INVESTIGATIONS RELATED TO DIETARY SODIUM IN CHRONIC HEART FAILURE

by

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A thesis submitted in conformity with the requirements for the degree of Doctor of Philosophy

Graduate Department of Nutritional Sciences

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ABSTRACT

Sodium restriction is the primary dietary therapy for individuals with heart failure (HF); however, there is little information available to support or refute the use of sodium restriction to manage HF. The overall goal of this work was to generate data related to dietary sodium in patients with chronic HF that would contribute to the development of evidence-based guidelines.

The specific objectives were to investigate the optimal methods for measuring sodium intake in HF, to describe the habitual consumption of sodium and other nutrients in HF, and to evaluate the relationship between sodium intake and clinical outcomes in HF. We studied stable ambulatory HF patients who were optimally medicated and participating in multidisciplinary HF programs.

We determined that: (1) a strong relationship exists between 24-hour urine collections and food records for sodium intake assessment in non-HF cardiac patients and HF patients not taking loop diuretics. However, the relationship between urinary sodium excretion and sodium intake in HF patients taking loop diuretics was disturbed, suggesting that food records may be a better method for estimating sodium intake in this group. (2) Mean sodium intake in HF and non-HF cardiac patients was similar, and approximately half
of patients in each group had sodium intake levels that exceeded the Dietary Reference Intakes tolerable upper level of 2300 mg/d. We also found that both groups had inadequate intakes of several nutrients, including potassium, calcium, magnesium, folate, and vitamin D and E. (3) Finally, we showed that a high sodium diet (>2800 mg/day) in HF was associated with risk of acute decompensated HF, all-cause hospitalization, and all-cause mortality over a median 3 year follow-up period. This is the first published study that prospectively related sodium intake to clinical outcomes in HF.

In summary, these data provide novel contributions related to the measurement of sodium intake that can be used in clinical or academic settings. We also describe inadequacies in intake of several vitamins and minerals, which could be addressed through dietary counselling. Finally, we importantly offer insight into a threshold of sodium intake (>2800 mg/day) that could contribute to adverse clinical outcomes in HF.
ACKNOWLEDGEMENTS

The first acknowledgement is to the patients who participated in this research. Elective visits to the hospital are not always easy for individuals with heart failure, and I am sincerely grateful for the efforts they put towards our research program, which were usually made with the good intention of helping future heart failure patients. The investigations in this thesis would not be possible without these volunteers.

I would like to thank both of my supervisors. My deepest and most sincere gratitude is for Dr. Gary Newton. His mentorship, support and confidence have empowered me to strive towards goals, that previously I never would have dreamed were possible, enabling me to develop both as a professional and more importantly as a person. It has been fun, rewarding, and a true privilege working with him in building our nutrition and heart failure research program. Dr. Johane Allard, has always been available to provide advice, guidance and unwavering support during my Masters and doctoral studies. She has taught me much about being a leader in clinical nutritional sciences and has provided an enriching environment to cultivate my critical thinking and clinical nutrition expertise.

My thesis committee members, Dr. Tony Hanley and Dr. John Floras, have spent many hours contributing to my progress throughout my graduate program and have provided invaluable feedback on my thesis and overall development of my scientific thinking. Dr. Tom Wolever served as my Departmental defense examiner and facilitated a challenging, engaging and overall enjoyable Departmental defense. I also thank my External examiner, Dr. Norm Campbell from the University of Calgary, who attended my exam in-person and provided a thoughtful examination of my work, particularly related to dietary sodium and health.

This research would also not have been possible without the dedication of our research staff. Vanessa Floras and Mavra Ahmed made significant contributions to the work presented in this thesis. Throughout a 5- and 3-year period, respectively, they assisted with many aspects of these studies, including patient recruitment and food record analysis. The
fact that I trusted them with my data is a testament to how truly wonderful they are! Dr. Joan Ivanov was also especially helpful in providing analytic and statistical guidance. Wilson Chan also made significant technical contributions, which made the management of our nutritional data much easier. Other individuals also made contributions to the studies in this thesis are acknowledged within each individual investigation.

Members of the Division of Cardiology and Department of Nutrition at Mount Sinai Hospital have been like an extended family to me since I moved to Toronto in 2001. The cardiologists, nurses, dietitians and other graduate students in these departments have contributed greatly to both my dietetic and graduate training. Especially including dietitians Sandra Brazel, Joy Langlois, Fran Berkoff and Marlene Choleva, who helped me begin my journey and have provided much needed friendship and support along the way. The other graduate students in our Cardiology program have been wonderful to learn from and collaborate with, especially Andrew Liuni. Several cardiologists assisted with patient recruitment and have provided invaluable feedback pertaining to my research and my progress as a student, especially Drs. John Floras, Susanna Mak, and Eduardo Azevedo.

Finally, I most importantly must thank my family for their support and understanding (i.e. tolerance!) during my graduate program. I thank my parents, Beverley and Gary, my sister Stephanie, and my best friend Mary Claire for their unconditional love and support. Also SL&C provided much needed escapes, and always provided the answers with their beauty. My absolute greatest gratitude is for my husband, Abdul, who has been a source of strength, love, and compassion throughout all my years of training and in life. Although I am moving onto my next adventure, I find happiness and comfort knowing all of you will remain by my side.

This research was supported by grants from the Heart and Stroke Foundation of Ontario, the Canadian Institutes of Health Research, and from the generous donation of Mr. Alexander Epstein.
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LIST OF ABBREVIATIONS

ACE/ACEI  Angiotensin converting enzyme inhibitor
ADHF  Acute decompensated heart failure
AI  Adequate Intake
ANOVA  Analysis of variance
ARB  Angiotensin receptor blocker
BMI  Body mass index
BNP  Brain natriuretic peptide
BP  Blood pressure
CCHS  Canadian Community Health Survey
CHARM  Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity
CI  Confidence Interval
DASH  Dietary Approaches to Stop Hypertension
DRI  Dietary Reference Intakes
EAR  Estimated Average Requirement
ECF  Extracellular fluid
eGFR  Estimated glomerular filtration rate
FFQ  Food frequency questionnaire
FR  Food record
GWTF-HF  Get With the Guidelines Heart Failure
HF  Heart failure
HR  Hazard Ratio
LD  Loop diuretic
LV  Left ventricle
NHANES  National Nutrition and Health Examination Survey
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<tr>
<th>Acronym</th>
<th>Definition</th>
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<tr>
<td>NYHA</td>
<td>New York Heart Association</td>
</tr>
<tr>
<td>OPTIMIZE-HF</td>
<td>Organized program to initiate lifesaving treatment in hospitalized patients with heart failure</td>
</tr>
<tr>
<td>RAAS</td>
<td>Renin-angiotensin-aldosterone system</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomized controlled trial</td>
</tr>
<tr>
<td>RDA</td>
<td>Recommended Dietary Allowance</td>
</tr>
<tr>
<td>REE</td>
<td>Resting energy expenditure</td>
</tr>
<tr>
<td>RR</td>
<td>Relative Risk</td>
</tr>
<tr>
<td>UC</td>
<td>Urine collection</td>
</tr>
<tr>
<td>UL</td>
<td>Tolerable Upper Level</td>
</tr>
<tr>
<td>SD</td>
<td>Standard Deviation</td>
</tr>
<tr>
<td>SNS</td>
<td>Sympathetic nervous system</td>
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</table>
UNITS OF CONVERSION FOR SODIUM

1 g sodium = 1000 mg of sodium
1 mmol sodium = 23 mg of sodium
1 g sodium chloride or salt = 400 mg sodium
1 teaspoon sodium = 2300 mg of sodium
PUBLICATIONS AND PRESENTATIONS ARISING FROM DISSERTATION

Publications and presentations as of June 14, 2011.

Peer-Reviewed Publications


Book Chapters


Other Published Contributions

2. Arcand J. “Cardiovascular Disease: Heart Failure”. In Practice Based Evidence Nutrition (2010). Published online by Dietitians of Canada.

Oral Presentations


**Poster Presentations**


CHAPTER 1: LITERATURE REVIEW

1.1. Dietary Sodium: Physiology, Intake and Measurement

1.1.1. General Introduction

Sodium, an essential nutrient, is tightly regulated by the human body. However when consumed in excessive amounts it has adverse cardiovascular and non-cardiovascular health effects. On average, Canadians consume over twice the recommended sodium intake level daily, which is due primarily to the excessive quantities permeating processed and packaged foods. This section will describe dietary sodium in healthy populations, while subsequent chapters will focus on sodium and nutrition in the setting of chronic heart failure (HF).

1.1.2. A Brief Overview of Sodium Physiology and Regulation

Sodium is required for a range of physiologic processes. It is involved in the transport of molecules across cell membranes as well as the maintenance of electrochemical gradients via the Na/K ATPase pump. Sodium is concentrated in the extracellular (140-145 mmol/L), rather than intracellular (10 mmol/L) compartments. The osmotic properties of sodium make it a determinant of the extracellular fluid (ECF) volume, including plasma and interstitial volumes. Therefore, total body sodium determines blood volume and thus blood pressure. Because of the possibility of cardiovascular overload or collapse from either sodium excess or depletion, mammalians have developed sophisticated feedback mechanisms to precisely regulate sodium intake and excretion, enabling humans to survive at extremes of sodium exposure.

Several excellent publications review sodium regulation and physiology. Briefly, absorption of dietary sodium occurs in both the small and large intestine. It is estimated that
98% of ingested sodium is absorbed, regardless of the magnitude of sodium consumed. Dietary sodium intake typically far exceeds physiologic requirements; therefore, when sweating is not excessive, the sodium surplus is excreted in the urine. This regulation is facilitated by the kidneys, which alter sodium excretion rates to match sodium consumption. Therefore human populations tolerate and survive at dramatically different levels of habitual sodium intake. For example, the multi-national Intersalt study found sodium consumption to be 21 mg/d in the Brazilian Yanomamo tribe, and individuals in China on average consumed 5650 mg/day. Experimental studies also show that most healthy individuals can adapt to extreme changes in sodium intake, including a decrease from 1500 mmol/day (34,500 mg/day) to 10 mmol/day (230 mg/day), without significant changes to extracellular fluid volume or plasma sodium concentration. Tight regulation of total body sodium is required to maintain extracellular fluid volume, ensuring organ perfusion and preventing cardiovascular volume overload or collapse. Regulation of sodium balance occurs through a complex interplay between neurohumoral and intra-renal mechanisms, which ultimately aim to maintain ECF volume and arterial blood pressure.

In the kidney, autoregulation of sodium reabsorption and excretion occurs in the renal tubules, mediated by glomerular filtration of sodium and by substances that act directly on the renal tubules. The most basic mechanism controlling sodium excretion is pressure natriuresis and pressure diuresis mechanisms; both of which are activated in response to changes in ECF volume and/or changes in arterial pressure. Changes in tubular reabsorption of sodium and water also occurs in response to an increase or decrease in sodium delivery to the nephron. Such changes are detected by the macula densa, which causes afferent arteriolar constriction or dilation, thus altering sodium filtration. However, intra-renal mechanisms are insufficient to independently maintain ECF volume and blood pressure. Therefore, maintenance of sodium balance also involves neurohormonal feedback mechanism, including natriuretic peptides, the renin-angiotensin-aldosterone-system (RAAS) and the sympathetic nervous system.
During periods of sodium deprivation the sympathetic nervous system is activated.\textsuperscript{11-13} Increased efferent renal sympathetic activity reduces sodium and water excretion through constriction of the renal arterioles, subsequently causing increased tubular reabsorption of sodium and water. Should sodium depletion result in a reduction in blood volume great enough to cause a systemic fall in arterial pressure, the mechanical stretch of the arterial baroreceptor nerve endings situated in the aorta and carotid sinus would be reduced, causing further activation of the sympathetic nervous system.

Sympathetic nervous system activation during sodium deprivation also results in renin release,\textsuperscript{14} which activates the RAAS.\textsuperscript{15,16} Higher amounts of circulating renin increase levels of angiotensin II, which promotes renal arteriolar vasoconstriction. This constriction reduces total renal blood flow, thereby reducing sodium filtration. Angiotensin II and aldosterone act on the proximal and distal renal tubule to increase sodium reabsorption. Aldosterone also acts on the brain to increase salt appetite.\textsuperscript{17} Therefore, in healthy individuals sodium balance is maintained through an integration of several neurohumoral mechanisms, ultimately enabling tight homeostatic control of total body sodium.

### 1.1.3. Dietary Reference Intakes for Sodium

The Dietary Reference Intakes (DRI) were developed by the Institute of Medicine and are comprised of a set of nutrient-specific reference values for defined age and sex categories.\textsuperscript{18} The DRI values contain recommended intake levels that were created to reduce the risk of nutrient deficiency and risk of nutrient excess.\textsuperscript{19} The first of the DRI values is the Estimated Average Requirement (EAR). The EAR is the amount of a given nutrient that meets the needs of 50% of the population; therefore it is used to establish nutritional inadequacy of a group or population.\textsuperscript{20-22} However, for daily requirements of individuals the Recommended Daily Allowance (RDA) has been established. The RDA is set two standard deviations from the EAR, thereby meeting the nutritional requirements for 97-98% of individuals. The EAR, and thus RDA, are only established when sufficient dose-response data are available. When there is insufficient evidence to establish an EAR and RDA, an Adequate
Intake (AI) level is generated. The AI level is often based on available observational and experimental data, and is set at a level considered to meet the needs of most of the population. The final reference level is the Tolerable Upper Level (UL), which is the highest possible daily nutrient intake that can be consumed without the risk of adverse health effects, including nutrient toxicity or onset of acute or chronic disease.

The DRI values for sodium include an AI and UL, which are reported in Table 1-1. The AI has been established to replace insensible sodium losses (i.e. sweat) and to ensure adequate consumption of other nutrients. The UL for sodium has been established to reduce the risk of developing hypertension and related cardiovascular and non-cardiovascular conditions in the general population. Since sodium is most likely to be consumed in excess, public health messages for sodium focus on limiting intake below the adult UL of 2300 mg.
Table 1-1. Dietary Reference Intake levels for sodium by age category

<table>
<thead>
<tr>
<th>Age Category</th>
<th>Adequate Intake Level (mg/day)</th>
<th>Tolerable Upper Level (mg/day)</th>
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<tbody>
<tr>
<td>1 to 3 years</td>
<td>1000 mg</td>
<td>1500 mg</td>
</tr>
<tr>
<td>4 to 8 years</td>
<td>1200 mg</td>
<td>1900 mg</td>
</tr>
<tr>
<td>9 to 13 years</td>
<td>1500 mg</td>
<td>2200 mg</td>
</tr>
<tr>
<td>14-50 years</td>
<td>1500 mg</td>
<td>2300 mg</td>
</tr>
<tr>
<td>51 to 70 years</td>
<td>1300 mg</td>
<td>2300 mg</td>
</tr>
<tr>
<td>Over 70 years</td>
<td>1200 mg</td>
<td>2300 mg</td>
</tr>
</tbody>
</table>
1.1.4. Sources of Sodium in Food

The majority of sodium in the western diet is already present in food, especially foods that have been processed. It is estimated that only 5-10% of sodium in the diet is from discretionary salt, either added at the table or during cooking. Two comprehensive, systematic evaluations of the food supply in Australia and the United Kingdom found that the processed foods containing the highest amounts of sodium (mg/100g) were sauces and spreads, processed meat, smoked and canned fish, pickled vegetables, snack foods such as potato chips, and sauces including tomato sauce, Asian sauces, and marinades. However, the relative frequency of consumption of sodium-containing foods is a better determinant of sodium consumption. A recent analysis of the Canadian Community Health Survey v2.2 (CCHS) examined the relative contribution of food group categories to sodium intake. Among all participants > 1 year of age, bread contributed the most sodium to the diet (14% contribution, 430 mg/day). Although bread is not considered a high sodium food, it is a major contributor to total sodium intake because it is consumed in such large quantities. Other foods contributing large amounts of sodium included processed meats (9% contribution, 276 mg/day), pasta dishes (6% contribution, 176 mg/day), cheese (5% contribution, 167 mg/day), and vegetables that are canned, pickled, smoked or dried (5% contribution, 159 mg/day). Similar findings were observed in other countries. In the United States, foods contributing the most sodium to the diets of the 2005-06 National Health and Nutrition Examination Survey (NHANES) participants were breads (7.3%), chicken and mixed chicken dishes, pizza (6.8%), pasta and pasta dishes (6.3%), cold cuts (5.1%), and condiments (4.4%). Indeed, these data demonstrate the large contribution of processed foods to overall sodium intake.

Sodium plays a principal role in the composition, sensory properties and preservation of food. One of the primary roles of sodium is to improve taste and flavour. Sodium also has the ability to enhance other flavours including increasing sweet tastes, masking metallic or chemical off-notes, and balancing the overall flavour profile of foods. Despite modern day advances in food packaging, storage, and transportation, sodium still plays a central role.
in food preservation and food safety. Sodium reduces the water activity in foods which controls microbial growth. The addition of sodium to foods may also limit the rate of microbial growth by interacting with cellular enzymes, and by reducing the solubility of oxygen, which retards the growth of microorganisms. Sodium also has an important role in the structural characteristics of food. In baked goods, salt controls the stickiness of dough and is a primary component of leavening agents such as sodium bicarbonate. In processed meat products, sodium increases the water binding of muscle tissues which results in improved tenderness. Furthermore, sodium can solubilize meat proteins which results in the “gluing” of meat pieces together, as in the case of restructured meats (i.e. sausage, bologna). The addition of sodium during processing and storage greatly increases the sodium content in foods which naturally contain minimal amounts of sodium. Ultimately, the addition of sodium during food processing greatly contributes to mean daily sodium intake of individuals.

1.1.5. Sodium Intake in the Canadian Population

Canadians consume excessive amounts of sodium compared to recommended intake levels. The CCHS v2.2 evaluated a representative cohort of approximately 35,000 Canadians and determined that sodium intake is 3098 mg/day among participants > 1 year of age. This estimate was obtained using data from 24-hour recalls; however, data collection did not include an assessment of sodium added at the table or during cooking. Using the assumption that 5-10% of sodium is discretionary and the reported frequency of use of discretionary salt, mean sodium intake in Canada is estimated to be 3400 mg/day. This mean sodium intake level is over double the recommended AI of 1500 mg for adults and 1200 mg for children and the elderly. It is also well above the UL of 2300 mg, further demonstrating that sodium intake levels in Canada are problematic.

To date, only subgroup analyses by age and sex and have been conducted for the CCHS v2.2 cohort. Mean sodium intake exceeds both the AI and UL for each age and sex category. Among those Canadians > 19 years, the average daily sodium intake is 3587 mg/d for men and 2684 mg/d for women. Over 90% of all older children and males between 15 and
50 years have a mean sodium intake that is above the UL. In the same cohort, mean sodium intake was highest in the adolescents and young adults, and declined with age. This is presumably related to the caloric content of the diet, since sodium intake is directly related to energy intake. In the United States National Nutrition and Health Examination Survey (NHANES) 2005-06 cohort, Caucasians had higher mean daily sodium intakes (3524 mg/d), compared to African Americans (3257 mg/d) and Mexican Americans (3162 mg/d). In this same cohort, those with the lowest income level (3222 mg/d) also had the lowest mean daily sodium consumption, compared those with higher income levels (3534 mg/d). Such analyses in population subgroups have not yet been conducted for the Canadian population as a whole.

1.1.6. Adverse Effects of Excess Dietary Sodium

The relationship between excess dietary sodium, high blood pressure, and subsequent cardiovascular disease is well established. In a recent meta-analysis of 15 observational studies, a high sodium diet was associated positively with cardiovascular risk including stroke and incident cardiovascular disease. Furthermore, data from the NHANES Epidemiologic Follow-up Study suggests that high sodium intake (>2600 mg/d) increases risk of incident HF. It has also been associated with increased LV mass and impaired vascular function, which may occur independently of blood pressure. However, high blood pressure resulting from excess sodium intake is considered to be the primary mediator of adverse cardiovascular events.

Approximately twenty percent of Canadians have hypertension, which often occurs with advancing age, greater body mass, and a diet high in sodium. There is a linear relationship between sodium and blood pressure. Habitual sodium intake that exceeds 2300 mg/day is considered to increase the risk of developing hypertension. Dietary sodium reduction has a blood pressure lowering effect in both normotensives and hypertensives. A meta-analysis of sodium restriction trials of >4 weeks duration found that sodium reduction of 1.7 g/d resulted in a 2.0 mmHg systolic and 1.0 mmHg diastolic blood pressure decrease in normotensives, and a respective 5.0 mmHg and 2.7 mmHg systolic and diastolic blood
pressure decrease in hypertensives. Therefore, the blood pressure lowering effect sodium restriction is considered an effective therapeutic option for those with hypertension, particularly among those with resistant hypertension. Another dietary approach to blood pressure management is the Dietary Approaches to Stop Hypertension (DASH) diet. The DASH trial enrolled pre-hypertensives and tested three levels of sodium in combination with either an “unhealthy” western-type diet pattern or a “healthful” diet pattern that included foods rich in potassium, calcium, magnesium, whole grains, and poly- and monounsaturated fats and low in saturated fat. For both dietary patterns there were significant reductions in both systolic and diastolic blood pressure occurring in a linear fashion as sodium in the diet decreased. However, blood pressure reduction was greatest when the lowest sodium diet was combined with the healthy DASH diet, as compared to the western diet. This effect was largely related to the interactions between sodium and other nutrients on blood pressure, particularly potassium, as has been observed in other studies. Sodium restriction combined with a DASH-style diet is now the primary dietary therapy for hypertension.

Evidence that excess dietary sodium contributes also to non-cardiovascular conditions has been summarized by DeWardener and MacGregor. For example, increased urinary sodium excretion promotes increases urinary calcium losses, which ultimately results in increased bone turnover and lower bone mineral density. There is also a causal relationship between recurrent kidney stones and high sodium intake. Furthermore, the multi-national Intersalt study observed a strong positive relationship between level of sodium intake and incidence of gastric cancer. Other data associates high sodium intake with asthma. The DRI levels for sodium, as established by the Institute of Medicine, include both cardiovascular and non-cardiovascular effects of excess sodium when developing guideline nutrient intake recommendations for the population.

1.1.7. Population-Wide Sodium Reduction Initiatives

Modest reductions in sodium intake are considered to substantially reduce cardiovascular morbidity and mortality, as well as health care costs. Population-wide
sodium reduction initiatives have been endorsed by international health agencies (i.e. World Health Organization and Pan-American Health Organization), federal governments abroad (i.e. United Kingdom, Finland, Australia) and by non-government health organizations (i.e. World Action on Salt and Health, American Heart Association). Health Canada assembled a multi-stakeholder Sodium Working Group to generate a strategy for sodium reduction in Canada. They recommend a multi-level approach to promote lowering of sodium in the diets of Canadians from 3400 mg/day to 2300 mg/day by 2016. The eventual goal is that 95% of Canadian population will have a sodium intake <2300 mg/day. Public health approaches include: 1) voluntary reduction of sodium in foods by the food industry, 2) a public health educational campaign aimed at increasing awareness of sodium among Canadians, 3) additional research in developing new food technologies and understanding the health effects of sodium, and 4) planned, periodic monitoring and evaluation of sodium intake levels. Ultimately, such initiatives aim to create a healthy food environment and reduce the risk of cardiovascular disease among Canadians.

1.2. AN OVERVIEW OF HEART FAILURE AND ITS MANAGEMENT

1.2.1. Heart Failure

Heart failure is a complex clinical syndrome resulting from any structural or functional cardiac disorder that impairs the ability of the ventricles to eject (systolic dysfunction) or fill (preserved systolic function) with blood. Heart failure symptoms develop when the heart is unable to perfuse peripheral tissues, or can only do so under high cardiac filling pressures or volumes. The cardinal clinical manifestations of HF include shortness of breath, fatigue, and accumulation of fluid in the lungs or periphery. Heart failure is a progressive condition. The failing heart undergoes several structural and molecular changes that lead to a progression of disease and ultimately results in death.

