Tetralogy of Fallot repair results in activation of the renin–angiotensin–aldosterone system


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Fluid retention is a common problem following transannular patch repair of tetralogy of Fallot. The present study was undertaken to evaluate whether humoral substances may contribute to this process. Patients undergoing tetralogy of Fallot repair using a transannular patch technique were compared to patients undergoing simple ventricular septal defect repair. Hormone levels were determined by radioimmunoassay. Fluid retention was defined as pleural effusions persisting beyond 5 days. The data demonstrate that patients undergoing tetralogy of Fallot repair had elevated levels of anti-diuretic hormone, renin, angiotensin II, and aldosterone as compared to a group with ventricular septal defect. The elevation in hormone levels in the tetralogy of Fallot group was principally accounted for by those who developed effusions postoperatively. These results suggest that activation of the renin–angiotensin–aldosterone system may be one of the contributing factors to fluid retention following tetralogy of Fallot repair.

Key Words: Tetralogy, effusion, renin, angiotensin.

Introduction

Tetralogy of Fallot repair may be complicated by excessive fluid retention in the postoperative period. This process is manifested by persistent pleural drainage. When present, the process may increase the duration of mechanical ventilation, time in the intensive care unit, and total length of hospital stay. Thus, fluid retention is a contributor to morbidity following tetralogy of Fallot repair.

Tetralogy of Fallot is often associated with severe hypoplasia of the right ventricular outflow tract[1,2]. Under these circumstances, surgery using a transannular patch may be required[3]. This technique provides an unobstructed pathway for blood to egress from the ventricle. However, the procedure also renders the pulmonary valve insufficient, and these patients are particularly susceptible to excessive fluid retention. This predisposition to fluid retention is probably multifactorial; potential contributing factors include diastolic dysfunction[4], diminished cardiac output, pulmonary insufficiency with secondary volume load to the right heart, and increased central venous pressure[5,6].

Since hormones are critical to normal fluid balance, we hypothesized that humoral factors may contribute to abnormal fluid homeostasis noted following tetralogy of Fallot repair. The present study was performed to evaluate the hormonal response of patients undergoing transannular patch repair of tetralogy of Fallot.

Methods

Fourteen patients who underwent repair of tetralogy of Fallot, in which a transannular patch technique was used, were enrolled in the study. The hormonal response of these patients was studied and compared to ten patients who underwent ventricular septal defect repair. Patient characteristics of the two groups are summarized in Table 1. Permission for enrolment in the study was granted by the parents, and the study protocol had been approved by the Children's Hospital Institutional Review Board.

Venous blood samples were obtained from the patients on the day prior to surgery and then 1 h, 24 h and 5 days following surgery. Sera and plasma were separated and stored at -70 °C prior to assay. The samples were analysed at the Nichols Institute Reference Laboratories, San Juan Capistrano, California. Plasma anti-diuretic hormone was measured by radioimmunoassay following acidified bentonite extraction with...
Results

Fourteen patients with tetralogy of Fallot and ten patients with ventricular septal defect underwent surgical repair without operative mortality. There were no significant residual ventricular septal defects and none of the patients experienced heart block. The length of cross-clamp and bypass times as well as the incidence of persistent effusions and low cardiac output are shown in Table 2. All 24 patients were discharged from the hospital and, to date, there has been no late mortality. In addition, none of these patients have required re-operation.

The endocrinological response of these two groups is summarized in Fig. 1. Both procedures resulted in early increases in antidiuretic hormone, cortisol, and aldosterone, but the early increases in antidiuretic hormone and aldosterone were more exaggerated in the group undergoing tetralogy of Fallot repair. By the 5th postoperative day, antidiuretic hormone and cortisol had returned to their baseline values. Aldosterone remained elevated in the tetralogy of Fallot group on the 5th day, but had returned to baseline in the ventricular septal defect group. Renin and angiotensin II levels were significantly different between the two groups. Patients undergoing ventricular septal defect repair demonstrated no changes in these levels throughout the study. In contrast, the tetralogy of Fallot group demonstrated increased levels of renin and angiotensin II, with the highest levels noted on the 5th postoperative day.

