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Original Article

Perioperative administration of angiotensin converting enzyme inhibitors decreases the severity and duration of pleural effusions following bidirectional cavopulmonary anastomosis

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Abstract *Background: .* Pleural effusions after bidirectional cavopulmonary anastomosis remain a significant cause of morbidity. Prolonged effusions in such patients have been associated with persistent elevations in plasma renin and angiotensin II. *Methods:* We conducted a controlled study in 36 patients (median age 8 months) undergoing bidirectional cavopulmonary anastomosis. Enalapril (5 mcg/kg) was administered intravenously within 1 hour of surgery and every 12 hours thereafter in 18 patients; when these patients were tolerating feeds, enalapril was switched to enteral captopril (3 mg/kg/day) every 8 hours. The other 18 patients did not receive perioperative angiotensin converting enzyme inhibitors. Using standardized criteria for discontinuation of chest tubes (< 2 mL/kg/day), volume and duration of pleural drainage were compared between groups. *Results.* There were no differences between groups in demographic, diagnostic, or hemodynamic factors. There was no difference in cardiopulmonary bypass time between groups and no difference in postoperative pulmonary arterial pressures. The duration of pleural drainage was shorter (2.2± 1.4 vs 5.9± 1.4 days, p< 0.001) and the volume less during the first 24 hours (4.7± 1.2 vs 7.7± 2.1 mL/kg, p< 0.001) and overall (10.6± 2.4 vs 19.6± 4.5 mL/kg, p< 0.001) in patients who received angiotensin converting enzyme inhibitors than those who did not. Readmission for persistent effusions was required in 3 patients who did not receive angiotensin converting enzyme inhibitors and none who did (p= 0.11). *Conclusions.* Perioperative administration of angiotensin converting enzyme inhibitors is associated with decreased severity and duration of pleural effusions following bidirectional cavopulmonary anastomosis.

Keywords: single ventricle; bidirectional Glenn; angiotensin II

PLEURAL EFFUSIONS ARE A SIGNIFICANT CAUSE OF postoperative morbidity after bidirectional cavopulmonary anastomosis and modified Fontan procedures.[1–10] The duration of significant effusions in such patients if often substantially longer than in patients who have undergone other surgical procedures for congenital heart disease. The etiology of prolonged postoperative effusions after bidirectional cavopulmonary anastomosis and Fontan procedures is not completely understood, but is probably related to a combination of hemodynamic and hormonal factors. Central venous pressure is elevated following cavopulmonary connection, which leads to relative lymphatic hypertension. The pleural cavities are normally drained via lymphatic channels, and elevated hydrostatic pressure in the thoracic duct would thus be expected to alter the balance of Starling forces involved in fluid flux and to impede normal lymphatic drainage of pleural fluid accordingly. Also, the renin-angiotensin-aldosterone, cortisol, atrial natriuteric factor, and antidiuretic hormone axes are perturbed after bidirectional cavopul-

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monary anastomosis and modified Fontan procedures, and these factors are also likely to interfere with normal fluid homeostasis.[10–12] Angiotensin converting enzyme inhibitors, which block the conversion of angiotensin I to angiotensin II by the angiotensin converting enzyme, are commonly used in the treatment of hypertension in pediatric patients, and for afterload reduction in patients with certain forms of congenital heart disease, cardiomyopathy, or decreased ventricular function due to other causes. Although their primary therapeutic effect depends on the decrease in serum angiotensin II, which acts as a vasoconstrictor, they also lead to decreases in aldosterone, which is secreted from the adrenal glands in response to angiotensin II binding, and bradykinin, by blocking the enzyme that cleaves its precursor. The effects of angiotensin converting enzyme inhibitors on these pathways have important clinical uses as well. In this study, we tested the hypothesis that perioperative administration of angiotensin converting enzyme inhibitors can be used to decrease the duration and severity of pleural effusions following bidirectional cavopulmonary anastomosis.

Patients and Methods

Patients and surgical procedures

During a 17-month period from 1997–98, 36 consecutive patients who underwent bidirectional cavopulmonary anastomosis as intermediate palliation for functionally univentricular congenital heart disease were studied. All procedures were performed by a single group of surgeons at either the University of California, San Francisco Medical Center or Children's Hospital in Oakland, CA. Patients ranged in age from 3 to 46 months (median 8 months), and 34 had undergone 1 or more prior palliative procedures. Diagnoses included tricuspid atresia in 10 patients, double-inlet left or right ventricle in 9, hypoplastic left heart syndrome or variants thereof in 8, Ebstein's malformation in 3, unbalanced atrioventricular septal defect in 2, pulmonary atresia with intact ventricular septum in one, and other complex functionally univentricular defects in 3. Hypoplasia or stenosis of one or both branch pulmonary arteries was diagnosed in 7 patients. At cardiac catheterization prior to bidirectional cavopulmonary anastomosis, calculated pulmonary vascular resistance was 2.7± 1.3 U/kg and end-diastolic ventricular pressure was 6.3± 2.7 mmHg. No patients were receiving maintenance therapy with angiotensin converting enzyme inhibitors prior to bidirectional cavopulmonary anastomosis.

