The Response to Catechol Amine Infusion During Salicylate-Induced Hypermetabolism in Man

By Robert J. T. Joy, M.D., and Frank K. Austen, M.D.

The increase in oxygen consumption produced in man by salicylate administration is not associated with a rise in pulse rate or an increase in responsiveness to infusions of epinephrine or norepinephrine. It is suggested that the effects of thyroid hormone on the cardiovascular system are more dependent on the concentration of circulating thyroid hormone per se than on the concomitant increase in tissue oxygen consumption.

There is considerable evidence that an important effect of thyroid hormone on the cardiovascular system is to increase its responsiveness to endogenous epinephrine and norepinephrine. The lethal dose of epinephrine in rats is markedly reduced by thyroid administration. Brewster et al. showed that the tachycardia produced in dogs by thyroid feeding is abolished by sympathetic block. Eppinger and Levine demonstrated in euthyroid patients that thyroidectomy significantly diminished the response in pulse rate to a given dose of intramuscular injection of adrenalin. Schneckloth et al. observed an exaggerated rise in blood pressure during norepinephrine infusion in thyrotoxic patients as compared to their response after treatment. It has not been possible, however, to determine whether these effects of thyroid hormone on the cardiovascular system are dependent upon the concentration of circulating thyroid hormone or on the rate of tissue oxygen consumption.

Salicylate administration offers an opportunity to study the effects of hypermetabolism in man in the absence of an increased concentration of circulating thyroid hormone. Salicylates increase the basal metabolic rate (BMR) while simultaneously depressing other indices of thyroid function, such as the serum protein-bound iodine (PBI) concentration, the thyroidal uptake of I\textsuperscript{131}, and thyroid clearance of I\textsuperscript{131}. The clinical findings generally regarded as characteristic of hyperthyroidism are lacking. The most striking difference is the failure of salicylate-induced hypermetabolism to increase the waking or sleeping pulse rate. Even a patient with myxedema, in whom the BMR was increased from −35 to +35 per cent by salicylate administration, did not exhibit an increment in pulse rate. Similarly, in 2 thyrotoxic patients with a tachycardia while sleeping, the administration of salicylates failed to increase the pulse rate while further elevating the oxygen consumption. Moreover, Alexander and Johnson found that patients with myxedema, restored to the same metabolic rate with tri-iodothyronine and salicylate, showed an increase in pulse rate with the former but not with the latter.

In view of the evidence that sensitization to adrenal medullary secretion is an important action of the thyroid hormone, a study was undertaken of the cardiovascular reactivity to epinephrine and norepinephrine infusion during salicylate-induced hypermetabolism. The purpose was to determine whether or not increased tissue oxygen consumption per se would increase the responsiveness to these catechol amines.

**Methods**

Three male volunteers, age 22, with early rheumatoid arthritis, were selected from the previous study. They received 7.2 to 8.1 Gm. of sodium salicylate daily in 6 divided doses. The serum salicylate concentration and BMR were determined at weekly intervals and on the day of each infusion study. Oxygen consumption was measured by the closed-circuit technic, and the BMR...
CATECHOL AMINE INFUSION AND SALICYLATES

was obtained from the factor tables. PBI determinations were obtained several times before, during and after salicylate administration. Sedimentation rate, C-reactive protein, and serum electrolytes were determined once each week.

The response to intravenous epinephrine and norepinephrine was observed twice for each drug during the control period. The infusion was repeated once with each drug 24 hours, 7 days, and 7 to 8 weeks after continuous salicylate administration, and again 5 to 8 weeks after discontinuation of salicylates. During the infusion period, the patient was supine, comfortable, in a quiet isolated room, and for 1 to 2 hours postprandial. A solution of 5 per cent dextrose in water and the appropriate infusion mixture of catechol amine were connected by a three-way stopcock to an indwelling polyethylene catheter in the antecubital vein. The rate of flow was controlled at 1 ml/min. by a sigma pump. The test dose of epinephrine and norepinephrine was determined by gradually increasing its concentration in the infusion mixture until a satisfactory response was obtained. The latter was arbitrarily defined as an increase in mean pulse rate with epinephrine of 10/min. over the base line and a mean rise in mean blood pressure (one third the pulse pressure added to the diastolic) of 10 mm. Hg with norepinephrine. The test dose range in 3 patients was 0.20 to 0.25 µg./Kg./min. for epinephrine, and 0.24 to 0.28 µg./Kg./min. for norepinephrine.

