Differing Relationship of Nocturnal Fluid Shifts to Sleep Apnea
in Men and Women with Heart Failure

Kasai et al: Fluid Shift and OSA in Women with HF

Takatoshi Kasai, MD, PhD1,2; Shveta S. Motwani, MD1,2; Dai Yumino, MD, PhD1,2;
Susanna Mak, MD, PhD3,4; Gary E. Newton, MD3,4; T. Douglas Bradley, MD1,2,3

1Sleep Research Laboratory of the Toronto Rehabilitation Institute, 2Centre for Sleep Medicine
and Circadian Biology, University of Toronto; 3Departments of Medicine of the Toronto General
Hospital of the University Health Network; and 4Mount Sinai Hospital, Toronto, Canada.

Correspondence to:
T. Douglas Bradley, MD
Toronto General Hospital of the University Health Network, 9N-943, 200 Elizabeth Street,
Toronto, ON, M5G 2C4, Canada.
Tel: 416-340-4719, FAX: 416-340-4197, email: douglas.bradley@utoronto.ca

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Abstract

Background—In men with heart failure (HF), nocturnal rostral fluid shift is associated with an overnight increase in the neck circumference (NC) and with severity of obstructive sleep apnea (OSA). Because the prevalence of OSA is lower in women than in men with HF, we hypothesized that less fluid would shift into the neck in association with less severe OSA in women than in men with HF.

Methods and Results—In 35 men and 30 women with HF, we assessed overnight changes in NC (ΔNC) and leg fluid volume (ΔLFV) before and after polysomnography. The severity of OSA was assessed by the apnea-hypopnea index (AHI). Although the ΔLFV did not differ significantly between men and women (-131±90 versus -180±132ml, P=0.081), in women, ΔNC was smaller (P<0.001) than in men. Furthermore, although in men, ΔLFV correlated inversely with ΔNC (r=-0.755, P<0.001) and AHI (r=-0.765, P<0.001), it did not in women.

Conclusions—Despite no difference in overnight displacement of fluid from the legs compared to in men, in women, less of this fluid reached the neck, and unlike men, there was no relationship between ΔLFV and either ΔNC or AHI. These findings suggest a differing relationship between overnight fluid shift from the legs and severity of OSA in women than in men with HF.

Key Words: edema; heart failure; sex; sleep apnea
In patients with heart failure (HF), obstructive sleep apnea (OSA) is associated with increased mortality rate,\(^1\) and its prevalence (12-53\%) is higher than in the general population, despite lower body weight.\(^2\)\(^-\)\(^4\) One reason for this higher prevalence of OSA may be greater fluid retention. We demonstrated that fluid accumulated in the legs while upright during the day can redistribute into the neck while recumbent during sleep. Such nocturnal rostral fluid shift could cause distension of the neck veins and/or edema of the peripharyngeal soft tissue and facilitate upper airway (UA) obstruction. Indeed, during the night, the volume of fluid displaced from the legs strongly related to the degree of overnight increase in neck circumference (NC) and severity of OSA in men with or without HF or with end-stage renal disease (ESRD).\(^5\)\(^-\)\(^8\) More recently, proof that nocturnal rostral fluid shift is a cause of OSA was provided by the observation that use of venous compression stockings in non-obese men with OSA and in patients with chronic venous insufficiency reduced fluid accumulation in the legs during the day, and the amount of rostral fluid shift at night that was accompanied by 36-37\% reductions in the frequency of apneas and hypopneas per hour of sleep (apnea-hypopnea index, AHI).\(^9\),\(^10\)

In patients with HF, women have a lower prevalence of OSA than men for unknown reasons.\(^2\) One possibility is a different pattern of gravity-dependent fluid movement out of the legs during sleep between the sexes. For example, compared to men, women may either have less fluid displaced from their legs overnight, or less of this fluid may accumulate in the neck. Despite a similar volume of fluid displaced from the legs in response to inflation of anti-shock trousers during wakefulness, UA collapsibility assessed by critical UA closing pressure increased significantly more in men than in women.\(^11\) Accordingly, there may be sex-related differences in response to fluid displacement from the legs that protect women from UA collapse compared to men. We therefore hypothesized that compared to men, women with HF would have a smaller
overnight increase in NC in association with a less severe degree of OSA than men despite no difference in the degree of overnight fluid displacement from the legs. To test this hypothesis, we compared relationships between nocturnal fluid displacement from the legs to overnight changes in neck circumference (ΔNC) and severity of OSA between men and women with HF.

