of the non-compacted septum essentially involves ventricular septation, either with an oversized patch, or by right ventricular apical exclusion. Outcomes of such procedures may be complicated by abnormal ventricular function requiring cardiac transplantation. In many circumstances, initial placement of an adjustable pulmonary arterial band remains a safer and desirable option.[14,16,17,30-32] The techniques of "over-sized pericardial patch", "composite patch", "double patch sandwiching the septum", "felt sandwich patch" have all been described, with or without transection of moderator band/septal trabeculations without left ventriculotomy.[1-8,79] The majority of patients required prolonged diuretics, angiotensin converting enzyme inhibitors, thereby suggesting impairment of left ventricular function in the postoperative period. The non-compacted septum can be notoriously difficult to identify before the initial repair. Once obvious defects have been closed, additional defects can be unmasked, and may require additional intervention.[1-8] If a large patch is used to cover the entire septum, it is desirable to address multiple points of fixation to avoid

the development of aneurysmal new septum.[4,5] Although the use of oversized pericardial patches yielded good results, residual defects are frequently reported, along with reduced right ventricular size, and late complications including cardiac cirrhosis, late opening of the oval fossa, and atrial tachyarrhythmias.[68]

It follows that there are wide variations in practice between centers in the approach to interventions for multiple muscular septal defects. Many surgeons prefer to repair mid muscular septal defects in the operating room using traditional techniques.[7-14,38,72] Recently, transcatheter device closure and hybrid techniques for closure of multiple muscular septal defects have reported encouraging early outcomes. Percutaneous device closure in infants below 5 kg poses a variety of challenges because of low body weight and poor venous access.[22-25,28,52-55] The stiff delivery catheters and sheath can splint open the tricuspid valve, mitral valve, and/or aortic valve, leading to arrhythmias, heart block and hemodynamic decompensation. In these clinical situations, a perventricular hybrid approach is a feasible "off pump" therapeutic option with acceptable mortality and morbidity.[23-25,51-55,69]

Recommendations were suggested in 2011 by the American Heart Association for device closure of multiple muscular septal defects. Infants weighing more than 5 kg, and children and adolescents with hemodynamically significant shunts were placed in Class IIA. In Class IIB were placed neonates, and infants weighing less than 5 kg with hemodynamically significant lesions and associated cardiac defects requiring cardiopulmonary bypass, albeit for initial hybrid perventricular closure off bypass, followed by surgical repair of the remaining defects. Neonates, infants and children with hemodynamically significant inlet multiple septal defects with inadequate space between the defect and the atrioventricular or arterial valves were not recommended for closure.[28] When considering these recommendations, it is those multiple defects located in the mid, apical, inferior, or anterior parts of the apical septum that are most amenable to closure in transcatheter fashion.[19-28,52-55] In recent years, with the introduction of the Amplatzer muscular and perimembranous occluders, the hybrid perventricular technique has been used for selected individuals with perimembranous and outlet defects to avoid surgical intervention, or to simplify operative repair.[67,73-78] In the multicentric trial on device closure carried out in the United States of America, almost three-quarters of individuals had only a single device inserted. In nearly one-fifth, however, it was necessary to use two devices, while three devices were needed in just over one-twentieth.[28] Other investigators have also reported successful closure with multiple devices.[28,52-55] The exclusion criteria of device closure include weight less than 3 kg, distances of less than 4 mm between the defects and valvar leaflets, pulmonary vascular resistance greater than 7 indexed Wood units, sepsis, more than trivial aortic or tricuspid regurgitation, obvious aortic valve prolapse, diameters greater than 10mm, preoperative arrhythmias, and contraindications to antiplatelet agents.[19-28] Patients with multiple ventricular septal defects with associated defects or undergoing hybrid procedures, represent a set of very particular clinical situations. A collaborative approach using transcatheter/hybrid device closure followed by surgical repair is emerging when preoperative evaluation is suggestive of relatively inaccessible location of the septal defect which may necessitate an incision in the systemic ventricle and those with complex associated lesions.[28-32,45,61,78] The advantages of percutaneous closure include avoidance of transection of trabeculations, avoidance of ventricular incisions and immediate confirmation of adequate closure. As already discussed, however, multiple adverse events have been reported in four series of intraoperative closure.[28,60,67-70]

