Radio-iodine in Treatment of Congenital Heart Disease with Severe Pulmonary Hypertension*

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The treatment of refractory cardiac pain and cardiac failure by radio-iodine has been in use for over 15 years (Blumgart, Freedberg, and Kurland, 1950, 1957; Jaffe et al., 1955; Chapman, 1958; Eliasch et al., 1959; Strong and Turner, 1962). The method has also been used to prevent the paroxysms of tachycardia and arrhythmias (Corday, Gold, and Jaffe, 1958; Liljefors, Einhorn, and Eliasch, 1966). The enthusiasm for this method has varied with the progress in pharmacotherapy and cardiac surgery. There are still, however, a number of cardiovascular conditions where no effective therapy is available. Congenital cardiovascular diseases accompanied by severe pulmonary hypertension and arterial hypoxia are frequently not able to be corrected by operation, for several reasons e.g. some combined anomalies, too great an operative risk in relation to the expected result, or a negative attitude on the part of the patients. Many of these patients become bed-ridden invalids. As far as we know no attempts have been made to evaluate the effect of treatment by radio-iodine in this type of condition. As the oxygen requirement of the tissues cannot be met in these patients because of arterial oxygen desaturation and low peripheral flow (Sandae, 1963), it is reasonable to assume that a lowering of oxygen requirements can improve the symptoms due to lack of oxygen.

The purpose of the present communication is to report clinical experience of treatment with relatively high doses of radio-iodine in cyanotic patients with congenital cardiac anomalies.

METHODS AND SUBJECTS

The clinical diagnosis was confirmed by heart catheterization (Varnauskas et al., 1963) and selective angiocardiography (Kjellberg et al., 1955). Criteria of the New York Heart Association (De Graff et al., 1942) were used to grade the functional cardiac disability. The functional state of thyroid gland was established by measurements of basal metabolic rate, protein-bound iodine, and radio-iodine uptake. Cholesterol in serum was also determined.

Treatment with radio-iodine was performed at the radio-isotope laboratory of the Jubileumskliniken of this hospital. A dose of 20 mc was given orally to all patients except one (R.S.) who received 12 mc. In patients O.M. and J.E. an additional dose of 20 mc, respectively, was given a few months later.

Cardiac size was measured radiologically (Jonsell, 1939).

After treatment the patients were followed clinically and by repeated laboratory tests to assess changes in thyroid function.

Treatment was given to 4 male and 5 female patients. Selected anthropometric and clinical data are presented in the Table. One patient (E.K.) had the cardiac anomaly but no pulmonary hypertension, but the pressure in the right ventricle was the same as in the left and he had a right-to-left shunt.

The individual course of the disease before treatment is presented in the Figure. The symptoms in early childhood could be assessed only vaguely. It appears, however, that the majority of the patients were quite well until the age of 15–20 years. Fatigue and dyspnea then began to increase on exertion.

Of the four patients with recurrent hemoptyses, one had developed this at the age of 8; it started considerably later in the other three patients. This symptom is quite frequent and occurs in about 33 per cent of patients with high pulmonary vascular resistance and right-to-left shunt (Wood, 1958).

Chronic cough, which is also a frequent complaint in cyanotic patients (Brown, Heath, and Whitaker, 1955), appeared at the age of 20 in one patient.

The progress of all these symptoms was fluctuating. The majority of the patients developed palpitations during exertion, and four of them also experienced oppression and/or pain in the chest.
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The rapid acceleration of the distressing symptoms began at somewhat younger ages among the men than the women. Only 2 remained in function group III, i.e. experiencing distress only on physical activity, while the remaining 7 became functionally incapacitated during recurrent intervals, even at rest, within a period of approximately one year. Two men developed manifest cardiac failure.

Pregnancy provoked an acute deterioration of the condition (from functional group III to group IV) accompanied by attacks of haemoptyses in patient O.S. at the age of 27. Dyspnoea at rest disappeared with the delivery of a healthy child, but haemoptyses remained, and she deteriorated again within the following 12 months to the same degree as during the pregnancy.

The course in patient J.E. also deserves comment. She was well and took part in gymnastics, experiencing only occasional exertional dyspnoea until the third decade of life. The distressing symptoms started at the age of 35 and progressed rapidly at the age of 40 when she had a long-lasting tachycardia attack following delivery. At the age of 52 and 54, respectively, she had two attacks of cerebral symptoms suggesting small cerebral embolus. She became disabled by the periods of dyspnoea at rest at 55 years of age.

At the time of treatment the youngest patient was a youth of 18 and the oldest a woman of 56 years. Seven patients were physically disabled at rest and belonged to function group IV. Two patients were in function group III but with frequent and profuse haemoptyses of 10-15 minutes' duration.

All patients exhibited cyanosis which increased during slight physical activity, such as undressing. Pulmonary arthropathy was absent only in patient O.M. All had more or less pronounced restrictive impairment of the pulmonary ventilation determined clinically as well as spirometrically.