Methods

Subjects

Polysomnography was performed prospectively on consecutive men and women with HF referred from the Mount Sinai Hospital Heart Failure Clinic in Toronto, irrespective of symptoms or signs of sleep apnea. None of the subjects participated in our previous study.6 Inclusion criteria were: age ≥18 years, HF due to ischemic or non-ischemic dilated cardiomyopathy for ≥6 months, left ventricular ejection fraction (LVEF) ≤45%, New York Heart Association (NYHA) class I-III, and clinically stable without medication changes for ≥1 month before polysomnography. Exclusion criteria were: decompensated HF, predominantly central sleep apnea (CSA, >50% central events) because CSA is rare in women,2 treated sleep apnea, tonsillar hypertrophy, unstable angina, myocardial infarction, or cardiac surgery within the previous 3 months, and pregnancy. The protocol was approved by the Toronto Rehabilitation Institute’s Research Ethics Board, and all subjects provided written consent before participation.

Patients’ characteristics and medications were recorded, and daytime sleepiness was assessed by the Epworth Sleepiness Scale, physical fitness by the Duke Activity Status Index (DASI), leg edema by a leg edema scale, and the amount of time spent sitting by an hourly diary before polysomnography as previously described.6 LVEF, estimated glomerular filtration rate (eGFR) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) level were assessed within
3 months before polysomnography. Menopausal status was assessed by directly asking each female subject.

**Weight, Leg Fluid Volume, Neck and Calf Circumferences**

Subjects’ weights were expressed both as body mass index (BMI), and as a percentage of the ideal weight (%IBW) based on sex, age and height, which is a better means of comparing body habitus between the sexes than BMI, since it takes into account differences in fat, muscle and bone composition between the sexes.\(^{11,12}\)

With subjects instrumented for polysomnography lying awake and supine with legs straight, we measured right leg fluid volume (LFV) by bioelectrical impedance as previously described (Hydra4200, Xitron Technologies Inc, San Diego, Calif).\(^{5,6,9-11,13-15}\) This well-validated technique (accuracy of within 5%; repeatability of within 0.3%) uses impedance to electric current within a body segment to measure its fluid content.\(^{16,17}\) We then measured the circumferences of the neck above the cricothyroid cartilage and of the thickest portion of the right calf by tape measure just before and after polysomnography as previously described.\(^{5,6}\) Lines were drawn at these levels with a marker pen to ensure that measurements after sleep were made at exactly the same level as those before sleep. On awakening the next morning, measurements made before sleep were repeated before scoring of polysomnography. The differences between LFV, NC and calf circumference before and after sleep were deemed the overnight changes in these variables.

**Polysomnography**

Subjects underwent overnight polysomnography using standard techniques and scoring
criteria for sleep stages and arousals. Subjects slept on a single pillow with the bed flat. Body position was recorded continuously by video recordings from which technicians scored time spent in particular positions epoch-by-epoch. Thoracoabdominal motion was monitored by respiratory inductance plethysmography, and nasal airflow by nasal pressure cannulae. Oxyhemoglobin saturation (SaO₂) was monitored by oximetry. Apneas and hypopneas were defined as >90% and 50-90% reduction in tidal volume from baseline, respectively, lasting ≥10s, and were classified as obstructive or central as previously described. Signals were recorded on a computerized sleep recording system (Sandman, Nellcor Puritan Bennett Ltd, Ottawa, Ontario, Canada) and scored by a technician blind to measurements of LFV, NC and calf circumference. The AHI for the whole night was quantified. In addition, the AHI was calculated for the first and second half of the night.

Statistical Analysis

The present study began as a pilot project involving 15 men and 15 women with HF. The sample size estimate was based on these subjects as follows. We planned a study in which AHI would regressed against ΔLFV within each sex. From pilot data, the standard deviations of the AHI and ΔLFV in men were 24 and 104, respectively, with a slope of 0.160. In women, the standard deviation of the AHI and ΔLFV in women were 14 and 115, respectively. The difference in the slopes of these regression lines was -0.116. Therefore, assuming a 2-tailed type I error of 0.05, we needed 30 men and 30 women to reject the null hypothesis that these slopes were equal with power of 0.8.