Pooling the available data for interventional closure of multiple defects reveals an incidence of such adverse events of between 2.8% and 45%. The reported complications are many and varied. They include arrhythmias, cardiac arrest, device embolization, residual shunting, cardiac perforation, and even procedure-related death.[19-28,60,66-70] When compared with surgery, in which complete heart block appears early postoperatively, complete heart block is unpredictable after device closure, and is a late problem. Direct compression, inflammatory reaction, and formation of scarring in the conduction tissues have all been variously incriminated as the causative mechanism of complete heart block.[19-28,66-70,73,80]

Study Limitations

The nature of the data currently available in the published literature carries its own inherent limitations. Patients with multiple defects and the Swiss-cheese septum undergoing different types of surgical procedures,

and transcatheter/hybrid closure are small in number, with incomplete follow-up. This makes it difficult to draw long-term conclusions at this stage. The numbers of patients reported with the different anatomical sub-sets, including the Swiss-cheese variety, were not large enough for analysis to be convincing, although the results are consistent with the clinical practice. Thus far, furthermore, patients have not been randomized between surgical, and interventional or hybrid closure, thus meaning that comparisons between the groups may be biased. Experienced hands, with highly specialized backup, must be available for safety. Whereas the long-term safety and efficacy of surgery are well documented, the long-term results of device closure are unknown. Future prospectively designed multicentric studies with larger sample sizes will be needed to substantiate our inferences made on the basis of from the published literature.

Conclusions

Based on the published literature, we conclude that color-Doppler flow mapping should allow precise delineation of the number, size, and location of multiple defects in infants and children, and facilitate planning of optimal strategy for intervention. The closure of Swiss-cheese defects still presents a technical challenge, and carries increased mortality. Use of an adjustable pulmonary arterial band is a desirable option in premature infants with low body weight, and body surface area less than $0.4m^2$, as it allows possible spontaneous closure of some smaller defects. Following its use, other defects can safely be closed on a bigger heart. Although oversized and Sandwich patch techniques are recommended for reconstituting the Swiss-cheese septum, biologic glue appears useful. Its downside is the need for extensive division or transection of right ventricular trabeculations for optimal visualization, with the potential long-term risk of myocardial and septal dysfunction.

Apical left or right ventriculotomies reliably provide access to apical defects, simplifying placement of patches, preserving ventricular volume compliance, and avoiding complications related to transection of trabeculations. With the current development of device closure, left ventriculotomy may be replaced in highly specialized centers by transcatheter or hybrid procedures. Perventricular device closure is here to stay. This means that surgeons should firmly embrace and study this new technology. For most teams, nonetheless, interventional or hybrid procedures are not recommended in premature infants, nor for those with low body weight or with the true Swiss-cheese septum.

Author's contribution

Author's name	Concept/ design	Data analysis/ interpretation	Drafting article	Critical revisi
Ujjwal Kumar Chowdhury	?	?	?	?
Robert H. Anderson	?	?	?	?
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Lakshmi Kumari Sankhyan	?	?	?	?
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Figure Legends

Figure 1: Schematic diagram of the location of defects in the apical muscular septum.

Figures 2A, 2B: Panel A: Transthoracic echocardiographic image with color flow showing multiple defects (red arrows) in the apical muscular septum (asterisk) which demonstrate a left to right shunt from left ventricle (LV) to right ventricle (RV). Panel B: Left ventricular angiogram in left anterior oblique view with cranial angulation demonstrating multiple oblique defects (asterisks) representing a Swiss-cheese septum.

Figures 3A-3F: Volume rendered (A) and oblique coronal (B) image showing the ventricular septum en-face and revealing the presence of multiple defects (various colored arrows). Short axis images at the mid ventricular level (C and D), at the ventricular apex (E) and four chamber image (F) profile the various defects (corresponding colored arrows).