Hemoglobin was raised up to 20 g./100 ml. in two patients only. Other patients had normal values except for J.U.B. who suffered from profuse haemoptyses. She had a sideropenic anemia.

The values for basal metabolic rate, protein-bound iodine, and cholesterol were within normal limits.

Four patients were on regular digitalis therapy. The trials with this drug were performed in the majority of patients; the treatment, however, was discontinued in some because of a doubtful effect and/or symptoms of intoxication. Narrow therapeutic range for this drug is frequently observed in this type of patient.

In six patients cardiac catheterization disclosed systolic pulmonary artery pressure at rest (95-144) almost equal to the systemic artery pressure. In one patient this pressure was 73 mm. Hg, (see Fig.). The catheterization data were not available in patient O.S., but the history record states that the pulmonary artery pressure was "high".

Arterial hypoxia (Fig.) was present in 6 patients. Normal arterial oxygen saturation was found in the patient with the lowest pulmonary artery pressure. These measurements were made at rest. In patient J.U.B. the saturation was also measured during slight exercise, showing a striking decrease from 81 per cent to 65 per cent. Sandoe (1963) observed that a more or less pronounced oxygen desaturation took place during exercise in 27 out of 33 patients with ventricular septal defect and varying degrees of pulmonary hypertension. Thus, it is reasonable to assume that resting values of intracardiac and pulmonary pressures as well as oxygen saturation do not reflect the situation existing during the major part of the day.

RESULTS

Overt physical and laboratory signs of hypothyroidism were induced, basal metabolic rate de-
creased to between −15 and −25 per cent, cholesterol increased to 300–400 mg./100 ml., and thyroid uptake of radio-iodine decreased. In 5 patients this was achieved by a dose of 20 mc and in one by 13 mc. In two patients the dose of 20 mc had to be repeated a few months later. The remaining patient developed only mild symptoms and signs of hypothyroidism but the treatment was not repeated because her haemoptyses had disappeared. Five patients required substitutional thyroid therapy sufficient to prevent the appearance of frank myxoödema (Eliasch et al., 1959; Strong and Turner, 1962). The slight general retardation of mental activity experienced by some patients was not considered to be a serious disadvantage.

The improvement of cardiac symptoms usually developed 2–3 months after treatment except in one male patient (Fig.) Dyspnoea at rest, palpitations, chest pain, haemoptyses, and chronic cough disappeared in the patients who had them, and exertional dyspnoea decreased. Functional capacity improved in all patients except one. Five who belonged to functional group IV improved to group II; two of the three patients who moved upwards one grade were in group III before treatment: the cessation of haemoptyses accompanied the decrease of exertional dyspnoea in these two patients. The functional change from group IV to III, i.e. one grade, was also accompanied by cessation of haemoptyses in patient J.F.

No cardiac improvement was noted in patient W.E. and he died 6 months later in progressive heart failure. He was the only one with atrial fibrillation. A similar outcome was also recorded in patient G.S., the other patient with congestive heart failure; dyspnoea at rest decreased somewhat but the peripheral congestion remained intractable. He died suddenly, however, two years after the treatment.

![Diagram](https://example.com/diagram.png)

**Fig.**—The course of the disease in each patient. Black area corresponds to functional group IV, squared area to group III, horizontal lines to group II, and white area to group I. The white vertical line in each column and the open arrows correspond to the time of radio-iodine administration. Short vertical strips on the top of the column for patients J.U.B., O.S., J.M., and J.E., respectively, indicate haemoptyses; small black triangles indicate chronic cough in patient O.M. Crosses indicate fatal cases. $P_{PA}$ and $RV$ = blood pressure in pulmonary artery and right ventricle respectively. $SaO_2\%$ = arterial oxygen saturation.
Two other patients (R.S. and O.M.) also died suddenly after being much improved for three and four years, respectively. Patient R.S. had started education in an industrial school, and patient O.M. was so well before death that she intermittently travelled abroad.

The improvement seemed to be related to the degree of thyroid dysfunction. This is supported by observation in patient J.U.B. After the initial improvement of 4 years she deteriorated suddenly to group III and attacks of hæmoptyses reappeared. This was apparently due to the increased dose of substitutional therapy which induced the euthyroid level. Re-establishment of hypothyroidism was accompanied by rapid improvement and disappearance of hæmoptysis.

Amenorrhæa developed in 3 patients who had regular menstruation before treatment. Reappearance of menstruation without any signs of regained thyroid activity was followed by increased dyspnoea on exertion (corresponding to functional group III) in patient O.S. The increased distress was confined to the pre-menstrual periods. Eventually menstruation disappeared again and the condition of the patient improved.

