

Association of Modifiable Risk Factors and Left Ventricular Ejection Fraction among Hospitalized Native Hawaiians and Pacific Islanders with Heart Failure

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Abstract

Background: Heart Failure (HF) disproportionately affects Native Hawaiians and Other Pacific Islanders (NHOPIs). This study examines risk factors associated with left ventricular ejection fraction (LVEF) among 151 hospitalized NHOPI HF patients enrolled at a single tertiary care hospital between June 2006 and April 2010.

Methods: Enrollment criteria: (1) NHOPI by self-identification. (2) Age \geq 21 yrs. (3) Diagnosis of HF defined: (a) left ventricular ejection fraction (LVEF) \leq 40% or LVEF \leq 60% with abnormal diastolic function and (b) classic HF signs/symptoms. LVEF was measured by echocardiography within 6 weeks of hospitalization. Clinical measures, medical history, and questionnaires were assessed using standardized protocols. Linear regression modeling was used to examine the association of significant correlates of LVEF, which were then included en bloc into the final model. A P-value $<$.05 was considered statistically significant.

Results: Of 151 participants, 69% were men, mean age 54.3 ± 13.5 years, blood pressure $112 \pm 20/69 \pm 15$ mmHg, and body mass index (BMI) 36.9 ± 9 kg/m². Twenty-five percent of participants were smokers, 45% used alcohol and 23% reported a history of methamphetamine use. Clinically, 72% had hypertension, 49% were diabetic and 37% had a prior myocardial infarction. Nearly 60% had moderate to severe LVEF ($<$ 35%). Higher LVEF was independently associated with female sex and greater BMI ($P <$.04) while pacemaker/defibrillator and methamphetamine use was independently associated with lower LVEF ($P <$.05).

Conclusions: Methamphetamine use and BMI may be important modifiable risk factors associated with LVEF and may be important targets for improving HF morbidity and mortality.

Introduction

Heart failure (HF) remains one of the leading causes of hospital costs and disproportionately affects racial and ethnic minorities compared with whites. Despite well known health disparities in heart disease and HF in particular, there remains a paucity of studies that have thoroughly examined the underlying cause of HF among high risk racial and ethnic minority populations.¹ Native Hawaiians and Other Pacific Islanders (NHOPIs) are known to bear an excess burden of heart disease morbidity and mortality and HF is a significant contributor.²⁻⁵ Yet it remains unclear as to why NHOPIs continue to suffer from increased heart disease disparities, including HF, when compared with other ethnic minority populations in the State of Hawai'i. A recent multi-ethnic study assessed incident cases of heart failure in six US communities over 4 years comparing White, African American, Hispanic and Chinese Americans and found that Chinese Americans (1.0/1000 person-years) had the lowest and African Americans the highest incident cases of HF (4.6/1000-person-years). However, the authors concluded that the increased incidence of HF in African Americans was largely related to

the higher prevalence of co-morbidities such as hypertension and diabetes as well as socioeconomic status.⁶ While among Hispanics and Whites (2nd and 3rd highest incidence of HF), increased left ventricular mass had a greater effect on etiology of HF. Although only four ethnic/racial groups were examined in this study, we have found similar differences between ethnic groups residing in Hawai'i in which underlying etiology of disease can vary across multiple ethnic groups and in several instances the Asian sub-group may actually out perform Whites as the "healthiest" racial group.^{7,8}

Thus, we were particularly interested in examining the clinical characteristics of HF among NHOPIs, as a group disaggregated from Asian Americans, to improve the granularity of our understanding of heart disease disparities among NHOPIs. In particular, NHOPIs with HF have been reported to develop HF at least 10 years earlier than the general HF population.⁹ Moreover, NHOPIs with HF were found to have a higher prevalence of methamphetamine use and some studies have even suggested that methamphetamine-induced HF may actually represent a reversible form of cardiomyopathy.¹⁰⁻¹³ To improve HF outcomes among NHOPIs, the Malama Pu'uwai Study (Caring for the Heart Study) a randomized control trial designed to test a culturally informed heart failure education program, was initiated at a single tertiary care hospital on Oahu, Hawai'i. The purpose of this study was to examine risk factors associated with left ventricular ejection fraction (LVEF) among hospitalized NHOPIs with heart failure (HF) at baseline in the Malama Pu'uwai Study. We chose to examine LVEF, a measurement of the percentage of blood ejected from the left ventricle per contraction, as it is commonly used to assess cardiovascular function. Cardiovascular function is important because it is associated with quality of life, prognosis, and ability to perform activities of daily living for patients living with HF.

