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Report

Report of the Working Group for Dietary Salt Reduction of the Japanese Society of Hypertension: (1) Rationale for Salt Restriction and Salt-Restriction Target Level for the Management of Hypertension

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Salt excess is well known to be involved in the pathophysiology of hypertension, and thus restriction of salt intake is widely recommended for management of the disease. Excessive salt intake induces blood pressure (BP)–dependent as well as –independent progression of cardiovascular disease. Although the human body is considered to be adapted to very low salt intake (0.5–3 g/day), restriction to such a low level of salt intake is extremely difficult to accomplish in developed countries. Significant BP reduction has been reported in large-scale clinical studies in which salt intake was decreased to less than 6 g/day, and the results of a meta-analysis have shown that systolic BP was reduced about 1 mmHg with every decrease in salt intake of 1 g/day in hypertensive subjects. Current guidelines for the treatment of hypertension, including Japanese guidelines, recommend dietary salt reduction to 6 g/day or less in hypertensive patients. However, it appears to be fairly difficult to attain this target of salt intake, especially in Japan. There is thus a need for feasible and effective measures to attain this salt restriction target. (*Hypertens Res* 2007; 30: 879–886)

Key Words: dietary salt, hypertension, cardiovascular disease, guidelines, large-scale clinical study

Introduction

Salt excess is well known to be involved in the pathophysiology of hypertension, and thus restriction of salt intake is widely recommended for management of the disease. Treatment guidelines for hypertension in Western countries recommend salt restriction to 6 g/day (sodium [Na] 100 mmol/day) or less for hypertensives (*1*, *2*). Because salt intake is higher in Japan than in Western countries, the 2000 version of the Guidelines for the Management of Hypertension (JSH 2000) from the Japanese Society of Hypertension (JSH) set the target of salt intake at 7 g/day or less (*3*). However, the target was revised to less than 6 g/day in the new Japanese guidelines (2004 version: JSH 2004) (*4*). To promote salt restriction for the management of hypertension, the JSH organized the Working Group for Dietary Salt Reduction in 2005. In this report, we summarize the rationale for restricting salt intake for the management of hypertension. The Japanese version of the working group report has been published previously (*5*).

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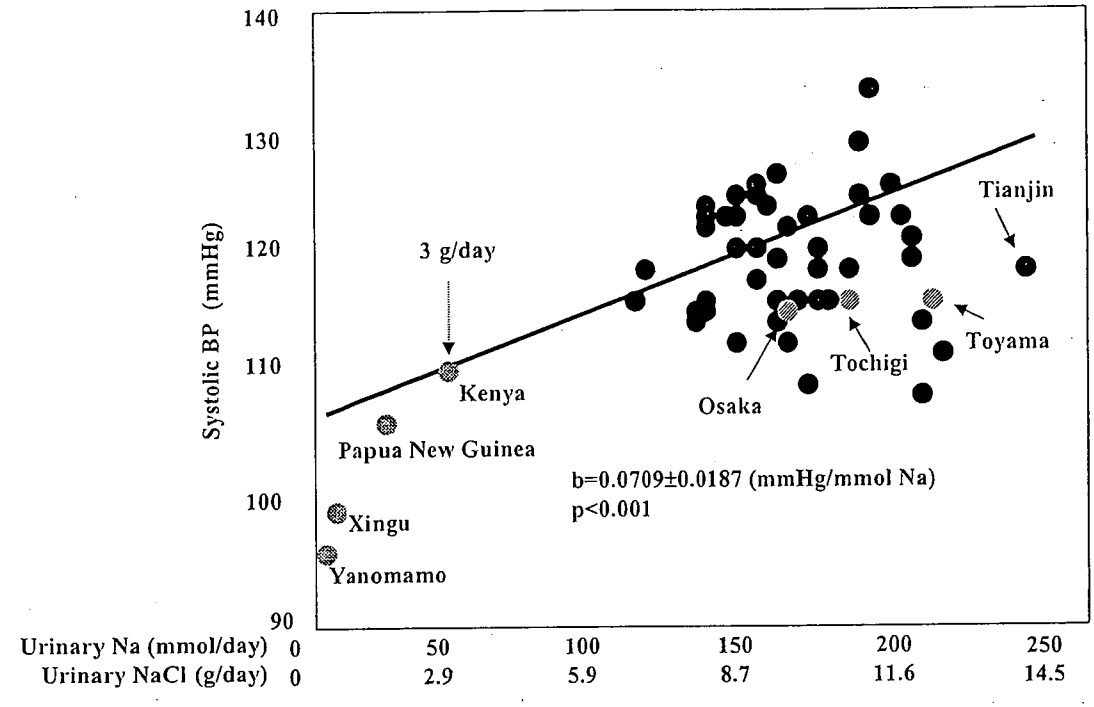

Fig. 1. *Relationship between salt intake and systolic blood pressure (BP) (from Intersalt Cooperative Research Group (8) with modification).*

Historical Background and Current Status of Salt Intake

Many land-dwelling animal species have difficulty gaining free access to salt and an innate salt appetite. In humans, low availability of salt has been a problem for millennia, and the period in which they could consume a large amount of salt has been very short in the history of mankind. It is estimated that humans in the Stone Age consumed salt at only 0.5–3 g/day (*6*), and the human body is considered to be adapted to such low salt intake. Physiologic studies have also suggested that the minimum salt requirement for human survival is about 0.5 g/day (*7*).

The amount of salt intake in humans shows wide regional and individual variations. The international cooperative Intersalt study, which investigated salt intake and blood pressure (BP) in various parts of the world, reported that salt intake ranged from less than 0.1 g/day in Yanomano, South America to about 15 g/day in Tianjin, China (*8*) (Fig. 1). Generally, salt intake is low in undeveloped regions and high in developed countries.

In Japan, the salt intake was traditionally high, especially in the Tohoku District (about 25 g/day in the 1950s) (*3*). Although the amount of salt consumption in Japanese has considerably decreased, the intake remains high, at about 11 g/day (*9*) (Fig. 2). Therefore, even today, most Japanese are consuming about 10 times the required amount of salt. In hypertensive patients treated on an outpatient basis, the mean salt intake estimated from the urinary Na excretion has also been reported to be high, at about 11 g/day (*10*) or 10 g/day (*11*). Salt intake is slightly higher in males than in females (*9*, *11*). Since this gender difference disappears when the values are corrected for body weight, it is considered to be ascribable to gender-related differences in physique (*11*).

Effects of Excessive Salt Intake

Hypertension

Many epidemiological, experimental, and clinical studies have clearly indicated that excessive salt intake is related to increases in BP and the progression of hypertension (*12*). For example, the Intersalt study found that salt intake was significantly correlated with BP; BP was extremely low particularly in groups with very low (less than 3 g/day) salt intake (*8*, *13*) (Fig. 1, Table 1). Moreover, little age-associated increase in BP was noted in these groups. Therefore, salt intake of less than 3 g/day is considered to be ideal for the prevention or treatment of hypertension.

Experimentally, the intake of excessive salt has been shown to induce or exacerbate hypertension in many models, including Dahl salt-sensitive rats and deoxycorticosterone acetate (DOCA)–salt hypertensive rats. Although the mechanism by which salt increases BP has not been completely elucidated, the kidney is considered to play an important role. The central

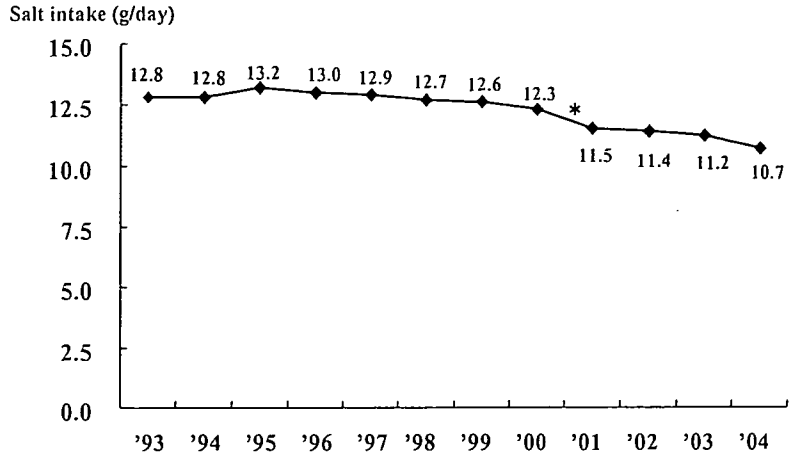

Fig. 2. *Trend of daily salt intake in Japan (based on data of Lifestyle-Related Disease Control Section, General Affairs Division, Health Bureau, Ministry of Health, Labor and Welfare (9)). *Calculated on the basis of the 4th edition of the Standard Tables of Food Composition in Japan until 2000 and 5th edition after 2001.*