Figures 4A-4F: Volume rendered (A) and oblique coronal (B) image showing the ventricular septum en-face and demonstrating the presence of multiple defects (various colored arrows). Oblique axial images at various levels (C to F) profile the respective defects (corresponding colored arrows).

Figures 5A-5F: Surgical photograph showing step-by-step passage of a thick No.3 black braided SUTUPAK silk (Ethicon, Johnson and Johnson Pvt. Ltds., USA) ligature (L) through the additional muscular ventricular septal defect (VSD) in a child with multiple discrete muscular septal defects. 5A: shows the small aorta (AO), distended right ventricle (RV), and tense hypertensive pulmonary artery (PA); 5B, 5C: a right angle forcep (F) is passed through the additional ventricular septal defect, and kissed against a DeBakey forcep which is inserted through the larger VSD. The tip of silk ligature is grasped and looped through the

additional septal defect. Traction on the silk ligature facilitated exposure of the margins of septal defect; 5D, 5E: two ventricular septal defects are closed separately using Dacron knitted polyester patches (BAARD® SAUVAGE® Filamentous, BARD peripheral vascular Inc, Temple, AZ, USA) and 5-0 interrupted pledgeted mattress sutures; 5F: shows the separately closed ventricular septal defect.

Figures 6A, 6B: Schematic drawing of Kitagawa's technique of insertion of an oversized patch on the left ventricular side of the defect.

Figures 7A, 7B: Mace's technique of surgical closure of the Swiss-cheese septum using a single large patch on the right ventricular side with intermediate fixation to prevent septal bulging.

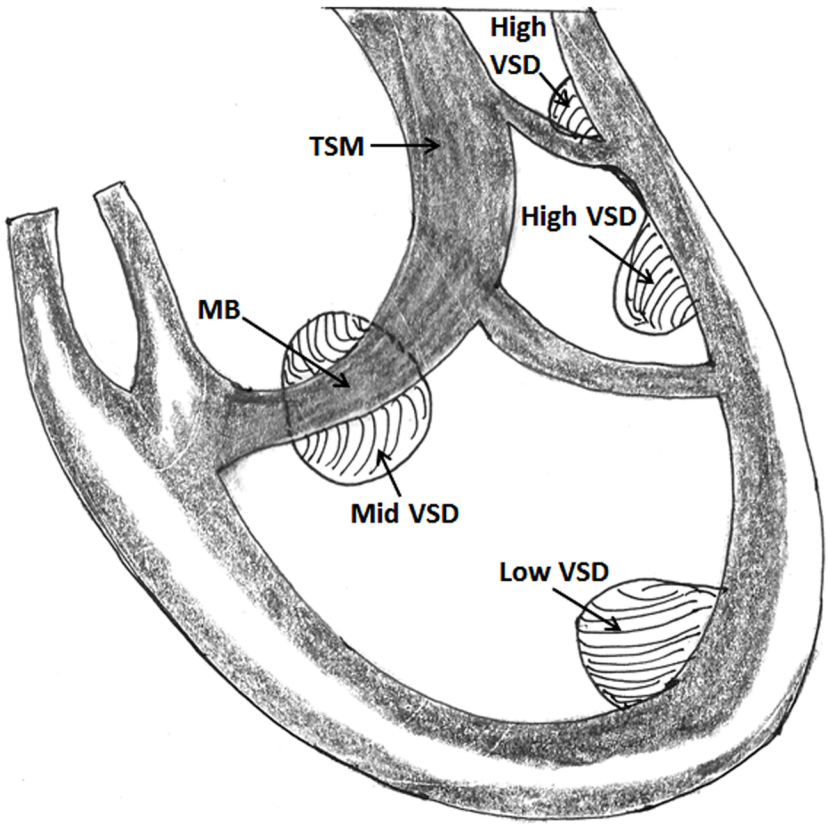
Figure 8: Ootaki's technique of sandwiching the apical defects between the two polyester felt patches.

