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Letters to the Editor

Sir,

Re: Reduction in levels of triidothyronine following the first stage of the Norwood reconstruction for hypoplastic left heart syndrome

In the report of reduced thyroid hormone levels in children after heart surgery,[1] no mention is made of what has historically been one of the most common causes of transient hypothyroidism in neonates, namely, the use of iodine-containing antiseptics. Use of these agents is still common in obstetrics, surgery, and neonatology. Topical iodine on the mother before delivery is absorbed so quickly that iodine in the blood of the umbilical cord increases by 50%. Transcutaneous absorption in neonates is even more extensive, and in some reports more than half of the babies with transient hypothyroidism had been exposed to iodine-containing antiseptics.[2] Do Mainwaring and his colleagues know what their institutional practice is, and can they be certain that these antiseptics were not used in the catheterisation laboratory, intensive care unit, and operating room?

Steven D. Colan MD
Department of Cardiology, Children's Hospital
300 Longwood Avenue
Boston, MA 02115, USA
Tel: 617 355 7893; Fax: 617 739 6282
E-mail: colan@alum.mit.edu

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Response

Sir,

We thank Dr Colan for his comments. We have no doubt that the pathophysiology of hypothyroidism in the neonate will be multifactorial, and the list of potential contributors that we provided in the third paragraph of our discussion was not intended to be entirely comprehensive.

It is important to recognize that the decrease in trioiodothyronine following cardiopulmonary bypass is quite distinct from neonatal transient hypothyroidism. Cardiopulmonary bypass induces the "euthyroid sick syndrome". This is a non-thyroidal illness which is characterized by enzymatic dysfunction in the conversion of thyroxine to triiodothyronine. Levels of thyroxine are generally in the normal range, and hence euthyroid, as are the levels of thyroid stimulating hormone. Levels of reverse triiodothyronine are abnormally elevated. While we did not measure such levels in this study, we,[1–3] and others,[4–7] have provided ample studies to demonstrate that the euthyroid sick syndrome is a consistent and important finding in newborns, infants, and in children undergoing cardiopulmonary bypass.

Neonatal transient hypothyroidism related to excess iodine is apparently the result of inhibition of synthesis of thyroxine. This is known as the Wolff-Chaikoff effect, and levels of thyroxine are abnormally low, while those of thyroid stimulating hormone may be normal or supranormal. Levels of reverse triiodothyronine remain normal in this condition. This is a classic form of primary hypothyroidism, and is in marked contradistinction to the changes seen following cardiopulmonary bypass. Indeed, the only data that possibly could be consistent with iodide-induced hypothyroidism is the elevated levels of thyroid stimulating hormone on the fifth postoperative day. But, at this point, the levels of free triiodothyronine have returned toward baseline, and the patients are well on their way to recovery.

The article that was referenced by Dr Colan states that more than half of all cases of neonatal transient hypothyroidism can be attributed to exposure to iodine. If the incidence of neonatal transient hypothyroidism is 1 in 2,700, then the incidence of neonatal transient hypothyroidism related to exposure to iodine is about 1 in 5,000. What is not stated in their study is how many babies were exposed to iodine who did *not* develop neonatal transient hypothyroidism. If we assume that one-tenth of all babies are exposed to iodine in and about the time of delivery, then there would be 499 with exposure to iodine who did not develop neonatal transient hypothyroidism for every one baby who did develop such a problem. In other words, it is not possible to determine, based on the data available in the article covered by Colan, whether their conclusion that

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"the practice of using iodine containing disinfectant should be withdrawn" is justified. Certainly, we have not been convinced as of yet, as we currently still feel that the benefits of povodine-iodine antiseptic outweigh the risks.

Dr Colan asked whether we know our institutional practice. The answer is that we know precisely what happens once the patients are within our institution, but have only an imprecise knowledge of what has transpired, such as exposure to iodine or material antibody history, prior to their arrival. We can state definitively that none of the patients underwent cardiac catheterization, as the diagnosis was determined by echocardiography. All of the patients, however, were exposed to povodone-iodine, both preoperatively for placement of lines, and intraoperatively, since this is our skin preparation of choice. Whether this exposure to iodine has any influence on alterations in thyroid hormones is uncertain based on the reasons stated above.

In summary, we thank Dr Colan for his interest and comments regarding our manuscript. We still believe that the dominant factor influencing the metabolism of thyroid hormones following cardiopulmonary bypass is the euthyroid sick syndrome. Iodide-induced hypothyroidism does not appear to be a major factor in the pathophysiology of changes in thyroid hormones in patients undergoing cardiopulmonary bypass, but we will add it our ever-growing list of things that may alter the metabolism of these hormones.

