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Clinical and Echocardiographic Evidence Suggesting Afterload Reduction as a Mechanism of Action of Tolazoline in Neonatal Hypoxemia

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SUMMARY. **The effect of tolazoline was assessed in 29 hypoxic neonates. Tolazoline was given in a bolus starting at 1 mg/kg and repeated or infused for 5–134 hours. A "good clinical response," defined as a rise in Pa_{O_2} of more than 20 mm Hg, was obtained in 23 (79%), 20 of this group were weaned from the respirator, and three died. Six infants did not respond initially and four died. Failure to respond to tolazoline or to be weaned from the ventilator was usually associated with severe additional pathology.**

Urine output (>1 ml/kg/h) was adequate in most neonates during therapy. In those with preexisting oliguria (<1 ml/kg/h), output improved during therapy. Blood pressure monitoring showed a fall in blood pressure in 19 patients during tolazoline administration, but true hypotension only occurred in four; in seven there was no fall and in three there was a rise in blood pressure.

Echocardiography was performed prior to therapy in 19 patients and repeated in 12 patients after 24 h. Additional "tracking" was performed at 10 min, 1 h, and 4 h in seven patients. Prior to therapy, right ventricular dysfunction was demonstrated by abnormal right ventricular systolic time intervals (RVSTIs) in 17 of the patients tested. A rapid improvement was evident during therapy especially with "tracking." Left ventricular dysfunction, assessed by left ventricular systolic time intervals (LVSTIs), ejection fraction (EF), shortening fraction (SF), and velocity of circumferential fiber shortening (VCF), was also evident prior to therapy and improved, though more gradually than the RVSTIs.

Tolazoline was therefore effective in neonatal hypoxia and improved cardiac dysfunction. A critical review of side effects and complications showed that (a) oliguria may precede therapy and renal impairment usually diminished, and (b) true hypotension was less of a problem than previously reported. As perfusion depends directly on blood pressure and inversely on vascular resistance, the systemic effect of tolazoline was to improve perfusion as a consequence of the fall in vascular resistance which improved ventricular function. We wish to introduce the hypothesis that afterload reduction is an additional therapeutic mechanism of tolazoline in neonatal hypoxemia.

KEY WORDS: **Afterload reduction — Tolazoline — Neonatal hypoxemia — Echocardiography**

Severe neonatal hypoxemia, in the absence of any structural cardiac malformation, with pulmonary vasoconstriction may adversely affect cardiac performance or the patient may present with cyanotic congenital heart disease [7, 23, 27]. Tolazoline therapy in neonatal hypoxemia remains controversial with reports suggesting that its usefulness is limited and that systemic hypotension, haemorrhagic problems, and renal failure are serious consequences which may be contraindications to its use [8, 14, 16, 29]. Recently, echocardiography has

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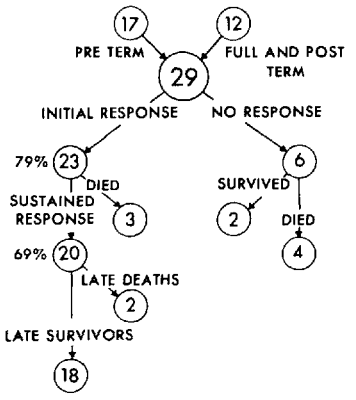

Fig. 1. Clinical response to tolazoline.

been used in an attempt to identify potential responders to tolazoline [14].

This report describes the use of echocardiography for monitoring the hemodynamic effects of therapy and critically examines the effects on blood pressure and urinary output in 29 cases of neonatal hypoxia. From the clinical and echocardiographic data, an additional therapeutic mechanism is hypothesized.