Values are expressed as mean±SD for normally distributed and as median [interquartile range] for non-normally distributed data unless indicated otherwise. To assess whether any
potential relationship between overnight change in LFV (ΔLFV) and ΔNC or AHI was sex-specific we used ANCOVA with an interaction term. In addition, continuous variables from men and women were compared by student t-test for normally distributed data or Mann-Whitney U-test for non-normally distributed data. Fisher’s exact test was used to compare nominal variables between the sexes. Within each sex, univariable relationships between AHI and independent variables were examined by simple linear regression analysis. We used both simple linear regression and exponential regression to analyze univariable relationships between ΔLFV and both ΔNC and AHI since previous studies in men reported exponential relationships between these variables.6 We expressed these relationships according the better fit of these two analyses. Multivariable forward stepwise linear regression with P<0.05 to enter and P>0.1 to remove were also performed. Independent variables included in the multivariable analysis for the AHI, were age, height, %IBW, NC before sleep, NYHA class, LVEF, eGFR, NT-proBNP, DASI, sitting time, degree of leg edema, percentage of time spent in the supine position, ΔNC, overnight changes in calf circumference, and ΔLFV. An additional stepwise multiple regression analysis with AHI as the dependent variable assessed the same independent variables except that BMI was substituted for %IBW. The AHI in the first and second halves of the night were compared within each sex by Wilcoxon signed-rank test.

Because seven men (but no women) had saphenous veins harvested for coronary bypass surgery, we assessed the relationship between the presence or absence of saphenous vein graft (SVG) and degree of leg edema. In women, the relationship between menopausal status and the AHI/ΔLFV relationship was also assessed by ANCOVA with an interaction term.

Within each sex, univariable and multivariable relationships between ΔLFV and independent variables were also examined by simple and stepwise multiple regression analyses,
respectively, with $P<0.05$ to enter and $P>0.1$ to remove. For $\Delta$LFV, independent variables included were age, height, %IBW, NYHA class, LVEF, eGFR, NT-proBNP, DASI, sitting time, and degree of leg edema. Similar analyses were also undertaken in which BMI was substituted for %IBW. $P<0.05$ indicated statistical significance. Analyses were performed by SPSS11.0 (SPSS Inc, Chicago, Ill).

Results

Characteristics of the Subjects

Sixty-five subjects were studied (35 men and 30 women). We found significant but modest relationships between $\Delta$NC and $\Delta$LFV ($r=-0.261$, $P=0.036$) and between AHI and $\Delta$LFV ($r=-0.310$, $P=0.012$) for all subjects. Because interactions between sex and $\Delta$NC/$\Delta$LFV ($P<0.001$), and AHI/$\Delta$LEV relationships ($P<0.001$) were significant, we analyzed data from men and women separately. Characteristics of the subjects are shown in Table 1. Compared to men, women had significantly lower NC, height and weight, but similar BMI. However, %IBW was significantly greater in women than in men. The DASI was significantly lower in women than in men. However, there were no significant differences between the sexes in the remaining variables including medications. Seven men had a history of cardiac bypass surgery with SVG. Nine women were premenopausal and 21 postmenopausal. No patients were taking steroids or sedatives at the time of the sleep studies.

Polysomnography Data

Total sleep time (TST), percentage of REM sleep and slow-wave sleep did not differ significantly between the sexes (Table 2). However, women had non-significant tendency to
spend a greater percentage of time in the supine position. There were no significant differences in leg edema scores, overnight reductions in weight, calf circumference and LFV between men and women. However, men experienced a much greater overnight increase in NC than women \((P<0.001)\). There was no significant difference in the frequency of nocturnal urination during sleep studies between men and women \((0.7±1.0 \text{ versus } 0.6±0.8 \text{ times per night in men and women, respectively, } P=0.781)\).

In men, there was an inverse exponential relationship between \(\Delta\text{LFV}\) and \(\Delta\text{NC}\) (Figure 1A), similar to that previously described. In contrast, there was no significant correlation between \(\Delta\text{LFV}\) and \(\Delta\text{NC}\) in women (Figure 1B). In both sexes, the AHI did not change from the first half to the second half of the night (from 22.4 [27.3] to 18.1 [33.9], \(P=0.829\) in men; and from 15.1 [20.0] to 22.4 [27.3], \(P=0.093\) in women).