The pulse rate was recorded by a continuously running electrocardiograph, and the blood pressure was determined every 2 min. by auscultation on the same arm. Base line data were secured in each test for 15 to 20 min. after the values became stable, then epinephrine or norepinephrine was infused for 30 min. In 2 subjects, JB and RPi, electrocardiograms revealed suppression of the sinoatrial node with an ectopic pacemaker during the presalicylate norepinephrine infusion. Subject JB also had periods of first-degree heart block with a P-R interval of 0.28, and subject RPi developed a supraventricular tachycardia after 20 min. of the presalicylate infusion. All subsequent norepinephrine infusions in this patient were limited to 20 min. The third patient, FK, showed a persistent bigeminal rhythm of atrial origin during the latter half of his postsalicylate epinephrine infusion. There were no instances of these minor arrhythmias during the salicylate administration period. Subject JB noted some tremulousness and mild agitation with each epinephrine infusion, and RPi had a similar experience during the first of the presalicylate epinephrine infusions; no unusual symptoms or signs were experienced during any of the norepinephrine tests.

Values for pulse rate, systolic, diastolic, and mean pressure (one-third the pulse pressure added to the diastolic) were averaged during the base line and catechol amine infusion periods. Values obtained during the first 5 min. of the catechol amine infusion were omitted from the average to allow time for a response to occur. The difference between the averages during the base line and the infusion period were considered as the response for each test. The rise in pulse rate with epinephrine and the increase in mean blood pressure with norepinephrine were found to be the most consistent responses and are used in this report.
RESULTS

The response to salicylate administration was that expected from the previous study. The serum salicylate concentration ranged from 21 to 25 mg. per cent at 24 hours, and thereafter remained higher, the mean values ranging from 29 to 39 mg. per cent. Oxygen consumption increased within 24 hours of salicylate administration (fig. 1); the mean increase for the whole salicylate period ranged from 43 to 86 ml./min./1.73 sq. meter. The PBI fell to a relatively constant value during the first week (fig. 1). There was no consistent change in baseline pulse rate or mean blood pressure. Salicylate administration did not produce any change from normal body temperature, and the serum concentrations of sodium, potassium, chloride, and bicarbonate remained within normal limits.

At no time during salicylate administration was there an augmented response to the epinephrine infusion (fig. 2). The response 24 hours after beginning salicylates was essentially the same as that obtained before and after salicylate administration. There was a tendency for the response to be depressed both 7 days and 7 to 8 weeks after continuous salicylate therapy. The time interval between the last infusion of the salicylate period and the preceding one was approximately the same as that between the last infusion of the salicylate period and the post salicylate test. Thus, the depressed response after 7 to 8 weeks of salicylate administration cannot be attributed to tachyphylaxis.

Similarly, at no time during salicylate administration was there an augmented response to norepinephrine infusion (fig. 3). The presalicylate and postsalicylate reactions were not as consistent as those obtained with epinephrine; however, the reproducibility was within the limits observed with this technic by Schneekloth et al. There was no consistent evidence of a depressed response during chronic salicylate therapy.

DISCUSSION

Salicylate-induced hypermetabolism in man, in contrast to hyperthyroid hypermetabolism,
does not increase the pulse rate* and is not associated with increased sensitivity to epinephrine or norepinephrine infusion. Equally striking differences between the cardiovascular effects of salicylate and thyroid have been demonstrated in the dog. Tenny and Miller10 have shown that in the dog the major cardiovascular adjustments to salicylate are an increase in cardiac output and a widening of the arteriovenous oxygen difference. It was assumed that the former was predominantly the result of increased stroke volume because there was only a slight increase in pulse rate. This has recently been confirmed by Walton and Darby17 who demonstrated by more direct methods that salicylate injection produces a prompt increase in the contractile force of the dog heart. On the other hand, Brewster et al.3 have shown that thyroid feeding in dogs causes a significant rise in pulse rate as well as an increase in ventricular stroke work, but no increase in the arteriovenous oxygen difference. The studies of Tenny and Miller10 with salicylate, and Brewster et al.3 with thyroid, are particularly pertinent because both used dogs in whom the BMR was increased to a similar extent. Hence, the difference between the cardiovascular effects of salicylate and thyroid in dog and man suggests that hypermetabolism per se may not be primarily responsible for the effect of thyroid hormone on the cardiovascular system.