Bidirectional cavopulmonary anastomosis was performed according to standard techniques.[2] When possible, cardiopulmonary bypass was avoided altogether, typically with the use of a temporary shunt between the superior caval vein and right atrium. Cardiopulmonary bypass was employed when concomitant intracardiac procedures or extensive pulmonary arterioplasty were required, or when adequate pulmonary perfusion could not be maintained solely with existing antegrade or shunt flow during creation of the cavopulmonary anastomosis. Bilateral bidirectional cavopulmonary anastomosis was performed in 3 patients with right and left superior caval veins. Additional procedures performed included pulmonary arterioplasty in 8 patients, repair of a regurgitant tricuspid valve in 2, modified Damus-Kaye-Stansel anastomosis in 2, and repair of supravalvar aortic stenosis at a prior cannulation site in one.

Angiotensin converting enzyme inhibition and postoperative pleural effusions

Patients were not strictly randomized to angiotensin converting enzyme inhibitors or no angiotensin converting enzyme inhibitors. Rather, the study arm was determined by site: patients undergoing surgery at Children's Hospital in Oakland were treated with angiotensin converting enzyme inhibitors, while patients undergoing surgery at the University of California Medical Center were not. Management and criterial for removal of chest tubes did not differ at the two sites. In the 18 patients who received perioperative angiotensin converting enzyme inhibitors, enalapril (5 mcg/kg) was administered by intravenous route within 1 hour of surgery and every 12 hours thereafter. Once these patients were tolerating enteral feeds, enalapril was switched to captopril (3 mg/kg/day), which was administered orally or by feeding tube every 8 hours. The other 18 patients did not receive perioperative angiotensin converting enzyme inhibitors. If it was felt to be clinically warranted, patients from this group were discharged on maintenance angiotensin converting enzyme inhibitor therapy, which was not grounds for exclusion from the study.

Data analysis

Preoperative and perioperative data were collected on retrospective review of patient records, and are expressed as median and range or mean ± standard deviation unless otherwise specified. Patients who did and did not receive perioperative angiotensin converting enzyme inhibitors were compared with respect to demographic variables, preoperative

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hemodynamics, use of cardiopulmonary bypass during surgery, duration of cardiopulmonary bypass, bidirectional cavopulmonary anastomosis pressure, volume of pleural drainage (first 24 hours after surgery, total), duration of pleural drainage (chest tubes discontinued when drainage was < 1 mL/kg/day for at least 24 hours), duration of postoperative hospitalization, and readmission for recurrent pleural effusions. Because of the potential importance of cardiopulmonary bypass, patients who underwent surgery with and without bypass were compared, both overall and within the study and control groups. Fisher's exact test and independent samples *t*-test were used to compare frequencies of dichotomous independent variables and mean values of continuous independent variables, respectively.

Results

Demographic, diagnostic, and surgical variables were not significantly different between patients who did and did not receive angiotensin converting enzyme inhibitors (Table 1). In patients who received angiotensin converting enzyme inhibitors, the duration of postoperative pleural drainage was shorter, the volume less both during the first 24 hours after surgery and overall, and the incidence of effusions requiring chest tube drainage for 7 or more days less than in those who did not (Table 2). When patients were analyzed according to whether they underwent surgery with cardiopulmonary bypass, the above differences remained ($p < 0.001$ in all cases). In both groups, approximately 40% of total pleural drainage occurred during the first 24 hours postoperatively. Patients who received angiotensin converting enzyme inhibitors were also less likely to require readmission for persistent pleural effusions (Table 2). There were no perioperative deaths, no reinterventions, and no complications aside from those related to pleural effusions.

