A Method for the Detection and Quantification of Impaired Sodium Excretion

Results of an Oral Sodium Tolerance Test in Normal Subjects and in Patients with Heart Disease

By Eugene Braunwald, M.D., William H. Plauth, Jr., M.D., and Andrew G. Morrow, M.D.

The inability to excrete ingested sodium is one of the most fundamental abnormalities that characterizes the congestive heart failure state. Indeed, most of the symptoms and physical signs that occur in heart failure—exertional dyspnea, orthopnea, edema, venous distention, hepatomegaly, and ascites—result in large measure from retention of sodium and water. A variety of methods is now available for quantifying certain aspects of circulatory function in man, including technics for measurement of cardiac output and of intravascular and intracardiac pressures. Radiologic, angiocardio- graphic, and electrocardiographic studies provide considerable information concerning the presence and degree of myocardial hypertrophy, and of other structural changes in the heart. None of these approaches, however, provides information concerning the patient's ability to excrete ingested sodium. When the physician wishes to determine whether this important function is impaired, he has, in the past, been forced to rely upon relatively crude technics. He determines whether there is abnormal fluid accumulation by history and physical examination, and relates these findings to the patient's past salt intake and diuretic therapy. This approach provides only a gross evaluation of the presence and of the degree of impairment of sodium excretion that occurs in patients with heart disease. In the present report a simple oral sodium tolerance test, designed to detect and quantify abnormalities of sodium excretion, is described. The results of the test in normal individuals and in patients with heart disease of various forms and severity are presented. Also, the test was applied to assess the effects of corrective cardiac operations and of an aldosterone antagonist on sodium excretion.

Methods and Patients

Initially all patients studied were given a diet containing 10 mEq. of sodium a day for a preliminary 4-day period, so that Na excretion had been reduced to an extremely low value by the time the actual test commenced. This preliminary period was followed by sodium administration for 8 days according to one of two schedules. In plan A, the patients ingested a total of 920 mEq. of Na during the test; 80 mEq. daily for the first 4 days, and 150 mEq. daily for the last 4 days. In patients with severe congestive heart failure, who were considered unlikely to tolerate the ingestion of 920 mEq. of Na in 8 days, the test was modified. In them, plan B was utilized and they received 320 mEq. of Na in 8 days. After the preliminary period on 10 mEq. of Na, these patients were given 30 mEq. of Na daily for the first 4 days of the test and 50 mEq. of Na daily during the last 4 days. In all patients the urine was collected in 24-hour samples during all 8 days of the test period, and was analyzed for Na, particular care being taken to assure that the urine collections were complete for the entire test period. The results of both test plans were expressed in terms of total Na excreted during the 8-day test period. Na retention was defined as the difference between the quantities of Na ingested and excreted, the small insensible and fecal losses being neglected.

The patients were maintained on an isocaloric, 10-mEq. Na diet throughout the study; this was supplemented with appropriate amounts of Na in the form of table salt, which was added to the food. Except for the three patients in whom the
effects of Aldactone on Na retention were specifically determined, diuretics were not given for at least 4 days prior to the test. All patients receiving digitalis were continued on maintenance doses throughout the study. When multiple Na tolerance tests were carried out in the same patient, the same preparation and dose of glycoside were administered throughout each study. All of the normal subjects and patients were ambulatory on the ward, which was maintained at a temperature of 68 to 70 F. Prior to each study, a postprandial 3-hour endogenous creatinine clearance was determined. In addition, before the tolerance test both right and left heart catheterizations were carried out in all patients with valvular or primary myocardial disease, and right heart catheterization was carried out in the patients with congenital heart disease or constrictive pericarditis. Serum Na, K, Cl, and CO₂ were determined on the day preceding and on the last day of the test period.