Richard D. Mainwaring MD, Jerald C. Nelson MD
Associate Professor of Surgery
University of Tennessee
Department of Surgery
956 Court, Suite G212
Memphis, TN 38163
Tel: 901 572 5958; Fax: 901 572 7107
E-mail: rmainwaring@utmem.edu

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Sir,

Re: Successful treatment using heparin of the bronchial cast syndrome after the Fontan procedure

We read with interest the article from McMahon et al.[1] describing a three year old boy suffering from the bronchial cast syndrome after the Fontan procedure. This boy died despite several bronchoscopic interventions, and different trials to reduce the elevated central pressure. We have recently cared for a three year old girl with hypoplastic left heart syndrome, who survived the third stage after the Norwood procedures, and received a fenestrated modified Fontan operation. Two days after closure of the fenestration, she developed severe dyspnoea due to bronchial casts, which required several bronchoscopies to improve the situation. Despite additional therapy with steroids and diuretics, the symptoms reoccurred, and again bronchial casts had to be removed. We therefore looked for further therapeutic options. Dr B. Stiller, from Berlin, informed us of her experience with a child treated with high molecular heparin, with an initial good response. Her case report has recently been accepted by Pediatric Cardiology. Like her, we started with 5,000 Units high molecular heparin given subcutaneously daily, and we were then able to stop all other medications without any relapse requiring intervention. Only once was a tiny piece of firm mucus coughed up during a viral infection. Treatment with heparin was reduced to alternate days after she had been free of symptoms for 4 months, and was finally stopped 2 months later. Unfortunately, after another 4 months, she suffered a sudden severe relapse, and died due to hypoxic organ failure.

We believe that the development of bronchial casts after the Fontan procedure follows the same pathway as described for protein-losing enteropathy. In such patients, Donelly and colleagues[2] elegantly demonstrated the great benefit of treatment with high-molecular heparin, with marked improvement of all symptoms. An increase in filtration pressure, and leaking lymphatic fluid, were the suggested pathomechanisms offered by Languepin and colleagues[3] for the bronchial casts seen in children with cardiopathies. There are some reports of improvement after reduction of the elevated central venous

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pressure.[4] In our case, bronchial casts developed shortly after closure of the fenestration, which also suggests a major influence of changes in pressure. Cardiac catheterisation, however, showed values in the normal range. As suggested by Buchhorn et al.,[5] the bronchial lymphatic system may be the more sensitive reactor.

The development of bronchial casts in patients with cardiac disease is a life-threatening disorder, which requires immediate action. If anatomic improvement of the lymphatic drainage cannot be achieved, then treatment with high-molecular heparin given sub cutaneously may prove to be helpful.

Jürgen Seidenberg, Reinald Motz MD
Elisabeth Kinderkrankenhaus
Städt. Kliniken Oldenburg gGmbH
Cloppenburger Strasse 363
26133 Oldenburg, Germany
Tel: +49 441 403 2024; Fax: +49 441 403 2887
E-mail: Seidenberg.juergen@kliniken-oldenburg.de

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Sir,

Re: Diuretics in the treatment of bronchial casts in congenital heart disease

I read with interest the report of McMahon et al.[1] describing a child who developed bronchial casts and subsequently died after having had a Fontan procedure carried out at the age of 2 years for pulmonary atresia with an intact ventricular septum. The authors, in their discussion, reviewed the literature concerning bronchial casts and suggested that the etiology was unknown and may be multifactorial. I will briefly describe a boy of 12 years who developed recurrent bronchial casts, initially treated with steroids and antibiotics but subsequently controlled by diuretics.

He presented on day one with cyanosis and was also found to have pulmonary atresia with an intact ventricular septum. As he had a reasonable right ventricular outflow, he was subjected to an atrial septostomy under echocardiographic guidance in the Intensive Care Unit, followed the next day by a pulmonary valvotomy and a modified right Blalock-Taussig shunt, being maintained initially on Prostaglandin E1. He subsequently, at the age of 21 months, had resection of the right ventricular outflow tract, and resection of right ventricular trabeculations in order to increase the right ventricular size. At the same time, he had a valvoplasty and reconstruction of the tricuspid valve because of its small size and moderately severe tricuspid incompetence. When aged 4½ years, he had further resection of the right ventricular outflow because of an increasing gradient, division of his shunt, and closure of his atrial septal defect. At the time, a pericardial monocusp was inserted at the pulmonary site. At the age of 9 years, because of decreasing exercise tolerance, he had a pulmonary homograft inserted with further repair of his tricuspid valve for severe tricuspid incompetence. At the age of 10½ years, he remained rather limited in his exercise tolerance. He had a very dilated right atrium, dilated right ventricle, moderate tricuspid incompetence, and free pulmonary incompetence. In addition, he had a small restrictive muscular ventricular septal defect that arose following his right ventricular resection. At about that time, he developed a loose cough, which failed to respond to steroids and bronchodilators when treated by the respiratory physician. The possibility of a mycoplasma pneumonia was considered, but he did not improve despite a prolonged course of erythromycin.

