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Role of Interventional Cardiology in the Treatment of Neonates - Part II - Balloon Angioplasty / Valvuloplasty

By P. Syamasundar Rao, MD

"Role of Interventional Cardiology in the Treatment of Neonates – Part II" is the second in a series of three articles by P. Syamasundar Rao, MD, Professor of Pediatrics and Medicine, Director, Division of Pediatric Cardiology, University of Texas-Houston Medical School. The first article was in September, and third article will appear in the November issue. The September and October issues are on the website in PDF files.

INTRODUCTION

There are many catheter-based interventional procedures (Table I) that are useful in the treatment of a neonate. In Part I [1] of this series of articles, non-surgical atrial septostomy was discussed. In the current presentation, balloon angioplasty/valvuloplasty for critical cardiac obstructive lesions will be reviewed, leaving the remaining items for discussion in the third part.

Until late 1970s, the entire transcatheter armamentarium in pediatric cardiac practice was limited to atrial septostomy. In 1980s, Gruntzig's balloon angioplasty technique [2] was extended to treat pulmonary valve stenosis[3], native aortic coarctation [4], post-surgical aortic recoarctation [5], aortic valve stenosis [6,7], mitral valve stenosis [8], subaortic membrane[9], branch pulmonary artery stenosis [10], pulmonary vein stenosis [11], stenotic bioprosthetic valves [12,13] and other obstructive vascular lesions [14-19]. Neonatal applications followed [5,20-23].

CRITICAL PULMONARY STENOSIS

The term critical pulmonary stenosis is applied when pulmonary valve obstruction results in supra-systemic right ventricular systolic pressure with resultant right to left shunt at the atrial level; these infants often have ductal-dependent pulmonary circulation. Following initiation of PGE1 infusion, percutaneous balloon pulmonary valvuloplasty should be undertaken. If the obstruction is less severe, the procedure may be performed at a later time, beyond the neonatal period.

Rubio-Alvarez and Limon-Lason [24,25] utilized a modified ureteral catheter to produce relief of pulmonary valve stenosis in the early 1950s. Semb and associates in 1979 [26] forcefully withdrew an inflated Berman angio-

Table I. Catheter Interventional Techniques Used in the Neonate

- Non-surgical atrial septostomy
- Balloon angioplasty/valvuloplasty
- Radiofrequency perforation of atretic pulmonary valve
- Transcatheter occlusion of shunts
- Stents

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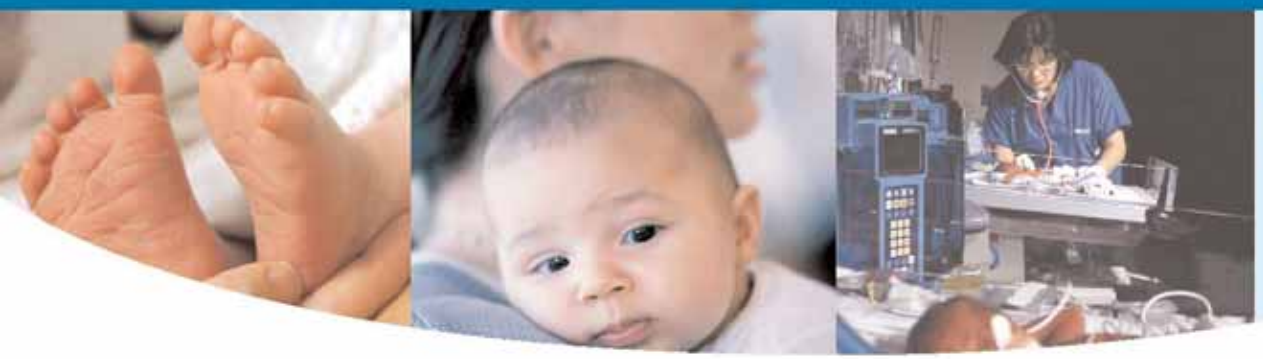

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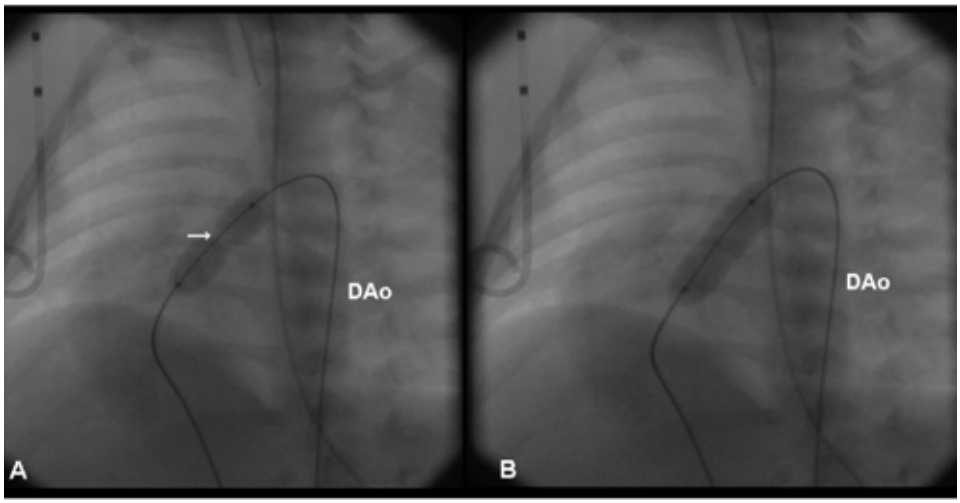

Figure 1. Selected cineflorographic frames in a sitting-up (15^0 LAO and 35^0 cranial) view demonstrating an angioplasty balloon across the stenotic pulmonary valve with waisting of the balloon (arrow) during the initial phase of balloon inflation (A); the waist has completely disappeared with further balloon inflation (B). Note the guide wire is passing through the ductus into the descending aorta (DAo).

graphic catheter across a stenotic pulmonary valve, causing relief of obstruction. In 1982, Kan et al[3] extended the techniques developed by Dotter[27], Gruntzig [2] and their associates and balloon dilated stenotic pulmonary valve with a double-lumen catheter carrying a non-elastic balloon [3]. This type of static balloon dilatation is what is used today and has become a standard therapy for pulmonary valve stenosis. The technique was initially used in neonatal critical pulmonary stenosis by Tynan et al [20]; subsequently several groups of cardiologists [28-33] applied balloon valvuloplasty to treat the neonates with success.

Balloon Pulmonary Valvuloplasty

Prostaglandin E1 infusion is begun to augment the pulmonary blood flow and to improve systemic arterial saturation. This is followed by cardiac catheterization and biplane (sitting-up and lateral views) right ventricular cineangiography, performed percutaneously via the right femoral vein. The pulmonary valve annulus is measured in both views and averaged. Both the angiographic and echocardiographic measurements are used to determine the pulmonary valve annulus diameter. A right coronary artery (Cordis), angled Glidecath (Meditech) or cobra (Cook) catheter, as per the operator's preference is placed in the right ventricular outflow tract and a floppy-tipped coronary guide wire is advanced across the pulmonary valve and then into the branch pulmonary arteries or into the descending aorta via the ductus (the latter is preferred). The catheter is then advanced across the pulmonary valve into the descending aorta. The guide wire is then exchanged with a guide wire that is suited to position the balloon dilatation catheter. While the initial recommendations were to use a balloon that is 1.2 to 1.4 times the pulmonary valve annulus, more recent recommendations are that we strive for a balloon/annulus ratio of 1.2 to 1.25 [34,35]. The selected balloon angioplasty catheter is advanced over the guide wire, but within the percutaneous sheath and positioned across the pulmonary valve. The bony landmarks, namely, ribs, sternum or other fixed land marks, are used for this purpose. A frozen video frame of the right ventricular cineangiogram displayed on the screen is helpful in this regard. The balloon is inflated with diluted contrast material (1 in 4) using any of the commercially available inflators, while monitoring the pressure of inflation. The inflation pressure is increased up to the manufacturer-recommended pressure or until disappearance of the balloon waist (Figure 1). If the balloon is not appropriately centered across the pulmonary valve, the position of the catheter is readjusted and balloon inflation repeated. Once satisfactory balloon inflation is achieved, one additional balloon inflation may be performed, as per the operator's preference. The balloon catheter is removed, leaving the guide wire in place, over which a multipurpose catheter is positioned which is used to record post-balloon pullback pressures. This is followed by right ventricular angiography.

Sometimes it may not be possible to advance an appropriately-sized balloon catheter across the severely stenotic pulmonary valve. In such instances, smaller 3 to 6 mm diameter balloon catheters may be used initially to predilate, then, use a larger, more appropriately-sized balloon catheter (Figure 2).