From a clinical perspective, two groups of patients can present with a HF syndrome, including those with preserved systolic function (left ventricular (LV) ejection fraction >50%)
or those with impaired systolic function (LV ejection fraction <40%). Those with preserved systolic function tend to be older, female and have hypertension as an etiology for HF. The patient population described and studied in this thesis includes only those patients with HF due to impaired systolic function. These patients largely reflect those populations studied in RCTs of HF medical and device therapies. Subsequently, most evidenced based guidelines for HF therapies are also based on this group of patients. Previously, the clinical relevance of HF due to preserved systolic function was uncertain, but in recent years has received more attention, subsequent to the initiation of the investigations in this thesis.

1.2.2. Brief Epidemiology of Heart Failure

The HF syndrome is the final stage of most chronic cardiac diseases. The most common etiologies of HF are hypertension and coronary artery disease; however other causes may include congenital heart disease, myocarditis, pregnancy, and cardiotoxins. Heart failure affects both men and women with the prevalence increasing dramatically with age. The prevalence of HF in Canadians ages 60-69 years is 2.2%, rising to 7.6% in those over age 80. Patients with HF usually have multiple comorbid diagnoses and experience high rates of morbidity and mortality. The 5 year mortality rate after an index hospitalization in Ontario is 69% with a median survival of only 2.4 years. In Canada, the 30-day and 1 year readmission rate following an index HF admission is 9% and 23%, respectively. Elderly HF patients are most vulnerable to readmission. For example, a 23% readmission rate within 30 day following a HF admission has been observed in an elderly Medicare cohort. HF admissions are also associated with a prolonged length of stay, estimated in Canada at 8.5-9.9 days. Ultimately, these poor outcomes greatly impact overall medical expenditures and emphasize the need for further research into novel treatment approaches for this important problem.
1.2.3. Brief Pathophysiology of Heart Failure and Sodium Retention

The pathophysiology of HF is a complex process involving hormonal, nervous, and hemodynamic disturbances, which eventually lead to sodium retention and the onset of HF symptoms. Structural heart disease or an insult causing myocardial damage often progresses to the point where the heart cannot provide sufficient blood flow to meet the body’s demands at normal cardiac filling pressures or volumes. Alterations to cardiac filling pressures and volumes cause hemodynamic instability. This provokes a complex set of compensatory mechanisms including activation of the sympathetic nervous system and the RAAS, both of which cause vasoconstriction and renal sodium and water retention. These compensatory mechanisms are collectively referred to as neurohumoral activation, an independent predictor of mortality in this patient population. The initial activation of these regulatory systems is essential for maintaining circulatory homeostasis. Unfortunately, however, chronic neurohumoral activation becomes pathologic, contributing to progressive cardiac impairment, leading to excessive sodium and fluid retention and ultimately symptomatic HF.

Sodium retention in HF is largely the result of the inability of the kidneys to excrete dietary sodium. Abnormal renal sodium handling is caused by reduced renal sodium filtration and/or abnormalities in sodium reabsorption. First, impaired sodium filtration can result from poor central hemodynamics (i.e. reduced cardiac output), which reduces delivery of blood, and thus sodium, to the renal tubules. High circulating levels of norepinephrine also causes renal arteriole constriction, thereby further reducing the amount of sodium filtered and thus renal excretion. Second, altered central hemodynamics activate compensatory defenses, predominantly the RAAS and sympathetic nervous systems, which respond by restoring plasma volume and renal perfusion via sodium retention. Norepinephrine and angiotensin II directly promote renal arteriole constriction, which reduces filtration and thus excretion of sodium. Angiotensin II and aldosterone also act directly on the proximal and distal renal tubules to increase reabsorption of sodium. When sodium retention becomes excessive, atrial natriuretic peptide and brain natriuretic peptide (BNP) are elevated, however the natriuretic
effects are attenuated in HF.\textsuperscript{69,86} As reviewed in section 1.2.5. and 1.4.1., knowledge of these pathophysiologic changes in HF has placed dietary sodium restriction and medical therapies blocking the adverse effects of the sympathetic nervous system and RAAS as the principal HF therapies. If not appropriately treated, or if treated-HF patients experience further activation of these pathophysiologic abnormalities, volume overload and episodes acute decompensation can ensue.

1.2.4. Acute Decompensated Heart Failure

Acute decompensated heart failure (ADHF) is a major cause of morbidity and mortality in HF patients,\textsuperscript{87} which typically requires emergency medical care often resulting in a hospital admission. Acute decompensated heart failure occurs when new or worsening HF signs and symptoms develop (i.e. dyspnea, fatigue, or edema) after a period of relative stability.\textsuperscript{88,89} Several clinical triggers may precipitate the onset of ADHF, such as worsening renal function, persistent neurohumoral activation, and deterioration of myocardial function.\textsuperscript{89,90} Progression of each of these pathophysiologic disturbances can promote sodium retention and volume overload. Lack of adherence to medications or dietary sodium restriction is also considered a risk factor for ADHF. The role of dietary sodium in such decompensation is reviewed extensively in section 1.4.. In Chapter 6 we demonstrate the association between ADHF and high sodium intake in ambulatory HF patients.

1.2.5. Overview of Medical Therapies to Treat Abnormal Renal Sodium Handling

Medical therapy is the primary treatment for HF. The cornerstone of HF management are agents that block the adverse effects of neurohumoral activation. These include beta-blockers,\textsuperscript{91} angiotensin converting enzyme (ACE) inhibitors,\textsuperscript{92,93} angiotensin receptor blockers (ARB)\textsuperscript{94} and aldosterone antagonists.\textsuperscript{95,96} Each of these classes of medication classes have now been proven to prolong survival in HF, while preventing the progression of myocardial damage by blocking the multiple adverse effects of norepinephrine and angiotensin II. They also improve renal sodium handling through direct effects on the renal
vasculature and through inhibition of the RAAS. Sodium retention often persists in patients taking optimal doses of on neurohumoral antagonists. These patients are often prescribed a diuretic to directly promote natriuresis in order to restore sodium balance.

1.2.6. Diuretic Therapy

Diuretics are given to most HF patients with evidence of volume overload, and are used in combination with other HF therapies such as ACE inhibitors and beta blockers. Loop diuretics, such as furosemide, are the most commonly used diuretics in HF management, and are the first-line therapy in treating ADHF because they offer symptomatic relief. Loop diuretics work directly on the renal tubules to inhibit sodium reabsorption, thus increasing urinary sodium excretion, reducing filling pressures and resolving pulmonary and peripheral edema. Specifically, these diuretics block the NaK2Cl symporter on the ascending limb of the loop of Henle, which is responsible for approximately 20-30% of sodium reabsorption. Individual responses to loop diuretics are heterogeneous, being influenced by factors such as renal perfusion and gastrointestinal absorptive capacity. As such, doses are prescribed on an individual basis, considering the degree of sodium retention and individual dose responsiveness. The natriuretic efficacy of loop diuretics may be improved by administering moderate doses throughout the day, or by combining the loop diuretic with a member of another diuretic class.

Unlike for other HF therapies, there are no randomized controlled trials (RCT) examining the effects of loop diuretics on clinical outcomes. The short and intermediate effects of loop diuretics have been reviewed. These include a reduction in jugular venous pressures, pulmonary and peripheral edema, and body weight, as well as an improvement in cardiac function, exercise tolerance, and quality of life. Despite these beneficial clinical effects, observational studies have found associations between loop diuretics and increased risk of mortality. Since loop diuretic dose and use is a marker of HF severity, interpreting such studies is challenging, particularly based on their observational nature. Indeed, several adverse clinical and physiologic effects have been documented
related loop diuretics, including activation of the sympathetic nervous system and RAAS,\textsuperscript{111,112} as well as hyponatremia and renal insufficiency with aggressive treatment,\textsuperscript{113} all of which may aggravate sodium retention. Loop diuretic use is also associated with metabolic abnormalities including metabolic alkalosis and increased urinary losses of potassium, magnesium and calcium in the urine.\textsuperscript{114} These effects are reviewed in detail in section 1.3.4. Despite these concerns, loop diuretics remain a vital component of HF management since they are the most efficacious in fluid removal.

Thiazide and potassium-sparing diuretics (i.e. spironolactone) are also used to treat HF, but they are considered adjunctive therapies as they not typically prescribed in doses that alone induce a profound natriuretic responses.\textsuperscript{115} Compared to loop diuretics, other diuretics have a much less potent natriuretic effect, which is based on their site of action in the renal tubules. Thiazides block 5 to 10\% of sodium reabsorption, while potassium-sparing diuretics only inhibit 1 to 2\% of sodium reabsorption. Thiazide diuretics, prescribed commonly to hypertensive patients,\textsuperscript{116} can be given in conjunction with loop diuretics to enhance natriuresis in HF patients,\textsuperscript{103} although no large trials have been performed in patients with established HF.\textsuperscript{106} In contrast, potassium-sparing diuretics are proven to reduce morbidity and mortality in HF,\textsuperscript{95,96} Spironolactone or eplerenone are used most often in combination with loop diuretics to offset the kaliuretic and hypokalemic effects of furosemide.\textsuperscript{117}

\section*{1.2.7. Nonpharmacologic Therapies for Heart Failure}

Nonpharmacologic therapies are advocated as adjunctive treatments for HF and its common comorbidities. These may include physical activity,\textsuperscript{118,119} therapies for sleep disorders such as sleep apnea,\textsuperscript{120} dietary sodium and fluid restriction,\textsuperscript{121} and other self-care activities such as daily weight monitoring.\textsuperscript{121} The role of dietary therapy in the management of HF will be the focus of the remaining sections of this Chapter.
1.3. NUTRITION IN HEART FAILURE

1.3.1. Energy Expenditure and Cardiac Cachexia

Heart failure is frequently associated with increased resting energy expenditure (REE). Studies suggest that REE is 10-22% higher in male ambulatory HF patients with Class III and IV symptoms, and that REE increases as HF symptoms worsen. However, one study on a proportionally greater number of less symptomatic patients found no differences in REE, when HF patients were compared to healthy controls. On the other hand, the most recent study by Aquani et al found that a largely male HF cohort with a BMI<25 had a REE 15% higher than an age and BMI matched control group. The authors suggest this increase in REE may be explained by the inclusion of patients with evidence of cardiac cachexia. To date, many studies have limited generalizability to broad HF populations, especially to women and those on the current optimal medical therapies for HF. Importantly, for example, all known published studies evaluating energy requirements have not included, or neglected to report, if the HF patients were taking beta blockers. This is relevant since beta blockers attenuate REE, reverse catabolism, and promote weight gain. ACE inhibitors have been postulated to have similar effects. The frequent use of these therapies for HF management is possibly one mechanism which reduces energy expenditure and delays the onset of cardiac cachexia.

Cardiac cachexia, defined as unintentional, nonedematous weight loss of >7.5% nonedematous body mass over 6 months, is the most recognized disorder of energy-protein metabolism in HF. Cachexia is important clinically since it independently predicts mortality in HF patients. Cardiac cachexia is estimated to occur in 16% ambulatory HF patients, typically among those with advanced disease. Cachexia is not related to inadequate energy or protein intake, but rather to underlying pathophysiologic disturbances that increase REE and promote muscle wasting. The primary mechanism is heightened activation of the sympathetic nervous system, which activates proinflammatory cytokines and other metabolic compounds promoting a hypermetabolic state. Nutritional interventions, such as a
high protein diet and amino acid supplementation, only modestly improve nutritional status and rarely have any effect on clinical status.\textsuperscript{126,138} Beta blockade, and anti-anorexic and anti-inflammatory therapies, including omega 3 fatty acids,\textsuperscript{139,140} are currently under consideration as therapies to treat cachexia in HF.\textsuperscript{141}

\textbf{1.3.2. Obesity in Heart Failure}

Although obesity is a risk factor for HF,\textsuperscript{142} patients with established HF and obesity may have an overall better prognosis compared to those with a normal body mass index (BMI).\textsuperscript{143-145} This is often referred to as the obesity paradox.\textsuperscript{146} A meta-analysis of nine observational studies concluded that overweight (BMI 25.0-29.9 kg/m\textsuperscript{2}) and obesity (BMI \geq30 kg/m\textsuperscript{2}) in HF is associated with a respective 16\% and 33\% lower risk all-cause mortality, and 19\% and 40\% lower risk of cardiovascular mortality, compared those with a normal BMI.\textsuperscript{147} A J or U shaped relationship has also been described,\textsuperscript{142,145} with the lowest rates of morbidity and mortality occurring among those with BMI 30.0-34.9 kg/m2.\textsuperscript{142} Little can be concluded for patients with a BMI >40 based on the small number of patients in this category. These outcomes appear to be independent of the presence of preserved or impaired systolic function, and despite adverse hemodynamic and metabolic profiles in patients who are obese, such as the presence of diabetes, hypertension, impaired exercise capacity, and worse HF symptoms.\textsuperscript{142,145,148} Insufficient metabolic reserve to match the hypercatabolic state of advanced disease is a postulated mechanism yielding such observations among under-weight and normal-weight patients.\textsuperscript{135} Obese patients may also tolerate higher medication dosages or may have been classified incorrectly as having HF.\textsuperscript{145} Importantly, RCTs have not been conducted to confirm if changes in body weight result in better or worse clinical outcomes. Regardless, current HF practice guidelines continue to recommend weight loss, particularly for those who are morbidly obese.\textsuperscript{89,149}
1.3.3. Diet in Heart Failure

Diet quality in HF as it relates to food intake as well as adequacy of macronutrient and vitamin and mineral intake has been studied in HF populations. Altered food intake in HF may have multiple causes. Compared to non-HF controls, HF patients are more likely to experience a lack of hunger and early satiety.\textsuperscript{150} HF-related symptoms including shortness of breath and nausea also impact eating patterns and a lack of energy impedes patients’ ability to shop, cook and eat.\textsuperscript{150} Patients report that emotions, such as nervousness, sadness, and loneliness, also affect food intake.\textsuperscript{150,151} Concurrent co-morbid conditions, such as diabetes, coronary artery disease, or renal disease also necessitate further dietary restrictions that may limit food selection. A low sodium diet alone has been shown to alter consumption of certain nutrients, due to the need to alter food intake patterns.\textsuperscript{152-154} Medications, including RAAS inhibitors, calcium channel blockers and certain diuretics may alter taste.\textsuperscript{155} Furosemide, should it be administered in doses to promote excessive sodium depletion, may also paradoxically increase craving for higher sodium foods.\textsuperscript{156-158} These are all important considerations when assessing a patients’ dietary intake in this setting.

A few nutritional balance studies have been conducted to determine if protein and energy intakes meet the requirements of HF patients. One group reported that HF patients are able to maintain a neutral or positive energy balance since they engage in low levels of physical activity.\textsuperscript{125} In contrast, Aquilani et al\textsuperscript{159} found that stable HF patients, compared to age and BMI matched controls, had a greater prevalence of negative calorie and nitrogen balance, and suggested that such patients consume insufficient energy and protein for their physical activity. Interestingly, however, their patients had a stable body weight. Cross-sectional surveys indicate that HF patients may\textsuperscript{160-162} or may not\textsuperscript{161} have adequate energy and protein intakes. However, one study that included a control group found that energy intake was similar to non-HF controls.\textsuperscript{163} These different findings may be due to different patient populations (i.e. inclusion of those with cardiac cachexia or not taking optimal medical therapies such as beta blockers), possible under-reporting, and/or inaccurate estimations of
energy requirements, which were typically generated by predictive equations. However, since the majority of HF patients are overweight or obese, with mean BMI ranging between 27 and 30 kg/m², it is likely that the majority of stable HF patients meet their energy needs through diet.

Diet quality, pertaining to specific macronutrients and vitamins and minerals, also has been studied in HF (Table 1-2). One cross-sectional investigation found HF patients to have poor intake of vegetables (3.3 ± 2.1 to 4.2 ± 1.6 servings/d), fruits and fruit juices (1.6 ± 1.2 to 1.9 ± 1.1 servings/d), milk and dairy products (1.0 ± 0.8 to 1.1 ± 0.9 servings/d), and meat and non-meat protein alternatives (1.7 ± 1.1 to 2.6 ± 1.1 serving/d). In contrast, the average consumption of bread, grains, and cereals was 3.8 ± 1.8 to 6.4 ± 2.9 servings/d, and the average consumption of fats, oils, and sweets was 2.7 ± 1.3 to 3.7 ± 2.3 servings/d. Other studies found that saturated fat and cholesterol were consumed in excess. Whether these differences in food consumption are comparable to an age-matched non-HF group are unknown. Certainly the sources of macronutrients directly affect the amounts of vitamins and minerals consumed.

1.3.4. Vitamins and Mineral Requirements in Heart Failure

Vitamin and mineral requirements in HF are not well understood. Apart from dietary sodium and fluid, vitamin and mineral recommendations for HF patients do not differ from the DRIs that were established for healthy individuals. This is pertinent in that Chapter 4 includes an assessment of adequacy of vitamin and mineral intake among HF patients and a non-HF control group. Recently data on particular nutrients have been published. Omega-3 fatty acid supplementation has been shown to have positive physiologic and clinical effects. The recently published Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico Heart Failure (GISSI-HF) trial, showed modest survival benefit with omega-3 fatty acid supplementation, compared to placebo. Vitamin D has also been studied. Vitamin D supplementation reduces levels of inflammatory markers in HF, but has no beneficial effects on functional status in HF and only modestly lowered plasma BNP.
levels. Chronic utilization of loop diuretics has several nutritional consequences, by potentially increasing the requirements of specific excreted nutrients. Because of the frequent use of loop diuretics in HF therapy, a brief discussion of such nutrients follows.

Nutritional deficiencies secondary to long term use of loop diuretics is common in HF patients. The Heart Failure Society of America recommends that patients on diuretic therapy consider multivitamin supplementation. Increased urinary losses of potassium, calcium, magnesium and thiamin are well-documented. Urinary calcium losses, estimated to be increased by up to 30-40%, cause subsequent hyperparathyroidism, decreases in bone mineral density, and ultimately a 2.5-3.9 fold increase in fracture risk. Only one small trial assessed calcium and vitamin D supplementation and showed no improvement in markers of bone turnover. Hypomagnesemia is also reported and it is estimated to occur in 19-37% of HF patients. Hypomagnesemia can be associated with ventricular arrhythmias and cardiovascular mortality. Magnesium supplementation improves intracellular magnesium levels, reduces the frequency of ventricular arrhythmias and may improve endothelial function in HF. Hypokalemia is perhaps the most common electrolyte abnormality attributed to chronic loop diuretic administration. Consequently, many patients require potassium supplementation or potassium-sparing diuretics. Hypokalemia is associated with poor prognosis in HF. However, there are no known trials of dietary or pharmacologic supplementation on outcomes. Thiamin deficiency is estimated to occur in 21-98% of HF patients, which presents clinically as wet beriberi. Intravenous or oral thiamine supplementation may improve indices of LV function; however studies to date have been small and inconclusive. Multivitamin supplementation has been tested in a RCT in a small cohort of HF patients. Beneficial effects on LV function and quality of life were demonstrated. Whether or not multivitamin or single-nutrient supplementation has beneficial effects on clinical outcomes in HF is unknown.

Many HF patients do not meet DRI requirements for several vitamins and minerals (Table 1-2). Specifically, a high prevalence of inadequacy of potassium, calcium, magnesium, and vitamin D have been reported. Only two of these
studies included a control group. One of these investigations found no difference in vitamin and mineral intakes between HF patients and non-HF controls, although there was likely insufficient power to detect a statistically significant difference between the two study groups. However another study with a similar sample size found significant differences among most nutrients. Both of these studies assessed dietary intake retrospectively via food frequency questionnaires (FFQ), which may not have been a valid method for providing accurate assessment of all the vitamins and minerals evaluated in these studies. A better estimate of nutrient intakes would be obtained by prospectively collecting dietary intake data via multiple day food records. In chapter 4, we describe vitamin and mineral intakes, as assessed by 6 days of food records, in a well-characterized stable group of HF patients and a non-HF cardiac control group.
Table 1-2: Studies examining vitamin and mineral intake in HF patients

<table>
<thead>
<tr>
<th>Author</th>
<th>Population</th>
<th>Measurement Technique</th>
<th>Dietary Intake</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lemon SC et al, 2009</td>
<td>574 patients, self-reported HF from NHANES 1999-2000, 2001-02, 2003-04, 2005-06</td>
<td>Single 24-hour recall</td>
<td>A high proportion of patients had inadequate potassium (97%), calcium (88%), magnesium (97%). Excessive intakes of saturated fat and cholesterol reported.</td>
</tr>
<tr>
<td>Lourenco BH et al,</td>
<td>125 ambulatory patients</td>
<td>Diet history questionnaire</td>
<td>A high proportion of patients had inadequate potassium (98%), calcium (96-100%), magnesium (76-83%). Inadequate intakes also reported for thiamin (31-35%) and phosphorus (15-14%).</td>
</tr>
<tr>
<td>2009</td>
<td>(Brazil)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Catapano G et al,</td>
<td>62 ambulatory HF pts NYHA Class III-IV 62 non-HF controls</td>
<td>Food Frequency Questionnaire</td>
<td>Data (controls, HF). A high proportion of patients had inadequate potassium (79%,66%), calcium (87%,69%), vitamin D (97%,98%), and thiamin (84%, 86%) intake RDA values used for comparisons not reported.</td>
</tr>
<tr>
<td>2008</td>
<td>(Italy)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grossniklaus DA et al</td>
<td>45 ambulatory patients with systolic</td>
<td>Block Food Frequency Questionnaire</td>
<td>Patients were stratified by adequacy of caloric intake, which determined mean intake of most nutrients. Significant differences for potassium, calcium, magnesium, sodium and all other vitamins and minerals were found between those with adequate (29%) versus inadequate (71%) caloric intake.</td>
</tr>
<tr>
<td>2008</td>
<td>(US)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Price RJG, et al, 2006</td>
<td>39 elderly HF patients. Recently discharged or ambulatory</td>
<td>7-day food record</td>
<td>Approximately half of patients (54%) had inadequate energy intakes. A high proportion had inadequate potassium (82%) and vitamin D (97%). Thiamin intake was inadequate in 10% of patients.</td>
</tr>
<tr>
<td>(UK)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gorelik O et al, 2003</td>
<td>57 elderly HF patients 40 non-HF controls</td>
<td>Food Frequency Questionnaire</td>
<td>Data (controls, HF). A high proportion of patients had inadequate caloric intake (70%, 60%), magnesium (81%,73%), calcium (81%,73%). Compared to other studies, a lower number of patients had inadequate potassium intakes (30%,19%)</td>
</tr>
<tr>
<td>(Israel)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: EAR = Estimated Average Requirement, HF=heart failure, NYHA = New York Heart Association, RDA=Recommended Dietary Allowance, NHANES=National Health and Nutrition Evaluation Survey
1.3.5. Fluid Intake Recommendations

Excess fluid retained in the majority of HF patients is predominantly due to the osmotic effect of sodium. Therefore, compared to sodium reduction, restriction of fluid intake alone is considered less effective in maintaining euvolemia. The Canadian Cardiovascular Society and Heart Failure Society of America recommend a 1.5-2 L/day fluid restriction for HF patients with severe hyponatremia (serum sodium <130 mmol/L), renal dysfunction, or ongoing fluid retention that is not easily controlled with diuretics or dietary sodium restriction. There are two studies evaluating the effect of a fluid restricted diet in HF in both ambulatory patients\textsuperscript{201} and in those admitted with ADHF.\textsuperscript{202} These studies failed to observe statistically significant findings related to clinical endpoints such as time to clinical stability, body weight, quality of life, and biochemical endpoints such as serum sodium, serum creatinine and brain natriuretic peptide. However, these studies were of small sample sizes and may have been insufficiently powered to detect statistically significant changes. Therefore, sodium restriction remains the primary dietary approach to managing fluid overload in HF.