Table 1. Comparison of Low Salt Intake Groups with Other Groups—Intersalt Study*

	Yanomamo	Xingu	Papua New Guinea	Kenya	Others (n=48)
Lifestyle					
Salt intake (g/day)	<0.06	0.35	1.6	3.0	9.4
Na/K ratio	<0.01	0.08	0.48	1.8	3.4
BMI (kg/m^2)	21.2	23.4	21.7	20.8	25.2
Regular drinkers (%)	0	0	8.7	30.7	53.0
Bood pressure					
Systolic BP (mmHg)	95.4	98.9	107.7	109.9	118.7
Diastolic BP (mmHg)	61.4	61.7	62.9	67.9	74.0
Hypertensives (%)	0	1.0	0.8	5.0	17.4
Age-associated increases in BP (mmHg/10 years)	−1.1	+0.6	−1.4	+2.4	+5.0

*From Stamler *et al.* (*13*) with permission. Na/K ratio, sodium/potassium ratio; BMI, body mass index; BP, blood pressure.

nervous system, various neurohumoral factors, and vasoactive substances may also be involved (*12*).

Many clinical reports have suggested that BP is increased by excessive salt intake. However, the increase in BP due to excessive salt intake varies widely among individuals, and many people remain normotensive even on a high-salt diet. In fact, hypertensives can be classified into salt-sensitive and non–salt-sensitive groups, because the responses of BP to a high-salt or low-salt diet are not uniform (*14*, *15*). Many factors, including genetic interference, renal function, and neurohumoral elements, are involved in the salt sensitivity of BP.

Cardiovascular Diseases

Salt excess is related to the occurrence and progression of cardiovascular diseases through its BP-increasing effects, but it has also been shown that salt exerts adverse effects on the cardiovascular system by different mechanisms in addition to rise in BP (*16*) (Table 2). Excessive salt intake causes left ventricular hypertrophy and thickening of the vascular wall independently of its effects on BP. According to a report from Finland, mortality from ischemic heart disease, stroke and all causes increased significantly with increases in salt intake even after correction for BP or other factors (*17*) (Table 3). Furthermore, salt intake has been shown to be an independent risk factor of stroke and heart failure (*18*, *19*). Dietary salt may also relate to impairment of platelet aggregation and renal function (*15*), so that salt excess is considered to confer a greater risk of cardiovascular diseases than would be expected by a mere increase in BP.

Other Disorders

Excessive salt intake is also related to several other disorders (*16*) (Table 2). An increase in salt intake elevates the urinary calcium (Ca) excretion and the incidence of urolithiasis. This loss of Ca through the kidney also decreases Ca in the bone and increases the risk of osteoporosis. Moreover, a relation-

Table 2. Adverse Effects of Salt Independent of BP

Cardiovascular system
Left ventricular hypertrophy
Thickening/hardening of vascular wall
Platelet aggregation
Cardiovascular disorders
Stroke
Ischemic heart disease, Heart failure
Impairment of renal function
Other disorders
Urolithiasis
Osteoporosis
Stomach cancer
Asthma

ship between salt intake and stomach cancer has been suggested by epidemiological studies. A high-salt environment has recently been reported to promote the propagation of *Helicobacter pyroli*. A relationship between salt intake and asthma has also been suspected. Thus, excessive salt intake is considered to exert various adverse effects.

Antihypertensive Effect of Salt Restriction

There is much evidence based on clinical studies that restriction of salt intake reduces BP in hypertensives. In Japan, Ito *et al.* reported the results of moderate restriction of salt intake in a small number of subjects. Blood pressure decreased slightly but not significantly when salt intake was reduced from 13 g/day to 7 g/day but significantly when it was rigorously restricted to 3 g/day (*20*). All large-scale clinical studies to date have been performed in Europe or America. Significant decreases in BP were observed in the Trials of Hypertension Prevention (TOHP)-Phase I (TOHP-I) (*21*), the Trial of Nonpharmacologic Interventions in the Elderly (TONE) (*22*), a report from He *et al.* (*23*), and the Dietary Approaches to Stop Hypertension (DASH)-Sodium trial (*24*), in all of which salt intake was reduced to less than 6 g/day (Table 4). But the decreases were not significant in the TOHP-II study (*25*), in which restriction of salt intake was milder. In the Hypertension Prevention Trial (HPT), salt intake was reduced to less than 6 g/day, but no significant decrease in BP was observed, probably because salt intake was also decreased in the control group (*26*). In the TONE, evaluations were also performed at various levels of salt restriction achieved, and salt intake to 5.64 g/day or less was effective for the maintenance of a normal BP after discontinuation of antihypertensive medication (*22*). On the basis of these results, many guidelines for the management of hypertension in Western countries recommend less than 6 g/day as a target for salt restriction (*1*, *2*).

According to a meta-analysis of randomized studies on the effect of moderate salt restriction, BP decreased by a mean of 5.0/2.7 mmHg in hypertensive subjects (*27*) (Fig. 3). The

Table 3. Hazard Ratios and 95% CI of Deaths Due to Ischemic Heart Disease, Stroke, and All Causes Associated with Increases in the Urinary Na Excretion (100 mmol/day) after Adjustment*

Cause of death	Hazard ratio (95% CI)
Ischemic heart disease	1.56 (1.15–2.12)
Stroke	1.36 (1.05–1.76)
All causes	1.22 (1.02–1.47)

*From Tumilehto *et al.* (*17*) with modification. CI, confidence interval; BP, blood pressure.

median urinary Na excretion was 161 mmol/day (conversion to salt: 9.5 g/day) on an unrestricted diet and 87 mmol/day (5.1 g/day) on a low-salt diet, with a median decrease in the urinary Na excretion of 78 mmol/day (4.6 g/day). In normotensive subjects, the mean decrease in BP was 2.0/1.0 mmHg, and the decrease in the urinary Na excretion was 74 mmol/day (4.4 g/day). A recent analysis showed a clear quantitative relationship between the degree of decrease in salt intake and BP in a salt intake range of 3–12 g/day (*27*). In hypertensives, the systolic BP is considered to decrease by about 1 mmHg with each decrease in salt intake of 1 g/day. If a person who has consumed salt at 12 g/day restricts salt intake to 6 g/day, a considerable decrease in BP is expected with a consequent decrease in the dose of antihypertensive medication and prevention of cardiovascular diseases.

There have been no large-scale clinical studies about the effects of salt reduction on BP in Japan. However, many short-term clinical studies have shown that the restriction of salt intake effectively lowers BP in hypertensive Japanese (*20*, *28–31*). The average reduction in mean BP with a low-salt diet in those studies was 5–10 mmHg, which was comparable to the results of a meta-analysis. It has been shown that there is a racial difference in the salt sensitivity of BP, with the sensitivity in blacks being greater than that in whites (*32*). Although there are no studies directly comparing the salt sensitivity among Japanese and other races, the salt sensitivity of BP in Japanese may be intermediate between those of blacks and whites.

However, the responses of BP to a decrease in salt intake show marked individual variation. The depressor effect of reduction in salt intake has been shown to be large in the elderly, patients with renal dysfunction, those with severe hypertension, and those with low-renin hypertension (*28*, *32*). However, because hypertension arises through the intricate interplay of many factors, it is not easy to predict the salt sensitivity of BP in individual patients, and evidence is not sufficient to warrant individualized recommendations of salt restriction.