On rare occasions, especially with hypoplastic right ventricle or in the presence of severe infundibular obstruction, it may not be feasible to cross the pulmonary valve anterogradely. In such situations, the guide wire and balloon catheter may be

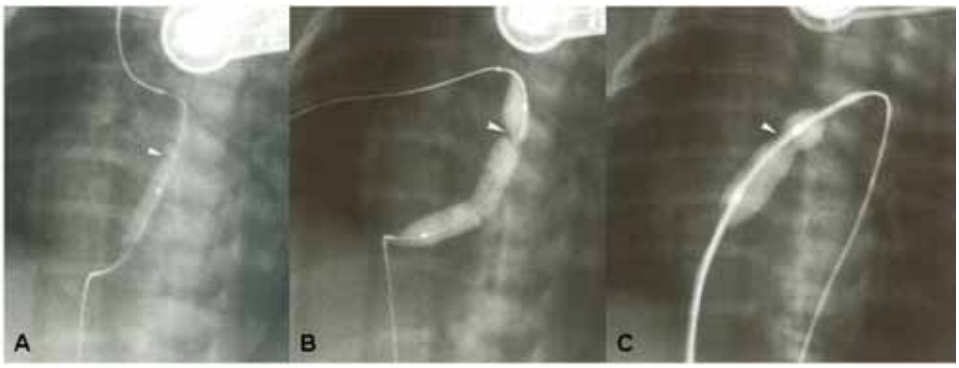

Figure 2. Selected cineflorographic frames in a sitting-up view illustrating use of progressively larger balloons in a one-day-old baby with critical pulmonary stenosis. A coronary guide wire was positioned across the pulmonary valve and a 3.5-F catheter carrying 4 mm diameter balloon was used to dilate the pulmonary valve (A); this is followed by a 6 mm (B) and an 8 mm (C) diameter balloons. Waisting of the balloons in the initial phases of balloon dilatation are shown. Further inflation of the balloons resulted in abolition of the waiting (not shown).

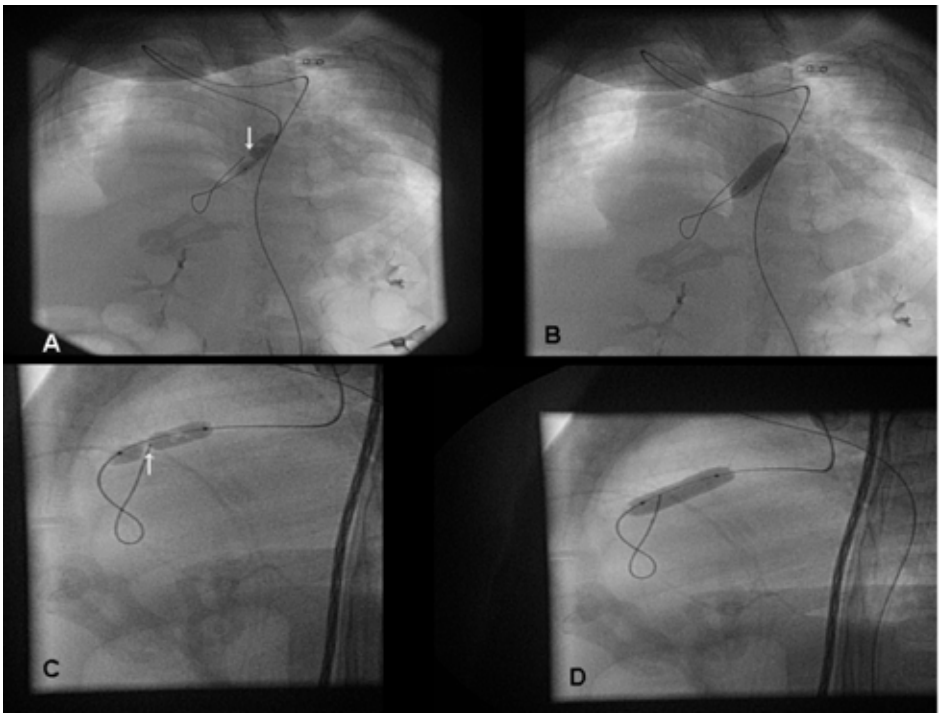

Figure 3. Selected cineflorographic frames in sitting-up and lateral views demonstrating an angioplasty balloon across the stenotic pulmonary valve with waisting of the balloon during the initial phase of balloon inflation (A & C); the guide wire and balloon angioplasty catheter were introduced retrogradely from the aorta through the ductus and pulmonary artery into the right ventricle across the pulmonary valve. The waist has completely disappeared with further balloon inflation (B & D).

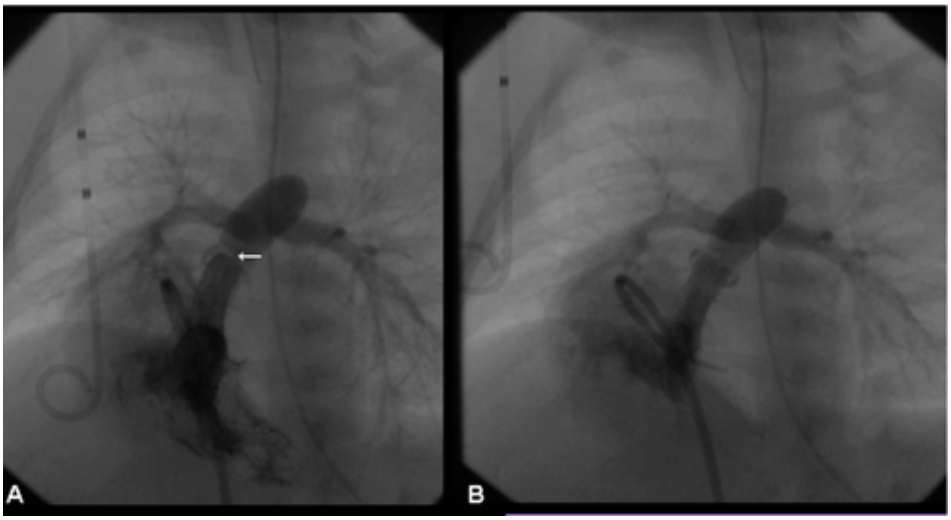

Figure 4. Selected right ventricular cineangiographic frames (from the neonate illustrated in figure 1) in a sitting-up view prior to (A) and immediately after (B) balloon pulmonary valvuloplasty; note the thin jet of contrast (arrow) across the thickened and domed pulmonary valve (A) prior to dilatation. The jet width has markedly increased following valvuloplasty (B).

positioned across the pulmonary valve retrogradely from the aorta through the ductus and pulmonary artery into the right ventricle across the pulmonary valve; an example is shown in Figure 3.

Results

Immediate success, as judged by decrease in pulmonary valve gradient, right ventricular peak systolic pressure and right ventricle to aortic systolic pressure ratio and improved flow across the right ventricular outflow tract by angiography (Figure 4) has been noted [20,28-33]. After a successful balloon procedure, extubation and discontinuation of PGE1 infusion are possible in the majority of patients. However, some neonates do not tolerate stopping prostaglandin infusion, developing severe arterial desaturation. As many as 25% patients [30,31] may require prostaglandin infusion for 3 to 21 days after balloon dilatation. Right to left shunt across the patent foramen ovale, presumably related to poor right ventricular compliance, is the reason for hypoxemia. Some of these infants may require prolonged infusion of PGE1 or creation of an aorto-pulmonary shunt to maintain adequate pulmonary flow. Placement of ductal stent is an alternative [36] but, the experience with ductal stents is limited.

Several studies demonstrated favorable intermediate-term outcome, paralleling surgical results [30,31,37]. For example, Tabatabaei et al [31] showed remodeling of the right ventricle and appropriate growth of all three component parts of the right ventricle. The residual gradients across the pulmonary valve (15 ± 9 mmHg) at follow-up six months to 8 years after balloon valvuloplasty were low. While the results of this approach are reasonably good, the need for re-intervention is higher (25%) than that in older children (8 to 10%), to address the complications associated with the procedure, hypoxemia due to right-to-left interatrial shunt secondary to decreased right ventricular compliance, residual obstruction or associated defects.

CRITICAL AORTIC STENOSIS

Very severe aortic valve stenosis with a high gradient, congestive heart failure or ductal-dependent systemic circulation may be labeled as critical obstructions. Balloon aortic valvuloplasty is an acceptable alternative to surgery in the treatment of critical aortic stenosis in the neonate [38,39]. After administering supportive therapy, including initiation of PGE1 infusion, if necessary, percutaneous balloon aortic valvuloplasty should be performed. Balloon aortic valvuloplasty may be performed at a later time, beyond neonatal period, in less severe obstructions.

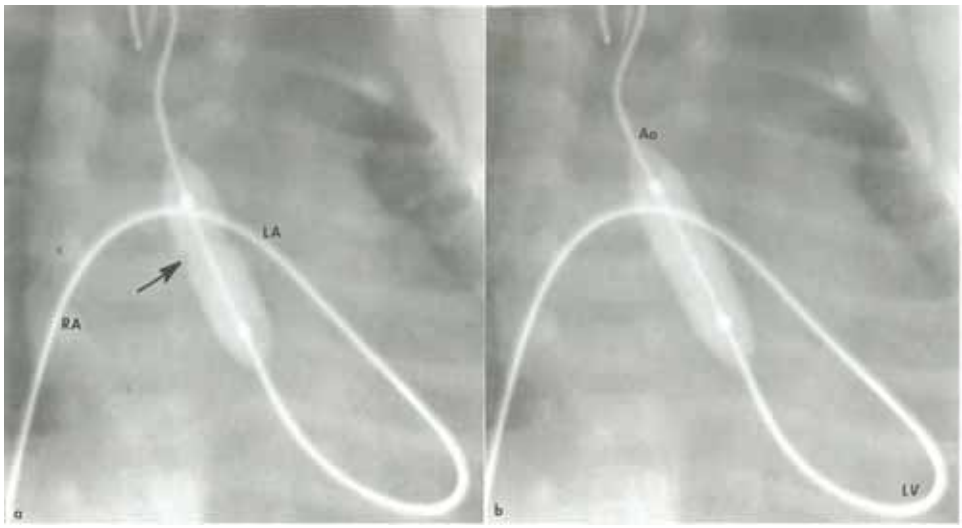

Figure 5. Selected cinefluorographic frames demonstrating the position of the balloon across the aortic valve introduced anterogradely from the umbilical vein, right atrium (RA), left atrium (LA), left ventricle (LV) and aorta (Ao). Note the waist (arrow) of the balloon (a) which was completely abolished after further inflation of the balloon (b).