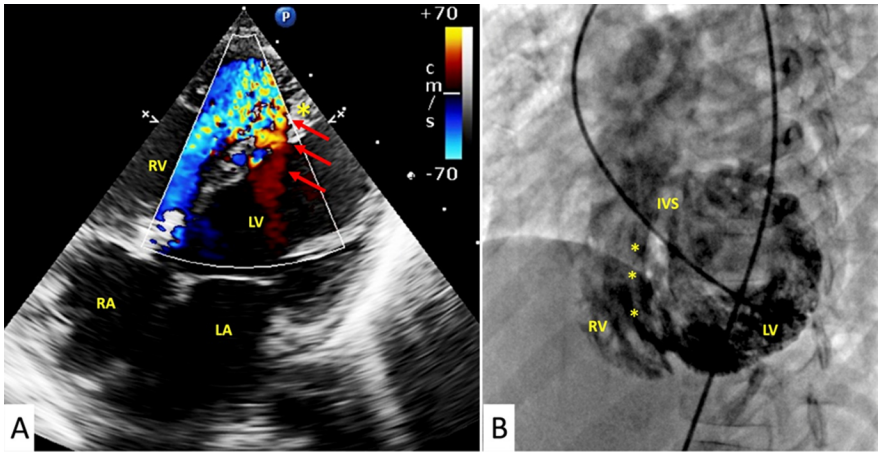
Figure 9: Kitagawa's technique of closure of multiple apical defects, sandwiching the septum with the anterior wall of the ventricle.

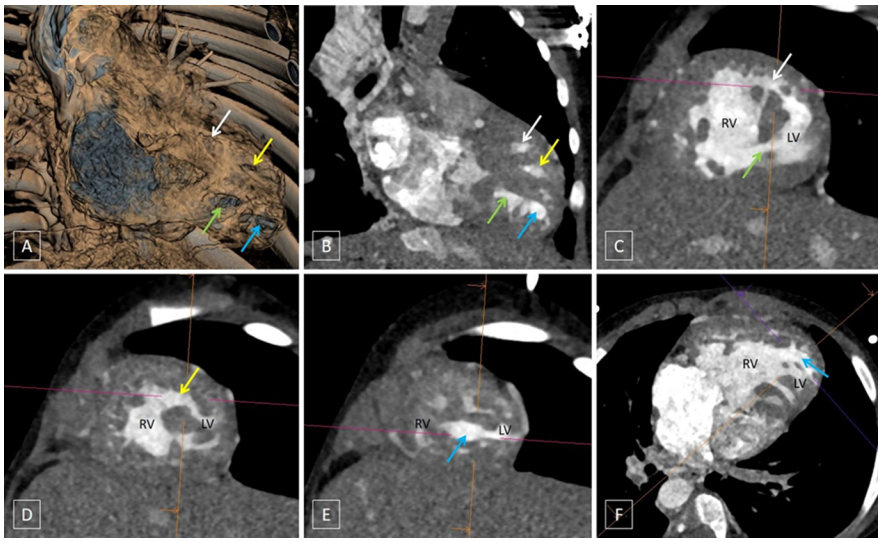
Figures 10A-10C: Surgical closure of apical defects through an apical right ventriculotomy.

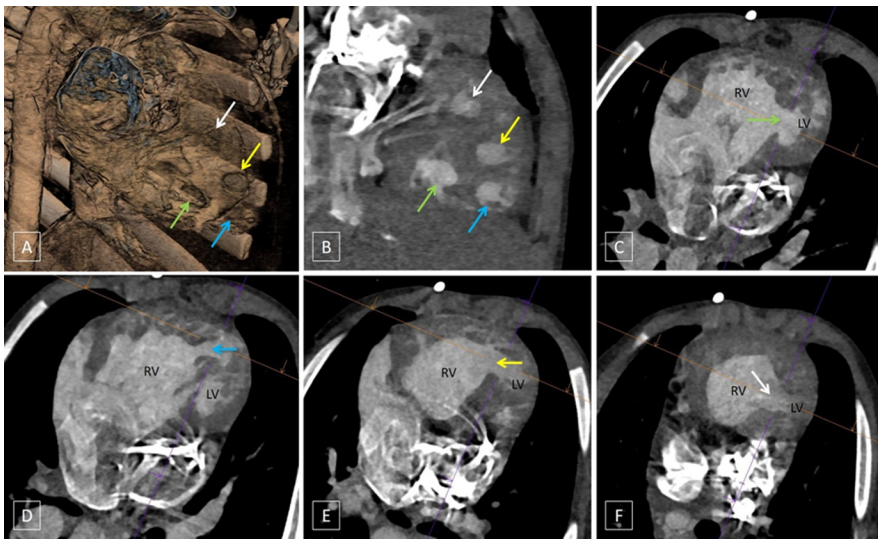
Figure 11: Surgical approach to apical defects through a modified apical left ventriculotomy.