He developed his first bronchial cast at that time, which persisted despite further antibiotics and steroid therapy. Bronchoscopy revealed essentially normal anatomy except for tenacious creamy secretions. A further cardiac catheter done at that time showed that his mean right atrial pressure was 16 mmHg. His right ventricle remained dilated with systolic pressure of 19 mmHg and an end diastolic pressure of 11 mmHg. The pressure in the pulmonary trunk was 18/12 mmHg.

He was discussed further with a view to a possible bi-directional Glenn, with or without the creation of a small atrial septal defect with further repair of his incompetent tricuspid and pulmonary valves.

As he had previously been subjected to multiple surgery and four sternotomies, it was decided to delay such intervention. Diuretics in the form of Frusemide and Spironolactone were commenced initially in a dose of 20 mg and 25 mg daily.

There was some improvement in his cough over the next month, with the passage of one bronchial cast. It was decided then to increase his diuretics further with an additional 15 mg and 12.5 mg of Frusemide and Spironolactone respectively at night. Since then, he has remained well, with no further casts despite his liver still being palpable one to two finger breadths below the right costal margin. His jugular venous pressure remains normal clinically. His exercise tolerance, however, is still reduced. His

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diuretics are now being decreased after he has been cast-free for more than two years. He remains well on 25 mg and 37.5 mg of Frusemide and Spironolactone respectively daily.

While initially considering the possibility that the bronchial casts may have been related to an inflammatory cause, it was apparent that the raised systemic venous pressure may well have been a contributing factor. Keeping such children dry with the help of diuretics, with or without limitation of fluids, may delay the need for further surgical intervention.

Samuel Menahem
Department of Cardiology
Royal Children's Hospital
Flemington Road
Parkville, Victoria 3052
Australia
Tel: +61 3 9345 5712; Fax: +61 3 9345 6001
E-mail: menahems@cryptic.rch.unimelb.edu.au

Reference

1. McMahon CJ, Nihill MR, Reber A. The bronchial cast syndrome after the Fontan procedure: further evidence of its etiology. Cardiol Young 2001; 11: 345–351.

Response

Sir,

I appreciate the comments of Drs Seidenberg and Motz, and those of Dr Menahem, regarding their experience of the "bronchial cast syndrome" in patients following a Fontan procedure. The former correspondence described production of bronchial casts after closure of the fenestration in a patient undergoing a Fontan procedure. This provides further insight into this refractory, and all too often fatal, condition. Comparison with the development of protein-losing enteropathy seems logical, although confirmation of a "common final pathway" is not yet substantiated. Regardless, the use of heparin as a therapeutic modality, providing a definite albeit transient reduction in the frequency of production of casts in the aforementioned patient, is an important observation. Presumably cellular effects upon the bronchial vascular endothelium and the endothelium of the lymphatic system mirror those occurring in the intestinal vascular endothelium in protein-losing enteropathy.

What is particularly interesting in this case, however, is the correlation of onset of symptoms with closure of the fenestration. This lends further credence to our belief that elevated central venous pressure is a primary template for the development of this complication. Interestingly, in this particular patient, the central venous pressure was reported as normal at cardiac catheterization, although one wonders whether the creation of a second fenestration in this case may have produced further palliation. Despite the transient palliation reported by Seidenberg and Motz, the natural history of the disease process was not significantly altered, with death ensuing a few months after the onset of symptoms. This mirrors the outcome of the patient we previously reported, with a transient but short-lived improvement, but with death occurring eight weeks following onset of symptoms.

The second case described by Dr Menahem illustrates, as in protein-losing enteropathy, that there is also a spectrum of severity in this disease process. This case further corroborates our hypothesis that elevated central venous pressure, at a mean right atrial pressure of 16 mmHg, is probably the underlying responsible pathophysiology. The introduction of diuretic therapy proved an effective therapy, presumably mediated by a reduction in the central venous pressure.

Despite the responsiveness of the above case to diuretic therapy, this complication often has an extremely high mortality. Its onset requires early investigation, with cardiac catheterization to rule out a remediable aetiology. Early therapeutic measures to reduce the central venous pressure, such as creation of a fenestration, and/or stenting of the stenotic Fontan circuit, may be required. Medical therapies, including aerosolized urokinase or tissue plasminogen activator to lyse the casts, steroids, diuretics, and now heparin, may also retard progression of this complex. Such a remission in symptoms, however, may be short-lived. Fortunately, the prevalence of this complication appears to be rare, although this is a confounding factor as large cohorts of patients are invariably required truly to determine efficacious therapies. This further emphasizes the importance of sharing the outcomes from single cases, given the rarity of this troublesome complication.

Colin J. McMahon MB, BCh, DCH, MRCP(UK)
Division of Pediatric Cardiology
Texas Children's Hospital
Houston 77030, Texas, USA
Tel: +1 832 824 5659; Fax: +1 832 825 5630
E-mail: cmcmahon@bcm.tmc.edu

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