Following successful application of Gruntzig's technique [2] to aortic coarctation [4,5,40] and pulmonary valve stenosis [3], Lababidi and his associates [6,7] utilized the technique of balloon dilatation to relieve aortic valve stenosis. His group further extended the technique to neonatal aortic valve stenosis [21]. Initially retrograde femoral arterial route was used for balloon aortic valvuloplasty [21,23,38,39]. Because of potential for injury of the femoral artery, alternative routes, namely, carotid [41], axillary [42], umbilical [43], or subscapular [44] artery and anterograde femoral venous [45,46] approaches for accomplishing the procedure have been attempted. More recently, anterograde, transumbilical venous route [47,48] has been introduced. Our preference is to use anterograde, transumbilical venous route initially and if that is not successful, retrograde, transumbilical arterial route is attempted, followed by carotid artery cutdown. Anterograde femoral venous and retrograde femoral arterial routes are the other available options.

Transumbilical Venous Balloon Aortic Valvuloplasty [47]

The umbilical venous catheter is exchanged with a 5-F sheath and the sheath tip positioned in the low right atrium. After obtaining the usual catheterization data including left ventricular angiography, the diameter of the aortic annulus is measured. A 4-F multi-A2 catheter (Cordis) with a slightly curved tip (special order) is introduced through the umbilical venous sheath and advanced into the left atrium across the patent foramen ovale and then into the left ventricle across the mitral valve. With the help of a J-shaped and/or a straight, soft-tipped 0.035-in Benston guide wires (Cook), the catheter is advanced into the aorta and the catheter tip positioned in the proximal descending aorta. At this juncture, the guide wire is exchanged with a 0.025-in J-tipped Amplatz extra stiff wire (Cook). A 6 to 8 mm diameter ultrathin (Meditech) or Tyshak II (Braun) balloon angioplasty catheter is advanced over this guide wire anterograde into the right atrium, left atrium, left ventricle and aorta, while maintaining a wide loop of the wire in the left ventricle. The balloon diameter should be 80 to 100% of the aortic valve annulus. Once the balloon is positioned across the aortic valve, the balloon is inflated with diluted contrast material (1 in 4) up to the manufacturer's recommended balloon inflation pressure, or until the waist of the balloon is abolished (Figure 5). Then the balloon dilatation catheter is removed and replaced with a 4-F multi-A2 (Cordis) catheter and its tip positioned in the aorta. After performing aortic root angiography, a pressure pullback recording across the aortic valve is undertaken. Left ventricular angiography is optional. Heparin is administered during the procedure to maintain adequate anticoagulation and Vancomycin for antibiotic coverage prophylactically because of extensive manipulation of the umbilical area during the procedure.

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Sometimes, despite multiple attempts, the tip of the guide wire may not be maneuvered into the descending aorta, or the balloon catheter positioned across the aortic valve. In such situations gooseneck micro-snare (Microvena, White Bear Lake, MN) is introduced through the 4-F multi-A2 catheter (Cordis) in the descending aorta via the umbilical artery. The snare

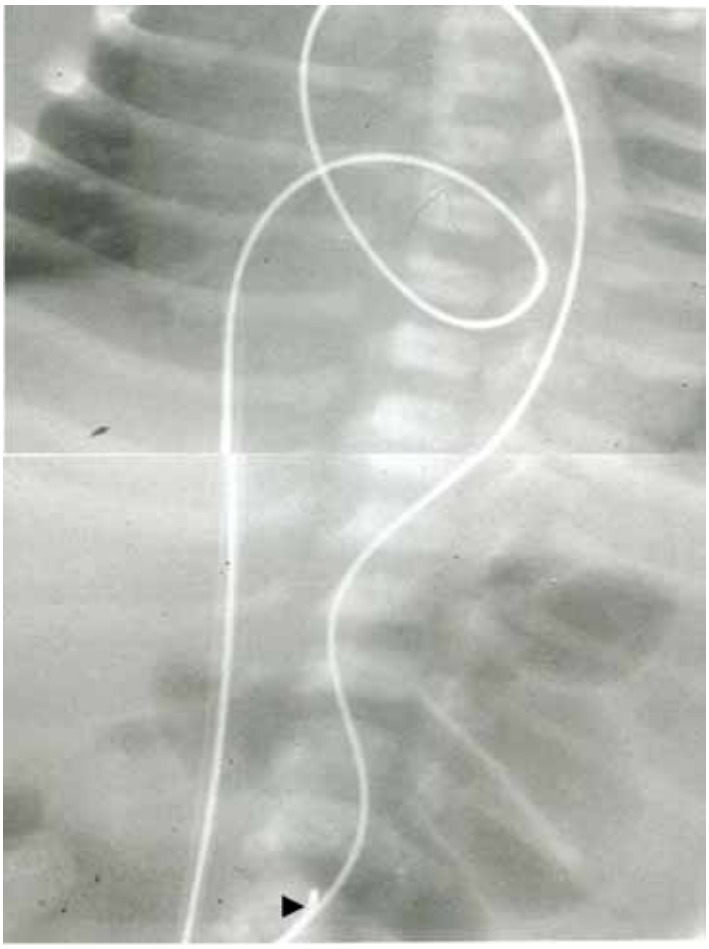

Figure 6. Selected cinefluorographic frames showing guide wire rail from the umbilical vein, right atrium, left atrium, left ventricle, ascending aorta and descending aorta. Note the snare (arrow-head at the bottom) holding the wire.

and the catheter are advanced into the aortic arch and the tip of the anterogradely placed 0.025-in Amplatz guide wire is snared and brought down into the descending aorta and held in place (Figure 6). Thus, an umbilical venous-to-umbilical arterial wire "rail" is established. With a gentle traction on the umbilical artery component of the rail and while maintaining the wire loop in the left ventricle, the balloon dilatation catheter may easily be advanced anterogradely across the aortic valve and balloon valvuloplasty performed. Once the procedure is successfully performed, the guide wire is released from the snare, and withdrawn from the umbilical vein; the presence of a catheter over the entire course of the guide wire within the heart protects the intra-cardiac structures from injury [47].

Trnasumbilical Arterial Balloon Aortic Valvuloplasty

The umbilical arterial catheter is exchanged with a 4-F multi-A2 catheter (Cordis) and positioned in the ascending aorta. A floppy-tipped coronary guide wire or a 0.035-in straight Benston guide wire (Cook), is advanced into the left ventricle across the aortic valve and the catheter advanced over the wire into the left ventricle and a left ventricular angiogram performed. Sometimes it may be difficult to cross the aortic valve and in such situation a number of other catheters and wires may have to used, as per the operator's choice. The remaining procedure is similar to that described in the preceding section. With the availability of balloon catheters that track well (for example Tyshak II), silicone-coated catheters, initially described for use in transumbilical arterial approach [43], are no longer necessary.

Retrograde Femoral Arterial Balloon Aortic Valvuloplasty

In this technique, a #4-F sheath is placed percutaneously in the femoral artery and a # 4-F multipurpose catheter is advanced into the ascending aorta and the remaining procedure is similar to transumbilical arterial procedure described in the preceding section. An example of balloon angioplasty catheter across the aortic valve is shown in Figure 7.

Balloon Aortic Valvuloplasty via Carotid Artery

Cut-down and isolation of the right carotid artery is performed by the cardiovascular surgery colleagues, and a #4-F sheath is placed via a purse string suture. The remaining procedure is similar to transumbilical arterial procedure described in the preceding section. Because of straight course of the catheter, it is much more easy to position the catheter/guide wire into the left ventricle across the aortic valve [41]. Following balloon aortic valvuloplasty, the catheters and sheaths are removed and the arteriotomy is closed by tightening the purse-string suture and the skin incision sutured; this may be performed either by the cardiovascular surgeon or the pediatric cardiologist depending upon the institutional practices.

Anterograde Femoral Venous Balloon Aortic Valvuloplasty

The femoral venous access is achieved with # 5-F sheath. The procedure is essentially similar to that described in the section on "Transumbilical venous balloon aortic valvuloplasty" except for the site from which the catheters are introduced.

Results

The results of balloon aortic valvuloplasty were tabulated elsewhere {49]; most authors found it useful in the management of sick babies with critical aortic stenosis with improvement in gradient and clinical status. However, poor results were found in 38 to 81% patients. The vast majority of failures appear to be related to either technical difficulties or are secondary to poor anatomic substrate, namely aortic valve dysplasia, aortic valve annular hypoplasia, hypoplastic left ventricle, mitral valve abnormalities and endocardial fibroelastosis. With the availability of miniaturized balloon angioplasty catheters and other materials, the technical difficulties have largely been eliminated.

Careful comparison of anterograde and retrograde techniques by Magee and associates [50] suggested similar results in terms of feasibility and gradient reduction. But, the retrograde approach resulted in higher mortality, more severe aortic insufficiency and greater incidence of arterial complications than with anterograde approach. They concluded that anterograde approach should be considered for neonates with severe aortic stenosis. More recent evaluation of this issue suggests that large balloon/annulus ratios are likely to be causing the aortic insufficiency, rather than route of balloon catheter entry.