Patients and Methods

The study comprised 29 newborns who received tolazoline. There were 17 newborns below 37 weeks gestation (mean birth weight 1580 g, range 880–2670 g) and 12 full- and postterm neonates (mean birth weight 3370 g, range 2180–3890 g). The mean gestational ages of the two groups were 31.1 and 41.1 weeks, respectively, and the mean 5-min Apgars were 7.1 (range 3–9) and 5.5 (range 2–10). All premature neonates had hyaline membrane disease, some with some asphyxia; meconium aspiration and hypoxia occurred in the rest. The hematocrit, blood glucose, serum calcium, and potassium were all within normal limits prior to tolazoline administration. Cyanotic heart disease or major cardiac structural malformations were excluded by physical examination, chest x-ray, electrocardiogram and, where possible, echocardiogram. All but one of these infants required ventilation with Fio_2 of 1. In one, the umbilical arterial Pao_2 was not available prior to therapy. The babies were electively hyperventilated with a fast rate to achieve a $PaCo_2$ level less than 30 mm Hg where possible. Twenty-eight neonates were also paralyzed with pancuronium; sodium bicarbonate was administered to correct a metabolic acidosis.

The indications for the use of tolazoline were (a) hypoxemia unresponsive to ventilation with a Pao_2 of less than 40 mm Hg, and/or (b) where there was concern about the peak inspiratory pressure exceeding 35 cm H_2O. This included patients with a prior pneumothorax or pulmonary interstitial emphysema. Marked instability of blood gases (flip-flop phenomenon) was a further indication for its use.

Tolazoline therapy was started at chronological ages from 7 to 93 h (mean 27). Intravenous infusions were given for a range of 5–134 h (mean 69). Tolazoline was initially given in a bolus of 1 mg/kg by scalp vein to go down the SVC and therefore flow predominantly into the right ventricle and out the pulmonary artery. If there was no response, this was increased to 2–4 mg/kg. If there was a positive response which was defined as an increase in Pao_2 of more than 20 mm Hg within 10 min, a continuous infusion was commenced and/or bolus doses repeated via the same route. Tolazoline was discontinued when the ventilator pressures and Fio_2 had fallen substantially and the patient appeared to be stable. The time for this varied with each patient. The blood pressure before and during tolazoline infusion was monitored by Dinemapp (Critikon) and taken prior to the first dose, monitored continuously for the first 20 min, and hourly thereafter. Infants who became hypotensive (as defined below) were treated initially by raising the legs and, if necessary, by volume expansion. Urinary output (by weighed diaper) and stool occult bloods were monitored prior to and throughout the period of infusion. Furosemide was given to six patients.

Before therapy, echocardiography was performed in 19 patients to obtain baseline indices of cardiac function and to exclude congenital cardiac lesions. In the remainder, echocardiography was either technically difficult to perform because of severe pulmonary disease or not done because of urgent need for therapy. Echocardiography was performed using an A.T.L. Mark III echocardiograph and 5 MHz unfocused transducer.

Left and right ventricular systolic time intervals were obtained and ejection fraction (EF), shortening fraction (SF), and the velocity of circumferential fiber shortening (VCF) were derived in the standard manner [13, 20]. In 12 patients, echocardiograms were performed prior to and 24 h after the initiation of therapy, and in seven of these 12 patients additional studies at 10 min, 1 h, and 4 h were performed during tolazoline administration.

Results

Out of 29 patients, 23 (79%) had an initial positive response to tolazoline (Fig. 1). Out of 23 initial responders, 20 were weaned off the ventilator (sustained response group). Four of the initial nonresponders died within 24 h with severe hyaline membrane disease, hypoplastic lungs, or severe asphyxiation. Two patients who initially did not respond, survived. Three patients who showed an initial response died with either fulminant Hemophilus influenza B septicemia or noninfective embolic endocarditis.

There were two late deaths that were unrelated to tolazoline.

The rise in Pao_2 in the patients who had responded, ranged from 22 to 392 mm Hg (mean 99).

Urine Output

A rate of urine production of 1 ml/kg/h was considered acceptable for patients more than 24 h old, and 0.5 ml/kg/h for those less than 24 h. Moderate oliguria was defined as a urinary output of 0.4–1.0 ml/kg/h, and severe oliguria was defined as less than 0.4 ml/kg/h. Twenty patients had an acceptable flow of urine prior to tolazoline therapy (Fig. 2). Three of

these patients received furosemide. Only two of this group developed oliguria and one patient died before the production of urine could be accurately assessed.

All six patients with urine flow of 0.4–1.0 ml/kg/h prior to therapy improved and only one received furosemide. Three patients had severe oliguria prior to therapy. In two, the urinary output improved with furosemide and the third patient remained oliguric and died.