The Na tolerance test, utilizing plan A (920 mEq of Na), was carried out in 13 normal volunteers, ranging in age from 18 to 26 years. In four of these 13 subjects the test was carried out on two separate occasions. Fifty-seven tests were performed in 41 adult patients with heart disease. Twenty-seven patients had rheumatic heart disease, with mitral stenosis as the major valvular lesion in 14 patients, mitral regurgitation in nine, aortic stenosis in two, and aortic regurgitation in two. Five patients had congenital heart disease (two patients with atrial septal defect, one patient each with patent ductus arteriosus, ventricular septal defect combined with pulmonic stenosis, and origin of the aorta and pulmonary artery from the right ventricle). Thirty patients had constrictive pericarditis and six patients were considered to have primary myocardial disease. Thirteen patients were studied both before and after a cardiac operation. A closed mitral valvulotomy was performed in six patients, replacement of a regurgitant mitral valve with a Starr-Edwards prosthesis in four patients, replacement of the aortic valve with a Starr-Edwards prosthesis in three patients—two with predominant aortic stenosis and one with predominant regurgitation. The influence of Aldactone A (100 mg a day) on the results of the Na tolerance test was determined in three patients. In three additional patients with valvular heart disease the test was begun but could not be completed because of the development of serious dyspnea on the sixth day.

The Na tolerance test utilizing plan B (320 mEq of Na) was carried out in seven normal young adult volunteers, in three of whom the test was carried out on two separate occasions. Eleven tests were performed in eight patients; four of them had predominant mitral regurgitation, and one patient each had combined mitral and aortic regurgitation, combined aortic and mitral stenosis, arteriosclerotic heart disease, and primary myocardial disease. Two patients were studied after operation, one of them on two separate occasions.

Results

Normal Subjects

In the 13 normal subjects in whom the

![Figure 1](http://circ.ahajournals.org/)  
**Figure 1**  
Representative examples of the Na tolerance tests in two normal subjects. The broken horizontal line in this and subsequent figures denotes the total quantity of Na administered during the eight days of the test.
Na tolerance test was carried out according to plan A, the total urinary excretion of Na during the 8-day test period ranged between 550 and 734 mEq., with an average value of 644 mEq. (SD, ± 54 mEq.) (fig. 1). The reproducibility of the test was examined in four subjects, in each of whom it was carried out twice. The differences in Na excretion between the two trials were 17, 51, 51, and 90 mEq. (Av., 52 mEq.). In the seven normal subjects in whom the Na tolerance test was carried out according to plan B, the total urinary excretion of Na during the 8-day test period ranged between 75 and 160 mEq., with an average value of 130 mEq. (SD, ± 35 mEq.) (fig. 1). The reproducibility of the test was examined in three subjects in each of whom it was carried out twice. The differences in Na excretion between the two trials were 9, 62, and 62 mEq. (Av., 44 mEq.).

Patients with Heart Disease, Plan A

A wide spectrum of responses to the Na tolerance test was observed in patients with heart disease. Among the 41 patients in whom the test was carried out according to plan A, there were 31 patients who excreted less than 550 mEq., the lowest value observed among the normal subjects. The impairment of Na excretion was considered to be extreme in four patients who excreted less than 20 mEq. (fig. 2). It was severe in five patients who excreted between 20 and 200 mEq., moderate in nine patients who excreted between 200 and 400 mEq., and was considered to be mild in 13 patients who excreted between 400 and 550 mEq. Na (fig. 3). In the other 10 patients the total Na excretion was within the normal range, exceeding 550 mEq. The hemodynamic abnormality was considered to be absent or mild in only three of these patients, a woman with a small ventricular septal defect and mild infundibular stenosis resulting in a systolic pressure gradient of 25 mm. Hg, a man with mitral regurgitation, but normal values of cardiac output and left atrial pressure at rest, and a man with idiopathic left ventricular enlargement and normal values of cardiac output.