Comparison between surgical and balloon methods has been made, but the issue is not settled [39,51]. However, based on the

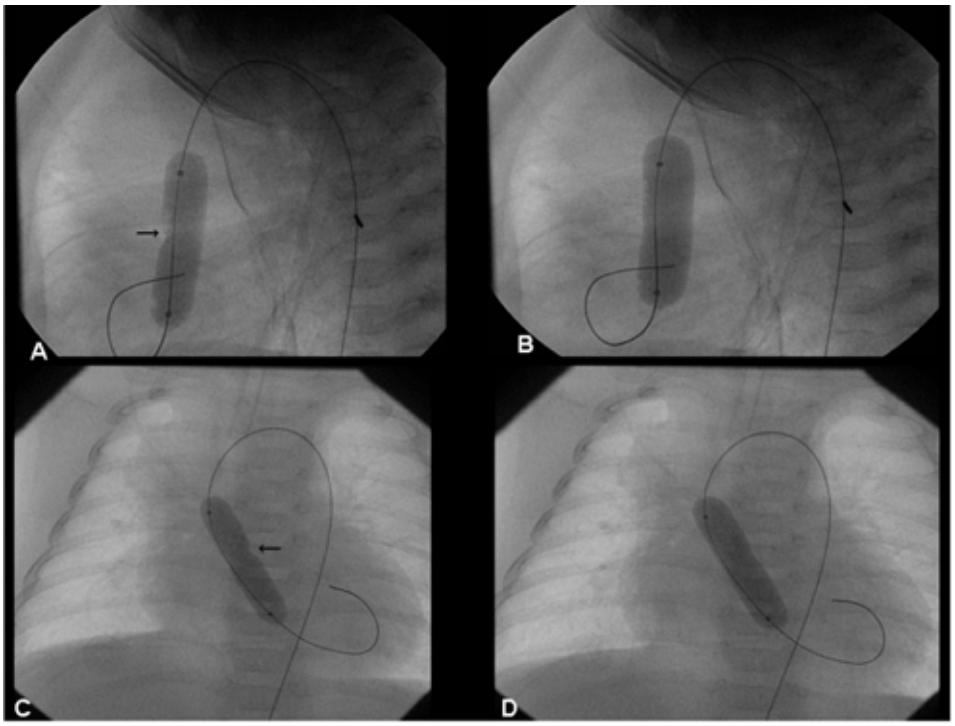

Figure 7. Selected cineflorographic frames in lateral (A & B) and anterio-posterior (C & D) views demonstrating an angioplasty balloon across the stenotic aortic valve with waisting of the balloon (arrows) during the initial phase of balloon inflation (A & C); the waist has completely disappeared with further balloon inflation (B & D).

available data, balloon valvuloplasty appears attractive in view of high surgical mortality at initial or repeat surgical aortic valvotomy in the neonate with critical aortic stenosis.

COARCTATION OF THE AORTA

Neonates with severe aortic coarctation causing congestive heart failure are candidates for intervention. An open ductus arteriosus may sometimes permit bypassing the obstruction and make it difficult to evaluate the degrees of obstruction should the ductus close spontaneously. Surgical intervention has been the main approach to treat these babies since first description of surgery by Crafoord and Nylin [52] and Gross and Hubbard [53] in mid 1940s. More recently, balloon angioplasty techniques have been utilized in the management of aortic coarctation.

Gruntzig's technique of balloon angioplasty[2] was adopted by Sos [40], Singer,[5] and Sperling[4] and their associates, to enlarge coarcted aortic segments in a postmortem specimen, postsurgical recoarctation and native coarctation respectively. This is followed by reports of successful use of this technique by several groups of investigators, including our own group. Because ofthe high rate of recurrence seen in neonates [54-57] and the association of varying degrees of hypoplasia of the transverse aortic arch and isthmus in coarctations presenting in the neonatal period, most groups of cardiologists prefer surgical treatment at this age.

However, balloon angioplasty in neonates and young infants has been very useful in critically ill babies, particularly in those in whom avoidance of anesthesia or aortic cross-clamping required for surgery is beneficial in the overall management. Such special circumstances include infants with shock-like syndrome [58], severe myocardial dysfunction and hypertensive cardiomyopathy[59], prior spontaneous cerebral hemorrhage [60] and biliary atresia awaiting liver transplantation [60,61].

Balloon Coarctation Angioplasty

The conventional retrograde femoral arterial approach for balloon angioplasty of aortic coarctation may produce arterial damage especially in neonates. Therefore, umbilical artery approach [58,62] and anterograde approach transvenously [63] via a transposed aorta or through the ventricular septal defect, when feasible, should be undertaken. When a femoral artery is catheter entry site, low profile balloons (for example Tyshak II balloons) that can be introduced through 4-F sheaths should be utilized; even Mini-Tyshack via 3-F sheaths may be appropriate [56].

If balloon angioplasty is contemplated, PGE1 should not be started since an open ductus may interfere with the effectiveness of balloon angioplasty. Cardiac catheterization and selective cineangiography are performed to confirm the clinical diagnosis, to exclude other cardiac defects and to assess suitability for balloon angioplasty. Once balloon angioplasty is decided upon a # 4-F multi-A2 (Cordis) catheter is introduced into the femoral artery percutaneously and is positioned across the aortic coarctation. If umbilical arterial route is used, the umbilical arterial catheter is exchanged with a 4-F multi-A2 catheter (Cordis) and positioned across the aortic coarctation. A 0.021 to 0.025 inch J-tipped guide wire is passed through the catheter into the ascending aorta and the tip of the wire positioned in the ascending aorta; If transvenous (femoral vein) anterograde approach is used a 4-F multi-A2 catheter (Cordis) is advanced via the transposed aorta or through the ventricular septal defect into the descending aorta across the coarctation and an appropriate-sized guide wire positioned in the descending

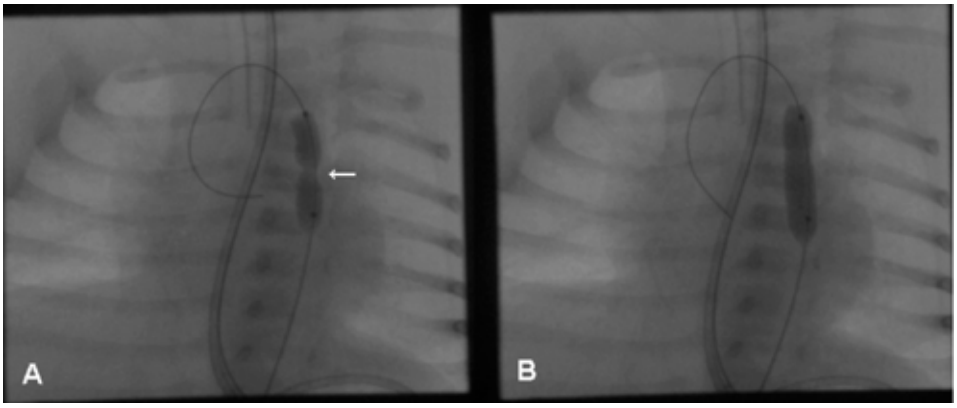

Figure 8. Selected cineflorograpic frames in 20^0 left anterior oblique projection demonstrating an angioplasty balloon across the aortic coarctation with waising (arrow) of the balloon (A) during the initial phases of balloon inflation. With further balloon inflation, the waist has completely disappeared (B).

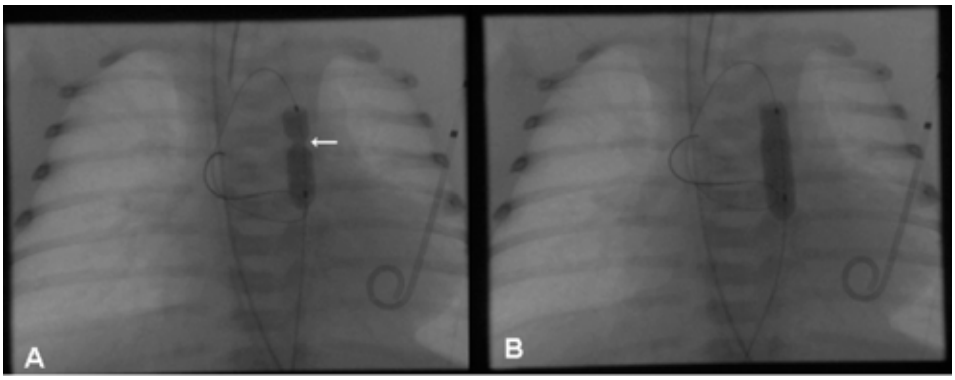

Figure 9. Selected cineflorographic frames in 20^0 left anterior oblique projection demonstrating balloon angioplasty of aortic coarctation using a 3-French system. The waising (arrow) of the balloon in A and its disappearance in B are shown.

aorta distal to the coarctation. The size of the balloon chosen for angioplasty is two or more times the size of the coarcted segment, but no larger than the size of the descending aorta at the level of the diaphragm, as measured from a frozen video recording. We usually choose a balloon that is midway between the size of the aortic isthmus (or transverse aortic arch) and the size of the descending aorta at the level of diaphragm. If there is not an adequate relief of obstruction (pressure gradient reduction to <20 mmHg and angiographic improvement), a balloon as large as the diameter of the descending aortic at the level of diaphragm is chosen for additional dilatation. The selected balloon angioplasty catheter is positioned across the aortic coarctation and the balloon is inflated (Figure 8) with diluted contrast material to approximately three to five atmospheres of pressure or higher, depending upon the manufacturer's recommendations. Monitoring pressure of

inflation via any of the commercially available pressure gauges is recommended. The balloon is inflated for a duration of 5 seconds. A total of two to four balloon inflations are performed 5 minutes apart. Aortography and measurement of pressure gradients across the coarctation site are performed. Because of concern for femoral artery injury, a 3-French system using mini-Tyshak balloon catheters (Braun) may be worthwhile considering (Figure 9).