Decreases in BP due to salt restriction are observed 24 h a day (*29*). Also, it has been reported that many salt-sensitive hypertensives are non-dippers, who show only small nocturnal decreases in BP, on a high-salt diet, but become dippers

Table 4. Antihypertensive Effects of Reductions in Salt Intake in Large-Scale Clinical Studies

Study (year of publication)	Subjects	Observation period	Group	Number of subjects	Intake or urinary excretion of salt (g/day)			Systolic BP (mmHg)			Diastolic BP (mmHg)		
					Before	After	Difference	Before	After	Difference	Before	After	Difference
HPT (1990) (*26*)	Healthy adults	6 months	Control	196	7.66	6.97	−0.69	123.9	121.8	−1.7±0.9	83.0	80.0	−0.4±0.7
			Salt reduction	196	7.55	5.89	−1.66	124.0	120.2	$p=0.126$	82.6	79.2	$p=0.664$
		3 years	Control	196	7.66	7.66	0	123.9	121.0	0.1±1.0	83.0	80.0	0.2±0.8
			Salt reduction	196	7.55	6.81	−0.74	124.0	121.2	$p=0.885$	82.6	79.8	$p=0.8$
TOHP-I (1992) (*21*)	Healthy adults*	6 months	Control**	417	9.20			125.1	121.9	−1.69	83.9	80.6	−0.85
			Salt reduction**	327	9.09	6.50	−2.59	124.8	119.9	$p<0.01$	83.7	79.6	$p<0.05$
TOHP-II (1997) (*25*)	Healthy adults	36 months	Control	596	11.95	11.33	−0.62	127.3	127.0	−0.4±0.4	85.8	83.4	−0.1±0.3
			Salt reduction	594	11.98	8.99	−2.99	127.7	127.0	$p=0.24$	86.1	83.2	$p=0.68$
TONE (1998) (*22*)	Healthy adults***	30 months	Control	147	8.53	8.51	−0.02		24.4%†	RR 0.69			
			Salt reduction	144	8.53	6.19	−2.34		37.8%†	$p<0.001$			
He *et al.* (2000) (*23*)	Healthy adults (from TOHP-I)	7 years	Control	70	8.69	7.5	−1.19	122.6	120.2	$p=0.01$	84.2	78.6	$p=0.08$
			Salt reduction	58	8.71	5.56	−3.15	122.7	117.0		83.8	76.6	
DASH-Sodium†† (2001) (*24*)	Healthy adults (including hypertensives)†††	30 days	DASH diet/Salt reduction	204	8.47	6.29	−2.18	128.1	126.8	$p<0.001$	83.1	82.5	n.s.
			Control/Salt reduction	208	8.29	6.24	−2.05	135.0	132.9	$p<0.05$	86.0	84.9	$p<0.01$

*Diastolic BP: 80–89 mmHg. **Frequency of hypertensives: 11.3% in the control group, 8.6% in the salt reduction group (RR 0.84, 95% CI 0.62–1.13). ***BP < 145/85 mmHg at ages 60–80 years. †Percentage of subjects not having reached the endpoint (diagnosis of hypertension, beginning of antihypertensive medication, cardiovascular event). ††Only the results of moderate salt reduction. †††BP > 120/80 mmHg, including mildly hypertensive (140–159/90–99 mmHg). BP, blood pressure; RR, relative risk; CI, confidence interval.

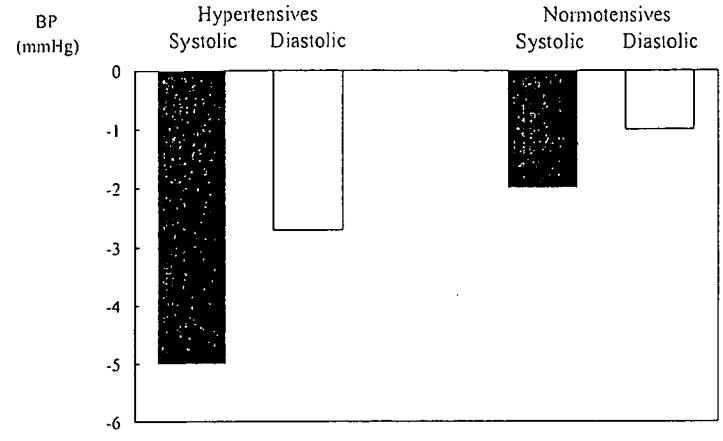

Fig. 3. *Effects of moderate salt reduction on BP according to a meta-analysis of randomized clinical trials (based on data of He et al. (27)).*

Table 5. Salt Reduction Accomplishment Rate in the TONE Study*

Salt reduction level	<5.6 g/day	>7.1 g/day
Control group	15.3%	67.7%
Salt reduction group	51.2%	29.7%
Weight control group	6.1%	79.6%
Salt reduction + weight control group	23.8%	49.0%

*From Espeland *et al.* (*36*) with modification.

with salt restriction (*31*).

Dietary intakes of potassium and sodium interact in the regulation of BP (*33*). Increasing potassium intake decreases BP mainly *via* natriuresis, and increasing sodium intake stimulates potassium excretion. A high potassium diet accomplished by means of fruit and vegetable intake is now widely recommended in the management of hypertension (*1*, *2*, *4*). The DASH-Sodium study has shown that a DASH (high potassium) diet and sodium restriction additively lower BP, but the effect of sodium restriction was greater under a normal diet than under the DASH diet (*24*). Thus a low sodium, high potassium diet is suitable for hypertensive subjects, but the BP-lowering effect of salt reduction appears to be attenuated by increasing potassium intake.

Restriction of salt intake also enhances the effects of some antihypertensive agents. This effect is particularly evident in inhibitors of the renin-angiotensin system. Sympatholytic agents are also expected to have similar effects.

An improvement of cardiovascular disease outcome can be expected with long-term restriction of sodium intake. The follow-up study of the TOHP-I and -II has shown that risk of a cardiovascular event is 30% lower among participants in the intervention (sodium restriction) group compared to those in the control group after adjustment for confounding factors (*34*). Therefore, sodium restriction not only lowers BP but may also reduce long-term risk of cardiovascular events.

Attainment and Maintenance of the Salt-Reduction

Lifestyle modifications, including salt restriction, are extremely important for the management of hypertension, but the difficulty of attaining and maintaining such changes is a problem (*35*). There have been few reports on the attainment rate of salt reduction in hypertensives, but in the TONE, a trial with elderly hypertensive subjects, the target of less than 5.6 g/day was attained by about half of the patients in the salt reduction guidance group and about 1/4 of the patients in the salt reduction plus weight control group (*36*) (Table 5). In Japan, in a trial in which physicians provided salt reduction guidance to hypertensives with a target of less than 6 g/day, mean salt intake decreased from 11.2 to 9.9 g/day, but the target was attained in only 12% of subjects (*10*, *35*). Also, while salt intake was lower in hypertensives intending to reduce salt intake than in those not intending, it was 9.4 and 10.6 g/day, respectively, with a minor difference (*11*). According to a report of the International Population Study on Macronutrients and Blood Pressure (INTERMAP), in Japanese subjects, among those practicing salt reduction, only 41.6% attained a target of less than 10 g/day, and the average salt intake estimated from the urinary Na excretion was 10.5 g/day (*37*). Therefore, attainment of the target of less than 6 g/day appears to be fairly difficult.

Limitations of long-term compliance to salt restriction and its effects have also been demonstrated. In the Treatment of Mild Hypertension Study (TOMHS), which provided 4-year lifestyle guidance to mildly hypertensive subjects, salt intake decreased by 2–3 g/day during the first year, but the decrease regressed to less than 1 g/day after 4 years (*38*). Moreover, a meta-analysis of long-term randomized interventional studies of 6 months or longer duration in normotensive and hyperten-

sive subjects showed that the mean decrease in salt intake was 2.1 g/day, and the mean decrease in BP was only 1.1/0.6 mmHg (*39*).

Salt-Reduction Target for the Management of Hypertension

Dietary salt appears to be related to hypertension, and excessive salt intake exerts adverse effects on the cardiovascular system independently of BP. While the antihypertensive effect of salt restriction is dependent on the degree of salt reduction, significant depressor effects have been confirmed at restriction levels of 6 g/day or less in large-scale clinical trials. Therefore, for the management of hypertension, the target of salt reduction should ideally be less than 6 g/day as in Western guidelines. In Japan, the target of salt reduction was set at 7 g/day or less in JSH 2000 (*3*) because of the traditionally high salt intake, but salt intake of Japanese has since decreased by about 1 g/day, so that it was considered reasonable to reset the target to less than 6 g/day in the subsequent JSH 2004 guidelines (*4*).

Presently, it appears to be difficult to attain the target of less than 6 g/day, but promotion of nationwide educational activities about the importance of the prevention and treatment of hypertension by salt restriction and its considerable preventive effect against cardiovascular and other diseases is considered to be a socially, economically, and medically important task. The establishment of feasible and effective measures by multi-faceted approaches is desirable for the attainment of the target of salt reduction.