Methods

The Malama Pu'uwai Study is a randomized control trial that is testing the efficacy of a culturally tailored HF education program to reduce re-hospitalizations and/or death compared to usual care among hospitalized NHOPI patients with HF. All subjects were recruited from a large, urban, university-affiliated tertiary care hospital within 6 weeks of a hospital discharge in which HF was listed either as the primary or secondary diagnosis. Only patients residing on O'ahu and Moloka'i were recruited for this study because of logistical considerations. Eligibility

criteria included: (1) Age ≥ 21 years old; (2) Ethnic/racial background self-identified as NHOPI (including Samoan, Tongan, Micronesian, other Pacific Islanders); (3) Clinical symptoms and signs of HF; (4) Left ventricular ejection fraction (LVEF) $\leq 40\%$ or $\leq 60\%$ with echocardiographic evidence of abnormal diastolic function. All participants gave written informed consent prior to enrollment.

Potential participants were recruited and enrolled through a stepwise process that was initiated at admission to the study hospital. On admission, patients were first screened by a trained cardiac nurse who identified potential patients based on whether they fulfilled the first three eligibility criteria. If so, the patient was then approached during the course of the index hospitalization by trained study recruiters who provided additional study information (design, duration, eligibility, etc) to the patient. If interested, patients were invited to contact the study office within 4-6 weeks following discharge or the study office would contact the participant for possible enrollment.

Between June 1, 2006 and April 30, 2010, the cardiac care service of the tertiary care study hospital admitted 1,033 patients. Of these cardiac service admissions, 506 patients were unavailable for study recruitment because they were admitted solely for ambulatory cardiac services, in/out surgery, etc, while 527 non-duplicated individuals were screened and found to meet initial demographic eligibility screening criteria. Of the 527 patients, 213 declined further information about the study, leaving 314 cardiac service inpatients (60%) that were willing to be contacted post-hospital discharge for possible study enrollment. Of the 314 NHOPI heart patients discharged, 135 patients (43%) declined study participation for the following reasons: (a) 8 patients died following hospital discharge, (b) 118 were unable to be contacted (disconnected phone number, wrong mailing address, moved away, etc) or later decided not to enroll in the study. Thus, 189 patients (60%) who had expressed a willingness to enroll and allow a thorough medical record review to formally determine study eligibility were contacted post-hospital discharge. Unfortunately, 21 patients who enrolled during the first 3 months of the study were later deemed ineligible after review of hospital medical records that revealed ineligibility such as serious illnesses that prohibited full participation in the study or required skilled nursing care at time of discharge ($n = 18$) or died prior to randomization ($n = 3$), or did not meet enrollment criteria ($n = 16$) and a single patient declined participation just prior to randomization ($n = 1$). Thus, 151 of the 189 NHOPI patients with heart failure, discharged from the index hospitalization (within 6 weeks) gave written informed consent, completed a baseline data examination and were formally randomized. Analysis of this baseline examination data serves as the primary focus of this paper.

Demographic information (eg, ethnicity, education, marital status) was self-reported at study entry. Clinical and anthropometric measurements (eg, blood pressure, pulse, height, weight, body mass index) were performed at enrollment according to standardized methods. Past and current medical history (eg, hypertension, diabetes, coronary artery disease), social his-

tory (eg, alcohol and smoking use) were obtained by patient self-reported and verified by medical record review of index hospitalization. Methamphetamine use was also assessed by self-report and verified by medical record review or positive toxicology screen. Trained interviewers administered the 10-item short form of the Center for Epidemiologic Studies of Depression (CES-D) and the 23-item Kansas City Cardiomyopathy Questionnaire (KCCQ).¹⁴

Data analysis was performed on all demographic, behavioral, clinical and cardiovascular factors and reported for the entire study population ($N = 151$) and stratified by sex (men and women) for descriptive purposes. Spearman correlation coefficient of all potential risk factors with LVEF was calculated. Linear regression modeling was performed using an en bloc approach to examine the association of significant correlates of LVEF adjusted for other covariates. *P* values $< .05$ were considered statistically significant. Data were analyzed using SAS version 9.1 (SAS Institute, Cary, NC).