**DISCUSSION**

The present series of 8 patients constitutes a homogeneous group with respect to clinical course and prognosis (Wood, 1958). The serious condition of the ninth patient, who had equal pressures in both ventricles, rendered his prognosis similar to that of the others even though he did not have their severe pulmonary hypertension.

The life expectancy in this type of congenital disease is much reduced. Wood (1958), who described a post-mortem series of 20 patients with cyanosis and large defects, found the average age was 33 years at the time of so-called natural death. The most common cause of death among his series was a hæmoptysis, and next came congestive failure and sudden death. Sandoe (1963), who thoroughly studied 87 patients with ventricular septal defect, the majority of them with pulmonary hypertension, reported that some patients died suddenly before the age of 20 from asystole or ventricular fibrillation. He found that the average duration of life was about 40 years. Congestive heart failure and hæmoptyses were the primary causes of death.

The present 4 fatal cases did not apparently deviate from those cited above, both with respect to age and cause of death. Individual variation in the outcome of the disease is, however, impossible to predict. Continued follow-up, and a larger series, are necessary to elucidate the effect of radio-iodine treatment on the prognosis.

The observation of clinical improvement which accompanied the development of hypothyroidism is conclusive. After early adolescence the disease is progressive (Sandoe, 1963). Some fluctuation in the severity of symptoms may be seen, and intervals between hæmoptyses may vary in length but they never abate or cease completely. That the beneficial effect was related to the decreased thyroid activity is emphasized by the relapse of functional deterioration and the reappearance of hæmoptyses provoked by too high a dose of substitutional therapy in one patient.

The mechanism for improvement is not altogether clear. The symptoms which were relieved are generally considered to be caused by pulmonary hypertension and/or arterial oxygen desaturation. Reduced demands for oxygen by the tissues seem to be the most obvious explanation. This reduction is at least in part achieved by the depressed calorigenic and hyperlactacidaemic effect of catecholamines in hypothyroidism. This depression is secondary to the diminished influence of thyroid hormones (Svedmyr, 1966). A decrease in cardiac output in connexion with a low oxygen consumption has been noted in cases of hypothyroidism both at rest and during exercise. (For the collected reports of cases previously published see Wade and Bishop, 1962.) Similar results at rest were also obtained in patients after hypophysectomy (Bojs et al., 1962). On theoretical grounds and present clinical observation it seems reasonable to assume that some decrease in pulmonary pressure had occurred due to a blood flow decrease as the result of radio-iodine treatment.

To what extent the pressor action of catecholamines is responsible for the functional component of pulmonary hypertension in man (Wood, 1958; Berlind et al., 1967) is not elucidated. Nevertheless, it is important to note that thyroid inactivation diminishes the pressor effect in dogs (Page and McCubbin, 1952).

The tendency towards arrhythmias is decreased by thyroid inactivation in animals (Sawyer and Brown, 1935) and also in human subjects (Shambaugh and Cutler, 1934; Raab, 1945; Corday et al., 1958; Liljefors et al., 1966).

Thus, it is conceivable that the major part of the total clinical improvement may be due to the depressed cardiovascular effect of catecholamines as a result of the diminished influence of thyroid hormones. The hæmodynamic and clinical effects of beta-adrenergic blocking agents (Schröder and Werkö, 1965; Hamer and Sowton, 1965) do not contradict this assumption.

Development of myxœdema heart should have an adverse effect. But the patients were not allowed...
to reach that level of myxœdema where this side-effect would be expected to develop.

It is sometimes stated that the hypercholesterolemia which accompanies induction of hypothyroidism may in turn induce or aggravate atherosclerosis. However, Blumgart et al. (1957) have shown from necropsy material that the incidence of atheroma is no greater than in control subjects.

Conclusions

In conclusion, the use of radio-iodine in the treatment of cyanotic patients with severe pulmonary hypertension is effective in ameliorating cardiovascular symptoms, including haemoptyses. Patients can return to a tolerable social life. The effect as to life expectancy is uncertain because the observation time has been too short and the series is too small for valid conclusions to be drawn.

There is nothing to suggest that the induction of a well-controlled hypothyroidism is accompanied by adverse effects on the cardiovascular system.

Summary

Nine patients with congenital cardiac anomalies causing cyanosis, eight of them also with severe pulmonary hypertension and one with equal pressures in both ventricles, were treated with relatively large doses of radio-iodine to induce hypothyroidism. The level of hypothyroidism was subsequently controlled by substitutional therapy to keep the improvement constant and to avoid frank myxœdema. Functional capacity, determined clinically, improved considerably. Five patients who belonged to functional group IV improved to group II. Two of the three remaining patients who moved upwards one grade were in functional group III and one in functional group IV before treatment. Only one patient did not improve; he died six months later in congestive heart failure. Three patients who had improved initially also died later: the cause of death was cardiac failure (2 years after the treatment) in one, and ventricular standstill or fibrillation in two (2 and 4½ years after treatment, respectively).

References


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