**Figure 2**

*A comparison of the Na tolerance test (plan A) in a patient with mitral regurgitation (M.R.) carried out preoperatively and four months following mitral valve replacement. R.A., right atrial pressure; m, mean; P.A., pulmonary artery pressure; L.A., left atrial pressure; v, left atrial v wave pressure; C.I., cardiac index; and Pulm. vasc. Resist., Pulmonary vascular resistance.*

*Circulation, Volume XXXII, August 1963*
Figure 3
A comparison of the Na tolerance test (plan A) in a patient with mitral stenosis (M.S.) carried out preoperatively and three months following mitral valvulotomy.

and pulmonary artery pressure. On the other hand, the other seven patients all had marked hemodynamic impairment and, on clinical grounds, their heart disease was considered severe enough to warrant operative treatment. This group included three patients with mitral regurgitation, two with mitral stenosis, one with calcific aortic stenosis, and one with origin of the aorta and pulmonary artery from the right ventricle.

There was no correlation between the severity of the impairment and the type of heart disease which was present. Two of the four patients with extreme impairment suffered from primary myocardial disease, one had mitral stenosis, and one had mitral regurgitation. The three patients with constrictive pericarditis all had relatively mild clinical manifestations of the disease, and their Na excretions were only moderately impaired (303, 347, and 381 mEq.). As already mentioned, the Na excretion was normal in two of the five patients with congenital heart disease. The two adult patients with atrial septal defects exhibited mild impairment, excreting 416 and 425 mEq., while the 60-year-old woman with a small patent ductus arteriosus had moderately severe impairment; she excreted only 259 mEq.

Ten of the 41 patients with heart disease had no recent history of edema, but the Na excretion was normal in only one of them, and in the other nine it ranged between 364 and 544 mEq. On the other hand, in the 31 patients with a history of edema, the Na excretion varied considerably, ranging from normal levels in nine patients, to extreme impairment. It is notable, however, that all 14 patients who excreted less than 350 mEq. had a history of edema.

When the patient's functional classifications (New York Heart Association) were related to Na excretion, it was observed that there was no overlap in the results of the Na tolerance test among the five patients in class IV, all of whom excreted less than 175 mEq., and the 14 patients in classes I or II, all of whom excreted more than 260 mEq. On the other hand, the Na tolerance varied widely among the 22 patients in class III, the Na excretion ranging from 5 to 779 mEq.

Comparisons were made between the Na excretion and a number of hemodynamic variables: mean right atrial pressure, mean
left atrial pressure, right ventricular end-diastolic pressure, left ventricular end-diastolic pressure, mean left atrioventricular diastolic pressure gradient, pulmonary artery systolic pressure, and cardiac index. No significant correlations were noted either when the entire series of 41 patients was considered or when the analysis was carried out within each specific diagnostic category. Similarly, there was no correlation between Na excretion and creatinine clearance.

In order to determine how closely changes in body weight during the 8-day test period reflected the level of Na retention during the tolerance test, these two variables were related to each other (fig. 4). It is apparent that the levels of Na excretion varied considerably among the patients who gained less than 1.5 Kg. However, in all 14 tests in which patients gained between 1.5 and 3.0 Kg., the Na excretion was abnormally low, ranging between 165 and 545 mEq., corresponding to levels of Na retention of between 370 and 755 mEq. In all 13 tests in which the patients gained more than 3.0 Kg., the Na excretion was less than 275 mEq., i.e., the Na retention exceeded 640 mEq.