Results

A total of 104 men and 47 women of NHOPI racial background ($N = 151$) were enrolled (Table 1). The mean age was 54.3 years, with men, on average, 4 years younger than women. Forty-four percent of patients were married and 36% had attended some college or attained a college degree. Smoking was reported in 25% of patients, any alcohol use within the past year in 45% and methamphetamine use in 23%, with men reporting a higher frequency of all 3 health behaviors compared to women (men vs women: smoking 27% vs 19%, alcohol 54% vs 26%, methamphetamine use 27% vs 15%).

Among recently hospitalized NHOPIs with HF, 72% reported a diagnosis of hypertension, nearly half (49%) had diabetes and more than one-third (37%) had a history of myocardial infarction (MI). (Table 2a) The mean BMI was 36 ± 9 kg/m², however, 15 participants (10%) are not included in this mean value because of weight in excess of 400 lbs. (the maximum limit of the weight scale) or inability to stand for height measurement. Thus, the mean BMI value is likely an underestimation of the true BMI for this population. Mean blood pressures were well within recommended treatment goals (< 130 mmHg systolic BP and < 80 mmHg diastolic) with mean values of 112 mmHg and 69 mmHg respectively.¹⁵ The most common class of HF medications used by patients were beta-blockers (72%), followed by diuretics (64%), and ACE/ARB medications (63%). Half of the patients were on aspirin and another 25% reported the use of warfarin for anticoagulation. The mean CES-D score was 10.1 in both sexes, which is consistent with elevated depressive symptoms. The mean KCCQ score was 62.3, similar to subjects with NYHA class II-III heart failure in a large cohort of outpatients with systolic dysfunction and similar to scores at 24-weeks following hospital discharge for more than 1400 HF patients in the Efficacy of Vasopressin Antagonism in HF Outcome Study with Tolvaptan (EVEREST) trial.^{16,17}

Nearly half (47%) of all patients had severe LVEF of $< 30\%$. (Table 2b) While another 11% were found to have moderate-

Table 1. Demographic and Behavioral Factors of Recently Hospitalized Native Hawaiians and Other Pacific Islanders with Heart Failure (N=151)

Characteristic	Women (n=47)	Men (n=104)	Combined (N=151)
Age (years, mean)	57.2	53.0	54.3
Marital status			
Married	15 (32%)	52 (50%)	67 (44%)
Divorced/Separated/Widowed	20 (43%)	27 (26%)	47 (31%)
Never married	12 (25%)	25 (24%)	37 (25%)
Education			
Less than H.S.	9 (19%)	18 (17%)	27 (18%)
High school	18 (38%)	52 (50%)	70 (46%)
Some college	9 (19%)	20 (10%)	29 (19%)
College graduate or more	11 (23%)	14 (13%)	25 (17%)
Smoking (in last 6 months)	9 (19%)	28 (27%)	37 (25%)
Alcohol (in last 12 months)	12 (26%)	56 (54%)	68 (45%)
Methamphetamine use (anytime)	7 (15%)	28 (27%)	35 (23%)

Table 2a. Clinical Characteristics of Recently Hospitalized Native Hawaiians & Other Pacific Islanders with Heart Failure (N=151)