An alternative explanation is that the failure of salicylate-induced hypermetabolism to increase the pulse rate or the responsiveness to the catechol amines is due to some direct inhibitory effect of salicylate on the heart. There is some basis for such a view. Tissues removed from salicylate-treated animals show an increase in oxygen consumption,18 and the addition of salicylate to isolated tissue preparations19, 20 or mitochondria18 raises oxygen consumption and depresses esterification of inorganic phosphate. Dinitrophenol21 and thyroxine22, 23 also uncouple oxidative phosphorylation, and this may be the mechanism whereby salicylate, dinitrophenol, and thyroxine increase oxygen consumption in the intact animal. Furthermore, Smith and Jeffrey24 have demonstrated by in vitro studies with the rat diaphragm that salicylate causes a depletion of the "high-energy phosphate" compounds, creatine phosphate and adenosine triphosphate. Moreover, Nayler25 has observed that, although salicylate and dinitrophenol alone have a positive inotropic action on the isolated frog heart, exposure to these agents prevents the inotropic response to the cardiac glycosides seen in the control perfusions. In view of this, Nayler25 has suggested that an adequate supply of "high-energy phosphate" compounds may be essential to the inotropic action of the cardiac glycosides. It is not inconceivable that salicylate in a similar way prevents certain responses to the increase in tissue oxygen consumption which accompanies its administration. However, this seems unlikely since thyroid is also an uncoupling agent and presumably could cause a similar depletion of "high-energy phosphate" compounds.

Concomitant with salicylate-induced hypermetabolism is a fall in the concentration of the PBI. If the level of circulating thyroid hormone determines the cardiovascular response to a catechol amine infusion, an actual reduction in sensitivity might be expected during salicylate administration. Such a tendency is evident in the epinephrine infusion studies. The response is normal at 24 hours, at which time the serum salicylate concentration and BMR are increased but the PBI is not significantly changed, whereas the response is diminished after 1 week at which time there is a reduction in the PBI. A similar trend is not evident in the norepinephrine studies. It may be that the epinephrine response is a more sensitive index of the level of thyroid activity than the norepinephrine response. Schneckloth et al.5 did not observe a

*The tachycardia observed in salicylate intoxication11 can be attributed to a number of factors, acting alone or in combination; increased work of breathing due to profound hyperventilation, electrolyte disturbances which can be either an alkalosis or acidosis,14 dehydration with hypotension, marked neuromuscular irritability,22 or anoxia from late respiratory depression.
diminution in the reaction of euthyroid patients to norepinephrine after thyroid ablation with radioiodine, whereas Eppinger and Levine noted a significant reduction in sensitivity to adrenalin in euthyroid patients after thyroidectomy.

The suggestion from our studies that hypermetabolism per se is not primarily responsible for the effect of thyroid hormone on the cardiovascular system is supported by other observations. Alexander and Johnson found that patients with myxedema, restored to the same metabolic rate with tri-iodothyronine and salicylates, developed angina pectoris and an increase in pulse rate only with the former. Furthermore, Oliver and Boyd noted the development of angina in 2 euthyroid patients with hypercholesterolemia during therapy with tri-iodothyroacetic acid (an analog of tri-iodothyronine) even though there was no concomitant measurable rise in BMR. These observations suggest that moderate hypermetabolism, when induced by salicylate administration, is well tolerated and that thyroid hormone increases the reactivity of the cardiovascular system by some means other than or in addition to increased tissue oxygen consumption.

**Summary**

The increase in oxygen consumption produced in man by salicylate therapy is not associated with an increment in pulse rate. The salicylate-induced rise in oxygen consumption does not increase responsiveness to infusions of epinephrine or norepinephrine. It is suggested that the effects of thyroid hormone on the cardiovascular system are more dependent on the concentration of circulating thyroid hormone per se than the concomitant increase in tissue oxygen consumption.

**Summary in Interlingua**

Le aumento del consumption de oxygeno que resulta in humanos ab le administration therapeutica de salicylato non se mostra associate con un acceleration del pulso. Le aumento in le consumption de oxygeno in consequentia del ingestion de salicylato non se mostra associate con un aumento in le responsivitate a infusiones de epinephrina o de levarterenol. Es suggeste que le effectos de hormon thyroide super le systema cardiovascular depende plus del concentration del hormon thyroide in le circulation que del concomitante augmento del consumption de oxygeno in le histos.

**Acknowledgment**

The authors would like to express their appreciation to Brig. Gen. Thomas W. Mattingly and Dr. Jan Wolff for their valuable suggestions during the progress of this investigation.

**References**

12. KELEX, W. J.: A rapid method for the de-


The Response to Catechol Amine Infusion During Salicylate-Induced Hypermetabolism in Man

ROBERT J. T. JOY and FRANK K. AUSTEN

Circ Res. 1958;6:678-683
doi: 10.1161/01.RES.6.6.678

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1958 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/6/6/678

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation Research can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation Research is online at:
http://circres.ahajournals.org/subscriptions/