Results

Reduction of peak systolic pressure gradients across the coarctation, increase in angiographic diameter of the coarcted segment (Figure 10), improvement of congestive heart failure and hypertension following balloon angioplasty, reviewed in detail elsewhere [22,60,64-66], have been observed by most workers. As pointed out earlier, the problem in the neonate is high rate of recurrence [54-57].

POST-SURGICAL AORTIC RECOARCTATION

Development of recoarctation following surgery is independent of the type of surgical repair; it has been observed following resection with end-to-end anastomosis, subclavian flap angioplasty, prosthetic patch repair, subclavian artery turn-down procedure and interposition tube grafts [67]. The younger the child at surgery, the higher is the chance for recoarctation.

Gruntzig's technique was applied to post-surgical coarctation by Singer and his associates[5]; this is followed by its use by others [68-70]

There is general agreement among cardiologists and surgeons that balloon angioplasty is the treatment of choice for post surgical aortic coarctations. However, the need for performing balloon angioplasty for recoarctation in the neonatal period is infrequent. The technique of balloon angioplasty for the management of post-surgical recoarctations is similar to that described above for native coarctation. The immediate and follow-up results of balloon angioplasty for post surgical recoarctation are essentially similar to those of native coarctations and have been reviewed in detail elsewhere [64,67,71].

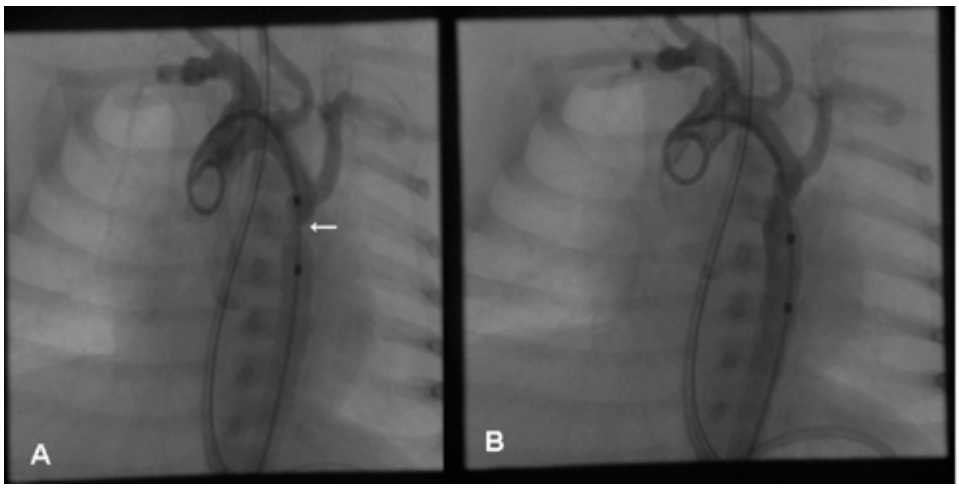

Figure 10. Selected aortic cineahgiographic frames in 20^0 left anterior oblique projection demonstrating narrowed coarcted aortic segment (arrow) prior to balloon angioplasty (A) which increased following balloon angioplasty (B).

PULMONARY STENOSIS ASSOCIATED WITH COMPLEX CONGENITAL HEART DEFECTS

In cyanotic congenital heart defects obstruction to pulmonary blood flow by stenotic or atretic pulmonary valve is an integral part of the cardiac malformation causing right-to-left shunt. The most common type of defect in this group is Tetralogy of Fallot. Other defects include transposition of the great arteries, double outlet right (or left) ventricle, single ventricle, tricuspid atresia, ventricular inversion (corrected transposition of the great arteries) and other types of univentricular hearts, all with nonrestrictive interventricular communication and severe pulmonary valve obstruction. These patients usually present with symptoms in the neonatal period or early in infancy. The degree of cyanosis and the level of hypoxemia determine the symptomatology. Some cyanotic heart defects with pulmonary oligemia can be surgically treated. Total surgical correction may not be possible in some patients because of anatomic complexity. Yet, they may require palliation to augment pulmonary blood flow and to improve systemic arterial desaturation. Surgical aortopulmonary shunts have conventionally been utilized in these situations.

Since the introduction of transluminal balloon dilatation techniques in children by Kan et al [3], we and others [72-75] have utilized balloon pulmonary valvuloplasty to augment pulmonary blood flow instead of systemic-to-pulmonary artery shunt and successfully relieved pulmonary oligemia and systemic arterial hypoxemia.

The indications for balloon valvuloplasty that we have used [74,76,77] were cardiac defects not amenable to surgical correction at the age and size at the time of presentation, but nevertheless required palliation for pulmonary oligemia. Relief of hypoxemia is the major reason for intervention. Hypoplasia of the pulmonary valve ring, main and/or branch pulmonary arteries are other indications even if symptoms are not present. The presence of two or more sites of obstruction (Figure 11A) is considered a prerequisite when employing balloon valvuloplasty [74.76,77], because if valvar stenosis is the sole obstruction, relief such an obstruction may result in marked increase in pulmonary blood flow and elevation of pulmonary artery pressure and resistance.

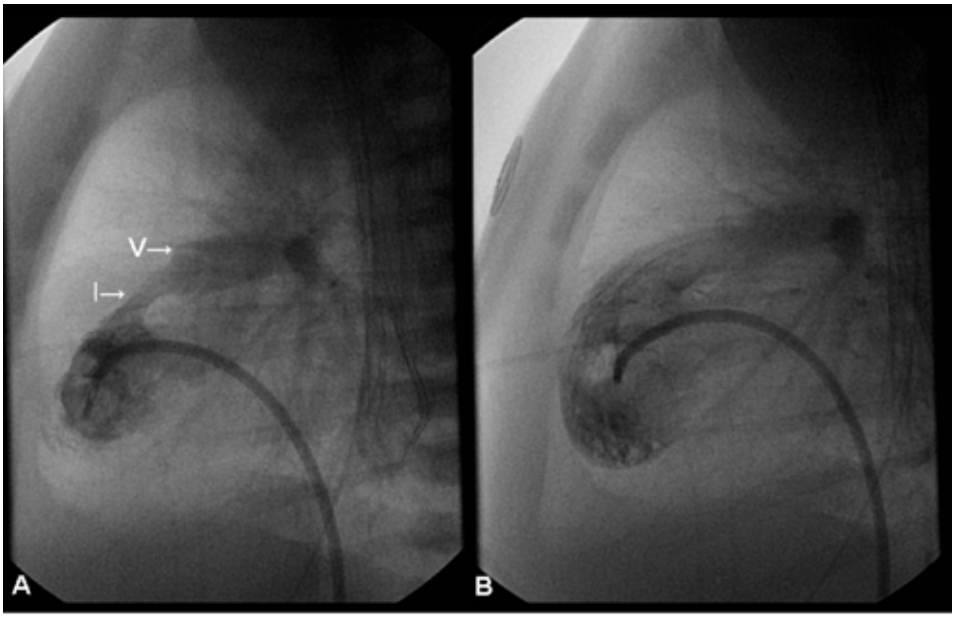

Figure 11. Selected right ventricular cineahgiographic frames prior to balloon dilatation (A) demonstrating both infundibular (I) and valvar (V) stenosis. Note the thickened and domed pulmonary valve leaflets. Following balloon valvuloplasty (B), the pulmonary valve leaflets open widely. Even the infundibular obstruction appears better.

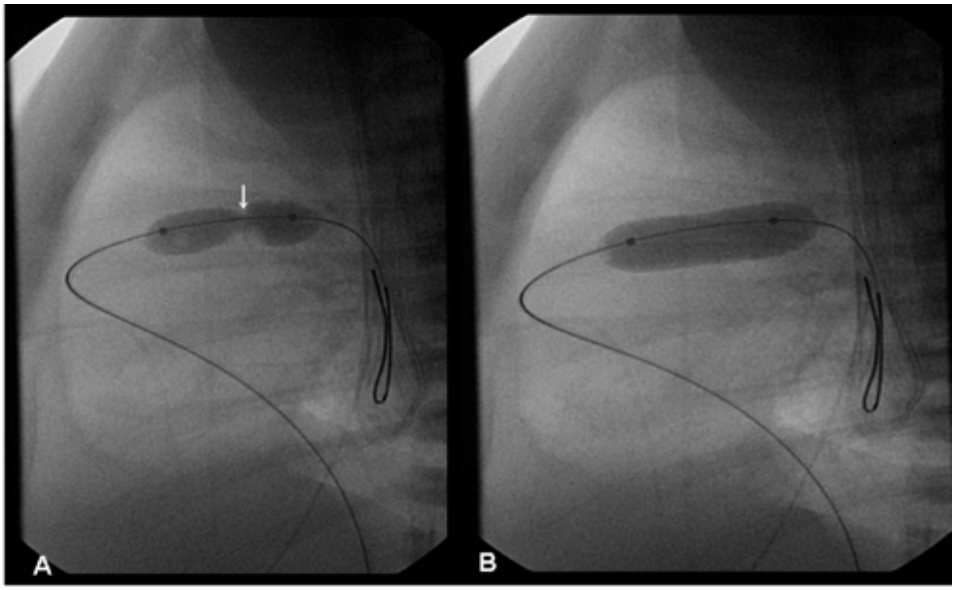

Figure 12. Selected cineflorograpic frames in lateral view demonstrating an angioplasty balloon across the stenotic pulmonary valve with waisting of the balloon (arrow) during the initial phase of balloon inflation (A); the waist has completely disappeared with further balloon inflation (B). This is the same patient whose right ventricular angiogram was demonstrated in Figure 11.