Clinical Characteristic	Women (n=47)	Men (n=104)	Combined (N=151)
Systolic BP (mmHg, mean, SD)	114±27	112 ± 20	112 ± 20
Diastolic BP (mmHg, mean, SD)	68 ± 16	70 ± 14	69 ± 15
Pulse (bpm, mean, SD)	73 ± 16	74 ± 14	74 ± 15
BMI (kg/m ² , mean, SD)	37 ± 10	35 ± 9	36 ± 9
H/O Hypertension (self-report)	37 (79%)	72 (69%)	109 (72%)
H/O Diabetes mellitus (self-report)	24 (51%)	50(48%)	74 (49%)
KCCQ Scores**	62.7±23.0	61.5±25.5	62.3±23.7
CES-D scores*	10.1 ± 6.2	10.1 ± 6.8	10.1 ± 6.6
Heart failure medications			
Beta-blockers	31 (66%)	84 (81%)	115 (76%)
ACEI/ARBs [§]	29 (62%)	66 (63%)	95 (63%)
Diuretics	32 (68%)	65 (63%)	97 (64%)
Aspirin	21 (45%)	55 (53%)	76 (50%)
Warfarin	13 (28%)	26 (25%)	39 (26%)

* 10-item version of the Center for Epidemiological Studies – Depression (CES-D) = scores of > 10 indicates presence of symptoms consistent with depression.

** 23-item, self-administered Kansas City Cardiomyopathy Questionnaire (KCCQ) instrument quantifies physical function, symptoms, social function and quality of life for patients with HF. Summary score ranges from 0-100, with higher scores reflecting better health status.

[§] ACEI=Angiotensin-converting enzyme inhibitor; ARBs=Angiotensin receptor blockers.

severe LVEF (30%-34%). Thus, nearly 60% of all enrolled patients had severe (< 30%) to moderate-severe (30%-34%) left ventricular ejection function. Men were more likely to have moderate-severe to severe heart failure (61%) compared with women (32%). Thus, not surprisingly, more men report having a pacemaker or defibrillator (30%) compared with women (15%) since one of the clinical indications for placing an implantable cardiac defibrillator is severe reduction in LVEF.

Table 3 shows that higher left ventricular ejection fraction

(LVEF) was significantly associated with female sex and BMI, while history of implantable pacemaker/defibrillator, smoking, alcohol, and methamphetamine use were all associated with lower LVEF (all *P*-values < .03). After adjusting for age and all significant factors of LVEF, four risk factors remained statistically significant. Female sex and BMI remained positively associated with LVEF (all *P*-values < .04), while presence of pacemaker/defibrillator and methamphetamine use was associated with reduced LVEF (all *P*-values < .05). (Table 4)

Table 2b. Cardiovascular Disease (CVD) Characteristics of Recently Hospitalized Native Hawaiians and Other Pacific Islanders with Heart Failure (N=145)

CVD Clinical Characteristic	Women (n=47)	Men (n=104)	Combined (N=151)
Systolic Ejection Fraction (EF)*			
Mild (45%-60%)	11 (24%)	19 (19%)	30(20%)
Mild-moderate (40%-44%)	8 (17%)	4(4%)	12(8%)
Moderate (35%-39%)	8(17%)	11 (11%)	19(13%)
Moderate-severe (30%-34%)	3 (7%)	13 (13%)	16 (11%)
Severe (<=30%)	14 (30%)	55 (54%)	69 (47%)
Unknown	2 (4%)	0 (0%)	2 (1%)
H/O Myocardial Infarction	17 (36%)	39 (38%)	56 (37%)
H/O CABG	10 (21%)	21 (20%)	31 (21%)
H/O Pacemaker/Defibrillator	7 (15%)	31 (30%)	38 (25%)
H/O Atrial fibrillation	12 (26%)	21 (20%)	33 (22%)

* Systolic ejection fraction as determined by echocardiography, heart catheterization, or nuclear scan. Women n=46; Men n=102 due to missing values.