1.4. DIETARY SODIUM IN HEART FAILURE

1.4.1. A Historical Perspective

Prior to the availability of current medical treatments, dietary sodium restriction was a core therapy for managing HF symptoms associated with volume overload.\textsuperscript{69, 203} It is unknown if dietary approaches were used in early times. As early as 100 BC – 475 BC, documented treatments to reduce fluid congestion included bloodletting, wet cupping, purging, vomiting, and sweating.\textsuperscript{204} In the 19\textsuperscript{th} century Karell published his milk cure, which is one of the earliest known diets used to manage volume overload in HF.\textsuperscript{205, 206} Dr. Karell
observed that his milk diet cured symptoms of HF and other diseases associated with “dropsy”. Specifically, this diet included the provision of 2 to 6 ounces of skim milk that were consumed slowly and at regularly-timed intervals. Consumption of medications and other foods were not permitted. Clearly, any benefits observed were likely related to the low sodium and fluid content of the diet, which may or may not have been apparent to Dr. Karell at that time.

Some of the earliest research on dietary sodium in HF occurred during the early to mid 1900’s, when sodium and fluid restriction were core HF therapies. It was observed that limiting sodium intake assisted patients in recovering from episodes of decompensation. It was also shown that HF patients were unable to excrete a sodium load. When dietary sodium was restricted, sodium balance improved, weight loss occurred, and HF symptoms diminished. Sodium restriction, when combined with digitalis and/or mercurial diuretics, caused an even greater negative sodium balance. Over the years, as new medical therapies were developed, enthusiasm for sodium restriction began to wane. Today, compared to older HF guidelines and texts, clinicians are offered little direction with regard to dietary sodium therapy. Indeed, the relevance of dietary sodium in HF has been challenged, particularly with the availability of medical therapies that target the sodium-retaining effects of the sympathetic nervous system and RAAS.

1.4.2. Guideline Recommendations

Most expert guideline recommendations suggest a 2000 to 3000 mg/day sodium diet for ambulatory patients with HF, with the goal of reducing HF symptoms and preventing ADHF hospitalizations. However, there is variability in such recommendations. The Canadian Cardiovascular Society and the Heart Failure Society of America advise 2000 to 3000 mg/day, especially for symptomatic patients taking loop diuretics. In contrast, the American Heart Association guidelines suggest that up to 3000 to 4000 mg/day of sodium may be appropriate. Differences in sodium guidelines are largely related to a lack of evidence for HF patients; indeed, current HF recommendations actually exceed the UL for sodium intake.
in healthy individuals. To date, RCTs in HF have not tested sodium intake independent of co-interventions, making it difficult to discern the independent contribution of sodium intake to clinical outcomes. Observational outcomes data are also limited in that sodium intake has never been quantified in patients. The following sections will review this data.

1.4.3. Dietary Sodium and Clinical Outcomes in HF: Clinical Trials

No large RCTs that have examined the independent contribution of sodium intake on clinical outcomes. However, sodium restriction has been tested as part of comprehensive HF care regimens. Trials of multidisciplinary HF disease management programs typically included sodium education as part of a broader intervention. These studies included participation in a HF clinic and focused on close monitoring and counselling for self-care behaviours such as symptom recognition, daily weighing, and medication adherence. A meta-analysis of 29 trials found these programs to be highly effective in improving outcomes including a 25% reduction in mortality, 26% reduction in HF hospitalization and 19% reduction in all-cause hospitalization. Subgroup analyses found that programs emphasizing self-care, including sodium education, had no effect on mortality, but significantly reduced HF hospitalization by 36% and all-cause hospitalization by 27%. These interventions also decreased overall medical costs, improved functional status and exercise capacity, and improved quality of life. Although the interventions tested were heterogeneous in both components and delivery, the multidisciplinary HF clinic has since become the accepted standard for HF management. Although education for adherence to sodium restriction was a component in these studies, changes to sodium intake were not measured and therefore any beneficial or adverse effects of sodium could not be measured.

Another RCT included sodium as part of a broad therapeutic intervention to improve volume status in HF patients. This group tested an alternative hypothesis: that moderate sodium intake (2760 mg/day, n=118), combined with high dose loop diuretics (250-500 mg, twice daily) and fluid restriction (1L/day) improved clinical outcomes, compared to a low sodium diet (1840 mg/day, n=114) combined with the same diuretic and fluid prescriptions.
After 6 months, patients following the low sodium diet regimen had a greater number of hospital readmissions (26% versus 8%, p<0.05), and the combined endpoint of hospital readmission and mortality (39% versus 13%, p<0.001). These findings are likely largely attributed to adverse renal and neurohumoral effects resulting from sodium depletion.\textsuperscript{225-227} The primary limitation in this study was the use of unconventional high loop diuretic doses (250-500 mg twice daily) that were not titrated downward once sodium excess was neutralized. Furthermore, only 9% of the patients in either treatment group were taking beta blockers. Therefore, the clinical relevance of this trial to contemporary HF practices is uncertain. Importantly, this treatment approach has not been endorsed by consensus committees.\textsuperscript{121, 228} Although some misinterpretation of this study has arisen it cannot be considered an evaluation of a purely dietary sodium intervention.\textsuperscript{229}

1.4.4. Dietary Sodium and Clinical Outcomes in HF: Observational Studies

Observational studies have also examined the relationship between sodium intake and clinical outcomes in HF patients. It is estimated that roughly 59% of hospital admissions for HF are due to sodium retention as the principal cause of HF decompensation.\textsuperscript{230} Sodium retention may result from changes to underlying clinical status, diuretic resistance, and nonadherence to medications and diet. Excess dietary sodium has been identified as a factor precipitating ADHF, estimated to cause between 1.3% to 45% of HF admissions (Table 1-3).\textsuperscript{165, 230-236} Poor sodium knowledge, as measured by a standardized test, has also been shown to independently predict hospitalization after 90 days.\textsuperscript{237} Recently Fonarow et al\textsuperscript{231} found an in-hospital mortality rate of 1.8% among patients who had dietary nonadherence as the primary factor precipitating hospitalization. At 60-90 days post-discharge, they also found that 6.5% and 35% of those initially classified as being dietary nonadherent either died or developed the combined endpoint of morality or hospital readmission, respectively. Ambedarkar et al\textsuperscript{165} noted similar findings among 54,322 admitted patients, 5.7% of whom were classified as nonadherent to diet. Of those admitted and classified as dietary nonadherent, approximately 1% died in-hospital. Both of these studies also reported a shorter
length of stay among dietary nonadherent patients, which was hypothesized to be due to a shorter time to clinical stability once dietary sodium and fluid restrictions were reinstated. These studies provide some evidence that nonadherence to sodium may increase risk of hospitalization and in-hospital mortality; however, these studies must be interpreted in light of their limitations as discussed below.

Observational studies conducted to date have several limitations. First, they included only hospitalized HF patients. Second, a broad, undescriptive definition of “dietary nonadherence” has been applied in most studies. This makes it unclear if nonadherence is defined in terms of dietary sodium, or fluid or both. Thus, it is difficult to draw specific conclusions concerning dietary sodium. Third, methods used to classify patients are often vague or include unvalidated retrospective dietary assessment techniques, as evident in Table 1-3. Most studies have assessed sodium intake during clinical interviews, although very few details regarding the methods used are reported. Indeed, even if these dietary assessment methods are sufficient to discriminate those who were adherent from those who were not, the methods were presumably insufficient to detect details regarding the actual level of sodium consumed prior to admission. No studies involving ambulatory patients with stable HF have examined prospectively how different levels of sodium intake contribute to clinical outcomes. Chapter 5 of this thesis directly addresses this knowledge gap.
## Table 1-3. Estimates of the prevalence of dietary nonadherence in HF patients

<table>
<thead>
<tr>
<th>Author</th>
<th>Design Population</th>
<th>Dietary Assessment Methodology</th>
<th>% patients with diet or sodium nonadherence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ambardekar AV. et al. (2009)</td>
<td>95,127 admitted patients from the GWTG-HF cohort</td>
<td>Ass’t method not reported. Unclear if sodium, or fluid or both was evaluated.</td>
<td>Total diet nonadherence was 4.6% (2.3% diet alone, 2.3% diet + medication)</td>
</tr>
<tr>
<td>Fonarow GC et al (2008)</td>
<td>OPTIMIZE-HF total hospital cohort (n=48,612) OPTIMIZE-HF follow-up cohort (n=5791), evaluated 60-90 days post-discharge.</td>
<td>Ass’t method not reported. Unclear if sodium, or fluid or both was evaluated.</td>
<td>Dietary nonadherence in: 5.2% total cohort 7.4% of the follow-up cohort At 60-90 day, dietary nonadherence occurred in: 6.8% who died 35% who died or readmitted</td>
</tr>
<tr>
<td>Vinson JM. et al (1990)</td>
<td>Prospective 90-day post-discharge hospitalization 140 patients admitted with ADHF</td>
<td>Ass’t method not reported. Unclear if sodium, or fluid or both was evaluated.</td>
<td>Dietary nonadherence precipitated hospitalization in 18% of pts; 47% of these pts were rehospitalized within 90 days.</td>
</tr>
<tr>
<td>Tsuyuki RT. et al (2001)</td>
<td>Prospective, 180 systolic HF patients with an episode of ADHF</td>
<td>Ass’t method not reported. Unclear if sodium, or fluid or both was evaluated.</td>
<td>22% of patients with ADHF had “excessive salt intake”</td>
</tr>
<tr>
<td>Bennet SJ et al (1998)</td>
<td>Retrospective chart review 585 admitted HF patients with ADHF</td>
<td>Diet history administered by a dietitian.</td>
<td>59% of patients had admission due to excess Na retention; 50% of these pts who were Rx sodium restriction were nonadherent</td>
</tr>
<tr>
<td>Michalsen A et al. (1998)</td>
<td>Cross-sectional, retrospective 179 admitted HF patients admitted with ADHF</td>
<td>Diet assessed during clinical interview. Nonadherence to sodium if pt “salted food at the table”; to fluid if pt consumed &gt;2.5L/d</td>
<td>45% consumed excess sodium, 43% consumed excess fluid 42% of admissions were the result of nonadherence with medications and/or diet</td>
</tr>
<tr>
<td>Chin MH. et al. (1997)</td>
<td>Prospective enrolment 436 admitted HF patients</td>
<td>Nonadherence to sodium was evaluated through chart review.</td>
<td>Nonadherent to sodium restriction: Total study population: 1.3% Previous HF diagnosis: 3% New onset HF: 0.01%</td>
</tr>
<tr>
<td>Ghali JK. et al. (1988)</td>
<td>Retrospective 101 admitted HF patients</td>
<td>Nonadherence to sodium was assessed, but methods used were not reported.</td>
<td>22% nonadherent to sodium restriction</td>
</tr>
</tbody>
</table>

Abbreviations: ADHF=Acute decompensated heart failure. GWTF-HF = Get With the Guidelines Heart Failure, HF=Heart failure, OPTIMIZE-HF=Organized program to initiate lifesaving treatment in hospitalized patients with heart failure
1.4.5. Physiologic and Clinical Effects of Dietary Sodium in HF

Short-term mechanistic studies have demonstrated that sodium restriction causes neurohumoral activation. Cody et al\textsuperscript{238} showed that extreme sodium restriction (230 mg/d) increased plasma norepinephrine and renin concentrations. Two more recent investigations studied fully medicated HF patients. Despite neurohumoral blockade, a lower sodium diet (1610 mg/d\textsuperscript{239} or 2300 mg/d\textsuperscript{240}), compared to higher sodium intakes, increased plasma norepinephrine, renin, and aldosterone. These neurohumoral effects of sodium depletion have been reported in non-HF subjects in response to both loop diuretics and reduced sodium intake.\textsuperscript{13, 111, 112} However, in the HF setting, these adverse physiologic effects are concerning since neurohumoral activation is associated with poor prognosis.\textsuperscript{82, 83}

In contrast, sodium restriction may positively impact clinical parameters in HF patients. Short and intermediate term studies demonstrate that moderate sodium restriction promotes weight loss,\textsuperscript{238-241} likely secondary to plasma volume contraction.\textsuperscript{239, 241} A low sodium diet has also been associated with reductions in mean arterial pressure, and lower cardiac filling pressures including pulmonary arterial pressure, and pulmonary wedge pressure.\textsuperscript{238, 239} BNP is also lowered in response to sodium restriction.\textsuperscript{240, 242} Conversely, a high sodium diet has been shown to increase LV end systolic and diastolic volumes.\textsuperscript{84} Although untested, sodium restriction may also be sympathoinhibitory if it lowers elevated cardiac filling pressures, which have been shown to stimulate cardiac sympathetic nerves.\textsuperscript{243} HF patients following a low sodium diet have also been shown to have improved HF signs and symptoms and higher levels of reported physical activity, but not improved exercise tolerance with testing.\textsuperscript{240, 241} Alvelos et al\textsuperscript{241} also demonstrated that patients adhering to a lower sodium diet over 3 months had improved quality of life in the domains of emotional aspects and sleeping disturbances as compared to a control group. Other clinical studies have been conducted, but have had insufficient power to detect statistically significant changes in clinical parameters.\textsuperscript{244-246} These findings suggest that sodium restriction may continue to have a clinically relevant role in managing HF, despite potentially inducing adverse neurohumoral effects.
1.4.6. Sodium Intake in Heart Failure Patients

Several cross-sectional studies have estimated average dietary sodium in various groups of HF patients (Table 1-4). Generally, HF patients consume excess sodium. Some studies have found that well over two thirds of HF patients consume >2000 mg of sodium per day.\textsuperscript{160, 162, 247} Actual estimates of mean sodium intake are variable. The highest level of sodium was observed in a group of American HF patients who had never been prescribed a low sodium diet (4967 ± 2524 mg/d); however this estimate was not different compared to those in the same study who had been prescribed a low sodium diet (4418 ± 2033 mg/d, p=NS).\textsuperscript{248} Other investigators have found lower levels of sodium consumption.\textsuperscript{160, 162, 163, 199} These variations are presumably due to the ethnic and regional differences in patients’ dietary patterns as well as differences in the dietary assessment techniques administered. Indeed, those studies that utilized a 24-hour urine collection for sodium intake assessment obtained higher sodium intake estimates,\textsuperscript{247-249} compared to a multiple day food record,\textsuperscript{160} or food frequency questionnaire.\textsuperscript{162, 163, 199} Chapter 2 reviews methodological considerations for assessing sodium intake in HF patients. Only one study to date, which used a FFQ to assess sodium intake, compared HF patients to age matched non-HF controls. They found no difference in sodium intake between the HF and control groups (1030 ± 635 mg/d vs. 1172 ± 621 mg/d, p=NS). In Chapter 5 we present data on sodium intakes of Canadian HF patients. Previously it was unknown if Canadian patients meet or exceed current dietary sodium recommendations.
Table 1-4. Cross-sectional studies evaluating dietary sodium intake in HF patients

<table>
<thead>
<tr>
<th>Author</th>
<th>Population</th>
<th>Measurement Technique</th>
<th>Dietary Sodium Intake</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lennie, T. et al (2008)</td>
<td>145 ambulatory HF patients</td>
<td>One 24-hour urine collection</td>
<td>3723±1970 mg; 60%&gt;3000 mg</td>
</tr>
<tr>
<td>Chung M et al (2008)</td>
<td>133 ambulatory HF patients</td>
<td>One 24-hour urine collection</td>
<td>Rx low sodium diet: 4418±2033 mg Not Rx a low sodium diet: 4967±2524 mg</td>
</tr>
<tr>
<td>Chung M. et al (2006)</td>
<td>68 ambulatory HF patients</td>
<td>One 24-hour urine collection</td>
<td>Total population: 3404±1786 mg; 72% &gt;2000 mg/d, 35% &gt;4000 mg/d Australia: 3168±1710 mg US: 3470±1817 mg</td>
</tr>
<tr>
<td>Price RJG, et al, 2006</td>
<td>39 elderly HF patients. Recently discharged or stable ambulatory</td>
<td>7-day food record</td>
<td>2955 ± 1020 mg/d; 82% &gt; 2000 mg/d, 44% &gt; 3000 mg/d</td>
</tr>
<tr>
<td>Lemon SC et al, 2005</td>
<td>574 patients, self-reported HF from NHANES 1999-2000, 2001-02, 2003-04, 2005-06</td>
<td>Single 24-hour recall</td>
<td>2728±94 mg/d (SEM); 77%&gt;2000 mg/d</td>
</tr>
<tr>
<td>Catapano G et al, 2008</td>
<td>62 ambulatory HF pts NYHA Class III-IV 62 non-HF controls</td>
<td>Food Frequency Questionnaire</td>
<td>Controls: 1508±971 mg/d, 77% &gt;RDA HF: 2132±802 mg/d, 73%&gt;RDA RDA values used for comparisons not reported.</td>
</tr>
<tr>
<td>Grossniklaus DA et al, 2008</td>
<td>45 ambulatory patients</td>
<td>Block Food Frequency Questionnaire</td>
<td>If adequate caloric intake: 3068 ± 928 mg/d If inadequate caloric intake: 2455 ± 881 mg/d</td>
</tr>
<tr>
<td>Gorelik O et al, 2003</td>
<td>57 elderly HF patients 40 non-HF controls</td>
<td>Food Frequency Questionnaire</td>
<td>Controls: 1172 ± 621 mg/d HF: 1030 ± 635 mg/d</td>
</tr>
</tbody>
</table>

Data presented ± standard deviation, unless otherwise indicated. 
Abbreviations: HF=Heart failure, NYHA=New York Heart Association, RDA=Recommended Dietary Allowance, SEM=Standard error of the mean
1.4.7. Factors Influencing Sodium Intake in Heart Failure

Many factors influence the amount of sodium consumed by HF patients. An analysis of 574 individuals with self-reported HF in the NHANES cohort identified the female sex, a higher education and income, and a diagnosis of hypertension to be associated with lower sodium intake.\textsuperscript{166} Furthermore, Amardekar et al\textsuperscript{165} found that admitted HF patients who were nonadherent to diet, medications, or both, tended to be younger, male, a smoker, have a higher BMI, higher blood pressure and have proportionally more HF signs and symptoms. Other factors influencing the level of sodium intake consumed have been studied. Generally, these include inadequate knowledge, social and financial barriers, and patient attitudes towards following a low sodium diet.

Inadequate sodium knowledge has been identified as a key factor related to sodium nonadherence in HF patients. Poor knowledge of sodium levels in food, as measured by standardized testing, has been associated with 90-day readmission in HF.\textsuperscript{237} Inadequate knowledge or misconceptions regarding the level of sodium in food impedes the ability to discriminate between high and low sodium foods. In a group of ambulatory HF patients, Neily et al\textsuperscript{250} found that patients had difficulty reading (42\%) and using (48\%) the Nutrition Facts Table and that 44\% were unable to sort foods into high and low sodium categories. Patients who had received previous dietary sodium counselling performed significantly better on these tests, suggesting that knowledge and skill development has a role in the ability to select low sodium foods. Indeed, patients may not receive a sufficient amount of education about lowering sodium intake\textsuperscript{251} or may teach themselves,\textsuperscript{252} which may explain why patients report misconceptions about sources sodium in food (i.e. that most sodium is from a salt shaker).\textsuperscript{252,253} Importantly, adequate knowledge of sodium content of foods does not guarantee adherence to a low sodium diet. In HF,\textsuperscript{247} chronic kidney disease,\textsuperscript{254} and hypertensive populations,\textsuperscript{255} no relationship has been observed between sodium knowledge and self-reported adherence to a low sodium diet, suggesting that other factors beyond basic knowledge may be involved.
Another factor influencing adherence is lack of understanding of the link between dietary sodium and HF symptoms.\textsuperscript{251, 252, 256} In an analysis of 501 HF patients, those patients unable to recall the rationale for sodium reduction in HF management were less likely to report adherence to sodium restriction.\textsuperscript{256} Also, sodium may not be identified as the primary factor influencing HF symptoms; rather, dietary fat or the whole diet may be considered a priority.\textsuperscript{251} One study found that women have a better understanding of the physiologic effects of sodium and more were better able to recall steps to lowering dietary sodium.\textsuperscript{247} However, Lennie et al found that perceived benefit of a low sodium diet was unrelated to 24-hour urine sodium excretion.\textsuperscript{249} This suggests that sufficient understanding of the biologic effects of excess dietary sodium may not be the sole influence on total sodium intake.

Social and lifestyle barriers to following a low sodium diet have been documented in HF.\textsuperscript{249, 251, 252} Poor availability and higher cost of lower sodium foods choices is commonly reported.\textsuperscript{249, 251, 252} Palatability of lower sodium alternatives is also a concern\textsuperscript{249} and patients report not choosing lower sodium foods to retain the pleasure and satisfaction obtained by their prior food choices.\textsuperscript{251} Patients also report that combining a low sodium diet with dietary restrictions is complex and confusing.\textsuperscript{251-253} Social aspects may impact adherence to a low sodium diet. Patients report that eating away from home is challenging,\textsuperscript{249, 252} especially because restaurant foods tend to be high in sodium and there may be few low sodium options available. In contrast, social pressure and encouragement from spouses, partners, and the health care team positively influence motivation to follow a low sodium diet.\textsuperscript{251, 252} Clearly, because there are multiple factors that influence adherence to a low sodium diet, patient education for dietary sodium reduction must address a range of issues and interventions should be patient focused and tailored to meet individual needs.

1.4.8. Interventions to Promote Adherence to a Sodium Restricted Diet

In the HF setting, specific educational approaches to promote adherence to diet are relatively understudied. However, those that have been tested to date are generally
efficacious in lowering sodium intake. Our group found that two counselling sessions by a dietitian, compared to usual care which was distribution of self-help literature, was more effective in lowering sodium intake in HF patients (-657 sodium/day versus -262 mg sodium/day, p<0.05). During our three month trial, patients randomized to the dietitian intervention group received two counselling sessions with a dietitian. The dietitian reviewed the rationale for sodium restriction, conducted a diet history, and developed tailored goals with the patient. Compared to the dietitian intervention group, the provision of self-help literature without instruction (control group) is not effective in lowering sodium intake, presumably because that approach assumes both literacy and self-motivation. Similarly, Keuhneman et al implemented a dietary sodium counselling protocol in a HF clinic, which involved four sessions with a dietitian over 6 to 9 months. Significant reductions in sodium intake were observed: 2300 ± 1100 g/day (baseline) to 1800 ± 600 mg/day at 2-3 months (p<0.001 vs. baseline), and 1800 ± 700 g/day at 6-9 months (P<0.003 vs. baseline). However, no control group was included. Dunbar and colleagues randomized 61 HF patients to a “standard education” group that included HF education by a nurse and individualized counselling with a dietitian, or to a family-focused approach involved “standard education” plus two a family counselling sessions. After 3 months, there was a trend towards reduced 24-hour urinary sodium excretion in the family focused group (3438 ± 1205 mg to 2612 ± 1255 mg, p = 0.057) but not in the standard education group (2945 ± 1606 mg/d to 2932 ± 1747 mg, p=NS). The authors concluded that a family-centred intervention may help patients achieve and adhere to a sodium restricted diet. This is relevant since social factors can promote or impede adherence with sodium restriction. Other studies of sodium restriction that involved diet counselling successfully reduced sodium intake in ambulatory HF patients, including clinical and mechanistic studies, although specific techniques to promote sodium reduction were not detailed.

Sodium intake in HF patients is modifiable, albeit this is difficult based on the prevailing high sodium food environment. Importantly, screening and monitoring of sodium intake in a HF clinic is necessary so that appropriate patients can be identified for dietary
counseling. However, conducting sodium intake surveillance is challenging since dietitians are not always readily available to perform such assessments in a HF clinic setting. Furthermore, specific methodologies to assess sodium intake in a HF population have not been evaluated. This is relevant since there may be several factors impeding utilization of certain methods in this population, which we address in Chapter 4 of this thesis.
CHAPTER 2: SCOPE AND HYPOTHESES OF THESIS

2.1. Scope and Objectives of Thesis

To address the lack of information related to sodium in HF, the studies presented in this thesis were designed to generate data that can serve as a foundation to test future hypotheses and to guide dietary therapies in clinical practice. The overall objectives of this work were: 1) to investigate the optimal methods for measurement of sodium intake in HF, 2) to describe the average consumption of sodium and other nutrients in HF, and 3) to evaluate the relationship between sodium intake and clinical outcomes in HF. Specific aims were:

1. to assess the strength of relationship between 24-hour urine collections and food records for assessment of sodium intake in stable, optimally medicated non-HF cardiac patients, HF patients not taking a loop diuretic, and HF patients taking a loop diuretic.