Blood Pressure Response

The average blood pressure pretolazoline therapy was 62/38 mm Hg, mean 46 [range (32–89)/(21–63) mean range 26–68]. Three patients were hypotensive prior to therapy; 19 patients had a variable fall in blood pressure immediately following therapy but only four of these were transiently hypotensive and responded quickly to leg raising. In seven patients there was no fall in blood pressure and in three the blood pressure actually rose. The average blood pressure following the first bolus of tolazoline was 55/34 mm Hg mean 43 [range (29–77)/(20–59) mean range 23–69]. Two of the patients with hypotension prior to therapy survived, whereas the third patient, who was severely acidotic, did not. Two of the four patients who showed a transient hypotensive reaction died also.

Echocardiography

The results of the mean left and right ventricular systolic time intervals, ejection fractions, shortening fractions, and velocity of circumferential fiber shortening for the 19 patients in whom these could be obtained before therapy and 12 patients in whom this was obtained 24 h after therapy are shown in Table 1 and in Figs. 3 and 4. The results of additional "tracking" of the systolic time indices at 10 min, 1 h, and 4 h after therapy in seven of these patients is shown in Fig. 5.

Discussion

The rate of response obtained in this study (79%) compares favorably with previous studies reporting an initial response in Pao_2 in 50%–69% of patients [8, 16, 19, 29]. In our experience, failure to respond rapidly was usually associated with an additional complicating factor. Failure to obtain an initial response was not a predictor of a fatal outcome nor did a positive response guarantee a favorable outcome.

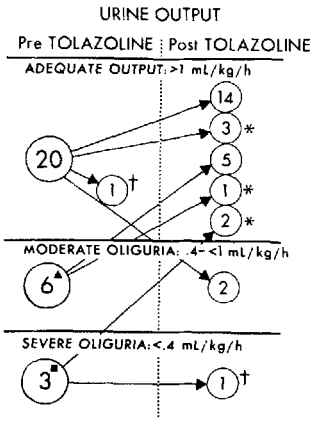

Fig. 2. Urine output before and after therapy: *, furosemide; ▲, 4 < 24 h of age; ■, 1 < 24 h of age.

Echocardiography

The pretherapy right ventricular systolic time intervals showed varying degrees of abnormality. These were frequently reversed when compared with the left ventricular systolic time intervals, indicating pulmonary hypertension and right ventricular dysfunction, as has also been shown by other workers [10, 14, 25, 31]. It has been suggested that normal RSVTIs prior to therapy are seen in patients who did not respond [14]. This was true in two of three of our patients in this category. As the third responded extremely well, we would still recommend a trial of tolazoline in all patients.

Echocardiography demonstrated that a number of our patients had left ventricular dysfunction, as others have described clinically [5, 8, 14, 16, 29], by echocardiography [14, 25, 31], and cardiac catheterization [5, 9, 16, 23, 26]. After 24 h, an improvement in LVSTIs, EF, and SF was seen with normal values in all but two patients, who also showed an improvement. VCF was less useful as an index as we found that the very short ejection times produced normal values no matter how poor other indices of left ventricular function were.

"Tracking" of these indices showed an extremely rapid improvement in RVSTIs and a more gradual improvement in LVSTIs and indices of LV function over 24 h. This rapid response of the RVSTIs correlates well with the rapid increase in Pao_2 seen in most patients. The increased pulmonary valve motion due to increased flow was dramatically demonstrated in one patient whose echocardiogram is shown in Fig. 6. The change in RVSTIs was a rapid improvement in very abnormal

Table 1. Results of echocardiography before and 24 h after initiation of therapy

	Before tolazoline				24 h after tolazoline			
	n	Mean	Range	SD	*n*	Mean	Range	SD
LVPEP/ET	19	0.48	0.27–0.68	±0.12	12	0.33	0.29–0.42	±0.06
RVPEP/ET	19	0.59	0.31–1.0	±0.19	12	0.34	0.25–0.57	±0.1
EF	19	55%	31–73	±9.8	12	58	50–73	±6.6
SF	19	0.301	0.17–0.45	±0.7	12	0.324	0.26–0.46	±0.57
VCF	19	2.13	1.16–3.85	±0.66	12	2.07	1.52–3.3	±0.50

EF, ejection fraction; LVPEP/ET, left ventricular preejection period/ejection time; RVPEP/ET, right ventricular preejection period/ejection time; SF, shortening fraction; VCF, velocity of circumferential fiber shortening.