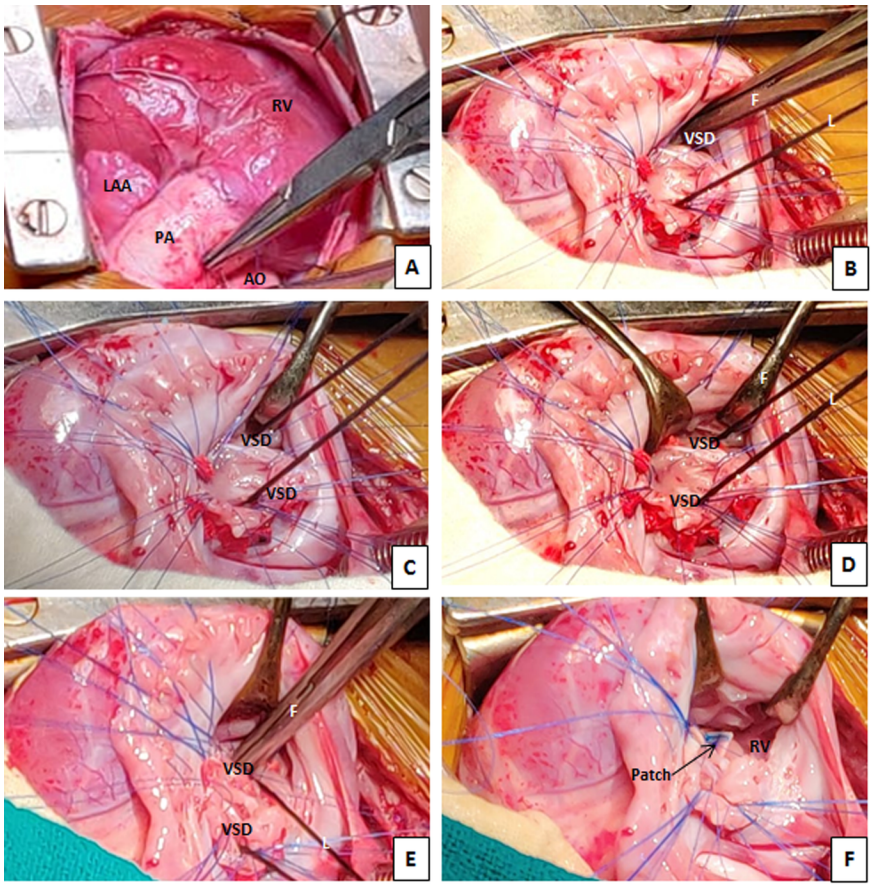
Figure 12: Wu's two-patch and right ventricular apex exclusion technique of repair of the Swiss-cheese septum.