Discussion

Pleural effusions after bidirectional cavopulmonary anastomosis

Although progress in the management of patients with functionally univentricular heart disease has reduced the impact of pleural effusions after bidirectional cavopulmonary anastomosis and Fontan procedures, effusions have remained a consistent and significant cause of morbidity [1–10]. A combination of hemodynamic and hormonal factors likely contributes to the relatively high frequency of prolonged pleural drainage in patients undergoing these procedures. Insofar as the

Table 1. Demographic, diagnostic, and surgical variables in patients who did and did not receive perioperative angiotensin converting enzyme inhibitors

Variable	ACE inhibition (n= 18)	No ACE inhibition (n= 18)	P value
Age (months)	14.3± 22.1	14.8± 14.7	0.95
Weight (kg)	8.1± 3.4	8.4± 3.4	0.84
Male sex (£ [%])	11 (61%)	11 (61%)	1.0
Preoperative pulmonary vascular resistance (U/kg)	3.1± 1.1	2.2± 1.4	0.15
Preoperative end-diastolic ventricular pressure (mmHg)	5.5± 2.4	7.0± 2.8	0.11
BCPA with cardiopulmonary bypass (£ [%])	10 (56%)	10 (56%)	1.0
Duration of cardiopulmonary bypass (min)	57± 65	34± 34	0.20

ACE= angiotensin converting enzyme, BCPA= bidirectional cavopulmonary anastomosis

Table 2. Postoperative variables in patients who did and did not receive perioperative angiotensin converting enzyme inhibitors

Variable	ACE inhibition (n= 18)	No ACE inhibition (n= 18)	P value
Postoperative BCPA pressure (mmHg)	11.8± 3.1	12.0± 4.6	0.87
Duration of pleural drainage (days)	2.2± 1.4	5.9± 1.4	< 0.001
Duration of drainage > 7 days (£ [%])	1 (6%)	4 (22%)	0.16
Volume of pleural drainage (mL/kg)			
First 24 hours	4.7± 1.2	7.7± 2.1	< 0.001
Total	10.6± 2.4	19.6± 4.5	< 0.001
Readmission for persistent effusions (£[%])	0 (0%)	3 (17%)	0.11

ACE= angiotensin converting enzyme, BCPA= bidirectional cavopulmonary anastomosis

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thoracic duct drains into the left subclavian vein, elevated pressure in the superior caval venous system produces lymphatic hypertension.[13] Because the pleural cavities are drained through the lymphatic system, lymphatic hypertension leads to impairment of normal drainage of pleural fluid.[14] Although lower pressure in the systemic venous/pulmonary arterial circuit has not been found to correlate with a decreased incidence of effusions following bidirectional cavopulmonary anastomosis or Fontan procedures, lowering pressure in a given patient may be expected to reduce lymphatic hypertension and its effect on reabsorption of pleural fluid. In addition to the hemodynamic factor of elevated systemic venous pressure, perturbation of hormonal axes involved in fluid and electrolyte homeostasis may have an effect on effusions after bidirectional cavopulmonary anastomosis and modified Fontan. Elevated plasma levels of renin, angiotensin, aldosterone, atrial natriuretic factor, and antidiuretic hormone, which have been documented after bidirectional cavopulmonary anastomosis and Fontan procedures,[10–12] are likely to promote fluid retention and thus to facilitate effusive complications.

Preoperative and surgical strategies aimed at acute and chronic reduction in systemic venous pressure are now generally considered important concepts in the staged palliation of functionally univentricular heart disease, and may contribute to reducing the incidence of persistent effusions.[5,15,16] Procedures to reduce total body water after cardiopulmonary bypass[6] and to decrease or eliminate excessive pulmonary blood flow[8] have also been reported to reduce effusions. Likewise, it is plausible that perioperative modulation of the hormonal milieu governing fluid homeostasis might be yet another effective means of decreasing the severity and duration of postoperative pleural drainage following bidirectional cavopulmonary anastomosis and Fontan operations.

Effect of angiotensin converting enzyme inhibition on pleural effusions

In this controlled study, we tested the hypothesis that administration of angiotensin converting enzyme inhibitors immediately after bidirectional cavopulmonary anastomosis and during the entire period of postoperative hospitalization would decrease the severity and duration of pleural effusions. We found that perioperative administration of angiotensin converting enzyme inhibitors at standard antihypertensive doses did indeed result in a significant decrease in the volume and duration of effusions after bidirectional cavopulmonary anastomosis. In patients who received angiotensin converting enzyme inhibitors, the volume of pleural drainage was significantly less during the first 24 hours postoperatively and during the entire duration of tube thoracostomy. The fraction of total pleural drainage that occurred during the first 24 hours after surgery was similar (~ 40%) in both groups. There was also a notable, though not statistically significant, difference in the incidence of readmission for persistent effusions, despite a shorter duration of hospitalization in patients who received angiotensin converting enzyme inhibitors. These results suggest that administration of angiotensin converting enzyme inhibitors immediately after bidirectional cavopulmonary anastomosis and in the early postoperative period can be used to decrease the severity as well as the duration of significant pleural effusions.