In 13 patients the Na tolerance test was carried out preoperatively and was repeated 2 to 8 months (Av., 4 mo.) after operation (fig. 5). During the preoperative study, 12 of the patients excreted less than 550 mEq. of Na, the lowest value observed among the normal subjects. Postoperatively, seven of these patients excreted a normal quantity of Na. In four of the other five, although the Na excretion increased markedly, by 294, 328, 358, and 378 mEq., the total remained abnormally low, i.e., less than 550 mEq. Preoperatively, the Na excretion was 39 mEq. In one patient (B.R.), in whom a Starr-Edwards prosthesis was inserted to correct mitral regurgitation, the excretion was only 10 mEq. during the postoperative study, but a cardiac catheterization following the test revealed residual regurgitation around the prosthesis, which ultimately necessitated a second operation. With this exception, the other 12 patients were proved to have hemodynamic benefit from operation (figs. 2 and 3), and in

---

**Figure 4**

Relation between cumulative Na excretion and retention and cumulative weight gain during the 8-day test period when plan A was employed. Open circles, normal subjects; closed circles, patients with heart disease.

**Figure 5**

A comparison of the results of the Na tolerance tests carried out before and after operation. M.S., mitral stenosis; M.I., mitral insufficiency; A.I., aortic insufficiency; A.S., aortic stenosis; and S.E. Repl., Starr-Edwards replacement.
all of them this was associated with either normal or greatly improved Na excretion.

In an attempt to determine the role played by aldosterone in the abnormal Na excretion in three patients with valvular heart disease, the Na tolerance test was carried out during a control study, and was repeated while Aldactone A (100 mg. a day) was administered during the 8-day test period. In each instance the Na excretion was higher in the second test when Aldactone was given, rising from 6 mEq. to 452 mEq., from 39 to 461 mEq., and from 435 to 676 mEq., respectively, in these three patients.

**Patients with Heart Disease, Plan B**

The total urinary excretion of Na was less than 75 mEq., the lowest value encountered among the normal subjects in six of the eight patients in whom the Na tolerance test was carried out according to plan B (total ingestion 320 mEq.). Extremely low values of Na excretion, 2 to 20 mEq., were observed in five patients (two with mitral regurgitation, and one each with combined aortic and mitral regurgitation, combined aortic and mitral stenosis, and primary myocardial disease). The excretion of Na was moderately depressed, 40 mEq., in a patient with arteriosclerotic heart disease, and normal values, 111 and 166 mEq., were noted in two patients with mitral regurgitation. As in the 41 patients with heart disease in whom plan A was utilized, there was no correlation between the degree of impairment of Na excretion, on the one hand, and the clinical history or any specific hemodynamic variable on the other.

An increase in Na excretion was observed in both patients with mitral regurgitation in whom the tolerance test was performed before and after mitral valve replacement, the values in the two patients rising from 16 to 154 mEq., and from 166 to 224 mEq., respectively (fig. 6).

**Discussion**

In spite of the widespread recognition that an abnormality in Na excretion exists in congestive heart failure, no standardized clinical method has been available for detecting the presence and measuring the severity of this abnormality. The Na tolerance test described in this report was developed to provide such a measurement. Several aspects of the test deserve comment. Prior to the administration of the Na load, a diet containing only 10 mEq. of Na a day for 4 days is administered, so that the daily Na excretion is always reduced to a low and similar level at the beginning of the test period. If the intake of Na were not controlled prior to the test, the

![Figure 6](image-url)

*A comparison of the Na tolerance test (plan B) in a patient with mitral insufficiency (M.I.), carried out preoperatively (left), one month postoperatively (center), and one year postoperatively (right).*

*Circulation, Volume XXXII, August 1965*
Na excretion during the first 2 or 3 days would be influenced by the patient's Na intake immediately prior to the test period. It is appreciated that this low dietary intake of Na stimulates aldosterone secretion, and consequently the Na excretion lagged behind the intake for the first 3 days of the test even in the normal subjects. Since the oral Na tolerance test is carried out after a period of reduced Na intake, the level of Na excretion reflects primarily the rate at which Na conserving mechanisms are turned off, and it is possible that this test may prove more sensitive in the detection of slight degrees of impaired excretion than the measurement of Na balance at steady levels of Na intake. The finding that the total excretion of Na was always less than the total amount administered during the test period may be attributed to the low Na intake prior to the test and the fact that the small quantities of Na excreted in feces and sweat were not measured.