Nine of the 14 patients undergoing tetralogy of Fallot repair had no significant fluid retention, whereas five patients required chest tube drainage for more than 5 days. A comparison of the renin, angiotensin II, and aldosterone response in these two subgroups of tetralogy of Fallot is shown in Figs 2–4. Patients who did not develop pleural effusions had only transient increases in these hormone levels. By the 5th postoperative day, these levels had returned to baseline. Thus, tetralogy of Fallot patients without effusions had a similar hormonal profile to the ventricular septal defect patients. Patients who developed pleural effusions demonstrated persistent increases in renin, angiotensin II, and aldosterone, and it was therefore this subgroup of the tetralogy of Fallot patients who accounted for the increased levels in the group as a whole.
Hormonal response following tetralogy repair

Pre-op

24 h

5 days

Figure 1 Endocrinological response of patients undergoing repair of ventricular septal defect (squares) and those undergoing repair of tetralogy of Fallot using a transannular patch technique (circles). ADH = anti-diuretic hormone.

The median length of hospital stay was 6 days in the ventricular septal defect group and ten days in the tetralogy of Fallot group. However, there was significant variability amongst the tetralogy of Fallot group. A comparison of hormone levels (renin, angiotensin II, and aldosterone determined on postoperative day 5) compared to length of stay is shown in Fig. 5. There was a significant correlation between renin ($r^2=0.73$, $P<0.01$) and angiotensin II ($r^2=0.84$, $P<0.01$) levels and length of hospital stay. The correlation between aldosterone ($r^2=0.36$, $P>0.05$) and length of stay was not significant.

Discussion

This study was performed to evaluate the relationship between hormonal changes and the development of the effusive process following tetralogy of Fallot repair. The data indicate that patients who develop effusions had significant elevations in renin, angiotensin II, and aldosterone. These results suggest that activation of the renin–angiotensin–aldosterone system may have a role in the etiology of fluid retention following repair of tetralogy of Fallot.

Activation of the renin–angiotensin–aldosterone axis results in a variety of physiological responses which may adversely affect fluid homeostasis. Angiotensin II is a potent constrictor of both the systemic and pulmonary vasculature. This vasoconstriction is mediated in part through antagonism of nitric oxide$^{14}$. Patients who

Figure 2 Renin response of patients undergoing transannular repair of tetralogy of Fallot separated into those with (solid bar) and without (hatched bar) effusions. *$P<0.05$ compared to effusion group.

Figure 3 Angiotensin II response of patients undergoing transannular repair of tetralogy of Fallot separated into those with (solid bar) and without (hatched bar) effusions. *$P<0.05$ compared to effusion group.
have had a transannular patch repair of tetralogy of Fallot may not tolerate an increase in pulmonary vascular resistance, since this would accentuate pulmonary insufficiency at the expense of forward flow. An increase in systemic vascular resistance would tend to decrease cardiac output due to the increased pressure load to the systemic ventricle. Angiotensin II has several local effects on the kidney, including decreased renal blood flow and glomerular filtration rate. Aldosterone influences kidney function as well; inhibiting the clearance of sodium and free water. This combined hormonal milieu at the kidney level may predispose patients to fluid retention. Renin has the singular biological effect of increasing angiotensin I release, and therefore would contribute to this process only through its effect on angiotensin availability.

The aetiology of renin-angiotensin-aldosterone system activation is probably multifactorial. Low cardiac output may be an important contributing factor, as it will result in the release of renin from the juxtaglomerular apparatus of the kidney. In our series, only three patients were felt to have low cardiac output based on their postoperative clinical course. Two of these patients subsequently developed persistent effusions, whereas one did not. Conversely, three of 11 patients judged to have adequate cardiac output subsequently developed effusions. The type of cardiopulmonary bypass (pulsatile vs non-pulsatile) may be another factor which affects the renin-angiotensin-aldosterone system, as it has been shown that pulsatile perfusion results in lower levels of angiotensin II and aldosterone in adult patients. All patients in our series experienced non-pulsatile perfusion, and thus this cannot account for the differences which we observed.

We have previously reported similar observations in patients undergoing the Fontan procedure, specifically, patients who develop effusions following the Fontan had persistent increases in renin and angiotensin II. While the Fontan procedure is used to palliate the single ventricle and tetralogy of Fallot operation repairs a dual ventricle system, the two operations result in many similarities in postoperative physiology. Both procedures are accompanied by an increased central venous pressure, a prerequisite for the development of effusions. However, not all patients with elevated central venous pressures develop effusions, and therefore other factors must contribute to the pathophysiology of this problem.

In conclusion, patients undergoing tetralogy of Fallot repair utilizing a transannular patch have a predilection for developing fluid retention. This study has demonstrated that those patients who have prolonged pleural drainage also have a markedly exaggerated hormonal response characterized by increased levels of renin, angiotensin II, and aldosterone. It remains unclear whether these hormonal alterations are a biological marker of the effusive process or actually play a role in mediating it. Further studies may elaborate on this association between effusions and hormonal changes.
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References