**Factors Related to AHI**

Univariable analyses revealed that, in men, the AHI correlated linearly and inversely with \(\Delta\text{LFV}\) (Figure 2A). Other significant correlates of AHI are shown in Table 3. Multivariable analysis revealed that the only significant correlate of the AHI in men was \(\Delta\text{LFV}\) (partial \(r=-0.753, P<0.001\)) and \(\%\text{IBW}\) (partial \(r=0.374, P=0.029\)), which together accounted for 64% of its variability \((r=0.802, P<0.001 \text{ for total model})\). When BMI was substituted for \(\%\text{IBW}\) in this multivariable analysis, the significant correlates of the AHI were \(\Delta\text{LFV}\) (partial \(r=-0.746, P<0.001\)) and BMI (partial \(r=0.346, P=0.045\)) which accounted for 64% of its variability \((r=0.797, P<0.001 \text{ for total model})\). Although there was a significant relationship between the presence or absence of SVG and degree of leg edema \((r=0.355, P=0.036)\) there was no significant relationship between presence or absence of SVG and AHI \((r=0.027, P=0.876)\).
In women, univariable analyses revealed no significant correlation between AHI and ΔLFV (Figure 2B). Univariable analysis demonstrated the percentage of supine sleep time and ΔNC tended to correlate with AHI, but not significantly (Table 3). Multivariable analyses showed no significant correlates of the AHI in women. When BMI was substituted for %IBW in this multivariable analysis, none of the variables correlated significantly with the AHI in women. There was no significant relationship between AHI and menopausal status ($r=0.253$, $P=0.177$) and no interaction between menopausal status and AHI/ΔLFV relationship ($P=0.960$).

**Factors Related to ΔLFV**

In men, significant univariable correlates of the ΔLFV are shown in Table 4. In multivariable analysis, the significant correlates of the ΔLFV in men were the DASI (partial $r=0.381$, $P=0.029$), sitting time (partial $r=-0.380$, $P=0.029$), and degree of leg edema (partial $r=-0.413$, $P=0.017$), which accounted for 56% of its variability ($r=-0.749$, $P<0.001$ for the total model). When BMI was substituted for %IBW in this multivariable analysis, the significant correlates of the AHI were the same as above. In women, significant univariable correlates of the ΔLFV are shown in Table 4. There was no significant relationship between ΔLFV and menopausal status ($r=-0.230$, $P=0.221$). Multivariable analyses revealed that the significant correlates of ΔLFV in women were sitting time (partial $r=-0.417$, $P=0.024$) and degree of leg edema (partial $r=-0.603$, $P=0.001$), which together accounted for 61% of its variability ($r=-0.778$, $P<0.001$ for total model). Substituting BMI for %IBW, the significant correlates of the ΔLFV were the same as above.
Discussion

These findings provide novel insights that may help to explain differences between the sexes in the severity of OSA in HF patients. First, the overnight increase in NC and AHI in men were greater than in women, despite no significant differences in degrees of leg edema, and ΔLFV. Second, ΔNC was strongly related to ΔLFV in men, but not in women. Third, the only significant correlate of the AHI in men was ΔLFV. However, in women, there was no relationship between the ΔLFV and the AHI. Finally, ΔLFV correlated directly with sitting time and degree of leg edema, and inversely with physical fitness in men, while in women, it correlated directly with sitting time and degree of leg edema. Taken together, these results confirm our previous findings in men with HF, that overnight rostral fluid displacement from the legs, related to sedentary living, contributes to the severity of OSA probably by causing nuchal fluid accumulation that increases collapsibility of the pharynx during sleep. Of greatest interest, however, were the intriguing observations that in women, the fluid displaced from the legs overnight did not accumulate in the neck to nearly the same extent as it did in men, and did not relate to the AHI. These observations suggest previously unrecognized mechanisms contributing the lower severity of OSA in women than in men with HF.

Obesity, a major risk factor for OSA in the general population, may predispose to OSA through pharyngeal fat deposition, that increases peripharyngeal soft tissue pressure, facilitating UA narrowing and collapse. However, many OSA patients are not obese. The observation that OSA is commoner in edematous states, than in the general population despite lower body weight led us to hypothesize that rostral fluid shift from edematous legs to nuchal structures could impinge on the UA and facilitate its collapse during sleep. In previous studies, we demonstrated that fluid displacement from the legs by inflatable trousers increased NC, narrowed
the UA and increased its resistance and collapsibility during wakefulness.\textsuperscript{13-15} Subsequently, we
demonstrated that overnight rostral fluid shift strongly correlated with severity of OSA in
association with an increase in NC in men with and without HF.\textsuperscript{5,6} Accordingly, some of the
fluid displaced from the legs accumulated in the neck and facilitated UA collapse. Proof of this
concept was provided by the observation that use of compression stockings in chronic venous
insufficiency patients with OSA reduced fluid accumulation in the legs during the day, and
rostral fluid shift at night accompanied by a 37\% reduction.\textsuperscript{10}