Conclusions

Excessive salt intake is closely related to the occurrence and progression of hypertension, and it also exerts adverse effects on the cardiovascular system independently of BP. The depressor effect of salt restriction is dose-dependent, and despite marked individual variation, BP has been shown to decrease about 1 mmHg on average with each decrease in salt intake of 1 g/day. Salt reduction is important for the prevention and treatment of hypertension, and there is reasonable evidence in support of the current salt-restriction target of less than 6 g/day (Na < 100 mmol/day). Salt reduction is particularly important in Japan, a country with high salt intake, but attaining the new target has proven difficult in Japanese hypertensives. There is thus a need to establish new effective measures for attaining the target.

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Report

Report of the Working Group for Dietary Salt Reduction of the Japanese Society of Hypertension: (2) Assessment of Salt Intake in the Management of Hypertension

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Restriction of dietary salt is widely recommended in the management of hypertension, but assessment of individual salt intake has drawn little attention. The understanding of salt intake is important as a guide for optimizing salt-restriction strategies. However, precise evaluation of salt intake is difficult. More reliable methods are more difficult to perform, whereas easier methods are less reliable. Thus, the method to assess salt intake should be determined as the situation demands. The Working Group for Dietary Salt Reduction of the Japanese Society of Hypertension recommends the assessment of individual salt intake using one of the following methods in the management of hypertension. 1) The measurement of the sodium (Na) excretion from 24-h urine sampling or nutritionist's analysis of the dietary contents, which are reliable but difficult to perform, are suitable for facilities specializing in the treatment of hypertension. 2) Estimation of the Na excretion from the Na/creatinine (Cr) ratio in spot urine is less reliable but practical and is suitable for general medical facilities. 3) Estimation using an electronic salt sensor equipped with a calculation formula is also less reliable but is simple enough that patients can use it themselves. The patients are considered to be compliant with the salt-restriction regimen if salt intake measured by whichever method is less than 6 g (100 mmol)/day. (*Hypertens Res* 2007; 30: 887–893)

Key Words: salt intake, food weighing, food questionnaire, urinary sodium excretion, hypertension

Introduction

Excessive salt or sodium (Na) intake causes hypertension, and restriction of salt intake is widely recommended for the management of hypertension. In the 2004 version of the Japanese Society of Hypertension (JSH) Guidelines for the Management of Hypertension (JSH 2004), the target of salt restriction was tightened from 7 g/day or less to less than 6 g/day (*1*). On the other hand, while the salt intake in Japan is decreasing, it is still high, being about 11 g/day (*2*). Also, salt intake shows considerable individual variation and daily fluctuation in the same individual.

An understanding of individual salt intake is considered to be important for successful salt reduction, because it leads to appropriate guidance and judgement of whether the target of salt restriction has been attained. However, there are several problems with the assessment of salt intake, and its imple-

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Table 1. Evaluation Methods of Salt Intake

Evaluation method	Reliability	Convenience
Evaluations based on dietary contents		
Weighing method	◎	×
Questionnaire method	○	△
Measurement before intake	◎	×
Evaluation using test paper or salt sensor	×	◎
Evaluations based on the measurement of urinary Na excretion		
24-h pooled urine	◎	×
Nighttime or early morning urine	○	△
The second urine sample after waking	○	△
Spot urine	△ (○*)	○
Evaluation using test paper or salt sensor	× (△**)	◎

◎, excellent; ○, good; △, fair; ×, poor. *When a formula for the estimation of the daily creatinine (Cr) excretion is used. **When a salt sensor installed with the formula is used.

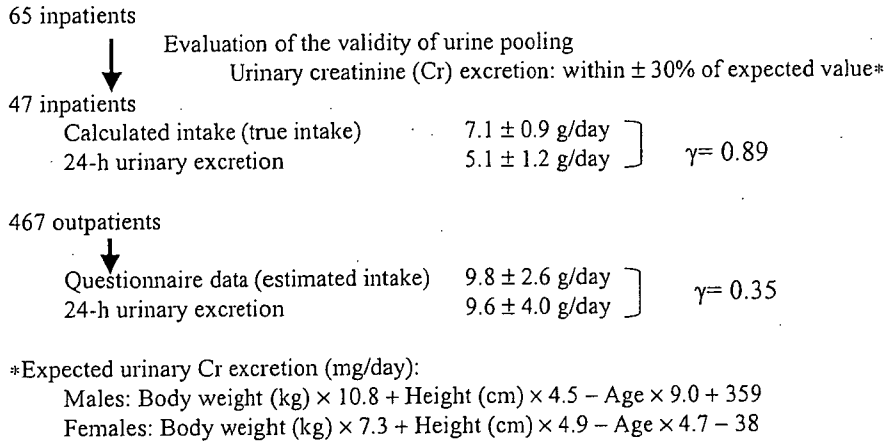

Fig. 1. *Calculated dietary salt intake and 24-h urinary excretion in inpatients and estimated salt intake based on a questionnaire and 24-h urinary excretion in outpatients (from data of Fukumoto et al. (9))*

mentation is often difficult. Most of the current guidelines for the management of hypertension do not mention the methodological aspect of assessing salt intake. While the guidelines of the World Health Organization and International Society of Hypertension (WHO/ISH) state that counseling by a skilled nutritionist and monitoring of the urinary Na level are necessary in most cases, they do not mention specific methods for these purposes (*3*).

This report describes variations and characteristics of salt intake–assessment methods and proposes the guidelines for the assessment of salt intake for the management of hypertension as part of the activities of the Working Group for Dietary Salt Reduction of the JSH. The Japanese version of the working group report has been published previously (*4*).

Methods to Assess Salt Intake

There are several methods for the assessment of salt intake. In general, however, the choice of method involves a compromise between accuracy and ease-of-use, with relatively precise methods being difficult to perform, and simpler methods being less reliable (Table 1). Also, because salt intake is not fixed in each person, its assessment is naturally subject to limitations in accuracy (*5*). Sodium, which is important in the occurrence and progression of hypertension, is primarily ingested as salt (NaCl). Since 1 g of salt is equivalent to 17 mmol (17 mEq) of Na, 6 g of salt is about 100 mmol (100 mEq) of Na. In terms of relative weight, a given amount of Na in salt would weigh 2.5 times more than the equivalent amount as pure Na (for example, 400 mg of Na is equal to 1 g of salt).

Assessment Based on Dietary Contents

Weighing Method

This method, by which salt intake is estimated by weighing

Table 2. Formula for the Estimation of the 24-h Sodium (Na) Excretion from Nighttime Urine Data and Estimated Cr Excretion (*18*)

24-h Na excretion (mmol/day)	
Male	$0.634 \times (Na_n/Cr_n) \times Pr.UCr_{24} + 104.7$
Female	$0.682 \times (Na_n/Cr_n) \times Pr.UCr_{24} + 62.6$
	Na_n: Na concentration in nighttime urine (mEq/L)
	Cr_n: Cr concentration in nighttime urine (g/L)
	$Pr.UCr_{24}$: estimated 24-h urinary Cr excretion (g/day)
	Male $0.027 \times$ LBM
	Female $0.022 \times$ LBM
	LBM = Body weight (kg) − Body fat mass (kg)

Cr, creatinine; LBM, lean body mass.

Table 3. Formula for the Estimation of the 24-h Na Excretion from Data in the Second Urine Sample after Waking and Estimated Cr Excretion (*19*)

24-h Na excretion (mmol/day) $= 16.3 \times \sqrt{(Na_{SMU}/Cr_{SMU})} \times Pr.UCr_{24}$
Na_{SMU}: Na concentration in 2nd urine sample after waking (mEq/L)
Cr_{SMU}: Cr concentration in 2nd urine sample after waking (mg/L)
$Pr.UCr_{24}$: estimated 24-h urinary Cr excretion (mg/day)
Male Body weight (kg) × 15.1 + Height (cm) × 7.4 − Age × 12.4 − 80
Female Body weight (kg) × 8.6 + Height (cm) × 5.1 − Age × 4.7 − 75

Cr, creatinine.

the food ingested by each subject, is highly reliable (*6*). Concerning Na, the values estimated from the food weight based on the Standard Tables of Food Composition in Japan (*7*) have been shown to be close to, and strongly correlated with, the actual values measured in the ingested food. However, this method is complicated and requires calculation by a nutritionist. Also, a 1-day survey is considered to be insufficient for accurate assessment of salt intake, which changes from day to day.

Questionnaire Method

By this method, dietary salt intake is estimated from data obtained by a questionnaire or interview performed over one to several days. While it is easier than the weighing method, this method still requires calculation by a nutritionist. Although there has been a report suggesting that its reliability is comparable to that of the weighing method (*8*), its accuracy is considered to be slightly inferior. Also, while the mean salt intake estimated by interview has been reported to agree with the value based on the 24-h urinary Na excretion, its correlation to actual salt intake was not high, and actual salt intake may be underestimated by this method (*9*) (Fig. 1).