The technique of balloon pulmonary valvuloplasty is essentially similar to that used for isolated valvar pulmonary stenosis, described in the preceding section; the position of the balloon catheter in a Tetralogy of Fallot patient is illustrated in Figure 12.

Results

Improvement in systemic arterial oxygen saturation, increase in pulmonary blood flow and pulmonary to systemic flow ratio (Qp:Qs) and decrease in pulmonary valve gradients (while infundibular and total right ventricular outflow gradients remain unchanged) following balloon valvuloplasty have been observed [74,76-79]. The pulmonary valve leaflets open better after valvuloplasty (Figure 11B).

Increase in the size of the pulmonary arteries and the left atrium/ventricle at follow-up has occurred such that some patients who were thought to have uncorrectable defects became good risk candidates for surgical correction [74-81].

Not all cyanotic heart defect patients with pulmonary stenosis are candidates for balloon pulmonary valvuloplasty. Based on our experience and that reported by others, we [74,76,78,79] recommended this procedure be performed in selected patients. The selection criteria that I recommend are, (a) the infant requires palliation of pulmonary oligemia, but is not a candidate for total surgical correction because of the size of the patient, the type of the defect or other anatomic aberrations; (b) valvar obstruction is a significant component of the right ventricular outflow tract obstruction; and (c) multiple obstructions in series are present so that there is residual subvalvar obstruction after relief of pulmonary valvar obstruction such that flooding of the lungs is prevented. Other indications are any type of contraindication for open heart surgery or refusal by parents/guardians for open heart surgical correction.

CONCLUSIONS

Severe pulmonary and aortic valvar obstruction may occur in the neonatal period and these obstructive lesions can be successfully treated by balloon valvuloplasty techniques. Milder forms of obstruction do not need intervention in the neonate. Aortic coarctation can be successfully relieved with balloon angioplasty in the neonatal period. However, there is a high rate of recurrence. Consequently, surgical repair is the first line therapeutic option in the neonatal period. If recoarctation develops following surgical repair, balloon angioplasty is the method of choice, although the true need for such intervention in the neonatal period is infrequent. Pulmonary valve stenosis associated with complex heart defects, causing hypoxemia can be successfully treated with balloon valvuloplasty and such intervention is used in highly selected cases.

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Choosing Antibiotics in Neonates At - Risk for Sepsis - A Study of Blood Cultures from Two Geographically Separated Neonatal Intensive Care Units

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KSA assisted in collecting the analysis of data; KKD is the guarantor and was responsible for the conceiving, planning and executing the study, and preparation of manuscript

INTRODUCTION

Infection continues to be a bugbear in the management of neonates. Commencing antibiotics in at-risk infants has become the norm of neonatal intensive care. Despite the availability of rapid methods of diagnosis and identification, the choice of the primary antibiotic continues to be based on recommendations of 'literature'. The present study was undertaken to determine the 'first line antibiotics' that would be optimal to commence in at- risk neonate while awaiting the blood cultures and sensitivity report. It is our belief that obtaining data from two hospitals separated geographically over 500 km, in different states, could provide comparative information that could facilitate a consensus in choosing the 'first-line' antibiotics in neonatal sepsis.

Materials and Methods

Isolates obtained from neonatal blood culture done over a 4-year period from January 1999 to December 2002 at the Kasturba Medical College, Manipal, Karnataka (Center A) and over an 18 month period, from March 2004 to August 2005, at the Malankara Orthodox Syrian Church Medical College, Kochi, Kerala (Center B) were retrospectively analyzed. The indications for blood cultures were the same at both centers. Cultures were done for evaluating at-risk neonates and in those infants clinically suspected to have sepsis. The age of presentation, identity of isolates, frequency and sensitivity to commonly used antibiotics were evaluated.

The search for the combination to cover the largest cluster of isolates was obtained by evaluating the sensitivity of isolates to any one of the antibiotics of the selected combination. The profile and sensitivity of isolates were also analyzed separately for both the centers, and the coefficient of correlation determined.

Isolates obtained in blood cultures of infants within 72 hours of life was considered "early onset sepsis" (EOS) and those beyond 72 hours considered as "late onset sepsis" (LOS). The sensitivity pattern of isolates based on the 'onset of sepsis' was also evaluated.

The principal investigator was the same and was head of the neonatal services at both the centers during the study period. Relevant statistical analysis was done using the SPSS version 7.5 statistical package.

Results

Three-thousand and seventy-seven samples of blood cultures were evaluated. (Table 1). Two thousand-five-hundred and forty-five of these were from Center A and 532 were from Center B. Isolates were reported in 697 (22.7%). Coagulase negative staphylococcus (CONS) constituted the largest group (37.6%) of these isolates. This was followed by Klebsiella species (18.5%), Pseudomonas (14.1%), Acinetobacter sp. (7%), Enterobacter sp. (4.9%) and other bacteria in varying percentages. The isolates were similar at both the centers though they varied in their frequency of occurrence (Table 1). While CONS was the most common isolate at both centers, Enterobacter sp. and Acinetobacter sp. were more common than Klebsiella at Center B.

Contaminants, which included aerobic spore bearing bacilli constituted 6% (42/697) of the total isolates, and were excluded from further analysis (Table 1). Six hundred-fifty-five isolates were therefore evaluated for sensitivity to commonly used antibiotics. Five hundred-twenty of these were from Center A and 135 from Center B.

The antibiotics sensitivity of individual isolates was evaluated (Table 2). Gram negative organisms like Enterobacter, Pseudomonas and Klebsiella, were more sensitive to Amikacin. Sensitivity to Ciprofloxacin was seen among both gram negative and gram positive bacteria.

The antibiotics sensitivity pattern of identical species of bacteria varied at both the centers (Table 2). The correlation for antibiotics sensitivity between the two centers was best for Enterobacter sp. and ($r = 0.8$, $p = 0.05$) least for COPS ($r = 0.04$, $p = 0.9$).

Individual antibiotics were evaluated for their 'antimicrobial cover' against the organisms isolated (Table 3). The largest cluster of isolates were sensitive to Aminoglycosides --. Amikacin (37.7%) followed by Gentamicin (36.6%)and Netilmycin (28.9%). The sensitivity of isolates to aminoglycosides was followed by Ciprofloxacin (23.8%), Cotrimoxozole (23.5%), Cefotaxime (22%) and Ampicillin (18.5%). Comparison of the 'antimicrobial cover' of individual antibiotics at Center A and Center B (Table 3) were not identical and correlated at $r = 0.57$ ($p = 0.07$).

Antibiotic combinations, commonly used in clinical practice were assessed for the widest coverage against the isolates (Table 4). Eg. The combination of Ampicillin and Amikacin was evaluated to see if the isolates were sensitive to either Ampicillin or Amikacin (Table 4). *Ampicillin + Amikacin* covered the largest cluster of bacteria (49%). This was followed by *Ciprofloxacin + Gentamicin* (46.4%), *Ciprofloxacin + Amikacin* (44%) and *Ampicillin + Gentamicin* (38.6%). The three-drug combination of *Cefotaxime + Ampicillin + Amikacin* covered 50.5%, while *Cefotaxime + Ampicillin + Gentamicin* covered 44.9% of the isolates . The numbers of isolates sensitive to the combination *Ampicillin + Amikacin* was compared to the combinations of other antibiotics and chi squared test applied. The numbers of isolates sensitive to *Ampicillin + Amikacin* were significantly more than *Ampicillin + Gentamicin* (chi square = 14.3, $p = 0.002$), *Cefotaxime + Amikacin* (chi square = 8.7, $p = 0.003$), and *Cefotaxime + Gentamicin* (chi square = 3.98, $p = 0.046$). However, *Ampicillin + Amikacin* was not significantly