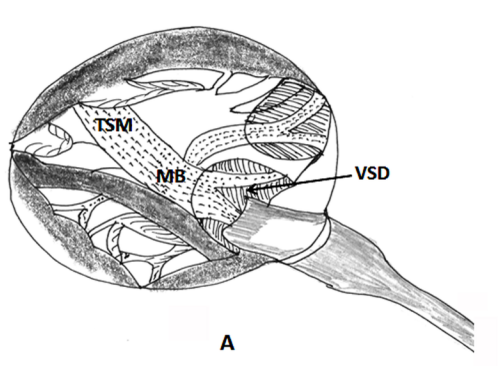


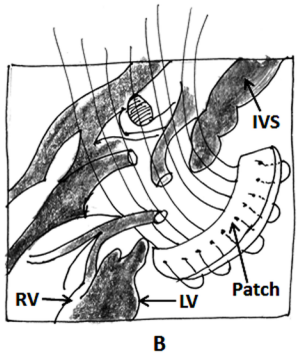


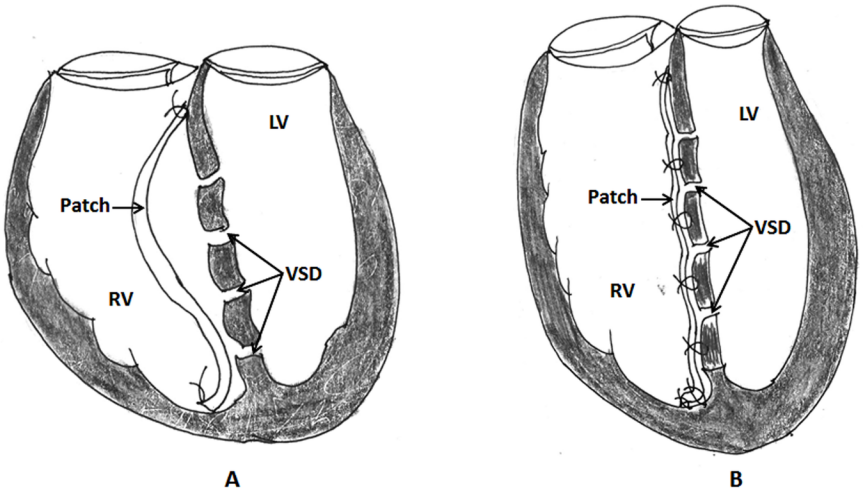


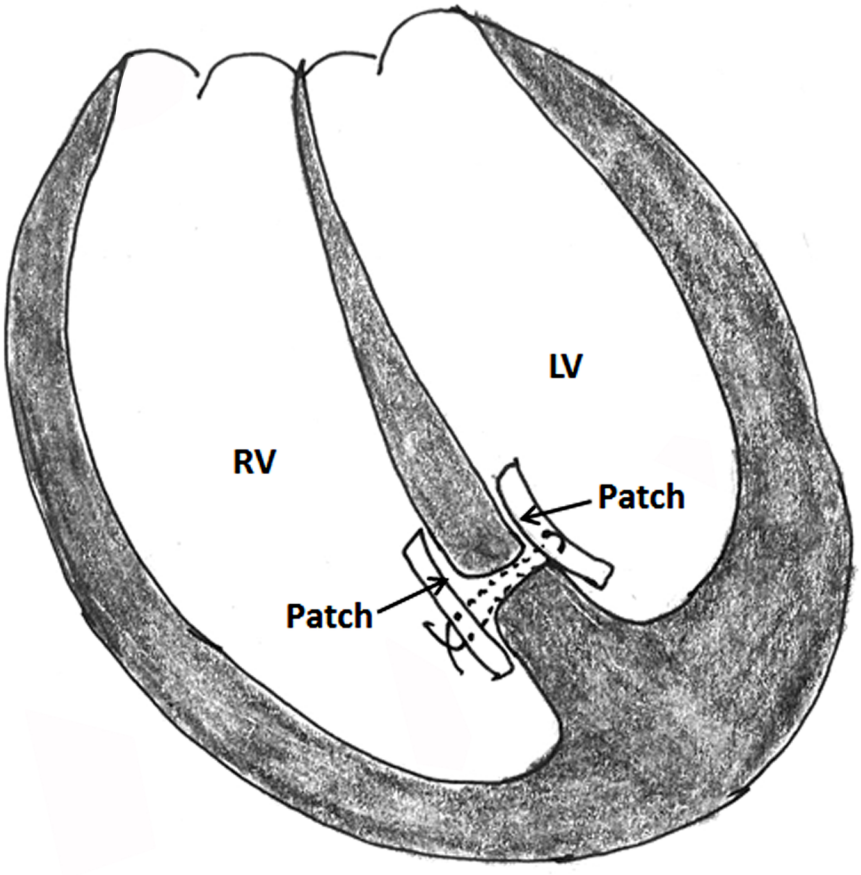