Measurement before Intake

In the measurement-before-intake method, daily salt intake is determined by measuring or estimating the salt content of food to be eaten before ingestion. If performed precisely, this method is highly reliable. Hospital meals and test meals for clinical research are examined by this method. Since the salt intake is revealed before ingestion of the meal, this method is useful for the practice of salt reduction. However, it is inconvenient to measure the salt content before each meal. Moreover, accurate determination requires calculation by a nutritionist, although rough calculation can be performed by untrained individuals.

Measurement of the Urinary Na Excretion

Measurement by 24-h Urine

In this method, urine is collected for 24 h, and salt intake is assessed by determining the urinary Na excretion. This method is considered to be reliable and is used in many clinical and epidemiological studies, including the international cooperative Intersalt study (*10*). However, it is relatively difficult to perform because of the necessity of 24-h urine sampling, and inadequate urine pooling leads to underestimation of salt intake. The nuisance of 24-h urine collection is slightly mitigated by the use of a portable urine sampler (Urinmate®), which allows fractionated partial urine sampling (*11*). For accurate assessment of salt intake, even the 24-h urine sampling method is insufficient if performed over only 1 day, and thus measurement over several days is considered necessary (*11*, *12*). In addition, while most of the ingested Na is excreted in urine, part of it is contained in feces or sweat. Salt intake determined from the Na excretion in 24-h urine has been shown to be 0.5–3 g/day lower than the true intake, and

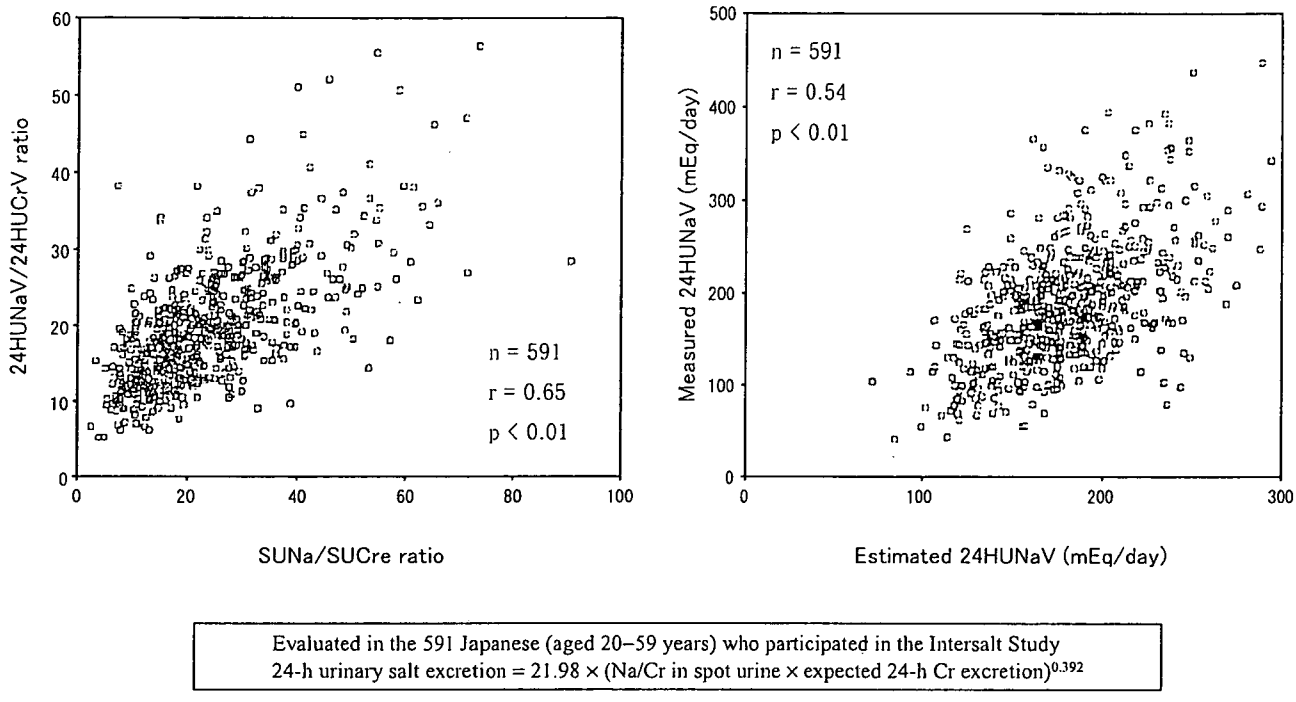

Fig. 2. *Evaluation of salt intake by spot urine. The left plot shows the relationship between the sodium (Na)/Cr ratio in spot urine (SUNa/SUCr ratio) and Na/Cr ratio in 24-h urine (24HUNaV/24HUCrV ratio). The right plot shows the relationship between the estimated 24-h urinary Na excretion by the calculation formula based on spot urine data (Estimated 24HUNaV) and measured 24-h urinary Na excretion (Measured 24HUNaV) (from Tanaka et al. (21) with modification).*

Table 4. Formula for the Estimation of the 24-h Na Excretion from Spot Urine Data and Estimated Cr Excretion (*21*)

24-h Na excretion (mmol/day) = $21.98 \times \{(Na_S/Cr_S) \times Pr.UCr_{24}\}^{0.392}$
Na_S: Na concentration in spot urine (mEq/L)
Cr_S: Cr concentration in spot urine (mg/L)
$Pr.UCr_{24}$: estimated 24-h urinary Cr excretion (mg/day)
$Pr.UCr_{24} = -2.04 \times Age + 14.89 \times Body\ weight\ (kg) + 16.14 \times Height\ (cm) - 2244.45$

Cr, creatinine.

it is underestimated even with complete urine collection (*9*, *12*, *13*) (Fig. 1).

Measurement by Nighttime and Overnight Urine

Sampling of nighttime or early morning (overnight) urine, which consists of nighttime urine, is often employed, because it is easier than 24-h urine sampling and still provides a relatively long-term sample. In addition, Na excretion in nighttime urine is well correlated with that in 24-h urine (*14*, *15*). However, Na excretion exhibits diurnal fluctuation, being about 20% lower during the nighttime than the daytime (*16*, *17*). Therefore, simple estimation of salt intake from the Na excretion in nighttime urine is considered to result in greater underestimation than that in 24-h collected urine. However, the 24-h Na excretion estimated by the following calculation using Na excretions in nighttime urine has been reported to be in relatively close agreement with the value determined in 24-h sampled urine (*18*) (Table 2). In this method, 24-h Na excretion was estimated by applying Na and creatinine (Cr) excretions in nighttime urine and estimated 24-h urinary Cr excretion, calculated using the lean body mass from the height, body weight, and body fat mass.

Measurement by the Second Urine Sample after Waking

In another previously reported method to estimate the daily urinary Na excretion, the Na and Cr concentrations in the second urine sample after waking, and the 24-h urinary Cr excretion estimated from height, body weight, and age, are applied to a calculation formula (*19*) (Table 3). The Na excretion estimated by this method is closely correlated with the value determined in 24-h pooled urine. However, its clinical use may be limited by the condition that the urine must be col-

Table 5. Guidelines for the Evaluation of Salt Intake

Evaluation method	Recommendability	Major application target
Measurement of the Na excretion in 24-h pooled urine, or Weighing or questionnaire survey by a nutritionist	Although highly reliable and recommendable, these methods are complicated. Recommended if the patients' cooperation and the facility's ability are secured	Special facilities for hypertension treatment
Estimation as Na/Cr ratio based on measurement of Na and Cr in spot urine samples*	Although the reliability is relatively low, the method is simple and recommended as a practical evaluation procedure	Medical facilities in general
Estimation in early morning urine (nighttime urine) using an electronic salt sensor installed with calculation formula**	Although the reliability is relatively low, the method is recommendable. It is convenient and can be performed by the patients themselves	Patients themselves

*Early morning urine (nighttime urine) may also be used; the reliability is increased by the use of the calculation formula incorporating the estimated 24-h Cr excretion (Tables 2–4). **Methods using test paper or a simple salt sensor are convenient but unreliable, and quantitative evaluation is difficult. Cr, creatinine.

lected as the second urine sample after waking and before breakfast.