2. to quantify and evaluate the adequacy of intake of dietary sodium and other vitamins and minerals in a group of ambulatory HF patients and a control group of non-HF cardiac patients.

3. to determine if a high sodium diet in stable, optimally medicated, ambulatory HF patients is associated with a primary endpoint of acute decompensated heart failure, or secondary endpoints including all-cause hospitalization and all cause mortality.
2.2. Specific Hypotheses

We hypothesized that:

1. a positive, significant relationship between 24-hour urine collections and food records for sodium intake assessment is present in non-HF cardiac patients and the HF patients not taking loop diuretics. Conversely, we hypothesized that there would be a weak or no relationship between 24-hour urine collections and food records for assessment of sodium intake in HF patients taking loop diuretics.

2. a large proportion of HF patients and non-HF cardiac patients will exceed recommended intakes and will have similar mean intakes of vitamin and minerals.

3. HF patients with the highest sodium intake are at greater risk of developing acute decompensated heart failure, all-cause hospitalization, and/or all-cause mortality over a median 3 year follow-up period.

2.3. Preview of Chapter 4

A 24-hour urine collection is the current gold standard for assessment of sodium intake. A relatively strong relationship has been observed between 24-hour urine collections and food records in healthy and hypertensive populations; however, no studies have evaluated the strength of the relationship between these two approaches in HF patients. We hypothesized that the natriuretic effect of loop diuretics modifies the relationship between 24-hour urine collections and food records. In this investigation we determined the strength of relationship between 24-hour urine collections and food records in non-HF cardiac patients, HF patients not taking a loop diuretic, and HF patients taking a loop diuretic. Our objective in conducting this investigation was to inform researchers and clinicians as to the optimal method for sodium intake assessment in HF patients.
2.4. Preview of Chapter 5

At the time this study was initiated there were few published studies comprehensively evaluating sodium intake HF patients. Using two 3-day food records we conducted a detailed analysis to quantify and evaluate adequacy of dietary intake in a stable, ambulatory group of HF patients and a non-HF group of cardiac control patients. We examined mean intakes of sodium and other vitamins and minerals and determined adequacy of intake compared to age and sex specific DRI values. Such data is relevant to describe sodium intakes in HF, and to identify nutritional inadequacies that can be addressed with dietary counselling.

2.5. Preview of Chapter 6

Observational studies have identified nonadherence to sodium restriction as a risk factor for acute decompensated HF. However, no studies have longitudinally evaluated clinical outcomes in relation to quantitative estimates of sodium intake. In this investigation, we measured sodium intake using two 3-day food records and followed patients for a median of 3 years to determine if high sodium intake is associated with adverse clinical outcomes. We specifically examined a primary endpoint of acute decompensated HF, and secondary endpoints of all-cause hospitalization and all-cause mortality. These data are among the first to describe the relationship between sodium intake and clinical outcomes in HF.
CHAPTER 3: GENERAL METHODS

3.1. A Review of the Literature on Assessment Methods for Sodium Intake

3.1.1. 24-hour Urine Collections

Twenty-four hour urinary excretion of sodium is the current gold standard for estimation of sodium intake.\textsuperscript{258} Urinary sodium over a 24-hour period is used as a proxy for daily sodium consumption, since the tight regulation of ingested sodium results in acute changes in sodium appearance in the urine.\textsuperscript{259} This has been shown in balance studies involving subjects on a known amount of sodium, including feeding studies\textsuperscript{260, 261} and studies using duplicate food samples.\textsuperscript{4, 262} Sodium excretion also matches sodium intake, regardless of the magnitude of the sodium load consumed.\textsuperscript{260} Acute, moderate variations in sodium intake are also reflected in the urine. For 10 days, Luft et al\textsuperscript{261} gave amounts of sodium fluctuating between 50 and 250 mmol/day (1150 and 5750 mg/day), to healthy individuals and observed a good relationship with the amount of sodium ingested and excreted (mean r=0.56). However, acute extreme increases or decreases in sodium intake (i.e. 1380 mg and 6900 mg sodium)\textsuperscript{259} may take up to three days for subsequent changes in the urine to appear.\textsuperscript{259, 263}

There are several strengths and limitations to the 24-hour urine collection. The benefit of this method is that it provides an objective measure of ingested sodium. In contrast to food reporting methods, this method is free of reporting bias and is not associated with analytic errors that may occur when working with food composition databases.\textsuperscript{264} The 24-hour urine collection is also ideal because it captures sodium excretion over a 24-hour period, eliminating confounding variations in time of sodium consumption and diurnal variations in sodium excretion. However, due to the large day-to-day variability in sodium intake,\textsuperscript{265-267} it is necessary to acquire sodium consumption data over several
days. Multiple 24-hour urine collections are cumbersome and may be complicated to acquire, especially in those with active lifestyles given that the large specimen containers must be transported with the individual during the collection periods and if several collection containers must be returned.Subjects may also not adhere to the collection protocol. Subjects may not collect each void or may not store the urine container at the proper temperature. Inappropriate timing of the urine collection could lead to over- or under-collection of urine volumes and thus lead to unusable or inaccurate samples. Furthermore, the measurement of total sodium loss can be confounded in sweat, vomit, or diarrhea. As a result of these limitations, other urine methods have been developed in hopes of establishing a more feasible and objective approach to assessing sodium intake.

3.1.2. Other Urinary Methods

The use of nocturnal and spot urine collections has been explored as an alternative objective estimate of sodium intake that reduces subject burden. Nocturnal urine collections have been investigated as an alternative to 24-hour urine collections for estimating sodium intake. This method only requires collection of each void occurring between 2200 and 0600 hours. However this method has not been widely adopted into clinical research.

Spot urine samples have received more recent attention as an alternative to the more cumbersome urinary collection methods. This method requires collection of one void and calculation of daily sodium excretion using a regression equation which considers urinary sodium, age, weight and height of the subject or using the sodium to creatinine ratio. The spot urine collection can be a random urine sample, the second void of the day, or collection of one void in the afternoon or early evening. There is lack of consensus as to which void is optimal. Recently Mann et al. compared spot urine collections to a full 24-hour urine collection. Their data suggest that an early evening spot collection (r=0.86, p<0.001) is better than either a random collection (r=0.17, p<0.33) or a morning collection (r=0.31, p=0.06) in the estimation of daily sodium intake.
These studies are relevant since they are exploring new alternative methods for estimating sodium excretion that could be easily applied to large populations or in clinical and research settings. For example, dipstick methods using a chloride titrator strip, for immediate quantification of sodium excretion, may be useful for monitoring sodium intake in a clinical setting.

Nocturnal and spot urine collections have several limitations. Both methods include several assumptions. For example, there is a high degree of inter-individual variability in creatinine excretion related to differences in muscle mass, which varies greatly by age, sex, and body size; therefore, the ability to use predictive equations to estimate 24-hour sodium excretion is uncertain. These methods also do not take into account diurnal fluctuations in sodium excretion, especially since nocturnal variations in natriuresis may occur, and/or possible variation in sodium excretion due to timing and the sodium content of meals. Further study into these methods is warranted, and such studies should include larger sample sizes and statistical methods which allow for better assessment of agreement between the gold standard 24-hour urine collection and the spot urine method. Based on the complexities of administering urinary excretion methods, investigators and clinicians often opt to use food reporting techniques, including food records, food recalls, and food frequency questionnaires.

### 3.1.3. Food Records

Food records are considered the best non-biologic method for assessing sodium intake based on their prospective and detailed nature. Subjects measure the amount of food and beverages prior to consumption and also measure and record any leftovers using a scale to determine the weight of foods (weighted food record) or volume household measures (i.e. measuring cups and spoons). Complete details on food record methodology used by our group are discussed in section 3.2.2.
Food records have been validated as a method to assess sodium intake (Table 3-1), and have been used in healthy and hypertensive adult populations. Food records tend to underestimate sodium intake. In a small group of healthy individuals, Schachter et al\(^4\) found that food records underestimated sodium intake by approximately 350 mg, when compared to duplicate food portions. However, most studies found a significant linear relationship between food records and 24-hour urinary excretion, regardless of whether the food record was weighted\(^{262, 279}\) or not.\(^{246, 267, 280-283}\) Observed correlation coefficients typically range between 0.30 and 0.68.\(^{246, 262, 267, 279-282}\) In contrast, only one study included adolescents and found a weak relationship between 24-hour urinary sodium excretion and food records (r=\(-0.40, p<0.05\)), and only 16% of participants provided a urine sample with a food record when requested, suggesting that these methods may not be easily administered to all population subgroups.\(^{283}\) However, Clark et al\(^{262}\) found a strong relationship between urine collections and food records for sodium in a group of adolescent girls. Therefore, generally, food records provide a reliable estimate of sodium intake in healthy populations, but may be challenging in certain subgroups of individuals. In disease states, a good relationship also exists between the food records and urine collections, as observed for hypertensive patients taking anti-hypertensive therapies.\(^{267}\) The utility of doing food records to assess sodium intake in HF patients has received little attention, as reviewed in section 3.1.6.

The strengths of food records have been reviewed.\(^{200, 258}\) Food records are considered the optimal food reporting method since they are prospective and allow for the collection of numerous details related to the food and beverages consumed. This includes timing of meals and snacks, capturing of specific brand names used, actual volume and weight amounts of foods consumed. Unlike a 24-hour urine collection, food records allow investigators to assess sodium intake as well as comprehensively evaluate the intake of a wide range of macronutrients and vitamins and minerals. Since food records require an individual to record food items as they are consumed, they are not associated with memory bias. To promote ease of recording, alternative methods have been proposed and tested, such as voice recording or digital images.\(^{284}\) Usually study participants are asked to record foods during a combination of weekdays and weekend days, to capture variations in food
consumption patterns. Data acquisition can occur over any number of days. Three and seven day food records are the most common, although the number of days collected will typically be dictated by the nutrient of interest, considering inter- and intra-subject variability in intake of a nutrient. Using a 24-hour urine collection, it has been estimated that acquisition of 3 to 14 collections would be required to estimate habitual sodium intake with less than 10% variation for a group of individuals. However, food records may require even more days. Bastiotis et al. determined that acquisition of 58 days (range 27-140 days) to determine true intake of an individual, but only 6 days to capture true average sodium intake of a group of individuals. As previously mentioned, there is a large day-to-day variability in sodium intake. Ultimately, when determining habitual sodium intake, acquiring multiple day food records is presumably much more feasible for the subject, compared to collecting multiple 24-hour urine collections.

Food records also have several limitations. The primary concern associated with food records is under-reporting or omission of perceived undesirable food items, as has been documented for obese individuals. In contrast to other dietary assessment techniques, such as FFQs, food records can be burdensome for both the participant and investigative team. Participant burden increases and food record quality may decrease with a greater number of recording days. Weighted food records also require additional effort from the participant, compared to food records that use volume measurements. From the investigator’s standpoint, food record analysis can be expensive and time-consuming. Food records also require extensive analysis by trained coders using specialized nutrient analysis software. Error in food record analysis may also occur from the nutritional composition database used. While several excellent nutritional analysis software programs are available, missing food items or nutrients may affect quantification of nutrients. Finally, like most food recording techniques, food records require literacy. Therefore, there are several factors to consider for optimizing food record quality and reducing errors in analysis.
### Table 3-1. A summary of studies comparing food records with 24-hour urine collections for sodium intake assessment

<table>
<thead>
<tr>
<th>Author</th>
<th>Subjects</th>
<th>Study Protocol</th>
<th>Relationship between Food Record and Urine Collections for Sodium</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>• 28 day FR</td>
<td>Correlations:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• 2 24-hr UC</td>
<td>FR and 24-hr UC:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Crude: $r=0.41$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Energy adjusted: $r=0.28$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Energy and Creatinine adjusted: $r=0.38$</td>
</tr>
<tr>
<td>Micheli, E, et al (2003)²⁸³</td>
<td>188 healthy children and adolescents, free-living</td>
<td>Simultaneous completion of:</td>
<td>24-hr $U_{Na}$ = 3726±1472 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• 1 day FR (n=188)</td>
<td>Correlations:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Overnight UC (n=188)</td>
<td>FR and 24-hr UC:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• 24 hr UC (n=31)</td>
<td>$r=-0.40$, $p&lt;0.05$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>FR and Overnight UC:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.09, $p&lt;0.001$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Bland-Altman 95% limits of agreement:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>FR vs. 24hr UC: -223 to 319 mmol (-5129 to 7199 mg)</td>
</tr>
<tr>
<td>McKeown, NM, et al (2001)²⁸¹</td>
<td>146 healthy middle age men and women, free-living</td>
<td>Simultaneous completion of:</td>
<td>Mean 24-hr $U_{Na}$: M: 3979±989 mg; F: 3013±759 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• 14 days FR</td>
<td>Correlations:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• 6 24-hr UC</td>
<td>Avg FR and UC:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>All: $r=0.48$, Men: $r=0.39$, Women: $r=0.17$</td>
</tr>
<tr>
<td>Bingham SA, et al (1995)²⁷⁹</td>
<td>160 healthy women, free-living</td>
<td>Simultaneous completion of:</td>
<td>Mean 24hr $U_{Na}$ = 2622±53 mg (SEM)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• 16 days of weighted FR</td>
<td>Correlations for average of collection period:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• 8 24-hr UC</td>
<td>FR and 24hr UC:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>$r=0.30$</td>
</tr>
<tr>
<td>Clark AJ, et al (1986)²⁶²</td>
<td>8 females 13-15 years, free-living</td>
<td>Simultaneous completion of:</td>
<td>Mean 24-hr $U_{Na}$ = 2387±130 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• 7 days FR</td>
<td>Correlations for average of 7 days:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• 7-24hr UC</td>
<td>FR and 24-hr UC:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>$r=0.678$ ($p=0.0002$)</td>
</tr>
</tbody>
</table>

Data presented as mean ± standard deviation, unless otherwise indicated.

Abbreviations: F=Female, M=Male, FR=food record, SEM=standard error of the mean, UC=Urine collection, 24hr $U_{Na}$=24-hour urinary sodium excretion
Table 3-1. A summary of studies comparing food records with 24-hour urine collections for sodium intake assessment (continued)

<table>
<thead>
<tr>
<th>Author</th>
<th>Subjects</th>
<th>Study Protocol</th>
<th>Relationship between Food Record and Urine Collections for Sodium</th>
</tr>
</thead>
</table>
| Caggiula AW, et al (1985)   | 55 hypertensive pts, free-living | Completion of: 6 days of FR, 24-hr UC completed on 6th FR day                     | Mean 24-hr $U_{Na} = 2599 \pm 288$ mg  
Correlations:  
1 day FR vs. 24-hr UC: $r=0.53$  
2 days FR vs. 24-hr UC: $r=0.61$  
3 days FR vs. 24-hr UC: $r=0.55$ |
| Pietinen P, et al (1982)    | 154 healthy adults, free-living | Completion of: 4 days of FR, 3 24-hr UC, completed on last 3 FR days             | Mean 24-hr $U_{Na}$: M: 4232±1242, F: 3174±1058 mg  
Correlations:  
Day 1 FR and Day 1 24-hr UC: $r=0.55$, $p<0.001$  
Day 2 FR and Day 2 24-hr UC: $r=0.47$, $p<0.001$  
Day 3 FR and Day 3 24-hr UC: $r=0.62$, $p<0.001$  
3 day mean FR and 3 day mean 24-hr UC: $r=0.62$, $p<0.001$ |

Data presented as mean ± standard deviation, unless otherwise indicated. 
Abbreviations: F=Female, M=Male, FR=food record, SEM=standard error of the mean, UC=Urine collection, 24hr $U_{Na}$=24-hour urinary sodium excretion.
3.1.4. Food Recall

The 24-hour food recall is another common method used to assess sodium intake. Because it is highly feasible, it is the dietary assessment technique chosen for large epidemiologic studies, including the NHANES and CCHS v2.2 cohorts, from which population sodium intake estimates were derived.\textsuperscript{28, 287} Subjects are required to recite all food and beverages consumed in the 24 hours preceding the interview date. This method is relatively inexpensive, easily administered, has low respondent burden and does not require literacy.\textsuperscript{288} Food recalls are usually unannounced and are administered by a trained interviewer who probes the subject for details portion sizes, brands used, preparation methods, time and type of meal consumption, as well as commonly omitted or forgotten foods.

However, the 24-hour recall technique is retrospective and tends to underestimate sodium intake, when compared with sodium estimates obtained from 24-hour urinary excretion.\textsuperscript{289, 290} Although, significant correlations between the two methods have been observed. One study found a correlation coefficient of 0.42 between a 24-hour recall and 24-hour urinary sodium excretion among 4960 healthy adult participants,\textsuperscript{291} while smaller studies similarly found correlation coefficients ranging from 0.30\textsuperscript{290, 292} to 0.43.\textsuperscript{293} One study also showed that, compared to 24-hour urinary excretion, no significant misclassification occurred when food recalls were used to categorize patients into quartiles of sodium intake.\textsuperscript{292} Comparatively, the strength of the relationship between food recalls and 24-hour urine collections are weaker than that between food records and 24-hour urine collections, which may occur due to memory bias, resulting in an over- or under- reporting of foods.\textsuperscript{292} Furthermore, acquisition of multiple food recalls may be required for gaining an estimate of habitual intake.\textsuperscript{288} Food recalls also pose some degree of burden on investigators based on the need to interview each subject, and also because of the time and expense related to dietary analysis. Considering some of these challenges, FFQs are often the preferred choice for dietary assessment in large cohorts of individuals.
3.1.5. Food Frequency Questionnaire

The food frequency questionnaire is a semi-quantitative dietary assessment tool often used in large epidemiologic studies to measure habitual food intake and changes in food intake over time. Only a few published studies have used FFQs to assess outcomes associated with sodium intake.\textsuperscript{294, 295} FFQs may underestimate sodium intake compared to urine collections and other food reporting methods.\textsuperscript{289} Validation studies for dietary sodium that compared FFQs with multiple day food records reported a range of correlation coefficients between 0.07 and 0.53.\textsuperscript{296-299} Although the correlation coefficients between FFQs and reference methods can be small pertaining to dietary sodium, better agreement between a FFQ and reference method are observed when the reference method is administered to capture habitual dietary intake. For example, Block et al. found a relatively stronger correlation coefficients for sodium when comparing a FFQ with 12 days of food records (r=0.43 and r=0.49) versus 8 days of food records (r=0.42 and r=0.31).\textsuperscript{296} Therefore, it is not surprising that studies validating a FFQ against one or two 24-hour urine collections and/or food recalls find poor agreement related sodium.\textsuperscript{297, 299} Comparisons between type of FFQ for sodium assessment have also been made. The Diet History Questionnaire and Block Questionnaire, compared to the Willet Questionnaire, performed best in estimating sodium intake using multiple food recalls as a reference method.\textsuperscript{299} Possible limitations related to FFQs in the estimation of sodium intake include their retrospective nature as well as the possibility that they may be limited in their ability to discriminate between high and low sodium food items. For example, frozen, packaged and restaurant-prepared food items, which tend to be much higher in sodium, may not be distinguishable from a fresh, homemade version of the same food. Despite the limitations of the FFQ, it is a tool that is easily administered and analyzed, and can be applied to large populations with ease.
3.1.6. Assessment of Sodium Intake in Heart Failure

Assessment of diet in HF is relatively understudied. This topic has been reviewed, and briefly described in a small HF cohort, however no studies have systematically evaluated dietary assessment methods in this population. This topic is particularly relevant given the heightened interest in studying dietary sodium in the HF population.

Dietary assessment methods for sodium intake in studies involving HF patients have included 24-hour urine collections, food records, food recalls, and food frequency questionnaires. However, many investigations examining dietary sodium in HF patients failed to use validated assessment techniques. Interestingly, one group reported using the spot urine collection method to demonstrate a relationship between sodium intake and BNP. They used a regression equation to estimate 24-hour urinary sodium excretion. Evaluation of methods for sodium intake assessment in HF is warranted, primarily because HF patients may possess attributes that impact assessment of sodium. For example, patients may require assistance with completion of food records if they have limited functional abilities. Furthermore, exposure to multiple medications that alter renal sodium handling may affect the appearance of sodium in the urine. This is particularly true for the loop diuretics, which exert a powerful natriuretic effect, as reviewed in section 1.2.6. Our work in Chapter 4 addresses these important issues, and highlights the need for further examination of dietary assessment methodologies in HF.

3.2. Application of Selected Dietary Assessment Methodologies

3.2.1. 24-Hour Urine Collections

The timed 24-hour urine collection was used to estimate sodium intake in Chapters 4 and 5 of this thesis. The purpose of the collection is to determine the total amount of sodium
excreted over a 24-hour period, as a proxy for the total amount of sodium consumed in a
given day. The details provided in this section pertain to the specific methods we applied in
our studies.

The standardized 24-hour urine collection protocol has been reviewed. The
participant collected each void over a specified 24-hour period, after the first void in the
morning. The first void on the morning the 24-hour urine collection begins is discarded. All
passed urine is retained in a provided container. The urine collection ends 24 hours later on
the following morning, and is considered complete once the first morning void is collected
into the container. Participants are requested to record that start and end times in their food
record, which was completed concurrently.

Participants in our studies completed two consecutive 24-hour urine collections. Each participant was provided with two 4L preservative-free containers with a screw-top lid, in which all urine was to be stored. Participants were instructed to collect each 24-hour collection into separate containers. Study personnel labelled the containers with the patients name and date, to ensure proper collection. For collection of the urine, men were provided with 1L urinal containers and women were given urinal “hats” which enabled urine to be collected and transferred into the primary 4L storage container. During the collection period, participants were instructed to store the storage containers in a cool place (i.e. refrigerator, cellar). When the urine collections were complete, patients were scheduled to promptly return both 4L storage containers to the laboratory.

Sample analysis was performed by the Mount Sinai Hospital Core Clinical Research Laboratory. Standard laboratory methods were used to measure electrolyte and creatinine content. For each storage container, urine volume was measured and a 30 ml aliquot was taken. Urinary sodium was determined using the ion selective electrode method and urinary creatinine was measured using an enzymatic colorimetric assay (Roche Diagnostics). The ion selective electrode module of the Roche/Hitachi systems (Bielefeld, Germany) was used for both analyses. Total 24-hour excretion was determined by multiplying the measured concentration by the total urine volume. Creatinine excretion was used to assess adequacy of
the urine collections.\textsuperscript{200, 303, 304} We excluded women with a creatinine excretion <4.5 mmol/24-hours and men with a creatinine excretion <8.8 mmol/24-hours, which are the values at the lower end of the normal reference values for urinary creatinine. Creatinine excretion below these values may indicate under-collection. In our studies, sodium excretion is reported in mmol/day; however, for comparative purposes we converted urinary sodium to mg/day using the molecular weight of sodium (23 mg/mmol).

3.2.2 Food Records

The purpose of food records is to generate a quantitative assessment of food intake over a pre-specified number of days. We used food records in each of the reported studies included in this thesis, although the purpose of using food records differed according to the specific investigation. In Chapters 5 and 6, we used two 3-day food records to gain an estimate of habitual consumption, while in Chapter 4 we conducted a validation study to determine the strength of relationship between food records and urine collections among sub-groups of HF patients.

Study personnel provided detailed education to each study participant regarding how to complete a food record. This included instruction to not alter food intake patterns during the recording period, so that the study investigators could “find out what food and drinks you usually consume, so we can see if there is a relationship between what you eat and drink and your heart disease”. Participants were provided with a booklet in which to record foods and beverages. The dates of recording, which were randomly decided by study personnel, were recorded on the front of the booklet. To ensure accuracy in nutrient intake estimation we requested that a high level of detail be recorded.