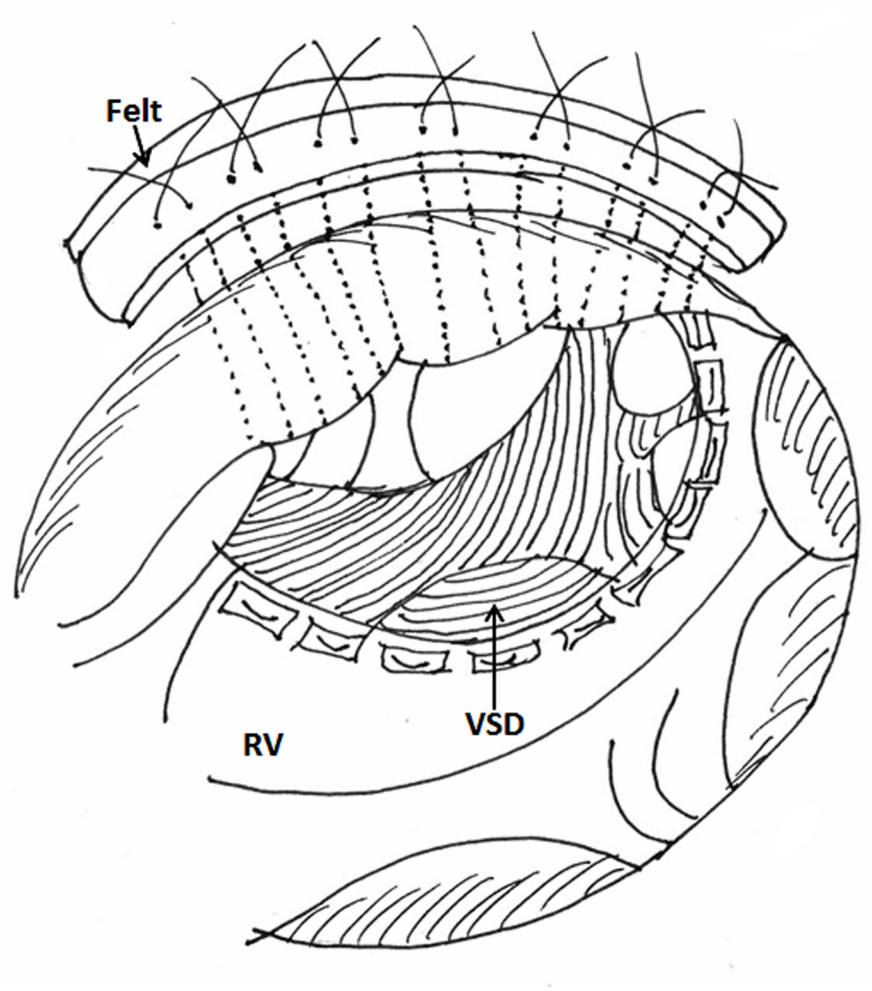


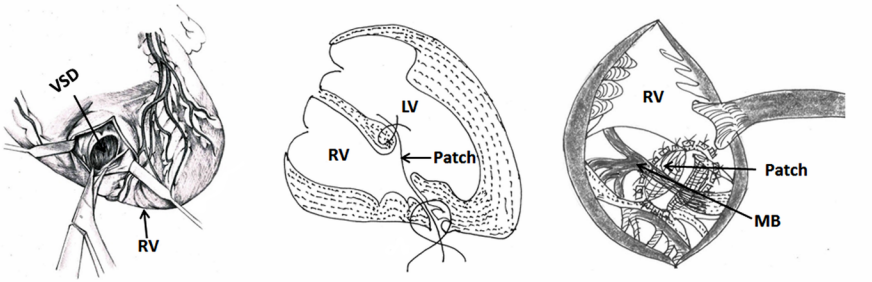












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