Mechanistic considerations

The mechanism(s) by which angiotensin converting enzyme inhibition reduces effusions after bidirectional cavopulmonary anastomosis cannot be determined from the present study. Presumably, however, it does so through modulation of hemodynamics and/or fluid homeostasis by reducing circulating angiotensin II and downstream products in the renin-angiotensin axis. Angiotensin II is a potent vasoconstrictor of the pulmonary circulation[17] and angiotensin converting enzyme blockade has been shown to result in decreased pulmonary vascular resistance in humans who are both normoxemic and hypoxemic, as is typically the case in those with a bidirectional cavopulmonary anastomosis.[18] Moreover, angiotensin II has been shown in animal models to increase venous tone,[19] and inhibition of its production to decrease central venous pressure.[20] The combination of decreased pulmonary vascular resistance and venous tone may improve the hydrostatic gradient for lymphatic reabsorption of pleural fluid. Of note, however, there was no significant difference in postoperative pulmonary arterial pressure between patients in our series who did and did not receive angiotensin converting enzyme inhibitors.

In addition to these potential hemodynamic effects, angiotensin converting enzyme inhibitors likely decrease fluid retention by preventing the abnormal elevation in angiotensin II and aldosterone after bidirectional cavopulmonary anastomosis.[10,11] The mechanism of action for such an effect would be prevention of conversion of angiotensin I to angiotensin II by angiotensin converting enzyme, thus inhibiting aldosterone secretion induced by binding of angiotensin II to receptors in the adrenal cortex.

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Clinical implications

Various operative and perioperative interventions have been reported to result in decreased effusions following superior and/or total cavopulmonary connection, including fenestration of the Fontan baffle/conduit,[5] modified ultrafiltration,[6] administration of aprotinin,[7] and preoperative embolization of systemic-pulmonary arterial collaterals.[8] In addition, some investigators have noted decreased effusions after the Fontan operation in patients who have undergone prior bidirectional cavopulmonary anastomosis.[9] Others have found that the incidence of significant effusions after bidirectional cavopulmonary anastomosis is lower in patients with the cavopulmonary connection as the sole source of pulmonary blood flow than in those with an additional source of flow to the lungs.[3,4] Perioperative administration of angiotensin converting enzyme inhibitors, an essentially benign therapy at the doses employed in this study, may be used in conjunction with some of the aforementioned techniques, which are not generally implemented for the primary purpose of decreasing effusions, to reduce further morbidity associated with postoperative pleural effusions after bidirectional cavopulmonary anastomosis.

Although the physiologic circulatory conditions in patients with a bidirectional cavopulmonary anastomosis or Fontan procedure are similar and postoperative effusions a problem with both, the results of this study cannot necessarily be extrapolated to patients undergoing a modified Fontan operation. Perturbations in the renin-angiotensin-aldosterone system occur following both bidirectional cavopulmonary anastomosis and Fontan operations, but elevations in renin and angiotensin II tend to persist for longer after a Fontan procedure.[10,11] While angiotensin converting enzyme inhibitors cannot be recommended for the reduction of effusions after a Fontan operation on the basis of this study, they are commonly employed for afterload reduction in Fontan patients, and are often initiated just prior to hospital discharge. The single published study of angiotensin converting enzyme inhibition in Fontan patients failed to demonstrate any functional or echocardiographic benefit, but this study did not look at early postoperative results, including pleural drainage.[21] Thus, beginning angiotensin converting enzyme inhibitor therapy earlier than usual (i.e., immediately after surgery) may be of benefit for the reasons discussed in this report as well. Given the encouraging results of the present study, research into the utility of angiotensin converting enzyme inhibitors for reducing effusions after the modified Fontan procedure is indicated.

Limitations of the study

The major limitation of the study was that patients were not strictly randomized to treatment or no treatment, but entered into the treatment group based on location of surgery. However, the same surgical group was responsible for management of patients at both institutions, and the same criterion for discontinuation of discontinuation was applied. Thus, we do not believe that our results were inordinately skewed by this enrollment strategy. Moreover, the volume of pleural drainage during the first 24 hours is independent of practices regarding chest tube removal. Another important limitation was that serum levels of renin, angiotensin II, and aldosterone were not measured.