Measurement by Spot Urine

Evaluation of salt intake using a spot urine sample collected at any time would be easy to perform. The Na excretion per amount of Cr in spot urine correlates relatively well with the Na excretion per amount of Cr in 24-h urine sampling (*20, 21*) (Fig. 2), but the correlation between the Na excretion in spot urine and that in 24-h pooled urine is not very high (*15, 20*). However, the estimated Na excretion calculated using a formula incorporating the estimated 24-h urinary Cr excretion (Table 4) is reportedly close to the actually measured 24-h urinary Na excretion (*21*) (Fig. 2). The method to estimate the daily Na intake from the Na excretion per gram of Cr calculated from the Na and Cr concentrations in spot urine is not very reliable but is simple and considered to be clinically useful.

Assessment Using Test Paper or a Salt Sensor

This method, by which salt intake is estimated by measuring the salt concentration in spot urine or overnight urine using test paper or an electronic salt sensor, is the simplest (*22, 23*). The test paper or salt sensor usually detects chloride (Cl) rather than Na, and the results of examination of overnight urine using a test paper have been shown to be correlated with salt intake estimated by a nutritional survey (*23*). However, these should be regarded as unreliable and semi-quantitative methods. Recently, a urinary salt sensor, which estimates salt intake by analyzing data in overnight urine using a preinstalled calculation formula, has become available and is expected to increase the reliability (*24*).

The salt concentration in food can be determined using test paper or a salt sensor. In one previous report, however, the salt concentration of miso soup was found to be unrelated to the urinary salt level (*23*). The estimation of daily salt intake from the salt concentration of a single food item is thus considered to be difficult.

Assessment of Salt Intake for the Management of Hypertension

As mentioned above, there are several problems with the assessment of salt intake. Even measurement of the dietary salt content and the 24-h urine sampling method, which are considered to be highly reliable, are not sufficiently accurate and are difficult to perform (Table 1). Although the examination of the Na/Cr ratio in spot urine and the test paper method are easier to perform, they are less reliable. Calculation using a formula and the data of nighttime or spot urine is more reliable but more complicated. Also, it should be noted that salt intake determined from the urinary Na excretion or by the questionnaire method tends to be underestimated.

Despite these problems, the assessment of salt intake in individual patients is useful for motivating patients to reduce their salt intake, as well as for guiding their progress and evaluating the results. Such assessment is strongly recommended for the management of hypertension, because it provides patients with concrete numerical values of their salt intake. The use of more reliable methods is desirable, if possible, but even less reliable methods are of clinical value.

The Working Group for Dietary Salt Reduction of the JSH proposes the guidelines shown in Table 5 for the assessment of salt intake for the management of hypertension. In the management of hypertensive patients, salt intake should be evaluated individually using one of the following methods whenever possible.

1) The measurement of the Na excretion in 24-h pooled urine or a nutritionist's analysis of the dietary contents: These

methods are reliable but often difficult to perform. They are recommended depending on the patients' cooperativeness and the facility's competence and are suited for facilities specializing in hypertension.

2) Estimation of the Na excretion from the Na/Cr ratio in spot urine: This method is less reliable, but it is easy to perform and is considered to be practical. Since the daily Cr excretion of Japanese is about 1 g (about 10 mmol) (*10*), salt intake is estimated to be about 6 g if the Na excretion per gram of Cr is 100 mmol. Therefore, this method is considered to be useful for salt reduction guidance. However, the urinary Cr excretion varies considerably according to the physique, age, and gender of patients. Therefore, note that true salt intake is lower in small females and higher in large males than the value estimated from the Na/Cr ratio. Overnight urine (nighttime urine) may also be used. The reliability can be increased by the use of a calculation formula (Tables 2–4).

3) Estimation using an electronic salt sensor equipped with a calculation formula in early morning urine (overnight urine): Although this method is less reliable, it can be recommended, because it is simple and can be performed by the patients themselves. However, the patient must purchase a salt sensor, or the medical facility must lend one to the patient, for home monitoring.

According to the guidelines for lifestyle modifications in the management of hypertension, the patient is considered to be compliant with the salt restriction regimen if the salt intake measured by whichever method is less than 6 g (100 mmol Na)/day and not if it is higher.

Conclusions

Although there are several methods for the assessment of salt intake, the precise determination of salt intake in individual patients is difficult. Reliable methods are difficult to perform, and simpler methods are less reliable. However, the assessment of salt intake is strongly recommended, because it is useful for informing patients of their salt intake and conducting salt restriction.

In the management of hypertension, it is desirable to assess salt intake by one of the following three methods whenever possible: 1) Measurement of the Na excretion in 24-h pooled urine or a nutritionist's analysis of the dietary contents: Although these are desirable methods because of their reliability, they are difficult to perform and are suited for facilities specializing in hypertension. 2) Estimation of the Na excretion from the Na/Cr ratio in spot urine: This is a less reliable but practical method and is suited for general medical facilities. Overnight urine (nighttime urine) may also be used, and the reliability is increased by the use of a calculation formula. 3) Estimation using an electronic salt sensor equipped with a calculation formula in overnight urine: While this method is less reliable, it can be recommended, because it is simple and can be performed by the patients themselves. The patient is judged to be compliant with the salt restriction regimen if salt intake (excretion) estimated by any of the methods is less than 6 g (100 mmol)/day but not if it is higher.

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Predictive factors for the intermediate-term patency of arterial grafts in aorta no-touch off-pump coronary revascularization

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Abstract

Objective: Graft flow is one of the important determinants of the arterial graft patency. To establish the optimal graft design, we examined detailed characteristics of the arterial composite and sequential grafts, and sought to delineate the risk factors of graft occlusion due to insufficient bypass flow. **Methods:** Angiograms of 2547 bypass grafts in 677 consecutive patients who underwent total arterial off-pump CABG without aortic manipulation followed by early postoperative angiography since December 2000 were reviewed. The angiographic flow was graded as A (antegrade), B (competitive), C (reversal), and O (occlusion). **Results:** The overall early graft patency rate was 98.2% (2502/2547). The rate of grade A was 91.3% (2325/2547), while the rates of grades B and C were 2.9% (73/2547) and 4.1% (104/2547), respectively. For the main trunk of the anterior descending branch (LAD), the graft patency rate was 99.3% (674/679). The grade A rate of the internal thoracic artery (ITA) grafts to LAD in an individual fashion was 99.5% (203/204), being comparable with that in the sequential or composite grafting which had two distal anastomoses (98.1%, 159/162; $p = 0.33$). The actuarial patency rates at 3 years were 84.7% for the bypass grafts with grade A flow and 33.9% for those with grade B/C flow, respectively ($p < 0.0001$). The multivariate Cox-regression analysis demonstrated that grade B/C ($p < 0.0001$, HR = 4.19) and 51–75% stenosis of the native coronary artery ($p = 0.02$, HR = 2.86) were significant predictors of graft occlusion. **Conclusions:** For the LAD, the results of graft flow in sequential ITA grafting or composite grafting with two distal anastomoses were comparable with that in individual ITA grafting. Prediction and prevention of competitive and reverse flow are mandatory for achieving the advantages of the arterial materials.

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Keywords: Coronary disease; Surgery; Angiography; Off-pump CABG; Arterial graft

1. Introduction

The arterial grafts have beneficial characteristics in terms of expectancy of long-term patency and improved late outcome after coronary artery bypass grafting (CABG) [1–3]. For the arterial grafts, the circumstance of the blood flow in the graft lumen is considered an important determinant of the patency. It has been reported that occlusion or string sign in the arterial grafts can typically occur when the stenosis in the native coronary artery is moderate, and that these physiologic changes in the luminal diameter occurred within 2 years [4–7]. We previously reported that reverse flow in the sequential or composite graft was commonly associated with the moderately stenotic right coronary artery (RCA) and composite or sequential grafting to more than four target branches [8]. In addition, the management of a coronary branch with critical stenosis played definitive roles [9].

The objectives of this study were (1) to delineate the effects of detailed characteristics of the target coronary branches and the bypass grafts on the occurrence of competitive flow, (2) to delineate the risk of graft occlusion, and (3) to establish a theoretical basis for optimizing the strategy for graft arrangement to the left anterior descending artery (LAD) and to non-LAD branches, which include the diagonal branch, left circumflex artery (LCX), and RCA.