The prevalence of OSA is 2-3 times higher in men than in women with HF\textsuperscript{2}, but the
reasons are not clear. Since women have smaller UA lumens than men, UA narrowing does not
explain their lower prevalence of OSA.\textsuperscript{21} However, women have a shorter pharynx than men that,
in theory, should make it less collapsible than in men.\textsuperscript{22} Because of the greater prevalence of
OSA in postmenopausal than in premenopausal women, low progesterone or estrogen levels has
been implicated in the pathogenesis of OSA.\textsuperscript{23} However, neither estrogen nor progesterone
alleviates OSA in postmenopausal women or men.\textsuperscript{23} Lower testosterone levels in women than
men might also play a role, but androgen blockade in men does not attenuate OSA.\textsuperscript{23} Therefore,
there is little evidence that differences in levels of sex hormones between women and men
contribute directly to differences in OSA prevalence.

Similarly, differences in nuchal fat distribution seem not to explain differences in OSA
prevalence between the sexes.\textsuperscript{24,25} Moreover, neither Rowley et al\textsuperscript{26} nor Su et al\textsuperscript{11} found any
difference in UA collapsibility between healthy men and women during sleep or wakefulness.
Therefore, none of these studies provides clear evidence to explain the lower prevalence of OSA
in women than in men with HF.
We previously demonstrated that lower body positive pressure increased UA collapsibility in men, but not in women despite a similar fluid volume displaced from the legs.\textsuperscript{11} Consistent with those findings, herein we found that for the same spontaneous $\Delta$LFV, men had a nine-fold greater increase in NC than women that was related to the AHI.\textsuperscript{5, 6} By contrast, there was no significant relationship between $\Delta$LFV and either $\Delta$NC or AHI in women. Thus, whereas in men a large amount of fluid accumulated in the neck overnight that was related to the AHI, in women a much smaller amount of fluid accumulated in the neck that was not related to the AHI. This lower fluid accumulation of in the necks of women at night may contribute to their lower severity of OSA than men. This is consistent with our observation that in patients with ESRD, there was a significant relationship between OSA severity and $\Delta$LFV in men, but not in women.\textsuperscript{8}

Although there was a significant univariable relationship between $\Delta$NC and AHI in men, the relationship was no longer significant in the multivariable analysis. There was, however, a significant strong univariable relationship between $\Delta$NC and $\Delta$LFV in men. Thus, the relationship between $\Delta$NC and AHI was attenuated by the $\Delta$LFV, and hence $\Delta$NC was excluded from the final model. These findings indicate that $\Delta$LFV is a more sensitive determinant of AHI than $\Delta$NC.

In a recent study, the absence of any change in the severity of OSA from the first to the second half of the night was advanced as an argument against the role of overnight rostral fluid displacement in the pathogenesis of OSA.\textsuperscript{27} In that study, the relationship between $\Delta$NC and AHI from beginning to the end of the night was also examined, but no relationship was found. However, because LFV was not assessed, no conclusions about the role of overnight fluid shifts in the pathogenesis of OSA could reasonably have been drawn from this observation. In addition, upon the transition from the standing to the supine position, most of fluid displacement from the
legs to the upper body occurs within 30-60 minutes. Consequently, a rapid fluid shift might induce a relatively quick change in UA characteristics at the beginning of the night without further significant changes overnight. If so, the AHI may not progress overnight as a result of continued fluid shift.

Since less fluid was displaced into the neck of women than in men, despite no significant difference in $\Delta$LFV between them, there would be less chance that fluid accumulated in sufficient quantities in nuchal tissues to increase peri-pharyngeal tissue pressure and narrow the UA. Consequently, fluid accumulation in the neck would not be as important to the pathogenesis of OSA in women as in men with HF. In women, a larger proportion of the fluid displaced from their legs must have accumulated elsewhere. For example, the gonadal veins of women are substantially larger than those of men and women have a large venous plexus around the uterus absent in men. In this regard, application of lower body negative pressure causes greater venous pooling in the pelvis of women than of men. Therefore, fluid spontaneously displaced from the legs overnight may accumulate to a relatively greater extent in the pelvis or abdomen than in the neck of women, than of men with HF. We also found no difference in the $\Delta$LFV between pre- and post-menopausal women suggesting that female hormonal status may not play a substantial role in the amount and pattern of overnight fluid shift, at least in patients with HF. However, we do not know whether this is true in subjects without HF.