References

1. Jacobs ML, Norwood WI. Fontan operation: influence of modifications on morbidity and mortality. Ann Thorac Surg 1994; 58: 945–952
2. Bradley SM, Mosca RS, Hennein HA, Crowley DC, Kulik TJ, Bove EL. Bidirectional superior cavopulmonary connection in young infants. Circulation 1996; 94[suppl II]: II-5–11
3. Mainwaring RD, Lamberti JJ, Uzark K, Spicer RL. Bidirectional Glenn: is accessory pulmonary blood flow good or bad? Circulation 1995; 92[suppl II]: II-294–297
4. McElhinney DB, Marianeschi SM, Reddy VM. Additional pulmonary blood flow with the bidirectional Glenn anastomosis: does it make a difference? Ann Thorac Surg 1998; 66: 668–672
5. Bridges ND. Fenestration of the Fontan baffle: benefits and complications. Pediatric Cardiac Surgery Annual of the Seminars in Thoracic and Cardiovascular Surgery 1998; 1: 9–13
6. Koutlas TC, Gaynor JW, Nicolson SC, Steven JM, Wernovsky G, Spray TL. Modified ultrafiltration reduces postoperative morbidity after cavopulmonary connection. Ann Thorac Surg 1997; 64: 37–43
7. Tweddell JS, Berger S, Frommelt PC, Pelech AN, Lewis DA, Fedderly RT, Frommelt MA, McManus TS, Mussatto KA, Kessel MW, Litwin SB. Aprotinin improves outcome of single-ventricle palliation. Ann Thorac Surg 1996; 62: 1329–1336
8. Spicer RL, Uzark KC, Moore JW, Mainwaring RD, Lamberti JJ. Aortopulmonary collateral vessels and prolonged pleural effusions after modified Fontan procedures. Am Heart J 1996; 131: 1164–1168
9. DeLeon SY, Idriss FS, Ilbawi MN, Muster AJ, Paul MH, Cole RB, Riggs TW, Berry TE. The role of the Glenn shunt in patients undergoing the Fontan operation. J Thorac Cardiovasc Surg 1983; 85: 669–677
10. Mainwaring RD, Lamberti JJ, Carter TL, Moore JW, Nelson JC. Renin, angiotensin II, and the development of effusions following bidirectional Glenn and Fontan procedures. J Card Surg 1995; 10: 111–118
11. Mainwaring RD, Lamberti JJ, Moore JW, Billman GF, Nelson JC. Comparison of the hormonal response after bidirectional Glenn and Fontan procedures. Ann Thorac Surg 1994; 57: 59–64
12. Stewart JM, Gewitz MH, Clark BJ, Seligman KP, Romano A, Zeballos GA, Chang A, Murdison K, Woolf PK, Norwood WI. The role of vasopressin and atrial natriuretic factor in postoperative fluid retention after the Fontan procedure. J Thorac Cardiovasc Surg 1991; 102: 821–829

https://doi.org/10.1017/S1047951101000105 Published online by Cambridge University Press

13. Szabo G, Mogyar Z. Effect of increased systemic venous pressure on lymph pressure and flow. Am J Physiol 1967; 122: 569–574
14. Laine GA, Allen SJ, Katz J, Gabel JC, Drake RE. Effect of systemic venous pressure on lymph flow and lung edema formation. J Appl Physiol 1986; 61: 1634–1638
15. Reddy VM, McElhinney DB, Moore P, Haas GS, Hanley FL. Outcomes after bidirectional cavopulmonary shunt in infants under six months of age. J Am Coll Cardiol 1997; 29: 1365–1370
16. McElhinney DB, Reddy VM, Silverman NH, Hanley FL. Modified Damus-Kaye-Stansel procedure for palliation of single ventricle with subaortic stenosis and arch obstruction in neonates and infants: mid-term outcomes and techniques for avoiding circulatory arrest. J Thorac Cardiovasc Surg 1997; 114: 718–726
17. Lipworth BJ, Dagg KD. Vasoconstrictor effects on angiotensin II on the pulmonary vascular bed. Chest 1994; 105: 1360–1364
18. Kiely DG, Cargill RI, Lipworth BJ. Angiotensin II receptor blockade and effects on pulmonary hemodynamics and hypoxic pulmonary vasoconstriction in humans. Chest 1996; 110: 698–703
19. Tabrizchi R, King KA, Pang CC. Direct and indirect effects of angiotensin II on venous tone in conscious rats. Eur J Pharmacol 1992; 219: 141–145
20. Chien Y, Frohlich ED, MacPhee AA, Pegram BL. Quinaprilat increases total body vascular compliance in rats with myocardial infarction. Chin Med J (Engl) 1992; 105: 382–389
21. Kouatli AA, Garcia JA, Zellers TM, Weinstein EM, Mahony L. Enalapril does not enhance exercise capacity in patients after Fontan procedure. Circulation 1997; 96: 1507–1512

https://doi.org/10.1017/S1047951101000105 Published online by Cambridge University Press