2. Methods

The pre- and postoperative coronary angiograms of 2547 bypass grafts in 677 consecutive patients, who underwent off-pump complete revascularization for coronary artery disease using only the internal thoracic artery (ITA) with or without the radial artery between December 2000 and May

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Table 1
Baseline characteristics

No. of patients	677
Age (years)	66.1 ± 9.1
Male/female	563/114
Hypertension	357 (52.7%)
Hyperlipidemia	332 (49.0%)
Diabetes	260 (38.4%)
Left ventricular end-diastolic volume index (ml/m^2)	84.9 ± 29.0
Left ventricular ejection fraction (%)	48.1 ± 11.7
Total distal anastomoses	2547
Distal anastomoses per patient	3.76 ± 1.01
Bypass conduits used	1023
In-situ ITA	293
Composite Y-graft	391
Composite I-graft	273
Composite K-graft	66

ITA, internal thoracic artery.

2006, were reviewed. The patients who had a bypass of the gastroepiploic artery, the inferior epigastric artery or the saphenous vein, those with individual grafts only, and those who did not undergo early postoperative coronary angiography were excluded. All patients provided written informed consent after explanation of the potential risks. All procedures were performed under social insurance coverage, and institutional approval was obtained. There were 563 men and 114 women, and their mean age was 66.1 ± 9.1 years. The number of distal anastomoses was 3.76 ± 1.01 per patient (Table 1).

Early postoperative coronary angiography was performed within a month after surgery. Cardiologists independently evaluated the native coronary artery stenosis and the graft patency. The maximal severity of stenosis was recorded for all target branches. The definitions of terms used in the present study are as follows. A patent graft meant that the graft had a complete continuity of the graft lumen throughout its entire length from the origin of the ITA to the target coronary branch, irrespective of the flow direction. Whenever the continuity of the graft lumen from an in-situ ITA graft to the anastomosis with the target coronary branch was interrupted at any level, or when repeated angioplasty was performed, they were defined as Grade O (occlusion). Grade A was defined as a situation in which antegrade graft flow was found in most of the multi-plane ITA angiographs. Grade B (competitive) was defined as a situation in which the target vessel was slightly opacified from the ITA graft injection, and the bypass graft did fill by retrograde flow from the native coronary injection. Grade C (reverse flow) was defined as a situation in which the distal anastomotic site was not opacified from the ITA graft injection at all, but it did fill clearly by retrograde flow from the native coronary injection. Flow grade was recorded for each target coronary branch, and these data were collected prospectively.

An individual bypass is defined as a bypass conduit having one in-situ ITA and one distal anastomosis. A non-individual bypass graft means a bypass conduit having two or more distal anastomoses, such as sequential or composite grafting. The in-situ ITA is ITA divided only at its distal portion.

2.1. Graft design strategy

The arrangement of the bypass conduits was primarily determined by the operative risk and positional relationship of the target sites. Our current standard technique since March 2003 was based on our previous angiographic studies and introduced for minimizing competitive and reverse flow. One in-situ ITA, usually the left, supplies the LAD territory, while an I-graft of the contralateral ITA, usually the right, and the radial artery supply the LCX and RCA territories in a clockwise orientation, via a side-to-side anastomosis with LCX and an end-to-side anastomosis with RCA. The counterclockwise orientation was occasionally chosen to avoid grafting to RCA branch with 75% stenosis at the end of the conduit, because reverse flow was commonly found at the distal end of the conduit with the end-to-side anastomosis [8,9]. Before introduction of this strategy, the I-graft was used only in a counterclockwise orientation for the safety of redo operation in the future. For patients aged more than 75 years or with considerable operative risks, such as chronic obstructive pulmonary disease or diabetes mellitus treated by insulin therapy, we harvested only a single ITA. In the present series, all ITA grafts were greater than 1.5 mm in diameter at the distal end.

2.2. Late angiographic results

Follow-up angiography was performed between 3 and 66 months after the operation for 325 bypass grafts in 91 patients with recurrent angina, or ischemic findings on electrocardiography or scintigraphy. The mean follow-up period was 29 ± 19 months.

2.3. Statistical analysis

The continuous variables are expressed as the mean values ± standard deviation (SD). The data of two independent groups were compared by Fisher's exact probability test. Longitudinal data were estimated by the Kaplan–Meier method and the difference of two groups was compared by log-rank method. Cox regression analysis was used to examine the significance of the variables in predicting graft occlusion. Statistical analyses were performed using SPSS software (SPSS 8.0 Inc., Chicago, IL). The differences in the outcomes were considered statistically significant when the p-value was less than 0.05.

3. Results

The overall graft patency rate was 98.2% (2502/2547), and the grade A rate was 91.3% (2325/2547). The actuarial graft patency rates at 3 years were 84.7% for the bypass grafts graded A and 33.9% for the bypass grafts graded B/C ($p < 0.0001$). The early patency rate of the bypass grafts to 51–75% stenotic coronary branches was 98.1% (1140/1162), and their grade A rate was 85.1% (989/1162), being significantly lower than that of the bypass grafts to 76–100% stenotic branches (96.5%, 1336/1385; $p < 0.0001$). For 75% stenotic branches, the actuarial graft patency rates at 3

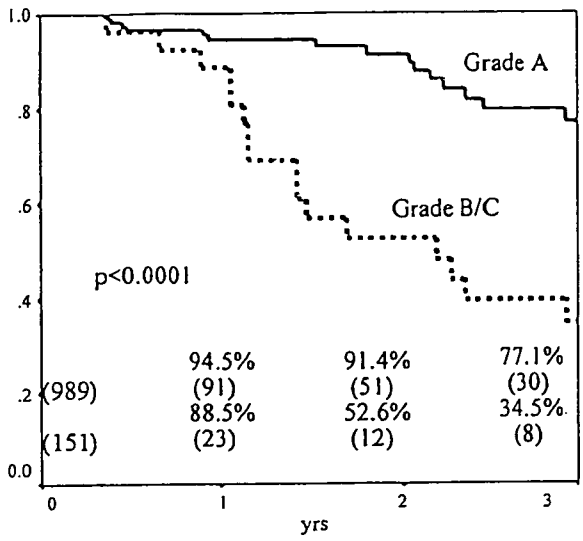

Fig. 1. The actuarial graft patency rate of the bypass grafts to 51–75% stenotic branches. Grade A vs grade B/C.

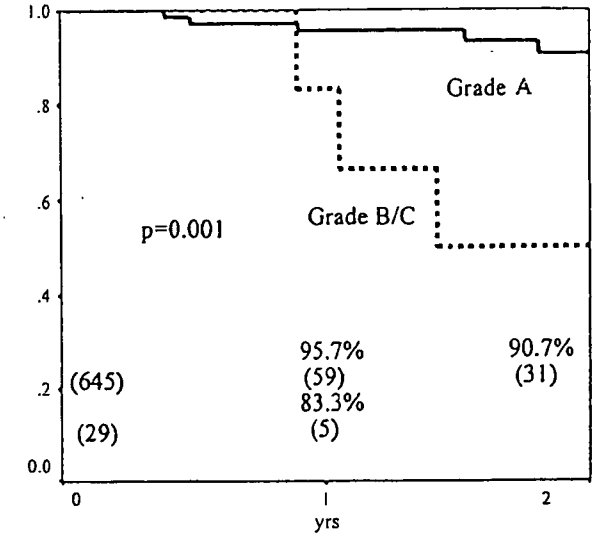

Fig. 2. The actuarial graft patency rate of the bypass grafts to the main trunk of LAD. Grade A vs grade B/C.

years were 77.1% for the bypass grafts graded A and 34.5% for the bypass grafts graded B/C ($p < 0.0001$) (Fig. 1).

Regarding the main trunk of LAD, the grade A rate of the in-situ ITA in individual fashion was 99.5% (203/204), and was significantly higher than that of non-individual conduit grafting (93.1%, 442/475; $p = 0.0001$), whereas the patency rates were similar ($p = 0.99$). The grade A rate of the conduit with two distal anastomoses was comparable with that of the individual grafting ($p = 0.33$) (Table 2). For the bypass grafts to LAD, the actuarial graft patency rates at 1 year were 95.7% for the bypass grafts graded A and 83.3% for the bypass grafts graded B/C ($p = 0.001$) (Fig. 2). The actuarial graft patency rates of the bypass graft to the LAD with 51–75% stenosis and those with 76–100% stenosis at 2 years were 79.9% and 96.7%, respectively ($p = 0.16$).