Table 1. Study Characteristics

Isolate	Counts (percentage)			Sensitive to common antibiotics, n			Resistant to common antibiotics, n		
	Combined N = 697 (%)	*Center A n=529 (%)*	Center *B n*=168 (%)	**Combined**	*Center A*	*Center B*	**Combined**	*Center A*	*Center B*
Acinetobacter	49 (7)	*32(6)*	*17(11)*	34	*19*	*15*	15	*13*	*2*
α hem strepto	10 (1.4)	*2(0.3)*	*8(4.8)*	8	*1*	*7*	2	*1*	*1*
β hem Strepto	2 (0.3)	*2(0.3)*	*0*	1	*1*		1	*1*	*0*
Candida	6 (0.9)	*1(0.15)*	*5(3.2)*				6	*1*	*5*
Citrobacter	14 (2)	*12(2.2)*	*2 (1.4)*	12	*10*	*2*	2	*2*	
Coag pos staph	32 (4.6)	*30(5.6)*	*2(1.4)*	20	*18*	*2*	12	*12*	
Coag neg Staph	262 (37.6)	*215(40.6)*	*47(28)*	186	*144*	*42*	76	*71*	*5*
Ecoli	10 (1.4)	*5(0.9)*	*5(3)*	6	*2*	*4*	4	*3*	*1*
Enterobacter	34 (4.9)	*9(1.7)*	*25*	26	*7*	*19*	8	*2*	*6*
Enterococi	8 (1.1)	*8(1.5)*	*0*	5	*5*		3	*3*	*0*
Klebsiella	129 (18.5)	*112(21.2)*	*17(10.1)*	74	*61*	*13*	55	*51*	*4*
Proteus	1(0.1)	*1(0.15)*	*0*				1	*1*	*0*
Pseudomonas	98 (14.1)	*91(17.2)*	*7(4.2)*	63	*58*	*5*	35	*33*	*2*
Aerobic spore + Contaminants	*42(6)*	*9(1.6)*	*33(19.6)*						
Total Isolates	697	*529*	*168*						
No isolates	2380	*2016*	*364*						
Total sample	3077	*2545*	*532*						
Isolates evaluated for sensitivity (Excl.contaminants)	**655**	*520*	*135*	**435**	*326*	*109*	**220**	*194*	*26*

Study period : Center A – 4 years, Center B - 18 months.

different to the combination of *Ciprofloxacin + Gentamicin* (chi square = 0.88, p = 0.34). Though a greater percentage of isolates were sensitive to the combination *Cefotaxime + Gentamicin* than *Cefotaxime + Amikacin,* the difference was not statistically significant (chi square = 0.9, p = 0.3) The differential evaluation of the centers showed that while in Center A coverage provided by *Ampicillin + Amikacin* (51.3%) was followed by *Ciprofloxacin + Gentamicin* (47.7%), in Center B the combination of *Ciprofloxacin + Gentamicin* (44.4%) covered a few more isolates than *Ampicillin + Amikacin* (43%).

The percentages of isolates sensitive to combination of antibiotics were similar at both the centers and correlated at, r = 0.8 (p = 0.008) (Table 4).

Three-hundred-eighty-nine (59%) isolates were EOS and 266 (41%) were LOS. The antibiotic sensitivity patterns of the isolate clusters of EOS and LOS were compared. The sensitivity patterns correlated well for individual antibiotics (r = 0.9, p = <0.01) (Table 5), as well as for the common combinations of antibiotics (r = 0.97, p = <0.01) (Table 6).

Thirty-three point six percent (33.6%) (220/655) of the isolates were resistant to all the commonly plated antibiotics. (Table 1). Multi-drug resistance was most common amongst Klebsiella, (43%), Pseudomonas (36%) Acinetobacter (30%) and CONS (29%).

One hundred-twenty-five of the 389 isolates of EOS and 87 of the 266 LOS were resistant to the commonly used antibiotics and their combination. There was no higher risk of resistance in LOS . (Relative Risk = 1.01 (0.91 – 1.12) at 95 % Confidence limits, p = 0.8, ns).

DISCUSSION

The at–risk approach to neonatal sepsis results in blood cultures being done in a large number of infants. As is the recommended practice, antibiotics are commenced as soon as blood is drawn for cultures and the drugs stopped if no organism is isolated. Should the cultures show some isolate, the antibiotics are altered based on the sensitivity pattern for drugs. As the clinical symptoms of sepsis are common to many other neonatal diseases, blood cultures continue to be the gold standard for confirming sepsis. As seen in the present study, such an ap-

Table 2. Antibiotic Sensitivity of individual Types of Bacteria to Common Antibiotics - Comparison Between Center A & Center B (in %)

	N	Amik	Ampi	Cefotax	Cefurox	Ceftazid	Ciprofl	Genta	Penicil	Vanco	Netil	Cotrimox.
Isolate Cor (p)	Cen.A											
	Cen B											
Corr.0.7 (p= 0.02) Acineto	32	40.6	12.5	18.8	6.2	0	28.1	25	0	6.2	34.3	21.8
	17	*35.2*	*5.8*	*17.6*	*11.8*	*5.8*	*70.5*	*47*	*17.6*	*0*	*41.1*	*58.8*
ά h strep corr: 0.3 p = 0.44	2	0	0	0	0	0	0	50	0	50	0	0
	8	*0*	*75*	*0*	*0*	*0*	*0*	*37.5*	*12.5*	*12.5*	*0*	*0*
Citro bact Corr=0.3 P = 0.37	12	16.7	16.7	25	16.7	0	25	50	0	8.4	58	8.4
	2	*100*	*0*	*50*	*0*	*0*	*50*	*0*	*50*	*0*	*100*	*50*
COPS Corr;0.04 P = 0.9	30	40	23.3	23.3	13.3	0	6.7	53.3	6.7	40	36.7	13.3
	2	*0*	*50*	*0*	*0*	*0*	*0*	*50*	*50*	*0*	*0*	*50*
CONS Corr:0.16 P= 0.63	215	40	32.5	30.6	27.4	1.3	22.3	47.9	4.6	26.5	32	18.6
	47	*4.2*	*27.7*	*2.1*	*0*	*0*	*2.1*	*51.1*	*21*	*2.1*	*2.1*	*61.7*
E.Coli Corr:0.1 P= 0.74	5	40	0	40	20	20	20	20	0	0	20	0
	5	*20*	*40*	*20*	*20*	*0*	*0*	*40*	*0*	*0*	*20*	*20*
Enterobact Corr:0.8 P = 0.05	9	66.7	11.1	0	22.2	0	33.3	11.1	0	0	22.2	11.1
	25	*64*	*0*	*4*	*4*	*0*	*16*	*8*	*0*	*0*	*48*	*8*
Klebsiella Corr:0.6 P = 0.04	112	40.1	1.8	22.3	8	0.9	29.4	18.7	0	0.9	21.4	21.4
	17	*23.5*	*5.9*	*0*	*0*	*0*	*29.4*	*23.6*	*0*	*0*	*23.5*	*52.9*
Pseudomon Corr:0.6 P = 0.04	91	47.2	9.8	25.2	12	1	29.6	38.4	1	2.1	35.1	23
	7	*57*	*0*	*14.3*	*0*	*28.5*	*42.9*	*14.3*	*14.3*	*0*	*42.9*	*0*

proach results in a large number of cultures not yielding any isolates.

The choice of primary antibiotics are based on the preferences of the neonatal center and more studies to clarify this have always been sought [1]. The presumptive or 'first-line' antibiotic therapy is aimed at commencing antibiotics that have a reasonable chance of being effective against the isolate, while awaiting specific sensitivity reports. Needless to say, the ideal combination should be effective against 100% of the isolates. The quest for the widest coverage, has resulted in neonatal centers preferring to use varied combinations of antibiotics, often based on anecdotal observations.

The variations in the bacteriological spectrum of sepsis observed by us at the two centers, supports the observations of other workers [2]. Though gram negative bacterial infections as a group were more common [3], coagulase negative staphylococcus (CONS) was seen to be the commonest bacteria isolated (Table 1). The resistance of CONS to multiple drugs including Cloxacillin, reiterates the observations of other workers [4] to the emerging trends of resistance in this common isolate. The observed sensitivity of CONS to aminoglycosides could give some solace. However, its sensitivity to specific aminoglycosides were different at both the centers, with more numbers of CONS isolated at Center A being sensitive to Amikacin, while Gentamicin covered more numbers of CONS at Center B. This variation in sensitivity to specific aminoglycosides was observed by us even amongst CONS isolated from a single center [5]. The emergence of Enterobacter sp. as an important cause for neonatal sepsis [6] was supported by the data from Center B.

Aminoglycosides, despite its wide usage seems to be effective against most of the gram negative infections and a large proportion of staphylococci [7]. It was our observation that quinolones follow aminoglycosides in their coverage of the numbers of organisms isolated (Tables 2 & 3), thus highlighting a greater role for these drugs in the management of infants at risk for sepsis [8,9].

Table 3. Antibiotic Sensitivity of Isolate Clusters to Common Drugs

	Total n = 655		Center A N = 520		Center B N = 135	
Antibiotic	**Sensitive N**	**% of total isolates**	n	%	n	%
Amikacin	**247**	**37.7**	212	40.8	35	25.9
Gentamicin	**240**	**36.6**	195	37.5	45	33.3
Netilmycin	**189**	**28.9**	159	30.6	30	22.2
Ciprofloxacin	**156**	**23.8**	130	25	26	19.3
Cotrimoxozole	**154**	**23.5**	101	19.4	53	39.3
Cefotaxime	**144**	**22**	136	26.2	8	5.9
Ampicillin	**121**	**18.5**	97	18.7	24	17.8
Cefuroxime	**97**	**14.8**	93	17.9	4	3
Vancomycin	**80**	**12.8**	78	15	2	1.5
Penicillin	**30**	**4.6**	13	2.5	17	12.6
Ceftazidime	**9**	**1.4**	6	1.2	3	2.2

Coefficient of correlation Center A vs Center B , r = 0.57, p = 0.07

Over 50% of the Klebsiella, Acinetobacter sp and Staphylococci were sensitive to Cotrimoxozole (Table 2). More isolates were found to be sensitive to this drug at Center B than at Center A. However, the non-availability of parenteral preparations, and the risk of its sulpha component displacing bilirubin from albumin binding sites, limits the use of Cotrimoxozole in early neonatal sepsis. The role of Cotrimoxozole could, nevertheless, be considered when neonates have to be managed at the outback community level, where the health care is delivered by the community health workers [10].