Table 3. Correlation of Potential Risk Factors of Left Ventricular Ejection Fraction (LVEF) in Recently Hospitalized Native Hawaiians & Other Pacific Islanders with Heart Failure (N=151)

Variable	Spearman's rho	P-value
Age	0.12	.15
Sex (female)	0.22	.006
Education	0.16	.06
Smoking (tobacco) [§]	-0.22	.008
Alcohol use [§]	-0.18	.03
Methamphetamine use [§]	-0.23	.006
Kansas City Cardiomyopathy Questionnaire (KCCQ) [§]	0.09	.27
Center for Epidemiologic Studies of Depression (CES-D) [§]	-0.05	.60
Body Mass (BMI) ^{§*}	0.28	.001
Systolic Blood Pressure [§]	0.09	.29
Diastolic Blood Pressure [§]	-0.11	.17
H/O Hypertension	0.05	.52
H/O Myocardial Infarction	0.02	.85
H/O CABG/PTCA	0.02	.84
H/O Rheumatic Heart Disease	-0.01	.89
H/O Atrial fibrillation	-0.09	.27
H/O Diabetes mellitus	0.05	.56
H/O Pacemaker/Defibrillator	-0.28	< .001

[§] = The following variables were analyzed with a reduced n because of missing data: smoking (n=148), alcohol use (n=148), methamphetamine use (n=147), KCCQ (n=139), CES-D (n=139), BMI (n=134), SBP (n=147), DBP (n=148).

* BMI, n=134 because of excessive weight >400 lbs. or because measured height was not possible (unable to stand due to wheel chair bound) by 15 participants.

Table 4. Regression Model of Clinical Risk Factors and Left Ventricular Ejection Fraction (LVEF) in Recently Hospitalized Native Hawaiians & Other Pacific Islanders with Heart Failure			
Variable	Coefficient	STD error	P-value
Age (per 5 yr. increments)	0.05	0.10	.613
Sex (women referent)	5.08	2.47	.042
Smoking (yes)	-4.89	2.54	.057
BMI (per 1.0 kg/m ²)	0.32	0.12	.009
Pacemaker/Defibrillator inserted (yes)	-7.69	2.54	.003
Methamphetamine use (yes)	-6.13	3.03	.045

Discussion

This study provides initial results on risk factors for reduced LVEF in hospitalized NHOPIs with heart failure. Thus, it provides new insight into the diversity of HF risk factors in another racial/ethnic minority population at increased risk for HF disparities. Of note, we found that NHOPIs were approximately 10-15 years younger than the usual general HF population and this finding parallels similarities in US Blacks with HF.¹⁸ The high prevalence of depression symptoms and reduced quality of life scores are also consistent with existing studies in other HF populations. For example, high rates of CES-D-assessed depression symptoms were noted in other HF populations but CES-D scores were not significantly associated with severity of LVEF.¹⁹⁻²¹ Our results are also consistent with these prior studies.

After adjusting for significant correlates of LVEF, female sex and BMI remained independently associated with LVEF. Several studies have reported that HF outcomes and severity of HF measures are worse in men compared to women.¹⁸ Our study is consistent with these results and provides further validation of our findings in a NHOPI HF patient population. The association of higher BMI and improved HF outcomes (mortality) has been reported by Curtis, et al, in more than 7,000 HF patients.²² This “obesity paradox” has also been observed in several smaller HF cohorts and was recently examined by Padwal, et al, in a meta-analysis of more than 23,000 patients with HF to assess risk for mortality. The authors stratified patients according to reduced versus preserved LVEF and found that despite adjustment for confounders, BMI of 30.0-34.9 kg/m² resulted in the lowest mortality with a U-shaped mortality curve across both LVEF categories.²³ The authors discuss potential explanations for the consistent findings of an “obesity paradox” and propose that a more definitive study would be needed to address the role of obesity and mortality in HF patients. In our study, BMI was also paradoxically associated with a higher LVEF and this is consistent with the most recent meta-analysis study by Padwal, et al. Similarly, it remains unclear in our patient population of NHOPIs as to why BMI seems to be a protective factor despite the missing data of the extremely obese participants in our study cohort at baseline (n=15 missing BMI due to weight > 400 lbs).

We also found a significant association between lower LVEF and the presence of implantable pacemaker/defibrillator and methamphetamine use after adjusting for other covariates.