Portion size was measured by a scale or by standard household measures (i.e. cups, teaspoons, milliliters), as indicated by the study design. Patients recorded the type of foods consumed, including brand names and identification of potential nutrient modified foods (i.e. low fat, low sodium). An envelope was included in the back cover of the food record,
and patients were asked to submit recipes as well as food labels or the Nutrition Facts Table of foods consumed. Other details such as time and place of consumption (i.e. restaurant) and method of preparation were also requested. Patients were asked to carefully record the addition of any and all condiments added to foods. If the patient used table salt that could not be measured by a scale or measuring spoons, they were requested to provide the number of shakes used. Regarding salt from a salt shaker, our laboratory determined that the average amount of sodium dispensed per shake from 10 different salt shakers, which was 0.12 g weight of sodium chloride per shake, and this estimate was used in sodium intake calculations. Prior to recording food intake, participants received a call from the study personnel to again review the instructions and to answer any additional questions that may have arisen.

Subjects were instructed to record the day of the week and date at the top of the food record page and, using a pen, list one food item or beverage per line. Upon completion of the food record, study personnel reviewed the data to ensure its completeness and requested additional details from the patient, if needed. This step has been shown to improve food record quality.\textsuperscript{305}

The ESHA Food Processor SQL (Salem, OR) was the nutrition analysis software and database used for food record analysis. The database was updated approximately every 6 months with the newest version. The ESHA software is produced by an American company and includes brand-specific data as well as nutrient values for generic food and beverages as provided by the United States Food and Drug Administration. The ESHA nutrient database also includes the most recent version of the Canadian Nutrient File, which are items that can be identified because they are in capital letters. The Canadian Nutrient File contains food items largely based on the United States Food and Drug Administration generic food and beverage items; however, certain items have been updated considering supplementation and fortification of certain nutrients and foods in Canada (i.e. folic acid). The Canadian Nutrient File, however, does not include brand-specific information for Canadian food and beverages. Although, if a patient submitted the Nutrition Facts Table for a food or if the
nutritional information was available online, the food record coder would find the closest matching food item available in the ESHA database. Importantly, the ESHA database can be modified to include recipes submitted by a patient. This proved to be a valuable feature and enhanced the accuracy of nutrient intake assessment.

Food record coders underwent a training program to understand the methodology prior to initiation of food record entry. Training focused on understanding foods, food measurements, and critical thinking and analytic skills when probing the patients for clarification and details related to recorded items, as well as for interpretation of food and beverages consumed, particularly for entry into the ESHA database. During the training process, coders also entered a series of food records, which were compared to a set of “gold standard” food records that were entered by a dietitian. Once there was little variability in the results of the nutritional analysis between the coder’s food record and the “gold standard” food records, the coder was considered prepared to independently enter food records. Food records were assigned a 5 digit random number so that coders could remain blinded to patient identity and patient group during the coding process. Food records were entered into ESHA Food Processor SQL, on one centralized computer, using the randomized number and a standardized naming convention used to refer to the respective study. All food records were checked for errors and corrected by a second food record coder. A registered dietitian (J. Arcand, M. Choleva) reviewed the final food record for accuracy.

Food record data was exported from the ESHA database using ESHAPort (Salem, OR), which is an import/export utility software program. The export of food records occurred when all study food records had been analyzed. The nutrition analysis results related to individual patient food records were exported directly to EXCEL, and the exported data format was further modified by a customized EXCEL macro.
CHAPTER 4: Evaluation of two methods for sodium intake assessment in cardiac patients with and without heart failure: the confounding effect of loop diuretics

A version of this manuscript has been published:

Evaluation of two methods for sodium intake assessment in cardiac patients with and without heart failure: the confounding effect of loop diuretics

Short title: Assessment of sodium intake in cardiac disease

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Disclosures: The authors have no conflicts of interest to disclose.

Funding Source: Heart and Stroke Foundation of Ontario (NA-5897).

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4.1. Abstract

**Background:** Twenty-four-hour urine collections are considered the optimal method for sodium intake assessment. Whether a diagnosis of HF or the use of loop diuretic (LD) therapy for HF compromises the validity of 24-hour urine collections as a surrogate marker for sodium intake is unknown.

**Objective:** To determine the strength of association and limits of agreement between 24-hour urine collections and food records for sodium intake assessment in non-HF cardiac patients, and in HF patients stratified by LD usage.

**Design:** Food records and 24-hour urine collections concurrently completed for two consecutive days. Correlation coefficients and the Bland-Altman method of agreement described the relationship between the techniques.

**Results:** Non-HF cardiac patients (n=96, 65±11 years) and HF patients not taking LD (n=47, 62±11 years) and HF patients taking LD (n=62, 60±12 years) were included. Correlation coefficients for sodium intake between food records and urine collections were r=0.624 (p<0.001) for non-HF cardiac patients, and r=0.678 (p<0.001) for HF patients not taking LD. However no significant association (r=0.132, p=0.312) was observed for HF patients taking LDs. The 95% limits of agreement between the non-HF cardiac patients and the HF patients not taking LD were similar, but were approximately 50% wider for HF patients taking LD.

**Conclusions:** For assessing sodium intake, food records agree well with 24-hour urine collections in non-HF patients with cardiovascular disease and in HF patients not receiving LD therapy; but not for HF patients taking LD. Therefore food records may provide the better estimate of sodium intake in HF patients on LD.
4.2. Introduction

Heart failure (HF) is the end stage of many cardiovascular disorders, including coronary artery disease and hypertension.\(^{68}\) Despite advances in medical and surgical therapies, HF is an increasingly common cardiovascular syndrome associated with high rates of morbidity and mortality.\(^{75}\) Sodium retention, a primary pathophysiologic feature of HF, is largely responsible for HF symptoms such as shortness of breath. Despite a paucity of data evaluating the current effectiveness of dietary recommendations in HF, sodium restriction remains the cornerstone of nutritional advice for such patients.\(^{67,68,306}\)

There is growing interest in establishing an evidence-based literature for sodium guidelines for individuals with HF. However there are no published studies evaluating methods for the quantification of sodium intake in HF patients. Since renal excretion of ingested sodium is almost complete among healthy individuals, the 24-hour urine collection is considered the gold standard to assess sodium intake.\(^{300}\) Food records, food frequency questionnaires, and 24-hour diet recalls are also used to estimate sodium consumption. Weighted food records are considered to be the best non-biologic dietary assessment technique since they provide prospective, quantitative data on a broad range of nutrients. Compared to 24-hour urine collections, food records are also more easily acquired over several days allowing an estimate of habitual consumption. This is an important consideration based on large day-to-day variability in sodium intake.\(^ {267,285}\) Studies have proven food records to be a valid method of sodium intake assessment in healthy and hypertensive individuals.\(^{5,267}\)

Whether food records or urine collections are appropriate tools to estimate sodium intake in HF patients has not been established. There are HF-specific circumstances that may impact the use of either method in the HF setting. For example, urine collection based estimates of sodium intake may be altered by increased urinary sodium excretion secondary to loop diuretic (LD) usage.\(^{307}\) The purpose of this study was to describe the strength of the relationship and the limits of agreement between food records and urine collections for a
group of stable, euvolemic, HF patients and a group of non-HF cardiac patients with normal left ventricular function. Our aim was to stratify HF patients based on LD use, in order to discern the impact of natriuretic therapy on the assessment of sodium intake.

4.3. Subjects

Ambulatory patients, ages 18-85 years, were consecutively enrolled from a multidisciplinary HF clinic and from general cardiology clinics. All patients were stable without hospitalization or emergency room visits in the three months prior to study entry. No patients were institutionalized and all patients consumed a self-selected diet. Heart failure patients had a left ventricular ejection fraction <40% by two dimensional echocardiography or radionuclide angiography. The HF group was prospectively stratified into a group without LD usage (> 3 months without therapy), and a group with chronic stable LD usage (> 3 months of therapy without a dosage change). The non-HF cardiac control patients had normal left ventricular function, no current or previous HF symptoms, and were not taking a LD. Non-HF patients had medically treated hypertension and/or stable coronary artery disease which was diagnosed by either a clinical event, positive non-invasive testing, or by coronary angiography. Both non-HF cardiac patients and HF patients were receiving optimal medical therapy including at least one of an angiotensin converting enzyme inhibitor, an angiotensin receptor blocker, or a beta blocker. Exclusion criteria for all groups included serum creatinine >140 µmol/L, serum sodium <130 mmol/L, and cardiac cachexia (unintentional weight loss >10% over 6 months). This study was approved by the Research Ethics Board of the Mount Sinai Hospital in Toronto, Canada. All patients provided written informed consent for their participation.

4.4. Methods

All participants simultaneously completed two 24-hour urine collections and two weighted food records on consecutive days selected by study investigators. Participants were
instructed to continue medications as directed by their physician and to continue usual daily activities and food patterns. To reduce sodium loss in sweat, patients were asked to limit exposure to excessive heat and participation in strenuous activity during the study.

4.4.1. Food Records

Participants were trained on how to complete weighted food records. Training included completion of a food record prior to study entry. Patients were instructed on the use of an electronic scale to weigh food and beverages. Patients were required to include the time and place of food and beverage consumption and to provide a detailed description of the food item including the cooking method, any nutritional modifications (e.g. low fat, low sodium), and additions such as condiments, spices or salt. They were encouraged to provide recipes as well as the Nutrition Facts label of foods consumed. If added salt from a shaker could not be weighed, patients were asked to record the number of shakes. When the study food records were complete, patients had a debriefing session with a dietitian to clarify food item descriptions and any missing food items. Food records were entered into ESHA Food Processor SQL (v. 10.5.2, ESHA Research, Salem, OR) by trained coders who were blinded to subject identity. Food records entered for analysis were checked twice for accuracy by independent coders and by the study dietitian. Intra-coder variability for calories and sodium was 0.05 and 0.03, respectively. Inter-coder variability was 0.07 for calories and 0.09 for sodium. Individual patients consuming <500 kcal/day were considered to be under-reporting their intake and were excluded from the analysis.

4.4.2. 24-Hour Urine Collections

Patients were also provided with detailed instruction on how to complete the 24-hour urine collection. Participants were instructed to discard the first morning void and to collect all urine over the following 24 hours including the first void on the next morning. They were given two preservative-free containers, one for each 24-hour period. During the collection
period, patients were asked to store collected urine in a cool place. Urine containers were scheduled for prompt return to the laboratory for analysis. For each day, urine volume was measured and a 30 ml aliquot was taken. Urinary sodium was determined using the ion selective electrode method and urinary creatinine was measured using an enzymatic colorimetric assay (Roche Diagnostics). The ion selective electrode module of the Roche/Hitachi systems (Bielefeld, Germany) was used for both analyses. Total 24-hour excretion was determined by multiplying the measured concentration by the total urine volume. Creatinine excretion was used to assess adequacy of the urine collections. We excluded women with a creatinine excretion <4.5 µmol/24-hours and men with a creatinine excretion <8.8 µmol/24-hours. Sodium excretion is reported in mmol/day; however, for comparative purposes we converted urinary sodium to mg/day using the molecular weight of sodium (23 mg/mmol).

4.4.3. Statistical Analysis

Continuous variables are described as means and standard deviations. Categorical variables are presented as frequencies and percentages. Continuous variables were analyzed using one factor analysis of variance to make one-way comparisons between the control group and the two HF groups. When the F ratio from the analysis of variance was significant, Scheffe’s post hoc test was used to determine pairwise differences. Chi-square tests were used for between group comparisons of categorical variables.

Using the mean sodium intake of the two days, the association between urinary sodium excretion and sodium estimated by food records was determined using Pearson’s correlation coefficient for each study group. Analysis of covariance was used to determine if there was a difference in the linear relationship for the methods between the two HF groups. The main effects were HF group, sodium intake assessed by food records, and the interaction between the two. General linear modelling was further used to determine if clinical variables modified the relationship between urinary sodium excretion and reported sodium intake. The Bland and Altman method of agreement was used to describe the
relationship between two measurement techniques. The y-axis of the Bland-Altman plot included the mean difference between methods, which was calculated by subtracting sodium estimated by urinary excretion with sodium estimated from food records. The x-axis included the average sodium intake which was calculated by taking the mean sodium intake estimated by urinary excretion and food records. The standard deviation of the mean difference was multiplied by 1.96 to derive the 95% limits of agreement. Regression equations were calculated for the Bland-Altman plots to determine if there was a relationship between the mean difference in sodium estimated between the techniques and the magnitude of sodium intake. If the slope of the regression line in these plots significantly differed from zero (p<0.05), the regression equation was provided so that the limits of agreement could be calculated for any given level of sodium intake. A nonparametric form of the Bland-Altman method was also conducted. This included determining the proportion of individuals meeting or exceeding selected cut-points for the mean difference between sodium assessment techniques. All statistical analyses were performed with SAS version 9.1 (SAS Institute Inc, Cary, NC). A p value of <0.05 was considered statistically significant.

4.5. Results

We enrolled 104 non-HF cardiac patients and 116 HF patients (Figure 4-1) between September 2006 and August 2009. Seven non-HF cardiac patients and six HF patients were excluded because they failed to return their urine samples and/or food records. One non-HF cardiac patient and one HF patient were excluded because of incomplete urine samples. The final analysis includes 96 non-HF cardiac control patients and 109 HF patients. When HF patients were stratified by LD use, 47 patients were not taking LD and 62 patients were taking LD.

Baseline characteristics of the study groups are presented in Table 4-1. There were no differences in sex distribution between the groups. Heart failure patients taking and not taking LD had a similar left ventricular ejection fraction. Patients taking LD had a
significantly lower systolic blood pressure compared to both the non-HF cardiac patients and HF patients not taking LD. There were differences between the three groups in comorbid conditions and medications. Generally, the non-HF cardiac patients had lower medication usage aside from thiazide diuretics, presumably for treatment of hypertension. All patients in the HF group on a LD were receiving furosemide with an average dose of 73 mg/day (range: 20 to 240 mg/day). The distribution of furosemide dosage in this group included 14 (23%) taking <40 mg/day, 37 (60%) taking 40-120 mg/day, and 11 (18%) taking >120 mg/day.
Figure 4-1. Flow diagram

Eligible patients consecutively approached from ambulatory clinics:
128 non-HF cardiac patients
132 HF patients (55 not on a LD, 77 on a LD)

Declined participation:
24 non-HF cardiac patients
16 HF patients (5 not on a LD, 11 on a LD)

Patients who agreed to undergo food recording and 24-hour urine collection:
104 non-HF cardiac patients
116 HF patients (50 not on a LD, 66 on a LD)

Patients who had missing or incomplete food records and/or urine collections:
8 non-HF cardiac patients
7 HF patients (3 not on a LD, 4 on a LD)

The final analysis included:
96 non-HF cardiac patients
109 HF patients (47 not on a LD, 62 on a LD)
Reported mean sodium intake and consumption of other macronutrients were similar among the non-HF cardiac patients and the two groups of HF patients (Table 4-3). Mean urinary sodium excretion was also similar among the groups (Table 4-2). The mean difference in sodium intake estimates (urinary sodium - food record sodium) was significantly greater for HF patients taking LD (764 ± 1535 mg), compared to the control patients (195 ± 1023 mg) and HF patients not taking LD (393 ± 1002 mg) (p<0.05).

Significant correlations were observed between urinary sodium excretion and sodium intake estimated by food records for the non-HF cardiac patients (r=0.624, p<0.001, Figure 4-2(a)) and for HF patients not taking LD (r=0.678, p<0.001, Figure 4-2(b)). However, there was no significant correlation between the two sodium assessment techniques for HF patients taking LD (r=0.131, p=0.312, Figure 4-2(c)). Analysis of covariance demonstrated significant differences in the linear relationship among the assessment techniques between the HF patients taking and not taking LD (p=0.039). The linear relationship between sodium estimated between urine collections and food records for patients taking LD remained non-significant (r=0.227, p=0.694) after adjusting for variables that may further alter sodium excretion including furosemide dose, spironolactone use, hydrochlorothiazide use, and systolic blood pressure.

The 95% limits of agreement for the difference in sodium intake estimated from food records and urine collections is presented in Figure 4-2. The limits of agreement were similar between the non-HF cardiac patients (-1810 mg to 2200 mg) and HF patients not taking LD (-1610 mg to 2396 mg). Comparatively, the limits of agreement were almost 50% wider for HF patients taking LD (-2245 mg to 3773 mg). Furthermore, the regression of the mean differences against the magnitude of sodium intake was significantly different from zero for the HF patients taking LD (Figure 4-3(c), p=0.015), but not for the non-HF cardiac patients (Figure 4-3(a), p=0.975) and HF patients not taking LD (Figure 4-3(b), p=0.232). For the non-parametric analysis (Table 4-4), approximately two thirds of non-HF cardiac patients and HF patients not taking LD, compared to less than half of HF patients taking LD, had a mean difference between methods less than 1000 mg of sodium. This discordance
between methods for the HF patients taking LD, compared to the other patient groups, was evident at all selected cut-points (Table 4-4).
### Table 4-1. Patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>Controls (n=96)</th>
<th>HF No Loop Diuretic (n=47)</th>
<th>HF Loop Diuretic (n=62)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>72 (74)</td>
<td>40 (85)</td>
<td>41 (66)</td>
</tr>
<tr>
<td>Age</td>
<td>65 ± 11</td>
<td>62 ± 11</td>
<td>60 ± 12&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>BMI (kg/m2)</td>
<td>28.0 ± 4.1</td>
<td>29.0 ± 6.9</td>
<td>29.5 ± 6.1</td>
</tr>
<tr>
<td>NYHA Class I-II</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class III-IV</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>5 (11)</td>
<td>16 (26)</td>
<td></td>
</tr>
<tr>
<td>LV ejection fraction</td>
<td>59 ± 7</td>
<td>29 ± 8&lt;sup&gt;a&lt;/sup&gt;</td>
<td>27 ± 7&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>129 ± 18</td>
<td>125 ± 16</td>
<td>115 ± 15&lt;sup&gt;a,b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>76 ± 10</td>
<td>75 ± 9</td>
<td>72 ± 9</td>
</tr>
<tr>
<td>Serum Creatinine (µmol/L)</td>
<td>88 ± 18</td>
<td>90 ± 19</td>
<td>94 ± 25</td>
</tr>
<tr>
<td>eGFR (ml/min)</td>
<td>79 ± 16</td>
<td>80 ± 18</td>
<td>74 ± 22</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>59 (61)</td>
<td>18 (38)</td>
<td>25 (40)&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Hypertension</td>
<td>52 (54)</td>
<td>17 (36)</td>
<td>24 (39)&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Diabetes</td>
<td>21 (22)</td>
<td>8 (17)</td>
<td>20 (32)&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>59 (61)</td>
<td>17 (36)</td>
<td>26 (42)&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Smoking History</td>
<td>6 (6)</td>
<td>10 (21)</td>
<td>6 (10)&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Mean Furosemide dose (mg/d)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>73 ± 58</td>
<td></td>
</tr>
<tr>
<td>Spironolactone</td>
<td>1 (1)</td>
<td>12 (26)</td>
<td>28 (45)&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Thiazide diuretics</td>
<td>22 (23)</td>
<td>7 (22)</td>
<td>2 (9)&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Beta Blocker</td>
<td>58 (60)</td>
<td>40 (85)</td>
<td>56 (90)&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>ACEI/ARB</td>
<td>64 (67)</td>
<td>47 (100)</td>
<td>62 (100)&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Vitamins/Minerals</td>
<td>56 (58)</td>
<td>16 (34)</td>
<td>19 (31)&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Continuous variables presented as mean ± SD. Categorical variables presented as n (%).

<sup>a</sup> p<0.05 versus Control group by ANOVA;  
<sup>b</sup> p<0.05 HF-no loop diuretic versus HF-loop diuretic groups  
<sup>c</sup> p<0.05 between groups

Abbreviations: NYHA = New York Heart Association Class, BP=blood pressure, LV = left ventricular, eGFR=estimated glomerular filtration rate; ACEI = Angiotensin converting enzyme inhibitor, ARB = angiotensin receptor blocker.
Table 4-2. Mean dietary intake calculated from study food records

<table>
<thead>
<tr>
<th></th>
<th>Controls (n=96)</th>
<th>HF No Loop Diuretic (n=47)</th>
<th>HF Loop Diuretic (n=62)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calories (kcal)</td>
<td>2084 ± 626</td>
<td>2067 ± 634</td>
<td>2041 ± 493</td>
</tr>
<tr>
<td>Sodium/1000 kcal</td>
<td>1315 ± 430</td>
<td>1353 ± 561</td>
<td>1240 ± 449</td>
</tr>
<tr>
<td>Potassium (mg)</td>
<td>3232 ± 990</td>
<td>2894 ± 913</td>
<td>3042 ± 1001</td>
</tr>
<tr>
<td>Fluid (ml)</td>
<td>2620 ± 978</td>
<td>2336 ± 629</td>
<td>2290 ± 672</td>
</tr>
<tr>
<td>Carbohydrate (g)</td>
<td>264 ± 95</td>
<td>257 ± 83</td>
<td>251 ± 72</td>
</tr>
<tr>
<td>Protein (g)</td>
<td>95 ± 31</td>
<td>89 ± 34</td>
<td>90 ± 27</td>
</tr>
<tr>
<td>Fat (g)</td>
<td>68 ± 29</td>
<td>73 ± 35</td>
<td>74 ± 33</td>
</tr>
</tbody>
</table>

Continuous variables mean ± SD. There were no differences in dietary intakes between the groups.
Table 4-3. Mean sodium intake and excretion among HF patients and controls

<table>
<thead>
<tr>
<th></th>
<th>Controls (n=96)</th>
<th>HF No Loop Diuretic (n=47)</th>
<th>HF Loop Diuretic (n=62)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume (L)</td>
<td>1.8 ± 0.9</td>
<td>1.6 ± 0.7</td>
<td>1.8 ± 0.6</td>
</tr>
<tr>
<td>Sodium excretion (mmol/d)</td>
<td>127 ± 51</td>
<td>136 ± 52</td>
<td>142 ± 58</td>
</tr>
<tr>
<td>Sodium excretion (mg/d)</td>
<td>2916 ± 1182</td>
<td>3121 ± 1176</td>
<td>3262 ± 1325</td>
</tr>
<tr>
<td>Calculated sodium intake (mg/d)</td>
<td>2721 ± 1180</td>
<td>2728 ± 1342</td>
<td>2498 ± 967</td>
</tr>
<tr>
<td>Mean difference in sodium (mg/d) (UC-FR)</td>
<td>195 ± 1023</td>
<td>393 ± 1022</td>
<td>764 ± 1535&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Mean sodium intake (mg/d) (UC+FR)/2</td>
<td>2716 ± 1221</td>
<td>2675 ± 1257</td>
<td>2522 ± 978</td>
</tr>
</tbody>
</table>

Continuous variables mean ± SD;
<sup>a</sup> p<0.05 versus Control group;
Abbreviations: UC = 24 hour urine collection; FR = Food record
Table 4-4. Proportion of patients meeting select cut-points for differences in sodium intake as estimated by urine collections and food records

<table>
<thead>
<tr>
<th>Difference in Sodium Between Methods (±)</th>
<th>≤ 500 mg</th>
<th>≤ 1000 mg</th>
<th>≤ 1500 mg</th>
<th>≤ 2000 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-HF cardiac patients (n=96)</td>
<td>41 (43%)</td>
<td>64 (67%)</td>
<td>82 (85%)</td>
<td>89 (93%)</td>
</tr>
<tr>
<td>HF patients not taking LD (n=47)</td>
<td>17 (36%)</td>
<td>33 (70%)</td>
<td>40 (85%)</td>
<td>43 (91%)</td>
</tr>
<tr>
<td>HF patients taking LD (n=63)</td>
<td>15 (24%)</td>
<td>29 (46%)</td>
<td>44 (70%)</td>
<td>49 (79%)</td>
</tr>
</tbody>
</table>

Categorical data presented as n(%).
Abbreviations: HF=heart failure; LD=loop diuretics
Figure 4-2a. Correlation between 24-hour urinary sodium excretion and sodium estimated from food records for non-heart failure cardiac patients

[r=0.624, p<0.001]
Figure 4-2b. Correlation between 24-hour urinary sodium excretion and sodium estimated from food records for heart failure patients not taking loop diuretics.
Figure 4-2c. Correlation between 24-hour urinary sodium excretion and sodium estimated from food records for heart failure patients taking loop diuretics.