The differences in the bacteriological profile is quoted as an important reason by clinicians to avoid a uniform approach to 'first-line' antibiotic therapy in at-risk neonates at various hospitals. The primary importance for the clinician while awaiting culture and sensitivity reports is to know which combination of antibiotics would cover the widest spectrum of probable bacteria in Neonatal sepsis.

The resistance to Ampicillin and a greater sensitivity to aminoglycosides have been often reported [11]. The isolates were evaluated by us for their sensitivity to either or any of the drugs in combination. Implying that if the combination were to be used there would a reasonable chance of at least one of the drugs in the combination being effective against the isolates. Despite, the limited sensitivity to Ampicillin (Table 3) the combination of *Ampicillin + Amikacin* was observed to be sensitive for the largest cluster of isolates (49%, Table 4).

Though more numbers of isolates were sensitive to Cefotaxime than Ampicillin (Table 3), combining them with aminoglycosides, yielded varying percentages of sensitivity. The sensitivity being categorized as (*Ampicillin + Amikacin*) > (*Cefotaxime + Gentamicin*) > (*Cefotaxime + Amikacin*) > (*Ampicillin + Gentamicin*) . It was observed that despite Amikacin providing a wider cover than Gentamicin (Table 3), the combination of '*Cefotaxime + Gentamicin*' covered more isolates than '*Cefotaxime + Amikacin*'. The difference however was not statistically significant (chi square = 0.9, p = 0.3). These observations indicate that in the present study, more organisms were sensitive-in-common to both Amikacin and Cefotaxime than to Gentamicin and Cefotaxime. Thus, the overlap in the sensitivity patterns of Cefotaxime and Amikacin narrows the presumptive coverage for this combination. Similarly, the total numbers of isolates sensitive to the combinations of *Ampicillin + Amikacin* and *Ciprofloxacin + Gentamicin* were comparable (p = 0.34, ns).

It must be appreciated that despite the variations in the patterns of bacterial isolates (Table 1) and varying sensitivity of individual isolates at both the centers (Table 2), the antimicrobial efficacy of antibiotic combinations (Table 4) were fairly similar (r = 0.8, p = 0.008). It was our observation that adding more number of antibiotics does not significantly increase the coverage eg. *Ampicillin + Amikacin + Cefotaxime* yielded only 1.5% increase in coverage as compared to *Ampicillin + Amikacin* (p = 0.6, ns). It is therefore, time for the clinician to contemplate if the benefit of empirical addition of more antibiotics to the combination is justifiable as the risk of toxicity would undoubtedly be higher.

It has been our attempt to evaluate if uniform antibiotic policy could be advocated despite the differences in bacteria isolated. This presumption was based on the fact that despite their variations, the different types of bacteria isolated, could be sensitive to the same antibiotic. It is therefore reasonable to surmise that the same antibiotic or combination of antibiotics, could cover a wide –though not necessarily identical - cluster of bacterial isolates at different neonatal centers. The isolates of Center A and Center B showed a wider variation in their sensitivity, to individual antibiotics than to combinations of antibiotics (r = 0.81, p = 0.008, Table 4). Thus reaffirming that a rational combination of antibiotics could be equally effective at different neonatal centers, having isolates of varying bacteriological profile and sensitivity.

It is often commented that choice of antibiotics for 'late onset sepsis' and 'early onset sepsis' should be different as the bacteriologic profiles would differ. It was our observation that the spectrum of antibiotic sensitivity of both EOS and LOS correlated well with each other (r = 0.9, p < 0.01) for single as well as combination antibiotics. Isolates in LOS did not show any higher risk for resistance to commonly used antibiotics than EOS. It could therefore be inferred that the suggested combination of antibiotics could be initiated in all high-risk neonates or those suspected to have sepsis – irrespective of the age of presentation.

While appreciating its limitations, it is felt that '*Penicillins + Aminoglycoside*' combination continues to be the optimal drugs for at –risk infants, while awaiting the specific culture-sensitivity reports. *Ampicillin + Amikacin* was the most optimal combination in the present study. Ampicillin - sulbactum [12] has not been used by us.

Ciprofloxacin and an aminoglycoside, seems to be another promising combination and require more attention. The poor CSF penetrability of Ciprofloxacin would, however, limit its value.

Table 4. Sensitivity of Isolate Clusters to Common *Combinations* of Drugs

	Total N = 655		Center A, n =520		Center B, n = 135	
Drug combination	**Numbers of Isolates sensitive**	**%**	Isolates sensitive	%	Isolates sensitive	**%**
Ampicillin + Gentamicin	253	**38.6**	203	**39**	50	**37**
Ampicillin + Amikacin	321	**49**	267	**51.3**	58	**43**
Ampicillin + Cefotaxime	268	**40.9**	184	**35.4**	30	**22**
Cefotaxime + Gentamicin	285	**43.5**	242	**46.5**	48	**35.6**
Cefotaxime + Amikacin	268	**40.9**	233	**44.8**	39	**28.9**
Cefotaxime + Amikacin + Ampicillin	331	**50.5**	274	**52.7**	61	**45.2**
Cefotaxime + Gentamicin + Ampicillin	294	**44.9**	241	**46.3**	53	**39.3**
Ciprofloxacin + Gentamicin	304	**46.4**	248	**47.7**	60	**44.4**
Ciprofloxacin + Amikacin	288	**44**	243	**46.7**	49	**36.3**

Coefficient of correlation Center A vs Center B, r = 0.81 (p = 0.008)

Table 5. Comparison of Isolates of EOS and LOS for Sensitivity to Drugs

	EOS - 389		LOS N = 266		Total = 655	
Antibiotic	N	**%**	N	**%**	N	%
Amikacin	160	**41.1**	87	**32.7**	247	37.7
Gentamicin	156	**40.1**	84	**31.6**	240	36.6
Netilmycin	122	**31.4**	67	**25.2**	189	28.9
Ciprofloxacin	106	**27.2**	50	**18.8**	156	23.8
Cotrimoxozole	85	**21.9**	69	**25.9**	154	23.5
Cefotaxime	103	**26.5**	41	**15.4**	144	22
Ampicillin	79	**20.3**	42	**15.8**	121	18.5
Cefuroxime	68	**23.5**	29	**10.9**	97	14.8
Vancomycin	51	**17.6**	29	**10.9**	80	12.8
Penicillin	16	**4.1**	14	**5.3**	30	4.6
Ceftazidime	5	**1.36**	4	**1.5**	9	1.4

EOS vs LOS coefficient of correlation, r = 0.9 (p =<0.01)

The fact that nearly 50% isolates required combinations other than *Ampicillin + Amikacin* highlights the absolute necessity of obtaining blood cultures in all at risk infants.

CONCLUSION

We feel that *Ampicillin + Amikacin* would be a good combination to use as the 'first line' antibiotics in neonatal sepsis, while awaiting blood culture reports. The variations in the bacterial flora of neonatal centers is no indication for substituting the standard 'first line' combination of a "penicillin" + an 'aminoglycoside' with more 'exotic' combination in at- risk neonates. A conservative approach while choosing antibiotics is perhaps better than embarking on combinations that include the 'latest' antibiotics for the 'elusive' 100% cover.

Increasing the numbers of antibiotics in the combination need not yield a proportionate increase in the antimicrobial cover (Table 4).

The high correlation between their antibiotic sensitivity patterns, and the absence of any greater risk for antibiotic resistance in LOS, seems to justify commencing the same combination of drugs, viz. *Ampicillin + Amikacin* as initial antibiotics in both early and late onset sepsis.

It can never be reiterated enough that blood cultures are mandatory in neonatal sepsis for rationalizing antibiotic therapy. Empirical cocktails of antibiotics based on anecdotal reports or personal preferences should never supercede the meticulous blood culture and sensitivity studies.

Larger studies involving more neonatal centers could perhaps be useful in recommending a uniform drug policy in treating neonates who are at-risk for sepsis.

KEY MESSAGE

- A combination of a penicillin and an aminoglycoside – Ampicillin and Amikacin is a satisfactory combination of antibiotics to commence in all infants suspected or presenting with features of sepsis while awaiting blood culture reports.
- Blood culture is a mandatory investigation in the treatment of neonatal sepsis.

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Table 6. Comparison of Isolates of EOS and LOS for Sensitivity to Common *Combinations* of Drugs

Drug combination	EOS N=389	%	LOS N = 266	%	total Isolates sensitive	% (655)
Ampicillin + Gentamicin	161	**41.4**	92	**34.6**	253	38.6
Ampicillin + Amikacin	206	**53**	115	**43.2**	321	49
Ampicillin + Cefotaxime	145	**37.3**	69	**25.9**	268	40.9
Cefotaxime + Gentamicin	189	**48.6**	101	**38**	285	43.5
Cefotaxime + Amikacin	178	**45.8**	94	**35.3**	268	40.9
Cefotaxime + Amikacin + Ampicillin	216	**55.5**	119	**44.7**	331	50.5
Cefotaxime + Gentamicin + Ampicillin	190	**48.8**	104	**39.1**	294	44.9
Ciprofloxacin + Gentamicin	200	**51.4**	108	**40.6**	304	46.4
Ciprofloxacin + Amikacin	186	**47.8**	106	**39.8**	288	44

EOS vs LOS, coefficient of correlation, r = 0.97 (p = <0.01)

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