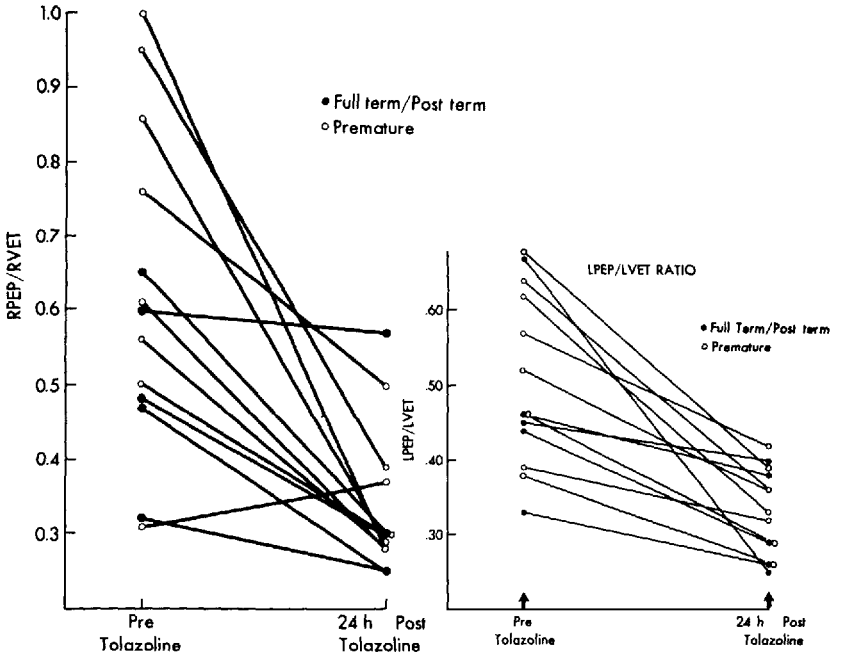

Fig. 3. Change in right and left ventricular systolic time intervals before and 24 h after commencement of tolazoline: *RPEP/RVET*, right preejection period/right ventricular ejection time.

values and not the normal fall that has been described in the first 24 h [11, 24]. This implies changes due to tolazoline. Whether this was due to a fall in pulmonary artery pressure as described by some workers (but not by others) or alterations in pulmonary vascular resistance with an increased cardiac output is not known. The work of Peckham and Fox [22] and Drummond et al. [4] with persistent fetal circulation suggests that no consistent change in P.A. pressure or Pao_2 can be attributable to tolazoline therapy. Variable responses have also been reported in the lamb experimental model [9, 18, 28, 30]. It is not the purpose of this paper to debate the pulmonary effects of tolazoline therapy.

Urine Output

Previous reports have stressed the frequency of oliguria in patients treated with tolazoline and it has been assumed that this has been due to therapy [8, 14]. There has been some animal work to support this view [21]. Poor renal perfusion due to cardiac failure would constitute a prerenal cause for impaired urinary output. The direct effect of tolazoline on the circulation, the secondary effects improving hypoxemia and cardiac performance, would increase renal perfusion and thereby urine output. The urinary output in our patients revealed normal or varying degrees of preexisting oliguria and in most cases an improvement in urinary output was seen during therapy, or normal output was maintained. The method of urinary collection used in this study does have limitations but the fact that the trend for urinary output clearly improved, and was not randomly scattered prior to and after therapy, supports this conclusion. Whether the observed improvement in renal function was due to changes in perfusion or some other intrarenal mechanism remains to be seen but it is incorrect to causually link oliguria to therapy, as has been suggested.