$r=0.131$
$p=0.312$
Figure 4-3a. Bland–Altman plot for agreement between 24-hour urinary sodium excretion and sodium estimated from food records for non-heart failure cardiac patients.
Figure 4-3b. Bland–Altman plot for agreement between 24-hour urinary sodium excretion and sodium estimated from food records for heart failure patients not taking loop diuretics.

- Mean Diff = 393 mg
- +1.96 SD = 2396 mg
- -1.96 SD = -1610 mg
Figure 4-3c. Bland–Altman plot for agreement between 24-hour urinary sodium excretion and sodium estimated from food records for heart failure patients taking loop diuretics.
4.6. Discussion

To our knowledge, this is the first study to evaluate two common methods used to quantify sodium intake in HF and general cardiac patients. We observed that 24-hour urine collections and food records are appropriate for assessing sodium intake in non-HF patients with cardiovascular disease and in HF patients not taking LD therapy. However, there was poor agreement between these two assessment techniques in HF patients taking LD therapy. These findings have important implications for clinical research in the HF setting. These data are also relevant because there are a paucity data available to guide sodium assessment in non-HF cardiac populations.

Urinary sodium excretion is the well accepted gold standard method to estimate sodium consumption, since 95% of ingested sodium is excreted in the urine.\(^4\) However, given the large day-to-day variability in sodium intake, it is necessary to acquire data over several days to estimate habitual sodium consumption.\(^285\) This limits the utility of urine collections with the important exception of investigations with very large numbers of patients.\(^6\) In these studies, as little as a single 24-hour collection may be sufficient to estimate sodium intake. Because of the challenge of urine collections over multiple days, food records have gained favour as a practical approach to determining intake of sodium, in addition to a broad range of other nutrients. Food records, however, have different limitations such as the misreporting of food and beverages consumed.\(^309\) Smaller clinical studies tend to use food records or food records in combination with 24-hour urine collections to assess habitual sodium intake.\(^241, 246, 310, 311\) Other methods such as food frequency questionnaires\(^299\) and diet recall methods\(^290, 293\) are retrospective and may provide less-reliable estimates of sodium consumption. For example, food frequency questionnaires have a limited ability to discriminate between a high and low sodium versions of similar food items (e.g. made-from-scratch versus canned soup).
Previous studies have generally confirmed a positive relationship between 24-hour urine collections and food records. In 55 hypertensive patients, Caggiula et al. observed significant correlations between one 24-hour urine collection and sodium intake reported from a one day ($r=0.53$), two day ($r=0.61$) and a six day ($r=0.61$) food record. Two thirds of these patients were on unidentified anti-hypertensive treatment. Holbrook and colleagues administered four sets of concurrent seven day food records and seven 24-hour urine collections to healthy subjects and also reported a strong correlation between methods ($r=0.76$, $p<0.001$). These earlier investigations have limited generalizability to present day practices, including utilization of contemporary medical treatments and the use of sophisticated nutritional analysis software now available to investigators. Furthermore, sodium assessment in the present day is more complex based on increased consumption of prepared and convenience foods. Finally, previous studies of urinary excretion methods did not include HF patients, a group with disturbed sodium homeostasis due to both the disease state and medical therapy. Indeed, methods to evaluate sodium intake in HF patients have only been reviewed but not tested systematically.

The current findings have implications for clinical studies involving both HF patients and patients with cardiovascular disease without HF. We discovered significant correlations and reasonable agreement in sodium estimates from urine collections and food records for the non-HF cardiac patients and for HF patients not taking LD. The non-parametric cut-point analysis in our study further highlights the relative consistency in the proportion of patients in these groups within all cut-points. Although absolute mean differences in sodium estimated between the methods may appear large (e.g. 1500 mg), these differences should be viewed relative to the high sodium content that currently exists in North American diet. Together, this agreement between methods suggests that urine collections and food records have similar utility in estimating sodium intake in cardiac populations without HF and in HF patients who are not taking LD.

The lack of correlation and agreement in the LD group of HF patients in the present study is a novel finding. For the HF patients taking LD therapy, there was a significantly
greater mean bias (764 mg) detected between the two techniques and the 95% limits of agreement were also much wider compared to the other two groups. We stratified HF patients by LD usage because these drugs exert a potent natriuretic effect compared to other diuretics (e.g. spironolactone, thiazides). Although it is generally assumed that sodium output will equal sodium input in HF patients at steady state, this hypothesis is yet to be proven. Indeed, unmedicated HF patients have impaired sodium excretion and develop a positive cumulative sodium balance following a high sodium diet. However, Damgaard et al recently showed that stable, compensated HF patients on optimal medical therapy were able to maintain a neutral sodium balance, similarly to non-HF controls, while following short-term high and low sodium diet regimens. Two thirds of the patients in this study were taking LD therapy. These experimental studies demonstrated a trend in sodium excretion consistent with the intervention administered (e.g. sodium loading or sodium depletion) that was constant over several days. Our patients were consuming self-selected diets. Since they had daily fluctuations in sodium intake, a plausible hypothesis is that day-to-day variations in salt load may not translate into similar variations in sodium excretion, even when at steady state. Therefore, 24-hour urinary sodium would not necessarily be a marker of sodium intake over the preceding 24 hours.

The lack of association between urine collections and food records in the HF patients on LD in the present study is also a challenging finding. The reasonable correlation and agreement in HF patients not taking LD and the non-HF cardiac patients group suggest that treatment with a potent diuretic is responsible for the loss of performance of food records, urine collections, or both. We argue above, based on biologic considerations, that urine collections are likely to be altered by the use of potent diuretics. In contrast, there is no obvious reason for food records to be disturbed by the ongoing use of diuretics. Furthermore, there were few differences between the two HF groups related to clinical and demographic data. We therefore assert that our data be interpreted to support food records to measure sodium intake in the setting of HF with LD treatment.
There are limitations associated with our study. We stratified our relatively small group of HF patients based on LD usage since LD have the greatest effect in directly enhancing renal sodium excretion; however, beta blockers, angiotensin converting enzyme inhibitors, and angiotensin receptor blockers also indirectly affect sodium balance by attenuating the underlying neurohumoral activation that is characteristic of the HF setting. However, use of these therapies was similar between the two HF groups. Furthermore, we studied HF patients who were medically stable without changes to LD for three months; therefore, we cannot determine if similar results would be observed in patients with recent adjustments in LD or in changes to their underlying clinical condition. We tested the agreement between two dietary assessment methodologies; however, this was not a balance study in which patients were admitted to a metabolic unit on a controlled amount of sodium. Furthermore, we assessed the adequacy of urine collections using the sex-specific reference standards for creatinine excretion and adequacy of food record recording by caloric intake. Indeed, it is difficult to ascertain that the data collected by these measures were completely representative to true intake and excretion, although this data represents the real-life experience when these methods are applied to a cardiovascular population.

4.7 Conclusion

In summary, this cross-sectional study assessing techniques to quantify sodium consumption demonstrated that food records and 24-hour urine collections are appropriate tools for assessing sodium intake in non-HF patients with cardiovascular disease and in HF patients not taking LD therapy. However, in HF patients taking LDs, there was a lack of relationship between urinary sodium and reported sodium intake, presumably due to altered sodium excretion. This suggests that, on an individual level, sodium intake is better assessed through food records in HF patients taking LDs.
4.8. Acknowledgements

Dr. Allard had full access to all of the data in the study and takes full responsibility for the integrity and accuracy of the data. Drs. Allard, Newton, Floras, Mak, Azevedo and Ms. Arcand take responsibility for the study design and concept. Ms. Arcand and Drs. Newton, Floras, Mak and Azevedo are responsible for data acquisition. Ms. Arcand and Drs. Allard and Newton conducted the statistical analysis and interpretation of the data as well as drafted the manuscript. All authors were involved in the critical revision of the manuscript. There are no conflicts of interest to report.

We wish to thank the following individuals for their assistance with data collection and food record analysis: Jordana Fenster RD, Tasha Cortese RD, Amanda Schwartz RD, Samantha Goren RD, Vanessa Floras BSc, BEd, Chelsea Kaplansky BSc, Mavra Ahmed BSc, Kitty Chan, Mariel VanWoudenberg BSc, Daniela Malta BSc, Marlene Choleva RD, and Diana Vasiliu RN. We would also like to thank the administrative staff and cardiologists in the general cardiology and heart function clinics who assisted with patient recruitment.
Figure Legends

**Figure 4-1 (a-c).**

**Title.** Correlation between urinary sodium excretion and sodium estimated from food records

**Figure.** Pearson’s correlation between urinary sodium excretion and estimated sodium from food record analysis for study groups (a) Non-HF cardiac patients, (b) HF patients not taking loop diuretics, (c) HF patients taking loop diuretics. There was a significant difference in the distribution of the data within the two HF groups (p=0.039).

**Figure 4-2 (a-c).**

**Title.** Bland-Altman plots for agreement between urinary sodium excretion and sodium estimated from food records

**Figure.** Estimated 95% limits of agreement between sodium estimated from food records (FR) and 24-hour urine collections (UC) using the Bland and Altman method. (a) Non-HF cardiac patients, (b) HF patients not taking loop diuretics, (c) HF patients taking loop diuretics. The regression of the mean difference significantly differed from zero among the HF patients taking LD therapy (p=0.015, Panel C).
CHAPTER 5: Nutritional inadequacies in stable heart failure patients

A version of this manuscript has been published:

Nutritional inadequacies in stable heart failure patients

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Disclosures: The authors have no conflicts of interest to disclose.

Funding Source: This study was funded by a grant-in-aid from the Heart and Stroke Foundation of Ontario (NA-5897).

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E-mail: gnewton@mtsinai.on.ca
5.1 Abstract

Sodium restriction is the primary nutritional strategy in heart failure (HF); however other diet-related concerns may also occur. We characterized dietary intake among stable HF patients and a non-HF cardiac control group to quantify and determine prevalence of inadequate micronutrient intake. Two 3-day food records were completed by 123 HF patients and 58 controls. A subset of each group provided two 24-hour urine collections. Mean intake of sodium (2540±1122 versus 2596±1184 mg/day, p=NS) and potassium (3190±980 versus 3114±828 mg/day, p=NS) were similar between the HF and control groups. Prevalence of inadequate potassium intake was 94% among HF patients and 91% among controls. Over 50% in each group had inadequate intakes of calcium, magnesium, folate, and vitamins D and E. In stable HF patients sodium intake was not excessive. However we demonstrated widespread dietary inadequacies of other vitamins and minerals. These findings highlight the importance of diet beyond that of sodium restriction.
5.2. Introduction

Sodium restriction remains the primary dietary recommendation for the treatment of chronic heart failure (HF). The American Heart Association guidelines recommend 3000 to 4000 mg/day in symptomatic patients and <2000 mg/day for end-stage patients. Despite these recommendations, the actual sodium requirement for HF patients is unknown. Dietary intake of other vitamins and minerals including potassium, thiamin, calcium, magnesium, zinc, and vitamin D are relevant in HF due to obligatory renal losses caused by loop diuretic therapy and the adverse cardiovascular and health effects of their deficiencies. There is minimal published information regarding consumption of vitamins and minerals in HF, and whether these nutrients are consumed in adequate amounts.

The primary objective of this study was to evaluate intake of vitamins and minerals from food in a group of stable HF patients compared to a relevant control group of cardiac patients without HF. Our secondary objective was to assess the prevalence of dietary inadequacy for these nutrients.

5.3. Methods

5.3.1. Study design

We performed a cross-sectional study in HF patients and control patients without HF. Heart failure patients were recruited from multidisciplinary HF programs and were eligible if they had a left ventricular ejection fraction less than 35%, stable HF symptoms, and stable medical therapy including an angiotensin converting enzyme inhibitor (ACEI), an angiotensin receptor blocker (ARB), or a beta blocker. Control patients had normal left ventricular function and were on medical therapy for coronary disease or hypertension,
without loop diuretic use. Exclusion criteria for both groups included serum creatinine >140 \(\mu\)mol/L, serum sodium <130 mmol/L, and an inability to consume a self-selected diet or record intake in a food record booklet. We also excluded patients with cardiac cachexia, defined as unintentional weight loss >10% over six months, and patients who had any hospitalizations or emergency room visits for three months prior to the study. Research Ethics Board approval was received at Toronto’s Mount Sinai and St. Michael’s Hospitals. All patients provided written informed consent.

5.3.2. Assessment of Dietary Intake

Dietary intake was assessed by two sets of 3-day food records on days selected by study investigators. Weekend and weekdays were included, and each record was completed 6-10 weeks apart to capture variation in grocery cycles and seasons. Patients recorded the time and place of consumption and included detailed information about each food item. Food amounts were measured with a scale or standard household measures. Upon completion, study investigators reviewed food record details with each subject. Food records were analyzed by three trained coders using a nutrient software program (ESHA Food Processor SQL v.10.1, ESHA Research). Coders were blinded and all records were checked twice by a different coder. Food records completeness was assessed by comparing reported energy intake to predicted energy intake using a predictive equation.\(^2\) Patients who under-reported caloric intake by >60% were excluded. The food record method has been validated for assessment of usual intakes of groups\(^5\) and has been used in the HF population.\(^{246, 310}\) Since we were interested in determining nutrient intakes from food, data on vitamin and supplements was not included in the estimation of nutrient intake in these subjects.

Since this study was completed prior to the investigation in Chapter 4, we did not have direction as to the best method to assess sodium intake in HF. Therefore, we also collected two 24-hour urine samples from a subset of consenting patients to provide an objective assessment of sodium and potassium excretion. Collections were completed at the same time as the first set of food records. Creatinine excretion standards were used to
determine completeness of the urine collections, and collections were excluded if they were less than 60% predicted value.

5.3.3. Statistical Analysis

A sample size of 56 patients per group was calculated to provide 80% power to detect a mean between group difference of 800 mg/day of sodium intake (alpha 0.05), based on our observation of a standard deviation for sodium intake of 1500 mg/day in HF patients. Between-group comparisons were conducted using an unpaired t test, chi-square test or Fisher’s Exact test. The DRI cut-point method was used to determine the prevalence of nutritional inadequacy. This method compares habitual intake of an individual to DRI for each vitamin and mineral. All data are expressed as mean ± standard deviation or as a percentage. A p value <0.05 was accepted as significant.

5.4. Results

A total of 135 HF patients and 75 control patients were enrolled. Twelve HF patients and 17 control patients were excluded for failure to complete their food records. No patients decompensated during the study period. The final analysis includes 123 HF patients and 58 control patients. There were no significant differences in baseline characteristics of patients who were excluded versus those who completed the study (data not shown).

Heart failure patients were younger than control patients, and had a higher body mass index (Table 5-1). Coronary disease was less common in the HF group (40% versus 63%, p=0.01). Medical therapy in the HF group included furosemide (81%), a beta-blocker (86%), an ACEI/ARB (98%), and spironolactone (43%). Medical therapy in the control group included a beta-blocker (55%), and an ACEI/ARB (57%). Fifty-three HF patients and 36 control patients also provided two 24 hour urine collections. There were no significant differences in baseline characteristics or dietary intakes of patients who provided urine collections versus those who did not (data not shown).
Thirty-two patients in the HF group had previously seen a dietitian, but none were counselled within 3 months of study participation or during the study period. No control patients had seen a dietitian prior to study enrolment.

Heart failure and control patients reported similar mean sodium and potassium intakes (Table 5-2). Based on the DRI upper limit of 2300 mg/day, 55% of HF patients and 52% of controls were consuming excess sodium by food records. Urinary sodium excretion was also similar between HF (136±58 mmol/day) and control patients (141±58 mmol/day)(p=0.682). Furthermore, no differences were observed in potassium excretion between HF (70±18 mmol/day) and control patients (70±25 mmol/day)(p=0.984). The DRI adequate intake level for potassium is 4700 mg/day. Based on this, over 90% of patients in both groups had inadequate potassium intake (Figure 5-1). Of the HF patients, 50% consumed >2.0 L/day and 83% consumed >1.5 L/day, although mean intake was similar between HF (2.2±0.8 L/day) and controls (2.3±0.8 L/day) (p=0.242). There were no significant differences for the intakes of multiple vitamins and minerals between the HF and the control group (Table 5-2). More than 50% of patients in each group had inadequate dietary intakes of calcium, magnesium, folate, vitamin E, vitamin D, and zinc (Figure 5-1).
Table 5-1. Patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>Control (n=58)</th>
<th>Heart Failure (n=123)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>43 (74)</td>
<td>94 (76)</td>
<td>0.882</td>
</tr>
<tr>
<td>Age (years)</td>
<td>64 ± 11</td>
<td>60 ± 13</td>
<td>0.024</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.0 ± 4.2</td>
<td>29.2 ± 6.0</td>
<td>0.020</td>
</tr>
<tr>
<td>CAD</td>
<td>36 (63)</td>
<td>49 (40)</td>
<td>0.006</td>
</tr>
<tr>
<td>Diabetes</td>
<td>11 (19)</td>
<td>41 (33)</td>
<td>0.079</td>
</tr>
<tr>
<td>Hypertension</td>
<td>25 (44)</td>
<td>32 (26)</td>
<td>0.026</td>
</tr>
<tr>
<td>LV ejection fraction (%)</td>
<td>63.0 ± 8.6</td>
<td>25.2 ± 9.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>127 ± 13</td>
<td>117 ± 18</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>77 ± 9</td>
<td>72 ± 9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>68 ± 11</td>
<td>71 ± 13</td>
<td>0.129</td>
</tr>
<tr>
<td>Serum Sodium (mmol/L)</td>
<td>140 ± 3</td>
<td>139 ± 3</td>
<td>0.010</td>
</tr>
<tr>
<td>Serum Potassium (mmol/L)</td>
<td>4.3 ± 0.5</td>
<td>4.3 ± 0.5</td>
<td>0.848</td>
</tr>
<tr>
<td>Serum Creatinine (µmol/L)</td>
<td>92 ± 25</td>
<td>100 ± 31</td>
<td>0.130</td>
</tr>
<tr>
<td>Furosemide</td>
<td>0 (0)</td>
<td>100 (81)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>0 (0)</td>
<td>53 (43)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Beta Blocker</td>
<td>32 (55)</td>
<td>106 (86)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ACE/ARB</td>
<td>33 (57)</td>
<td>120 (98)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Digoxin</td>
<td>2 (3)</td>
<td>59 (48)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Potassium Supplement</td>
<td>1 (2)</td>
<td>26 (21)</td>
<td>0.002</td>
</tr>
<tr>
<td>Vitamins/Mineral Supplement</td>
<td>18 (32)</td>
<td>36 (29)</td>
<td>0.888</td>
</tr>
<tr>
<td>Potassium supplement dose (mmol/day)*</td>
<td>0.6 ± 2.2</td>
<td>6.8 ± 16.5</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Results are expressed as mean ± standard deviation for continuous variables and frequency (percent) for categorical variables.

* Potassium supplement dose includes potassium supplemented from both pharmacologic and multivitamin supplements.
Table 5-2. Average daily intake of energy, macronutrients, and vitamin and minerals

<table>
<thead>
<tr>
<th></th>
<th>Control (n=58)</th>
<th>Heart Failure (n=123)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calories (kcal)</td>
<td>1768 ± 517</td>
<td>1756 ± 576</td>
<td>0.891</td>
</tr>
<tr>
<td>Sodium (mg)</td>
<td>2596 ± 1184</td>
<td>2540 ± 1122</td>
<td>0.765</td>
</tr>
<tr>
<td>Potassium (mg)</td>
<td>3114 ± 828</td>
<td>3190 ± 980</td>
<td>0.608</td>
</tr>
<tr>
<td>Fluid (ml)</td>
<td>2315 ± 769</td>
<td>2166 ± 807</td>
<td>0.242</td>
</tr>
<tr>
<td>% Carbohydrate</td>
<td>50 ± 9</td>
<td>51 ± 9</td>
<td>0.419</td>
</tr>
<tr>
<td>% Protein</td>
<td>20 ± 5</td>
<td>19 ± 4</td>
<td>0.867</td>
</tr>
<tr>
<td>% Fat</td>
<td>30 ± 7</td>
<td>30 ± 7</td>
<td>0.894</td>
</tr>
<tr>
<td>% saturated fat</td>
<td>9.0 ± 3.2</td>
<td>9.3 ± 3.0</td>
<td>0.471</td>
</tr>
<tr>
<td>% monounsaturated fat</td>
<td>8.9 ± 2.9</td>
<td>9.0 ± 2.9</td>
<td>0.855</td>
</tr>
<tr>
<td>% polyunsaturated fat</td>
<td>4.5 ± 1.9</td>
<td>3.9 ± 1.3</td>
<td>0.044</td>
</tr>
<tr>
<td>Calcium (mg)</td>
<td>813 ± 378</td>
<td>767 ± 365</td>
<td>0.437</td>
</tr>
<tr>
<td>Magnesium (mg)</td>
<td>335 ± 110</td>
<td>302 ± 106</td>
<td>0.054</td>
</tr>
<tr>
<td>Thiamin (mg)</td>
<td>1.6 ± 0.8</td>
<td>1.5 ± 0.6</td>
<td>0.265</td>
</tr>
<tr>
<td>Riboflavin (mg/d)</td>
<td>1.7 ± 0.7</td>
<td>1.6 ± 0.6</td>
<td>0.680</td>
</tr>
<tr>
<td>Niacin (mg)</td>
<td>25 ± 10</td>
<td>23 ± 8</td>
<td>0.180</td>
</tr>
<tr>
<td>Vitamin B6 (mg)</td>
<td>2.0 ± 0.8</td>
<td>2.1 ± 1.1</td>
<td>0.537</td>
</tr>
<tr>
<td>Folate (mcg)</td>
<td>304 ± 120</td>
<td>317 ± 138</td>
<td>0.558</td>
</tr>
<tr>
<td>Vitamin C (mg)</td>
<td>111 ± 65</td>
<td>144 ± 138</td>
<td>0.028</td>
</tr>
<tr>
<td>Vitamin E (mg)</td>
<td>3.7 ± 4.8</td>
<td>3.5 ± 3.3</td>
<td>0.730</td>
</tr>
<tr>
<td>Vitamin D (mcg)</td>
<td>3.0 ± 2.6</td>
<td>2.9 ± 2.7</td>
<td>0.756</td>
</tr>
<tr>
<td>Iron (mg)</td>
<td>14.4 ± 4.8</td>
<td>14.8 ± 5.2</td>
<td>0.673</td>
</tr>
<tr>
<td>Zinc (mg)</td>
<td>9.6 ± 3.7</td>
<td>9.4 ± 4.4</td>
<td>0.772</td>
</tr>
</tbody>
</table>

Results are expressed as mean ± standard deviation.
Figure 5-1. Nutritional inadequacy among heart failure patients and controls

The bar chart compares the percentage of patients with inadequate intake for various nutrients between heart failure patients and controls. Key nutrients include potassium, calcium, magnesium, thiamin, riboflavin, niacin, vitamin B6, folate, vitamin C, vitamin E, vitamin D, and zinc. The chart shows higher percentages of inadequacy among heart failure patients compared to controls for most nutrients.
5.4. Discussion

We observed that stable HF patients had similar intakes of vitamins and minerals when compared to control group of cardiac patients without HF. However, there were widespread nutritional inadequacies in both groups. Poor dietary intake was not specific to HF, although these patients may be at greater risk based on well-described nutritional abnormalities in the HF setting.

Inadequate nutritional intake has been described in small groups of HF patients who were elderly and hospitalized. A recent investigation also reported markedly lower dietary intake in an elderly HF group compared to age-matched controls. However, dietary intake was only assessed by retrospective questionnaire, with no validation by other methods. Importantly, investigations of energy and nitrogen balance, and nutritional biomarkers, have identified poor nutritional status in non-cachectic HF patients. There are likely several causes of altered nutritional status in HF including gastrointestinal malabsorption and urinary micronutrient losses from diuretic usage. Our observation of broad inadequacy suggests that diet likely contributes to poor nutritional status among HF patients. Several factors may impair food intake in HF patients such as early satiety, nausea, dietary restrictions, and shortness of breath. Lack of interest or inability to grocery shop and/or cook may further influence meal preparation and food consumption. Taken together, these observations highlight the importance of comprehensive nutritional counseling beyond sodium restriction.