While the association of history of pacemaker/defibrillator was not unexpected, the significant association between prior methamphetamine use and LVEF was a consistent finding that has been reported by other studies. Ito, et al, conducted a retrospective review of medical records for patients younger than 45 years of age who were discharged from the hospital with HF and reported that methamphetamine users had a significantly lower LVEF (32.9% ± 11.3%) than non-users (44.6% ± 17.8%). Our results are consistent with the finding of methamphetamine use as an independent risk factor for reduced LVEF. Several other studies have also reported on the link between long-term methamphetamine use and cardiomyopathy that may be reversible.^{9,24-30} In Yeo, et al’s, case-control study of 107 HF patients younger than 45 years of age and discharged from a tertiary care medical center in Hawai‘i, 43% were prior or current methamphetamine users, who had a 3.7-fold higher odds ratio for cardiomyopathy after adjusting for age, BMI, and renal failure compared to non-users.¹⁰ Moreover, NHOPIs accounted for 54% of the cardiomyopathy patients who had used methamphetamine and, in general, NHs were more likely to have used methamphetamine by age 12 years old compared to other racial/ethnic groups.^{9,31} Several small studies have reported on cardiomyopathy associated with methamphetamine use as yet another cardiovascular insult (ie, hypertension and cerebrovascular disease) related to habitual use of methamphetamine. Won, et al, recently reviewed the effects of methamphetamine-associated cardiomyopathy (MAC) and noted that several gaps in our understanding of prevalence, incidence, pathophysiology and therapeutics remain unanswered.¹³ However, what is clear, is that MAC was a phenomenon first recorded in Hawai‘i and other western regional states and has now slowly spread eastward across the United States. Thus, the authors recommend that greater recognition of MAC and how best to prevent and/or treat the condition be investigated as there is likely to be an increase of MAC with increased use of methamphetamine-like substances across other regions in the United States. Our study results supports the idea that MAC remains a significant underlying cause of HF hospitalization especially among NHOPIs and is associated with reduced LVEF. For policy makers and health care providers, recognition of MAC within hospitalized HF patients is important for treatment and especially prevention of repeat hospitalization and for designing comprehensive

treatment approaches to improve LVEF by also addressing other chronic problems such as methamphetamine use.

Interpretation of our results should also consider the limitations of the study. All of the study patients were recruited from a single tertiary care hospital and were confined to one racial/ethnic group (NHOPIs), although this referral medical center is the largest in the State and its patient population approximates the ethnic distribution of the State's population (ie, 18% Native Hawaiian ancestry). Acquisition of illicit drug use, tobacco and alcohol use were all self-reported which may have led to an underreporting of these health behaviors. Despite this potential bias for underreporting, we still found a significant association between smoking, alcohol and methamphetamine use with lower LVEF and this association persisted only for methamphetamine use following adjustment for other significant factors.

In summary, our results suggest that diagnosed HF seems to occur 10-15 years earlier in this select population of hospitalized NHOPIs. The significant positive association of LVEF with female sex, higher BMI and a negative association with presence of pacemaker/defibrillator and prior use of methamphetamine is consistent with prior studies on methamphetamine use and HF. To our knowledge, this is the first cross sectional study to characterize a relatively large sample of NHOPIs with diagnosed HF, and to identify significant modifiable risk factors that may guide the development of programs aimed at reducing the burden of HF in NHOPIs and other high-risk populations. For example, programs designed to reverse these HF trends may need to consider how best to address not only smoking and alcohol use but also the challenges of methamphetamine use to prevent and/or treat HF in NHOPI patients. The obesity paradox found in this study similar to other studies needs further investigation. Among NHOPIs in which morbid obesity (>40 kg/m²) is estimated to affect 25%-30% of adults and increased CVD mortality is well known in this population, suggests that perhaps other aspects of weight beyond a single static measure may be important. As Miller described, the characteristics of individuals suffering from heart failure, such as NHOPIs often do not align with those of the participants in studies that determine practice guidelines.³² Thus, further studies of HF risk factors, etiologies, types, and treatments among high risk populations such as racial and ethnic minorities is needed to reverse the HF burden and trends observed in the US population and other countries with racially and ethnically diverse populations.

Conflict of Interest

None of the authors identify any conflict of interest.

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