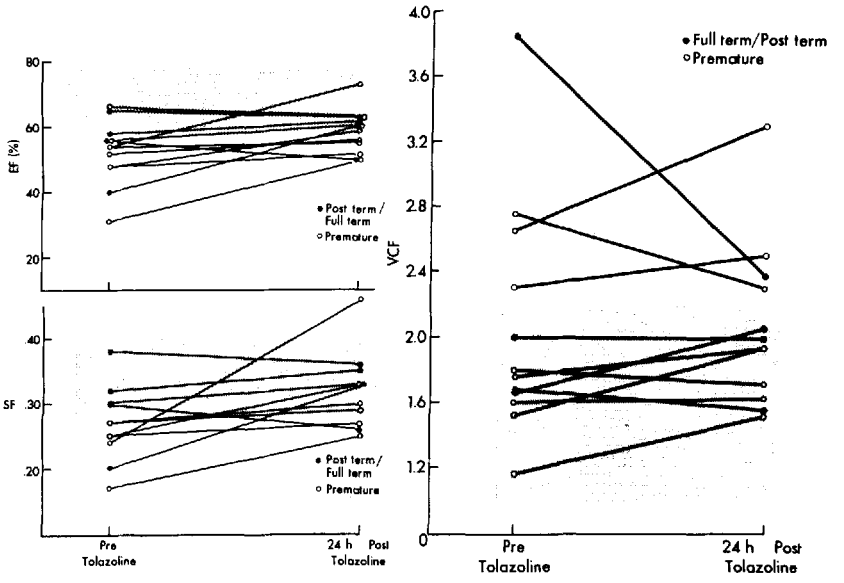

Fig. 4. Change in left ventricular function before and 24 h after commencement of tolazoline: *shaded area*, normal; *EF*, ejection fraction; *SF*, shortening fraction; *VCF*, velocity of circumferential fiber shortening.

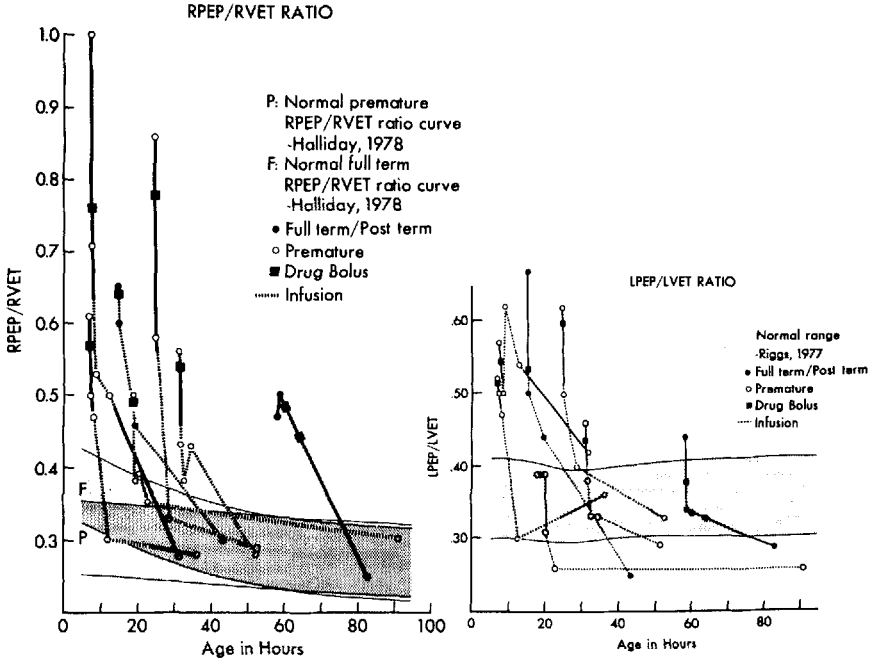

Fig. 5. Results of "tracking" of systolic time intervals with tolazoline therapy. Abbreviations as in Fig. 3.

Blood Pressure

Previous reports have stressed that the blood pressure drops with the use of tolazoline [8, 14, 16, 29], and one report defined a fall in blood pressure of greater than 25% as hypotension [29]. These decriptions and definitions are arbitrary and do not take into account the range of normal blood pressures which, in premature infants, is quite low [2, 15, 17, 32]. The emphasis on blood pressure levels in previous reports ignores the basic relationship of perfusion, i.e., blood flow, which depends on both the blood pressure and is inversely proportional to the vascular resistance. In our patients, a truly hypotensive fall [2, 15, 17, 32] in blood pressure was rare and in some cases the vasoconstrictive response to asphyxia produced mean blood pressures which were unnecessarily high if not hypertensive.