Measurement of the rate of excretion of salt administered intravenously would have been much more rapid and convenient than the 8-day oral tolerance test. However, the sudden expansion of intravascular volume could be hazardous in patients with serious heart disease, and it might provide little information in patients with mild heart disease, since, in them, paradoxical augmentation of Na excretion sometimes occurs after an intravenous salt load. In addition, the results of an acute test may be influenced by the level of circulating aldosterone at the moment the test is performed. All these problems are obviated by the 8-day oral Na tolerance test.

Although elucidation of the mechanism responsible for salt retention in heart failure was not the primary objective of the present study, it is of interest that the response to the Na load was markedly improved by the administration of Aldactone A, an aldosterone antagonist. This finding is compatible with the view that increases in the levels of circulating aldosterone may play an important role in the Na and H2O retention characteristic of heart failure. It was surprising that the results of the Na tolerance test did not correlate with any of the hemodynamic variables that were measured. These findings are at variance with those of Hollander and Judson, who observed a significant correlation between elevation of the right ventricular end-diastolic pressure and abnormal Na excretion. However, these investigators used the history of edema to determine whether or not Na excretion was impaired, and in this study little correlation was noted between such a history and the results of the Na tolerance test. Our finding of a lack of correlation between any of the intracardiac pressures, or the cardiac index, and Na excretion, must not be interpreted to indicate that a single hemodynamic abnormality is not ultimately responsible for impaired Na excretion in congestive heart failure. Indeed, in every patient augmentation of Na excretion following operation was always associated with demonstrable hemodynamic improvement (figs. 2, 3, and 6). In considering the entire group of patients it must be realized that the range of normal values of cardiac output and of intracardiac pressures is relatively wide. It therefore becomes understandable that no over-all correlation between any of these variables and the impairment of Na excretion was evident. Furthermore, even if the abnormality of Na excretion in congestive heart failure could ultimately be related to a depression of the cardiac output or an elevation of right atrial pressure, there is no reason to suppose that Na excretion would become impaired at the same level of the output or pressure in every patient.

It must be appreciated that the demonstration of an abnormal Na tolerance provides no information concerning the etiology of the impairment. Although the presence of heart disease was apparently responsible for all instances of impaired Na excretion described herein, primary renal disease or endocrine abnormalities can also, of course, affect Na excretion. Since Na excretion may normally be impaired just prior to menstruation, the test was not carried out during this phase of the ovulatory cycle in menstruating female patients. The endogenous creatinine clearance,
which averaged 91 ± 8 ml./min./1.73 M.² in the normal subjects, varied considerably among the patients with congestive heart failure, ranging from 52 to 110 ml./min./1.73 M.² (Av., 78 ± 16 ml./min.). Even the lowest creatinine clearances observed in the patients with heart failure cannot account, by themselves, for the abnormality in Na excretion, since many patients with primary renal disease exhibit more marked depression of the filtration rate without apparent impairment of Na excretion. Furthermore, we observed no correlation between the creatinine clearance and the level of Na excretion, which confirmed the impression that abnormalities of the glomerular filtration rate are not primarily responsible for the impaired Na excretion in heart failure.⁹

The striking augmentation of Na tolerance after corrective cardiac operations (fig. 5), provides objective evidence that, by correcting the hemodynamic abnormalities, the surgical procedures also improved those aspects of circulatory function that are related to Na excretion. However, the failure of improvement of Na tolerance in two of the patients postoperatively warrants special comment. In one of them, patient B. R., a prosthetic mitral valve had been inserted in the treatment of mitral regurgitation and his persistent failure to excrete Na led to the postoperative investigations which showed that the substantial regurgitation was taking place around the prosthetic valve. Eight months after successful reoperation, the Na excretion was still markedly impaired (24 mEq.), but the clinical signs of severe tricuspid regurgitation were still present. Similarly, in patient M. G., Na excretion was grossly abnormal in the early postoperative period (fig. 6), but rose to normal levels in the ensuing months. Preoperatively this patient had marked elevations of the pulmonary artery pressure and of the pulmonary vascular resistance, with clinical and hemodynamic evidence of tricuspid regurgitation. Her course suggests that these hemodynamic abnormalities resolved quite slowly after operation.