The majority of HF patients in our study had sodium intakes within HF guideline recommendations of 2000 to 3000 mg/day or 3000 to 4000 mg/day. Only 11% had a mean sodium intake >4 g/day and urinary sodium excretion was >4000 mg/day in only 26% of patients. This degree of adherence may reflect participation in a HF management program. Patients in this trial were stable over six months (three months before, and then three months during the study). Whether this level of sodium intake contributed to clinical
stability was not tested in this study. This is an important question, which would require a much larger investigation.

The DRI recommendation for healthy individuals places the tolerable upper limit of sodium intake at 2300 mg/day.\textsuperscript{2} This may actually result in additional dietary sodium restriction among HF patients. Unlike hypertension, the outcomes and clinical effects of different levels of sodium intake are generally untested in the HF setting. Historically dietary sodium restriction was essential for survival of HF patients.\textsuperscript{203} However, the role of sodium restriction in HF is now uncertain based on contemporary therapies, including diuretics and neurohumoral blockade. Furthermore, mechanistic studies have demonstrated neurohumoral activation in response to sodium restriction in HF \textsuperscript{239, 240}. A recent clinical trial observed worse outcomes in patients randomized to sodium restriction following a HF decompensation.\textsuperscript{225} Although excess sodium intake likely contributes to HF decompensation in individual patients, the success of medical treatment in maintaining sodium homeostasis, the lack of clinical data, and our data showing moderate intake in patients maintaining stability, should reduce enthusiasm for aggressive sodium restriction as a general strategy in stable HF patients (See Footnote, page 96).

We identified dietary inadequacies for multiple nutrients in both HF and control patients. Potassium intake was low, presumably based on a diet low in fruits and vegetables and high in refined-carbohydrates,\textsuperscript{316} although consumption of these foods was not quantified. The DRI for potassium is 4700 mg/day. However, there are no guidelines for potassium intake in HF. Hypokalemia is common in HF based on loop diuretic usage\textsuperscript{307} and elevated aldosterone levels.\textsuperscript{317} The importance of potassium depletion in HF has been highlighted in a recent study which observed increased mortality in among HF patients with a serum potassium <4 mmol/L.\textsuperscript{191} Counseling HF patients to increase dietary potassium may reduce the need for pharmacologic supplements, which do not yield the same health benefits of potassium ingested in food.\textsuperscript{318} Whether increasing dietary potassium improves outcomes and is safe in HF is an important and testable hypothesis.
We measured intake by food record analysis and 24-hour urinary excretion. The latter method is the gold standard for assessment of sodium intake, as excretion of consumed sodium is almost complete. Sodium excretion was higher than reported sodium intake, likely due to under-reporting. In contrast, potassium excretion was lower than reported intake. Potassium excretion is an accepted marker of potassium intake, although there is a weaker association, which may reflect both over-reporting and non-urinary potassium losses (i.e. fecal). No studies were identified that assess methods to quantify sodium and potassium intake in the HF setting. This is relevant since HF may be associated with multiple factors which impair recording of food intake and/or urinary collections. Whether the natriuretic effects of furosemide augments sodium excretion in a stable euvolemic HF patient is unknown. Therefore, we assessed nutrient intake with multiple-day food records to account for high day-to-day variability in diet.

There are limitations to our work. The DRI recommendations were generated for healthy populations. Heart failure and its therapy may lead to elevated nutritional requirements; therefore, our data may underestimate nutritional inadequacy for some nutrients. This study was performed in multidisciplinary HF clinics at academic hospitals and the generalizability of the present findings cannot be assumed. There were significant differences in age and BMI between these two patient populations. Whether these differences were a confounding factor influencing dietary intake was not assessed. We considered our dataset too small to do multiple comparisons with stratification. Finally, we did not evaluate nutrient balance, therefore we cannot address whether deficiencies resulted from poor intake despite identifying inadequate consumption of several vitamins and minerals.
5.5. Conclusion

We observed that HF patients had widespread dietary inadequacy including potassium, calcium, folate, and vitamins D and E. These findings highlight the importance of nutrition counselling, and provide a basis for the generation of nutritional hypotheses and investigations of dietary modification and supplementation in HF beyond that of sodium restriction.
5.6 Acknowledgements

We would like to thank the staff and cardiologists of the heart function clinics and general cardiology clinics at Mount Sinai Hospital and St. Michael’s Hospital in Toronto. We especially thank Chelsea Kaplansky and Sherri Schamehorn for their assistance in data collection and analysis.
Footnote

At the time of publication of this manuscript there was limited data related to sodium in heart failure. Our understanding was limited to mechanistic studies pointing to adverse neurohumoral activation in heart failure. However, there is a temporal evolution in our thoughts based on our findings in Chapter 6 and the recent investigation by Lennie et al., suggesting that higher sodium intake may indeed be associated with adverse outcomes in heart failure patients.

Figure Legend

Figure 5-1.

Title: Nutritional inadequacy among heart failure patients and controls

Caption: Proportion of heart failure (solid bars) and control patients (grey bars) not meeting Dietary Reference Intakes for vitamins and minerals. No significant differences were observed between groups. Recommended intake levels used in this analysis (M=males, F=Females): Potassium: 4700 mg; Calcium: 1200 mg; Magnesium: 350 mg (M), 265 mg (F); Thiamin: 1.0 mg (M), 0.9 mg (F); Riboflavin: 1.1 mg (M), 0.9 mg (F); Niacin: 12 mg (M), 11 mg (F); Vitamin B6: 1.4 mg (M), 1.6 mg (F); Folate: 320 µg; Vitamin C: 75 mg(M), 60 mg (F); Vitamin E: 12 mg; Vitamin D: 5 µg (≤50 years), 10 µg (51-70 years), 15 µg (≥71 years) Zinc: 9.4 mg (M), 6.8 mg (F).
CHAPTER 6: A high sodium diet is associated with acute decompensated heart failure in ambulatory heart failure patients: A prospective follow-up study

A version of this manuscript was published:


A high sodium diet is associated with acute decompensated heart failure in ambulatory heart failure patients: A prospective follow-up study

Short title: Dietary sodium and heart failure

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Disclosures: The authors have no conflicts of interest to disclose.

Funding Source: Heart and Stroke Foundation of Ontario (NA-5897).

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6.1. Abstract

**Background:** A low sodium diet is an accepted treatment for patients with heart failure (HF), although minimal evidence exists for any level of sodium intake in this population. Certain HF guidelines have liberalized dietary sodium recommendations, which actually exceed guidelines for healthy adults.

**Objectives:** We tested the hypothesis that high sodium intake is related to acute decompensated heart failure (ADHF) in ambulatory HF patients. Secondary outcomes included all-cause hospitalization and mortality.

**Design:** Medically stable, ambulatory patients with systolic HF (n=123, 60±13 years) were prospectively enrolled from two outpatient HF clinics from 2003-2007. Baseline estimates of dietary sodium and other nutrients were obtained from two 3-day food records.

**Results:** The median follow-up time was 3.0 years. Mean sodium intake was 1443 ± 297 mg/day, 2376 ± 253 mg/day, 3814 ± 882 mg/day in the lower, middle and upper tertiles, respectively. Cumulative ADHF event rate at three years was 12±6%, 15±7% and 46±11% in the low, middle, and upper tertiles (log-rank p=0.001). For ADHF, the upper tertile was associated with an adjusted hazard ratio of 2.55 (CI, 1.61-4.04, p<0.001). Time-to-event probabilities were significant for mortality (log-rank p=0.022) but not all-cause hospitalization (log-rank p=0.224). The high sodium tertile was associated with an adjusted hazard ratio of 1.39 (CI 1.06-1.83, p=0.018) for all-cause hospitalization and 3.54 (CI, 1.46-8.62, p=0.005) for mortality.

**Conclusions:** This is the first prospective evidence that ambulatory HF patients consuming higher amounts of sodium are at greater risk for an ADHF event. These data provide support for more stringent sodium intake guidelines than currently recommended for HF patients.
6.2. Introduction

Heart failure, an exceedingly common cardiac condition, is associated with high rates of morbidity and mortality including frequent hospital admissions. Sodium restriction has remained a core therapy for managing sodium and fluid retention in patients with acute and chronic heart failure. However, despite the theoretical basis for restricting sodium intake in heart failure patients, the role of dietary sodium in heart failure management has not been fully established in the current era of highly effective medical therapy. To date, there is no empirical evidence demonstrating beneficial or adverse outcomes associated with sodium intake in compensated, appropriately medicated heart failure patients, a group making up the majority of the heart failure population.

Recent data have highlighted an alternative hypothesis that sodium restriction may be harmful in heart failure patients. Two clinical trials of sodium restriction in heart failure patients following an episode of decompensation showed that a low sodium diet in combination with high dose diuretics and fluid restriction promotes increases in hospital readmission and death. Mechanistic investigations have also demonstrated adverse neurohumoral activation following short-term sodium restriction, further challenging the utility of sodium restriction in ambulatory heart failure patients. Practice guidelines for heart failure patients also demonstrate reduced enthusiasm for dietary sodium restriction. Limiting sodium intake to 2000 to 3000 mg/day is typically recommended, based on expert consensus, for patients with symptomatic heart failure on optimal medical therapy including diuretics. However, current American College of Cardiology/American Heart Association heart failure guidelines suggest a daily sodium intake up to 4000 mg may be appropriate for a similar patient group (Stage C heart failure). This sodium intake level is above the recommended tolerable upper intake of 2300 mg of sodium/day for the healthy adult population.
We tested the hypothesis that high sodium intake is associated with adverse outcomes including ADHF and secondary outcomes of all-cause hospitalization and mortality, in a cohort of stable, ambulatory, compensated heart failure patients.

6.3. Methods

6.3.1. Study participants

Patients included in this analysis were enrolled in a study assessing dietary intake in heart failure patients, which was the study presented in Chapter 5. Comprehensive dietary information from this cohort has been published elsewhere. 311 One hundred forty six patients were approached to participate. As eleven patients declined participation and twelve patients were excluded for failure to submit two sets of food records, data were available from 123 heart failure patients in the final analysis. The sample included eligible ambulatory heart failure patients who were consecutively enrolled between 2003 and 2007 from multidisciplinary heart failure programs in two tertiary care hospitals. Eligible patients were 18-85 years of age, had a left ventricular ejection fraction <35%, were stable without any hospitalizations or emergency room visits in the three months prior to study entry, and were taking optimal medical therapy including an angiotensin converting enzyme inhibitor, angiotensin receptor blocker, or a beta blocker. Patients were excluded if they had significant renal dysfunction defined by a serum creatinine >140 µmol/L, hyponatremia defined by serum sodium <130 mmol/L, or cardiac cachexia defined as unintentional weight loss >10% over six months. No patients were institutionalized (i.e. nursing home) and all patients consumed a self-selected diet. This study was approved by the Research Ethics Board at Mount Sinai Hospital and St. Michael’s Hospital, both in Toronto, Canada, and all patients gave written informed consent.
6.3.2. Assessment of Sodium Intake

Dietary intake was assessed by two 3-day food records: one at study entry and the other after 6-12 weeks. This approach was taken to capture variations in food selection resulting from seasonal and grocery-cycle factors. The mean intake reported by these records was used to estimate habitual intake of sodium and other nutrients. Patients were instructed to record all food and beverages consumed, and were blinded to the fact that sodium was one of the primary nutrients under investigation. Patients were required to weigh or measure their food using a scale or with standard household measures, which were provided to study participants. Patients recorded if salt was added at the table or during cooking. If the amount of salt could not be measured by a scale or volume measures, patients were asked to record the number of shakes added to the food so that sodium could be estimated. Recorded days were selected by study investigators and included at least one weekend day, since food intakes often differ between weekday and weekend days. All food records were reviewed by a dietitian to clarify food item descriptions and to identify any missing food items. Food records were analyzed by trained coders who were blinded to patient identity using a nutrient software program (ESHA Food Processor SQL v.10.1, ESHA Research, Salem, OR). Food records entered for analysis were checked twice for accuracy by independent coders and by the study dietitian. A subgroup of patients also completed two 24 hour urine collections for verification of reported sodium intake, which was previously reported \(^{311}\). However, multiple day food records at two time points were considered a feasible and ideal approach to capture the high day-to-day variability in sodium consumption.\(^{267}\)

6.3.3. Outcomes and Follow-up

The primary outcome for this study was ADHF. Secondary outcomes included all-cause hospitalization and death or transplantation. Outcomes were assessed from the time of enrolment to the completion date of (October 31, 2008). Events were identified through medical chart review and follow-up telephone interviews with patients and their families.
ADHF is a condition that often occurs in patients with pre-existing heart failure and is defined as an exacerbation of dyspnea, edema or fatigue requiring urgent medical treatment. The ADHF outcome in this analysis includes those patients hospitalized with a primary diagnosis of ADHF and patients visiting the emergency department for management of ADHF. Hospitalization and emergency department visits were confirmed by discharge summaries which were reviewed for classification of the primary diagnosis. The outcome of mortality included those who died and patients that received a heart transplant during the follow-up period. Confirmation of death and transplant was obtained by chart review and/or by contacting family members. Study outcomes were adjudicated by two cardiologists (G.N. and A.A.) blinded to dietary intake.

6.3.4. Statistical Analysis

All statistical analyses were performed with SAS version 9.1 (SAS Institute Inc, Cary, NC). Using PROC RANK, patients were divided into tertiles based on mean sodium intake. This approach was planned a priori, based on our previously published data, in order to split our sample into three groups constituting low, moderate, and high sodium intakes. Continuous variables were described using descriptive statistics including mean, median, and standard deviation. Frequencies were used for categorical variables. One-factor analysis of variance was used for univariate comparisons of continuous variables. When the F ratio from the analysis of variance was significant, Scheffe’s post hoc test was used to specify pairwise differences. The Pearson chi-square test was used to determine differences among tertiles as it relates to categorical variables.

The follow-up period was calculated as the time from the completion of the food records to the date of final data collection and follow-up for clinical events. For hypothesis testing, we truncated the follow-up period to three years, which was chosen based on a small number of patients followed beyond this time point. The cumulative event probability for time-to-event outcomes was calculated using the Kaplan-Meier method. Cox regression analysis was used to identify hazard ratios and 95% confidence intervals (CI). Cox
regression was first used to determine the independent predictors of the primary outcome. Clinically relevant covariates or those with a significant univariate hazard ratio, as defined by a p value <0.35, were included in the multivariate model. Cox regression analysis was also used to determine risk associated with high sodium intake. To test the hypothesis that high sodium intake is associated with increased risk of ADHF and secondary outcomes, the upper tertile was compared with the lowest and middle tertile. Covariates in the multivariate Cox model were selected based on clinical relevance or because a given covariate changed the effect of the high sodium tertile when included in the model. The covariates included age, sex, caloric intake, left ventricle ejection fraction, body mass index, furosemide use and beta blocker use. Since our sample size is small we developed two models: one partially adjusted model and one fully adjusted model which includes all covariates. The proportional hazards assumption was confirmed by visual examination of the log (minus log) curves. Significant p values were defined at an alpha level of <0.05.

6.4. Results

Follow-up data was available for all patients. No hospitalizations occurred during the 3 month period between dietary intake assessments. Mean sodium intake was 1443 ± 297 mg/day (900 to 1899 g/day), 2376 ± 253 mg/day (1 to 2799 g/day), and 3814 ± 882 g/day (2.8 to 5.9 g/day) in the low, middle and upper tertiles, respectively.

The mean follow-up time was 2.3 years (median 3.0 years; range 0.9 to 3.0 years). Patients in the lowest sodium tertile had a longer follow-up time (2.6 ± 0.8 years, p<0.05) compared to the highest sodium tertile (2.0 ± 0.9 years), but not compared to the middle sodium tertile (2.1 ± 0.9 years). Patients in this study had a mean age of 60 ± 13 years, a left ventricular ejection fraction of 25 ± 9%, and a body mass index of 29.2 ± 6.0 kg/m². Characteristics of patients in each sodium intake tertile are reported in Table 6-1. Compared to patients in the lower and middle tertiles, patients in the upper tertile had a significantly higher sodium intake, were more likely to be male, and had higher intake of calories, fluid and macronutrients (Table 6-2). Distribution of clinical characteristics and comorbidities
were similar between tertiles. Medication use was also similar among tertiles; however, differences in the frequency of beta blocker use was observed. The total number of months in which patients participated in the multidisciplinary heart failure program were similar between the tertiles (p=NS, data not shown). In addition, the number of clinic visits per patient in the year preceding enrolment in this study were similar between the tertiles (p=NS, data not shown).

Cumulative ADHF events for the lower, middle and upper tertiles were 5 ± 3%, 5 ± 3%, 17 ± 6% after one year; and 12 ± 6%, 15 ± 7%, and 46 ± 11% after three years (log-rank p=0.001, **Figure 6-1(a)**). The hazard ratio adjusted for age, sex, caloric intake and left ventricular ejection fraction was 2.36 (95% CI, 1.54 to 3.60, p<0.001), and was 2.55 (95% CI, 1.61 to 4.04, p<0.001) when the model was further adjusted for additional covariates including body mass index, beta blocker use, and furosemide use (**Table 6-3**). High sodium intake (>2.8 g/day) was the only independent predictor of the primary endpoint of ADHF (hazard ratio 1.66, 95% CI 1.23-2.24).

At three years, cumulative events for all-cause hospitalization were 40 ± 8%, 66 ± 9%, 54 ± 10% for patients in the lower, middle and upper tertiles, respectively, which was not significantly different among tertiles (log-rank p=0.224, **Figure 6-1(b)**). Risk of all-cause hospitalization in the highest sodium tertile was only significant after adjusting for covariates in both the partially and fully adjusted multivariable models (**Table 6-3**). The three year cumulative mortality was 8 ± 5% in the lower tertile, and 22 ± 8% in the highest tertile with no events observed in the middle tertile (log-rank p=0.022, **Figure 6-1(c)**). One patient in the lowest tertile and five patients in the highest tertile died of cardiovascular causes which included conditions such as worsening heart failure, myocardial infarction, and stroke. One patient in both the lowest and highest tertile died on non-cardiovascular causes (i.e. cancer, accidental). One patient in the lowest tertile had a heart transplant. Both adjusted and unadjusted hazard ratios for mortality were significant (**Table 6-3**).
### Table 6-1. Patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>≤ 1900 mg (n=41)</th>
<th>1901-2799 mg (n=41)</th>
<th>≥ 2800 mg (n=41)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>27 (66)</td>
<td>30 (73)</td>
<td>37 (90)</td>
<td>0.028</td>
</tr>
<tr>
<td>Age (years)</td>
<td>62 ± 12</td>
<td>59.9 ± 11</td>
<td>57.4 ± 14</td>
<td>0.256</td>
</tr>
<tr>
<td>Body Mass Index (kg/m$^2$)</td>
<td>28.3 ± 6.7</td>
<td>28.5 ± 4.8</td>
<td>30.8 ± 5.8</td>
<td>0.095</td>
</tr>
<tr>
<td>NYHA Class I-II</td>
<td>33 (80)</td>
<td>28 (68)</td>
<td>28 (68)</td>
<td>0.398</td>
</tr>
<tr>
<td>NYHA Class III-IV</td>
<td>8 (20)</td>
<td>13 (32)</td>
<td>13 (32)</td>
<td></td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>24 (8)</td>
<td>25 (10)</td>
<td>27 (10)</td>
<td>0.366</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>115 ± 17</td>
<td>120 ± 18</td>
<td>118 ± 18</td>
<td>0.446</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>70 ± 8</td>
<td>73 ± 9</td>
<td>72 ± 9</td>
<td>0.138</td>
</tr>
<tr>
<td>Heart Rate (bpm)</td>
<td>69 ± 11</td>
<td>73 ± 13</td>
<td>72 ± 16</td>
<td>0.372</td>
</tr>
<tr>
<td>Serum Sodium (mmol/L)</td>
<td>139 ± 2</td>
<td>138 ± 3</td>
<td>138 ± 3</td>
<td>0.824</td>
</tr>
<tr>
<td>Serum Creatinine (µmol/L)</td>
<td>102 ± 39</td>
<td>96 ± 25</td>
<td>102 ± 26</td>
<td>0.530</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>17 (41)</td>
<td>14 (34)</td>
<td>18 (44)</td>
<td>0.643</td>
</tr>
<tr>
<td>Diabetes</td>
<td>12 (29)</td>
<td>15 (37)</td>
<td>14 (34)</td>
<td>0.774</td>
</tr>
<tr>
<td>Hypertension</td>
<td>11 (27)</td>
<td>10 (24)</td>
<td>11 (27)</td>
<td>0.959</td>
</tr>
<tr>
<td>Current smoker</td>
<td>5 (12)</td>
<td>7 (17)</td>
<td>8 (20)</td>
<td>0.658</td>
</tr>
<tr>
<td>Furosemide</td>
<td>37 (90)</td>
<td>32 (78)</td>
<td>31 (76)</td>
<td>0.191</td>
</tr>
<tr>
<td>Furosemide Dose (mg/d)</td>
<td>78 ± 48</td>
<td>78 ± 46</td>
<td>94 ± 69</td>
<td>0.319</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>20 (49)</td>
<td>17 (41)</td>
<td>16 (39)</td>
<td>0.650</td>
</tr>
<tr>
<td>Beta Blocker</td>
<td>31 (76)</td>
<td>40 (98)</td>
<td>35 (85)</td>
<td>0.016</td>
</tr>
<tr>
<td>ACEI/ARB</td>
<td>41 (100)</td>
<td>40 (98)</td>
<td>40 (98)</td>
<td>0.602</td>
</tr>
</tbody>
</table>

One-way analysis of variance with Scheffe’s post-hoc analysis used to conduct between group comparisons. Continuous data presented as mean ± standard deviation, and categorical data presented as n (%).

Abbreviations: NYHA = New York Heart Association Class, LVEF = left ventricle ejection fraction, ACEI = Angiotensin converting enzyme inhibitor, ARB = angiotensin receptor blocker
Table 6-2. Mean dietary intake in patients divided by tertiles

<table>
<thead>
<tr>
<th>Mean Dietary Intake</th>
<th>≤ 1900 mg (n=41)</th>
<th>1901-2799 mg (n=41)</th>
<th>≥ 2800 mg (n=41)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium (g)</td>
<td>1443 ± 297</td>
<td>2376 ± 253 ‡</td>
<td>3814 ± 882 *†</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Calories (kcal)</td>
<td>1564 ± 341</td>
<td>1852 ± 428 ‡</td>
<td>2447 ± 580 *†</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Carbohydrate (g)</td>
<td>211 ± 63</td>
<td>233 74 ‡</td>
<td>300 ± 85 *†</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Protein (g)</td>
<td>76 ±19</td>
<td>92 ± 24</td>
<td>101 ± 26 †</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fat (g)</td>
<td>46 ± 18</td>
<td>61 ± 19 ‡</td>
<td>92 ± 31 *†</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fluid (L)</td>
<td>2.0 ± 0.6</td>
<td>2.1 ± 0.7</td>
<td>2.4 ± 1.0 *</td>
<td>0.015</td>
</tr>
</tbody>
</table>

One-way analysis of variance with Scheffe’s post-hoc analysis used to conduct between group comparisons. Data presented as mean (standard deviation).