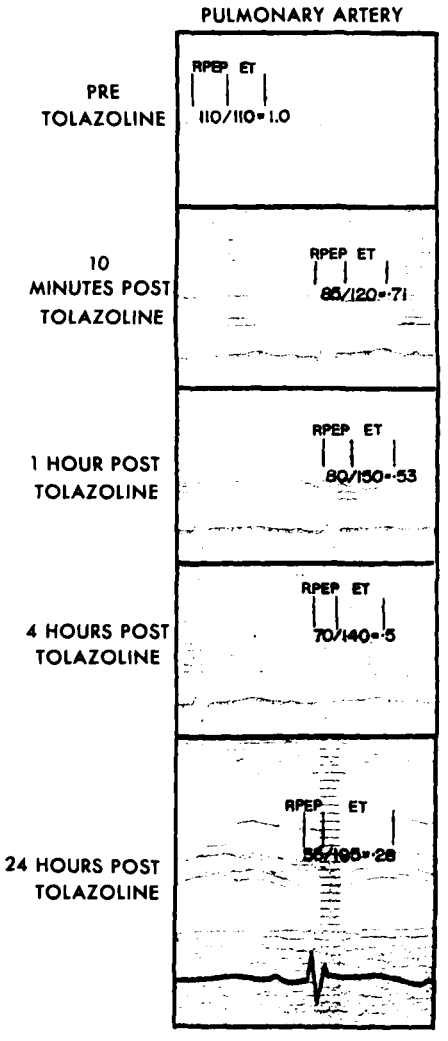

Fig. 6. Pulmonary valve echocardiogram demonstrating a rapid excursion and systolic time intervals with tolazoline. Abbreviations as in Fig. 4.

As previously discussed, the fall in blood pressure did not impair but rather improved both renal and, as will be discussed further, cardiac function.

Afterload Reduction

The relationship between flow (Q), pressure (P), and resistance (R) (i.e., Q = P/R) has already been alluded to and the technique of afterload reduction consists of manipulating this relationship to improve cardiac output (i.e., flow) without a significant loss of mean blood pressure. As the most expensive part of the cardiac cycle in terms of myocardial oxygen consumption is at the peak of systole, reduction of the impedance to left ventricular ejection may result in a significant improvement in cardiac output [1, 3]. The actual reduction of the mean blood pressure may be relatively small. The marked left ventricular dysfunction noted in some of our patients, and remarked upon in other reports, may have benefited from the fall in blood pressure as a form of afterload reduction.

Although direct cardiac output measurements were not performed in this study, the indirect evidence consisting of the improvement in perfusion and left ventricular indices on echocardiography is consistent with this hypothesis. This agrees with some of the animal experimental models which demonstrated that tolazoline increased cardiac output and decreased systemic and pulmonary vascular resistances with relative sparing of the mean blood pressure [18, 28]. As tolazoline has not been reported to have a direct inotropic effect, the observed improvement in systemic perfusion must be due to an increased left ventricular output facilitated by a fall in the vascular resistance. In addition to alpha-blocking agents, the use of inotropic agents has been suggested in PFC. Reports have appeared of the success of dopamine alone [6] or with tolazoline [12] and require further evaluation. Other factors which must be considered as contributory were the improvement in myocardial oxygenation and fall in right ventricular pressure.

The authors wish to stress that this paper reports a clinical study and it was not possible to control some of the variables or directly measure some parameters as would be possible in an experimental animal model. Nevertheless, we feel that these clinical observations warrant further investigation to confirm the proposed hypothesis.

In conclusion, a high percentage of our hypoxic neonates (79%) showed a marked improvement with tolazoline therapy. A critical examination of the so-called complications suggests that preexisting renal impairment was improved and true hypotension due to tolazoline was much less of a problem than previously described. Echocardiography detected biventricular cardiac dysfunction which was improved by tolazoline. We wish to introduce the concept of afterload reduction as one of the mechanisms responsible for the improvement in cardiac function.

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