For the non-LAD branches, including the diagonal, LCX, and RCA branches, the grade A rate of the in-situ ITA was comparable to that of the Y- or K-graft or I-graft (90.8% vs 89.9%; $p = 0.87$), and the grade A rate of the individual grafts was comparable to that of the sequential and composite grafts (91.9% vs 89.9%; $p = 0.99$) (Table 3). The patency rate of the bypass grafts to 51–75% stenotic branches was similar

Table 2
Early angiographic results: flow grading of bypass grafts to main trunk of left anterior descending artery

		No. of anastomoses	Grade A	Grade A rate (%)	Grade B	%	Grade C	%	Grade O	Patency rate (%)
Native coronary stenosis	51–75%	313	288	92.0 [1]	16	5.1	6	1.9	3	99.0 [3]
	76–90%	205	196	95.6 [2]	2	1.0	5	2.4	2	99.0 [4]
	91–100%	161	161	100 [2]	0	0	0	0	0	100 [4]
Diameter of target branch	<1.5 mm	72	68	94.4 [5]	2	2.8	1	1.4	1	98.6
	≥1.5 mm	546	523	95.8 [6]	10	1.8	10	1.8	3	99.5
	Not recorded	61	54	88.5	6	9.8	0	0	1	98.4
Graft material anastomosed	ITA	679	645	95.0	18	2.7	11	1.6	5	99.3
	RA	0	0	–	0	–	0	–	0	–
	Free ITA	0	0	–	0	–	0	–	0	–
Anastomotic fashion	End-to-side (graft end)	675	642	95.1	17	2.5	11	1.6	5	99.3
	Side-to-side (sequential)	4	3	75.0	1	25.0	0	0	0	100
Conduit type	In-situ ITA	275	272	98.9 [7]	1	0.4	0	0	2	99.3
	Y-graft	343	318	92.7 [8]	17	5.0	5	1.5	3	99.1
	K-graft	61	55	90.2 [8]	0	0	6	9.8	0	100
	I-graft	0	0	–	0	–	0	–	0	–
No. of distal anastomoses of conduit	1 (individual)	204	203	99.5 [9,13]	0	0	0	0	1	99.5 [11]
	2	162	159	98.1 [10,14]	2	1.2	0	0	1	99.4 [12]
	3	204	188	92.2 [10]	12	5.9	2	1.0	2	99.0 [12]
	4~	109	95	87.2 [10]	4	3.7	9	8.3	1	99.1 [12]
Total		679	645	95.0	18	2.7	11	1.6	5	99.3

ITA, internal thoracic artery; RA, radial artery. [1] vs [2], $p = 0.001$; [3] vs [4], $p = 0.67$; [5] vs [6], $p = 0.54$; [7] vs [8], $p = 0.0001$; [9] vs [10], $p < 0.0001$; [11] vs [12], $p > 0.99$; [13] vs [14], $p = 0.33$.

Table 3
Early angiographic results: flow grading of bypass grafts to diagonal branch, LCX, and RCA

		No. of anastomoses	Grade A	Grade A rate (%)	Grade B	%	Grade C	%	Grade O	Patency rate (%)
Target branch	Diagonal	391	368	94.1 [1]	9	2.3	7	1.8	7	98.2 [4]
	Circumflex	804	738	91.8 [2]	19	2.4	36	4.5	11	98.6 [5]
	Right coronary	673	574	85.3 [3]	27	4.0	50	7.4	22	96.7 [6]
Native coronary stenosis	51–75%	849	701	82.6 [7]	48	5.7	81	9.5	19	97.8 [9]
	76–90%	500	469	93.8 [8]	7	1.4	12	2.4	12	97.6 [10]
	91–100%	519	510	98.3 [8]	0	0	0	0	9	98.3 [10]
Diameter of target branch	<1.5 mm	614	553	90.1	15	2.4	27	4.4	19	96.9
	>1.5 mm	1121	1015	90.5	34	3.0	57	5.1	15	98.7
	Not recorded	133	112	84.2	6	4.5	9	6.8	6	95.5
Graft material anastomosed	ITA	166	147	88.6 [11]	4	2.4	7	4.2	8	95.2
	RA	1654	1488	90.0 [12]	51	3.1	83	5.0	32	98.1
	Free ITA	48	45	93.8	0	0	3	6.3	0	100
Anastomotic fashion	End-to-side (graft end)	869	709	81.6 [17]	48	5.5	80	9.2	32	96.3
	Side-to-side (sequential proximal)	999	971	97.2 [18]	7	0.7	13	1.3	8	99.2
Conduit type	In-situ ITA	109	99	90.8 [13]	1	0.9	1	0.9	8	92.7
	Y-graft	842	749	89.0 [14]	25	3.0	50	5.9	18	97.9
	K-graft	185	161	87.0 [14]	10	5.4	13	7.0	1	99.5
	I-graft	732	671	91.7 [14]	19	2.6	29	4.0	13	98.2
No. of distal anastomoses of conduit	1 (individual)	37	34	91.9 [15]	0	0	0	0	3	91.9
	2	360	319	88.6 [16]	15	4.2	12	3.3	14	96.1
	3	780	701	89.9 [16]	26	3.3	40	5.1	13	98.3
	4~	691	626	90.6 [16]	14	2.0	41	5.9	10	98.6
Total		1868	1680	89.9	55	2.9	93	5.0	40	97.9

ITA, internal thoracic artery; LCX, left circumflex artery; RA, radial artery; RCA, right coronary artery. [1] vs [3], $p < 0.0001$; [2] vs [3], $p < 0.0001$; [4] vs [6], $p = 0.18$; [5] vs [6], $p = 0.02$; [7] vs [8], $p < 0.0001$; [9] vs [10], $p = 0.87$; [11] vs [12], $p = 0.59$; [13] vs [14], $p = 0.87$; [15] vs [16], $p > 0.99$; [17] vs [18], $p < 0.0001$.

to that of the bypass grafts to 76–100% stenotic branches (97.8% vs 97.9%; $p = 0.87$), while the grade A rate of the bypass grafts to 51–75% stenotic branches was significantly lower than that of the bypass grafts to 76–100% stenotic branches (82.6% vs 96.1%; $p < 0.0001$). The actuarial graft patency rates at 2 years were 94.5% for the bypass grafts graded A and 57.6% for the bypass grafts graded B/C ($p < 0.0001$). The actuarial graft patency rate of the bypass grafts to branches with 76–100% stenosis at 2 years was 89.8%, being significantly higher than that of the bypass grafts to branches with 51–75% stenosis (82.2%; $p = 0.009$). The actuarial graft patency rate of the bypass grafts in the end-to-side fashion at 2 years was 80.5%, being significantly lower than that of the bypass grafts in the side-to-side fashion (91.4%; $p = 0.01$) (Fig. 3A). The actuarial graft patency rates at 2 years were 85.6% for the I-grafts graded A and 88.8% for the bypass grafts graded B/C ($p = 0.31$) (Fig. 3B).

As shown in Table 4, the univariate Cox regression analysis demonstrated that the RCA territory, 51–75% stenosis, small coronary branch (diameter < 1.5 mm), and grade B/C were significant predictors of graft occlusion. The multivariate Cox regression analysis identified 51–75% stenosis (HR = 2.86, $p = 0.02$) and grade B/C (HR = 4.19, $p < 0.0001$) as significant predictors.

4. Discussion

A composite graft allowed total arterial revascularization with excellent graft patency rate and lower incidence of perioperative cardiac and cerebrovascular events [10,11]. Although various arrangements of the in-situ and free arterial grafts have already been reported [3,12,13], no optimal strategy for graft arrangement has been established yet. We have applied our grading system of angiographic graft flow for 5.5 years. The results of the present study imply some suggestions regarding the strategy for graft arrangement.

For the main trunk of the LAD, the use of the in-situ ITA graft has been generally accepted as a standard strategy, which provides a long-term patency and improves the late survival after CABG. The in-situ ITA in an individual fashion may be ideal for the main trunk of the LAD; however, sequential and composite grafting to the LAD and a diagonal branch is an important option of choice. Dion et al. reported that the long-term patency of sequential grafting with the in-situ ITA to the LAD and a diagonal branch was identical to that of the individual in-situ ITA [14]. We previously reported that early angiographic results of the Y-graft to the LAD and a diagonal branch were similar to that of sequential grafting [9]. As shown in Table 2, our present study demonstrated that, in the LAD region, the sequential graft and the Y-graft to two distal anastomoses were as reliable as individual grafting. We consider that the in-situ ITA, which is anastomosed to the LAD, can be connected with at least one diagonal branch by sequential or composite grafting without disturbance of graft flow to the main trunk of the LAD. Different from bypass grafts to LCX or RCA, the difference between the patency rate of bypass grafts to LAD 51–75% and that of bypass grafts to 76–100% stenosis was not significant. The in-situ ITA grafts could confidently supply the