* p<0.05 Upper tertile (≥ 2800 mg/d) versus Lower tertile (≤ 1900 mg/d); † p<0.05 Upper Tertile (≥ 2800 mg/d) versus Middle tertile (1901-2799 mg/d); ‡ p<0.05 Middle tertile (1901-2799 mg/d) versus Lower tertile (≤ 1900 mg/d)
Table 6-3. Hazard ratios associated with outcomes for heart failure patients with high sodium intake

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Hazard Ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≥ 2800 mg sodium/day, n=123</td>
<td></td>
</tr>
<tr>
<td>Acute decompensated heart failure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Univariate model</td>
<td>1.66 (1.23 to 2.24)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Multivariate model 1*</td>
<td>2.36 (1.54 to 3.60)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Multivariate model 2†</td>
<td>2.55 (1.61 to 4.04)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>All-Cause Hospitalization</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Univariate model</td>
<td>1.20 (0.97 to 1.47)</td>
<td>0.089</td>
</tr>
<tr>
<td>Multivariate model 1*</td>
<td>1.37 (1.04 to 1.79)</td>
<td>0.023</td>
</tr>
<tr>
<td>Multivariate model 2†</td>
<td>1.39 (1.06 to 1.83)</td>
<td>0.018</td>
</tr>
<tr>
<td>Mortality‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Univariate model</td>
<td>1.72 (1.08 to 2.73)</td>
<td>0.022</td>
</tr>
<tr>
<td>Multivariate model 1*</td>
<td>2.41 (1.31 to 4.47)</td>
<td>0.005</td>
</tr>
<tr>
<td>Multivariate model 2†</td>
<td>3.54 (1.46 to 8.62)</td>
<td>0.005</td>
</tr>
</tbody>
</table>

The cox proportional hazards model was used to determine the hazard ratio associated with high sodium intake. Data presented as hazard ratio (95% confidence intervals (CI)).

* Multivariate model 1: includes covariates age, sex, caloric intake and left ventricle ejection fraction.

† Multivariate model 2: model 1 + covariates beta blockers, furosemide and body mass index.

‡ Mortality includes patients who had a transplant during the follow-up period.
Figure 6-1a. Kaplan-Meier plot for risk of acute decompensated heart failure in heart failure patients by sodium intake tertiles.
Figure 6-1b. Kaplan-Meier plot for risk of all-cause hospitalization in heart failure patients by sodium intake tertiles

Log rank p=0.224

Number at risk:

- ≤ 1900 mg sodium/day: 41, 36, 25, 18
- 2000-2700 mg sodium/day: 41, 31, 17, 15
- ≥ 2800 mg sodium/day: 41, 28, 13, 10
Figure 6-1a. Kaplan-Meier plot for risk of all-cause mortality in heart failure patients by sodium intake tertiles

Log rank $p=0.022$

Number at risk:

- $\leq 1900$ mg sodium/day: 41, 36, 25, 18
- 2000-2700 mg sodium/day: 41, 31, 17, 15
- $\geq 2800$ mg sodium/day: 41, 28, 13, 10
6.5 Discussion

This is the first study to demonstrate any relationship between dietary sodium and subsequent clinical outcomes in stable compensated heart failure patients. Specifically, our study demonstrates that heart failure patients consuming a high sodium diet (>2800 mg sodium/day), compared to those consuming lower amounts of dietary sodium, have a higher incidence of early ADHF. Further, we found that patients consuming a high sodium diet had a 2.5-fold increased risk of ADHF, as well as an elevated risk for all-cause hospitalization and mortality when adjusted for covariates. By demonstrating increased risk associated with high sodium intake levels, this analysis challenges recent data concluding that lower sodium diets are associated with adverse outcomes in heart failure, and suggests that current heart failure guidelines should be more aggressive in recommending lower sodium intake. These findings are particularly novel and relevant since they apply to a broad group of ambulatory heart failure patients with systolic heart failure, who are already receiving optimal medical therapy.

In the past, the therapeutic importance of sodium restriction in the setting of heart failure was well accepted. The recent controversy associated with dietary sodium restriction in heart failure has risen from contradictory findings reported by retrospective observational studies and by more recent clinical and mechanistic investigations. Observational studies which identified a high sodium diet as a risk factor for heart failure hospitalization assessed dietary sodium retrospectively and did not rely on validated dietary assessment techniques, such as 24-hour urines collections or food records to classify sodium intake. Disease management trials have included a low sodium diet as part of a multidisciplinary approach; however, since these studies tested several concurrent interventions, the independent contribution of a low sodium diet to outcomes could not be assessed. Other small clinical studies which restricted sodium intake as an educational intervention for heart failure patients were underpowered to explore outcomes. Finally, mechanistic investigations have demonstrated adverse neurohumoral activation in heart failure patients following short-term dietary sodium restriction.
More recently, Paterna et al. conducted a randomized controlled trial in 252 heart failure patients who had a recent ADHF hospitalization. Patients were randomized to receive a sodium restricted diet (80 mmol/day, 1840 mg/day) or a “normal” sodium diet (120 mmol/day, 2760 mg/day). Along with sodium restriction, patients were simultaneously prescribed a fluid restriction (1-2 L/day), as well as a high dose of furosemide (250 or 500 mg twice daily) at study randomization, which remained unadjusted over the study period. Based on these co-interventions, it is difficult to elucidate the sole contribution of the levels of sodium intake to clinical outcomes. Furthermore, concerns related to background medical therapy limit the generalizability to the general heart failure population, as only 9% of patients in each study group were receiving beta blocker therapy. Nevertheless, these investigators demonstrated that patients receiving the sodium restricted diet had an increased risk of hospitalization and the combined endpoint of hospitalization and mortality after 6 months. These findings are contrary to the data presented in the current study. Certainly, the concurrent interventions in the study by Paterna et al. may have contributed to adverse outcomes, as loop diuretic therapy is associated with neurohormonal activation and mortality in heart failure. This is relevant in context of the already described neurohormonal activation that occurs when dietary sodium is restricted. Furthermore, we studied ambulatory patients who were euvoelemic with longstanding stable heart failure on optimal medical therapy, a group which is highly generalizable to the larger heart failure population. Our study took an observational approach to evaluating clinical outcomes associated with sodium intake. Although causality cannot be proven using observational data, this is the first study linking high sodium intake to adverse outcomes in this relatively low-risk group of heart failure patients.

A high sodium diet has been associated with adverse outcomes in healthy populations, including incident hypertension and related outcomes of stroke and heart failure. The Dietary Reference Intake recommendation for sodium for healthy adults (ages 14 to 50) is an adequate intake level of 1500 mg/day, and a tolerable upper level of 2300 mg/day. The average sodium intake of most individuals with a North American diet far exceeds these recommendations. Our recent report from the same patient cohort identified
that sodium intake was similar in stable heart failure patients compared to an age matched control group.\textsuperscript{311} For patients living with established heart failure, excessive sodium intake has even greater consequences since abnormalities in renal sodium handling promote sodium and fluid retention.\textsuperscript{84} Although medical therapies including beta blockers and ACE inhibitors aim to correct renal sodium handling, our data indicate that a lower sodium diet may be required to assist in maintaining euvolemia and clinical stability over the long term. Based on the average intakes in our tertiles, our data suggest that the sodium intake recommendation for stable heart failure patients should not be dissimilar from the established tolerable upper level for healthy adults of 2300 mg/day. This is more aggressive than current heart failure treatment guidelines, which recommend up to a 3000 to 4000 mg/day sodium diet.\textsuperscript{67} Whether heart failure patients would benefit from an even lower amount of sodium intake, similar to the DRI adequate intake level of 1500 mg/day, will require further study. This may be especially true for patients in refractory heart failure, where a daily sodium intake $\leq$ 2000 mg/day is recommended.\textsuperscript{67, 68, 306, 321}

The sample of heart failure patients studied was relatively small; however, we included a well-characterized group with rigorous dietary assessment for classification of sodium intake. Despite the relatively small sample size, this is the first observation relating sodium intake to any outcome for patients with stable chronic heart failure. It could be argued that patients nonadherent to sodium intake guidelines are also more likely to be nonadherent to medical therapies and other beneficial lifestyle factors. Indeed, an analysis of the CHARM trial data found that adherence to medical therapy was an indicator of better outcomes, regardless if adherence was to the placebo or treatment drug.\textsuperscript{325} Adherence to medical therapies was not measured in this study, based on the complexities of applying proper measurement techniques. However, there are relevant differences in factors influencing adherence diet and medication. For example, adherence to sodium restriction is dependent on the knowledge of the sodium content of foods, access to low sodium foods, desire to follow a low sodium diet, and related social and lifestyle factors allowing for sodium reduction.\textsuperscript{252} In contrast, medication adherence is more likely related to the cost of the medication, potential side effects, as well as memory and dosing schedules.\textsuperscript{326} There are
no studies directly comparing the relationship between diet and medication adherence, therefore each should be considered independently.

6.6. Conclusion

In conclusion, the findings of this study provide insight into the role of dietary sodium in the management of heart failure patients who are clinically stable and receiving optimal medical therapy. This is the first evidence that stable heart failure patients who consume high amounts of sodium are at greater risk for early ADHF hospitalization compared to patients consuming lower levels of dietary sodium.
6.7. Acknowledgements

Dr. Newton had full access to all of the data in the study and takes full responsibility for the integrity and accuracy of the data. Drs. Newton, Allard, Ivanov Al-Hesayen, Mak, Azevedo and Ms. Arcand are for the study design and concept. Ms. Arcand, Floras and Sasson were responsible for logistical and administrative details as well as data acquisition and analysis and database management. Ms. Arcand and Drs. Newton, Mak and Azevedo are responsible for data acquisition. Drs. Newton and Al-Hesayen adjudicated clinical outcome data. Ms. Arcand and Drs. Ivanov and Newton conducted the statistical analysis and interpretation of the data. Ms. Arcand drafted the manuscript and all authors were involved in the critical revision of the manuscript. There are no conflicts of interest to disclose.

We would like to thank the clinical and administrative staff of the heart function clinics at Mount Sinai Hospital and St. Michael’s Hospital. We would also like to thank Mavra Ahmed and Chelsea Kaplansky for their assistance with data collection and analysis.
Figure Legend

Figure 6-1(a-c)

Figure. Kaplan Meier plots for sodium intake and clinical outcomes (a) Acute decompensated heart failure, (b) All-cause hospitalization, (c) Mortality. The mortality variable includes patients who received a heart transplant. The mean sodium intake was 1.4 ± 0.3 g/day in the lower tertile (red line), 2.4 ± 0.3 g/day in the middle tertile (black line) and 3.8 ± 0.8 g/day in the upper tertile (blue line).
CHAPTER 7: DISCUSSION

7.1 General Discussion

The HF syndrome is the end-stage of almost all chronic cardiac diseases and is associated with a large burden of illness. Care for patients in the multidisciplinary HF clinic generally includes dietary counseling as a core element. The traditional dietary advice is to restrict sodium, and to a lesser extent fluid intake, although evidence in support of this practice is very limited. The concept of limiting sodium intake is rooted in historical treatment practices preceding the discovery of diuretics. With the current availability of highly effective medications to treat HF, the role of dietary sodium restriction is unclear. This is reflected in HF treatment guidelines, which only discuss sodium restriction in general terms. 67, 68, 306, 321

Due to lack of data related to dietary sodium in this patient population, our group investigated several aspects of sodium intake in the setting of HF. The overriding objective of this work was to generate data related to dietary sodium in patients with chronic HF that would ultimately contribute to the development of evidence-based guidelines in this important patient population. We have conducted three investigations that address issues related to dietary sodium intake assessment, and evaluation of habitual sodium consumption and outcomes related to dietary sodium in ambulatory HF patients. These studies are highly relevant in the context of HF disease management and they provide a valuable foundation upon which future work can be based.

Previously it was assumed that sodium excretion would match sodium intake if a HF patient was optimally medicated and clinically stable at steady state. Therefore, a 24-hour urine collection was considered an appropriate method to estimate sodium intake in HF. In Chapter 4, we tested the hypothesis that 24-hour sodium excretion would not match sodium intake in HF patients taking loop diuretics. We found a strong relationship between sodium
estimated by 24-hour urine collections and food records for a group of non-HF cardiac patients and a group of HF patients not taking loop diuretics, which was similar to other published studies as described in Section 3.1.3. However, consistent with our hypothesis, there was no relationship between sodium intake and excretion in the group of HF patients taking loop diuretics. We interpreted these data as evidence that the natriuretic effect of the loop diuretics impairs the utility of urine collections in estimating habitual sodium intake.

Prior to our study, there were no investigations that systematically evaluated methods for sodium intake assessment in HF patients. However, discreetly imbedded within one published study was the reported the correlation between a 3-day food record and one 24-hour urine collection in 61 HF patients participating in a 3-month dietary sodium education program.\textsuperscript{246} Significant correlations between methods were observed at baseline ($r=0.43$, $p<0.001$) and at end of study ($r=0.59$, $p<0.001$). Medical therapy was not reported, therefore no inferences can be made as to whether loop diuretic therapy may have influenced the strength of relationship between methods in that analysis, as we found in our investigation.

Our findings confirmed a significant relationship between food records and 24-hour urine collections in non-HF cardiac patients and in HF patients not taking loop diuretics. We interpret these findings as to suggest that HF-related neurohumoral activation treated with beta blockers and RAAS blockers promotes sodium homeostasis such that sodium intake matches excretion. Although earlier work demonstrated that unmedicated HF patients had an inability to excrete a sodium load, Damgaard et al\textsuperscript{239} recently reported that HF patients treated with beta blockers and RAAS blockers were able to maintain sodium balance, similar to a non-HF control group, when following high and a low sodium diet regimens. Therefore, it is not surprising that the performance of urine collections and food records was similar between the non-HF cardiac patients and the HF patients not taking loop diuretics.

In summary, our data provide novel evidence that food records or urine collections are appropriate for determining sodium intake in patients not taking loop diuretics, but that only food records may be appropriate for estimating sodium intake in the HF patients.
receiving loop diuretics. These findings have important implications in the measurement and surveillance of sodium intake in both HF and non-HF cardiovascular populations.

As mentioned in section 3.1.6, previous investigations have used a variety of methods to assess sodium intake in HF patients. In Chapter 5 and 6 we chose to use two 3 day food records to estimate habitual sodium intake. At the present time there is no definitive method for this purpose. However, based on the confounding effects of loop diuretics on urinary sodium excretion, our results suggest that food records may be a better approach in this population. Because our sample size was relatively small, further studies are needed to reproduce our findings before widespread application or recommendation regarding the optimal dietary sodium assessment tool for HF patients can be implemented. Until future studies confirm our findings, food records should ideally at least be co-administered with urine collections.

Our second investigation, reported in Chapter 5, examined habitual sodium intake in a medically stable ambulatory HF population. We found that the amount of sodium consumed did not differ in a HF population, as compared to a non-HF cardiac control group. More than half of the patients in both patient groups had sodium intake levels beyond the DRI UL of 2300 mg/day. We also found that many HF patients have inadequate intakes of several vitamins and minerals, including potassium, calcium, magnesium, folate, and vitamin D and E. Of these nutrients, potassium, calcium and magnesium are of particular concern since excessive urinary losses may occur in patients who are taking loop diuretics. Indeed, as described in section 1.3.4., patients who have poor nutritional status related to these nutrients have shown to have adverse clinical outcomes, particularly with respect to potassium. As reviewed, there are few RCT’s of vitamin and/or mineral supplementation in HF and whether dietary modification or supplementation strategies are beneficial is unknown. Based on the lack of evidence, sodium and fluid restriction remain the core dietary therapies for HF patients.
The current recommended daily sodium intake for HF patients is 2000 to 3000 mg/day. However, these levels are supported by little evidence and thus based largely upon expert consensus.\textsuperscript{67, 68, 306, 321} In our investigation in Chapter 6 we took a novel approach to evaluating clinical outcomes associated with sodium intake in HF patients. We prospectively measured sodium intake and after a median 3 years follow-up, we found that \textgreater{}2800 mg sodium intake per day was associated with increased risk of ADHF, all-cause hospitalization, and mortality. This was the first study to prospectively associate any level of measured sodium intake with clinical outcomes in the HF population.

After our publication, Lennie et al\textsuperscript{320} reported on the relationship between sodium intake and a composite outcome of mortality, CV-related hospitalization, and CV-related emergency room visits in 302 impaired systolic and preserved systolic HF patients. Consistent with our observations, they showed that highly symptomatic patients (NYHA Class III/IV) consuming \textgreater{}3000 mg of sodium/day had an increased risk in developing their composite endpoint. However, they also demonstrated that mildly symptomatic patients (NYHA Class I/II) consuming \textgreater{}3000 mg/day had a lower risk of developing the composite endpoint, suggesting that high sodium intake is protective in mildly symptomatic HF. This study was limited by several factors including a study group that was very heterogeneous, the stratification of patients based only on subjective NYHA classification, and the use of only a single 24 hour urine collection to measure sodium intake. This is relevant in light of our findings in Chapter 4, since two thirds of this population was taking loop diuretics. Similar to our results, further investigation to confirm these results are needed, especially focusing on minimally symptomatic patients.

7.2 Future Directions

Future work related to the study of nutrition in HF needs to be multidirectional. Our work provides a foundation for future investigations to test new hypotheses to elucidate the role of sodium in HF management and generate strategies related to diet and nutrition in clinical settings.
Related to dietary assessment, in the clinical setting a HF nurse or cardiologist typically monitors dietary sodium intake during the clinical examination. If managed in a primary care setting, the general practitioner conducts dietary sodium monitoring. Those patients with sodium nonadherence and recurrent admissions are counselled on dietary sodium in-clinic or referred for dietary counselling from a dietitian, if available. The challenge is, however, accurately identifying those patients who require, or would benefit from, dietary intervention. There are no published methodologies to easily and accurately monitor sodium intake in any healthy or clinical population. Indeed, constraints in both time and dietary expertise among clinicians clearly limit proper dietary assessment. Such methods would have to be easy for the clinician to administer and interpret. This could be in the form of a short FFQ or diet screener, possibly even completed independently by the patient prior to seeing their care-provider, similar to the patient-generated subjective global assessment that is validated for cancer patients. Indeed, a spot urine sample with sodium measured by a dipstick test has been suggested as a novel approach for sodium intake monitoring in hypertension; however this method is not ideal based on limitations as reviewed in section 3.1.2. Therefore, future investigations should focus on the creation and validation of practical methods to accurately classify sodium intake in HF patients and identify those in need of a sodium educational intervention.

Investigation into how clinical dietary assessment techniques can be applied to the research setting is also needed. As mentioned, our findings should be replicated. We did not conduct a controlled balance study, which is an approach that could confirm that loop diuretics were indeed responsible for the failure of urine collections to perform well in sodium assessment. Whether or not these results hold true in a broader HF population is unknown. For example, we included patients who were predominantly NYHA Class II and III. It is possible that methods would agree differently in those with or without more severe symptoms, particularly since many patients with Class IV have impaired renal dysfunction and greater functional limitations. Finally, we studied patients with systolic heart failure, whether or not these results would hold true for those with preserved systolic function is unknown, particularly since they tend to have different demographic and clinical profile.
The validity of other known dietary assessment methods should be tested in HF populations. A FFQ would be particularly useful for assessing sodium intake in large observational studies. Despite the possible limitations of FFQs in assessing sodium intake, as outlined in Section 3.1.5, applying this validated tool to larger populations would be superior to clinician-derived classification of dietary sodium nonadherence, as was used in most observational studies that identified sodium as a factor precipitating HF hospitalization (Section 1.4.4). Our study in Chapter 6 was the first study to actually measure sodium intake using 6 days of food records and examine cardiovascular outcomes related to high sodium intake in otherwise stable ambulatory HF patients. Mechanistic studies have traditionally utilized 24-hour urinary sodium to monitor adherence to prescribed dietary regimens. Cross-sectional surveys have used a variety of validated and non-validated methods, including spot urines, 24-hour urinary sodium, food records, food recalls and FFQs. Validation of these methods for a HF population is warranted. However, new dietary assessment methods should also be created and considered to better meet the needs of HF patients and HF researchers.

Despite the challenges associated with studying sodium in HF, it is necessary to generate evidence-based guidelines to direct dietary therapy. It is important to know if there is indeed a causal relationship between sodium restriction and adverse outcomes, as suggested by the subsequent publication by Lennie et al.\textsuperscript{320} and also by mechanistic studies demonstrating neurohumoral activation in response to sodium restriction.\textsuperscript{238,239} Conversely, if sodium restriction did confer a therapeutic benefit in the context of current medical therapies, this would reinforce the relevance of sodium restriction in HF patients.

An RCT of sodium restriction in HF patients would be the strongest evidence to support or refute the application of dietary sodium restriction in HF. There are several possible answers as to why there is yet to be an RCT of dietary sodium in HF. The fundamental challenge to an RCT is delivering a low sodium diet over the long term, particularly with the excess amounts of sodium in the current food supply. Indeed, the DASH trial included sodium restriction, although those patients were provided with food
rather than choosing a self-selected diet.\textsuperscript{52} Other factors also make studying sodium difficult, including the large sample size required, the non-blinded nature of such a study, and the lack of a placebo controlled group. Additionally, there is the possibility of confounding variables, including changes to medical regimens, which may impact sodium balance and alter any effects of the sodium intervention. However, it could be argued that such challenges with confounding interventions would reflect the real-world experience of a free-living HF patient and thus be generalizable to clinical practice.

A large observational study would be an intuitive next step for examining dietary sodium in HF. This would include an adequately powered, multicentre study to longitudinally evaluate clinical outcomes related to dietary sodium in this population. This would confirm smaller studies, such as the one we have published in Chapter 6, and would allow for examination of subgroups of patients. Specifically, analyses could contrast symptomatic versus asymptomatic patients. Exploration into the role of sodium in HF patients with preserved systolic function would be novel, as this is a largely under-studied group possessing demographic and clinical features that greatly differ from HF patients with impaired systolic function. There are also no clinical studies that have included patients with refractory, end-stage HF. Theoretically, this group would appear to benefit from sodium restriction, based on decreased responsiveness to medical therapies and impairments to renal function; however no studies have confirmed this. A large observational study would also provide additional information on the threshold of sodium that contributes to adverse clinical events. These observational data would inform investigators regarding the best RCT format, including the outcomes and populations to be studied, as well as levels of sodium to be tested. Examining clinical outcomes related to sodium restriction in an RCT fashion is ultimately the best way to shed light on a topic that has become somewhat controversial and uncertain in light of the many advances made in the medical and surgical treatment of HF. Despite these advanced therapies, however, poor clinical outcomes continue to exist for this population. This highlights the need for novel treatments, including sodium and/or other dietary modifications, which may prove to be promising in prolonging survival, reducing
hospitalisations, improving symptoms, and bettering the quality of life for those living with HF.
CHAPTER 8: SUMMARY AND CONCLUSIONS

Sodium restriction is the primary dietary therapy for HF patients; however, there are little data to support or refute the use of sodium restriction and other dietary therapies in HF patients. The overall objective of this work was to conduct investigations that would contribute to the body of knowledge concerning dietary sodium in the management of HF, and to generate data that could be applied directly to the HF patient population in a clinical setting or used to create and test hypotheses in future investigations.

We observed that food records perform similarly to 24-hour urine collections (the gold standard) for the assessment of sodium intake in cardiac patients without HF and in HF patients who do not take loop diuretics. However, we found no relationship between 24-hour urine collections and food records for sodium intake assessment in HF patients taking loop diuretics. Given the similarities between the two HF patient populations studied, we concluded that the potent natriuretic effect of loop diuretics was responsible for the lack of agreement between urinary and food reporting methods. Therefore, either food records or 24-hour urine collections are appropriate for non-HF and HF patients not taking loop diuretics, but food records are likely the optimal method for HF patients taking loop diuretics.

We also observed that approximately half of the HF patients attending a Canadian multidisciplinary HF clinic consume sodium in excess of the DRI UL of 2300 mg/d, an estimate not dissimilar from a non-HF cardiac control group. We also found that several nutrients including potassium, calcium, magnesium, folate, and vitamin D and E, are consumed in inadequate quantities, compared to their respective DRI reference values.
In our third study, we observed that a high sodium diet (>2800 mg/d) was associated with risk of acute decompensated HF, all-cause hospitalization, and all-cause mortality over a median 3 year follow-up period in HF. This was the first published investigation assessing clinical outcomes related to any level of sodium intake in a stable ambulatory HF population. These novel data provides a basis for future work aiming to generate evidence for dietary sodium modification in HF patients.
CHAPTER 9: REFERENCES


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