The potential clinical usefulness of the Na tolerance test may be illustrated by the findings in a 41-year-old woman with a small ventricular septal defect and mild obstruction to right ventricular outflow, and a 45-year-old man with mitral regurgitation, mild cardiac enlargement, but normal values of the mean left atrial pressure and cardiac output at rest. Although the hemodynamic abnormality in both of these patients was relatively mild, they complained of troublesome fluid accumulation and had been urged by their referring physicians to have corrective operations. The demonstration that there was no impairment of Na excretion, even when they were stressed with a large Na load, provided objective evidence that operation would probably not influence this symptom. In contrast, the demonstration of unequivocal impairment of Na excretion in three patients with mitral valve disease, but with only minimal elevations of left atrial pressure, provided the only evidence of disturbed circulatory function and, when taken together with the patients' symptomatic disabilities, proved to be the major indication for operation. As a consequence of corrective surgery these three patients have not only exhibited clinical improvement, but have also demonstrated return of Na excretion to normal. Thus, the oral Na tolerance test is likely to be of the greatest clinical value in patients in whom the results of the clinical examination and the usual laboratory tests for circulatory failure are inconclusive, and in evaluating the effects of drugs and other interventions on the ability of patients with heart disease to excrete Na.

Summary

An oral sodium tolerance test was devised to detect and quantify impaired Na excretion in patients with heart failure. Following a 4-day period during which daily Na intake was limited to 10 mEq., 80 mEq. of Na were administered daily for 4 days and 150 mEq. for another 4 days. The total urinary Na excretion during the 8-day test period was determined. Thirteen normal subjects excreted between 550 and 734 mEq. of Na. Of 41 pa-
tients with heart disease, 31 excreted subnormal amounts of Na, between 10 and 550 mEq, and only 10 excreted normal quantities. An alternate plan, in which 320 mEq of Na was administered in 8 days, was also utilized in patients in whom the standard 920-mEq Na load was considered inadvisable. There was no correlation between the impairment of Na excretion, as estimated by the Na tolerance test, and the etiology of the heart disease, the glomerular filtration rate, or any hemodynamic variable. Patients with marked functional disability excreted less Na than those with few symptoms, and the patients with the most severe impairment of Na excretion all had a history of edema. Striking improvement in Na tolerance followed corrective cardiac operations. The Na tolerance test was found of particular usefulness in the evaluation of patients in whom clinical examination and hemodynamic studies gave no conclusive evidence as to the presence or absence of congestive heart failure.

References

The Enigma of Creativity

The creative process is often not responsive to conscious efforts to initiate or control it. It does not proceed methodically or in programmatic fashion. It meanders. It is unpredictable, digressive, capricious. As one scientist put it, "I can schedule my lab hours, but I can't schedule my best ideas." Obviously in any complex performance the process must at some point be brought under conscious discipline and control. But the role of the unconscious mind in creative work is clearly substantial.—John W. Gardner. Self-Renewal. The Individual and the Innovative Society. New York, Harper & Row, Publishers, 1963, p. 34.
A Method for the Detection and Quantification of Impaired Sodium Excretion: Results of an Oral Sodium Tolerance Test in Normal Subjects and in Patients with Heart Disease

EUGENE BRAUNWALD, WILLIAM H. PLAUTH, JR. and ANDREW G. MORROW

Circulation. 1965;32:223-231
doi: 10.1161/01.CIR.32.2.223

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1965 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/32/2/223

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation 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 is online at: http://circ.ahajournals.org/subscriptions/