$\Delta$LFV correlated with sitting time, lower physical fitness and greater leg edema in men, and with sitting time and greater leg edema in women. Thus, in general, the degree of $\Delta$LFV in both men and women with HF, was related to sedentary living. However, these factors appear to be related to the pathogenesis of OSA only in men. Therefore, exercise training even without weight loss may attenuate OSA more in men than in women by preventing fluid accumulation in
the legs during the daytime. Indeed, vigorous physical activity is associated with a lower prevalence of OSA to a greater extent in men than in women.\textsuperscript{32} In addition, exercise training without concomitant weight loss has been shown to attenuate OSA more prominently in men than in women with and without HF.\textsuperscript{33,34} However, overnight fluid shift was not measured and the mechanism for this beneficial effect was not determined.

Our study is subject to some limitations. First, we did not measure intra-abdominal or pelvic blood volume due to technical limitations. Therefore, we have no direct evidence that fluid displaced from the legs overnight accumulated in these areas to a greater extent in women than in men. Consequently, studies assessing fluid volume status in the abdomen, pelvis and other areas of the body will be required to test the hypothesis that a greater degree of fluid sequestration in these vascular beds is related to a lower prevalence and severity of OSA in women than in men. Second, subjects in the present study were relatively young for HF patients probably because they were enrolled from a university-affiliated tertiary referral clinic that, as usual for such clinics, sees a younger population than in a typical community HF population. This is because a larger proportion of patients in this tertiary referral clinic have non-ischemic/idiopathic dilated cardiomyopathy and require more extensive investigations than most HF patients, and because they may be referred for heart transplantation. Nevertheless, in reports of sleep apnea prevalences in HF patients from other groups, the mean age of approximately 60 years was similar to ours.\textsuperscript{35-38} Therefore, subjects in the present study should be representative of tertiary referral HF clinics. Third, we excluded patients with predominant CSA, because CSA is rare in women with HF, and therefore we would not be able to compare men and women for this condition.\textsuperscript{2} Therefore, further studies will be required to determine whether the findings of the present study are applicable to patients with predominant CSA. Fourth, because we studied only
HF patients, we do not know whether the differing relationships of overnight rostral fluid shift to OSA between the sexes applies to individuals without HF. Finally, there might be other confounding factors which were not specifically assessed in this study, but which may affect the relationship between severity of OSA and ΔLFV.

In conclusion, our findings suggest that differences in the overnight pattern of fluid redistribution between the sexes may help to explain the lower severity of OSA in women than in men with HF. They also suggest that sub-nuchal sequestration of blood and body fluid may protect women against the development of OSA in other fluid retaining states such as pregnancy and renal failure. Further studies will be required to determine whether overnight fluid redistribution from the legs into the abdomen and pelvis differs between men and women with or without HF.

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Operating grant MOP-82731 from the Canadian Institutes of Health Research. T. Kasai was supported by an unrestricted research fellowship from Fuji-Respironics Inc. D. Yumino was supported by an unrestricted research fellowship from Fuji-Respironics Inc and Toronto Rehabilitation Institute.

Disclosures

None.
References


### Table 1. Characteristics of the patients

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<th>Men</th>
<th>Women</th>
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<tr>
<td></td>
<td>(n=35)</td>
<td>(n=30)</td>
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<td>96.2±20.0</td>
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<td>IBW, % of predicted</td>
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<td>10 (33)</td>
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<td>Ischemic cardiomyopathy, n (%)</td>
<td>14 (40)</td>
<td>6 (20)</td>
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<td>Saphenous vein stripping for coronary bypass, n (%)</td>
<td>7 (20)</td>
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<td>Systolic blood pressure, mmHg</td>
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<td>124±16</td>
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<td>Diastolic blood pressure, mmHg</td>
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<td>29 (97)</td>
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<td>Value 2</td>
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<td>Beta Blockers, n (%)</td>
<td>30 (86)</td>
<td>24 (80)</td>
<td>0.742</td>
</tr>
<tr>
<td>Aspirin, n (%)</td>
<td>18 (51)</td>
<td>16 (53)</td>
<td>1.000</td>
</tr>
</tbody>
</table>

Values are expressed as mean±SD for normally distributed and as median [interquartile range] for non-normally distributed unless indicated otherwise.

Abbreviations: ACE, angiotensin-converting enzyme; and AT2, angiotensin-2 receptor
Table 2. Polysomnographic data

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>TST, min</td>
<td>251.8±81.5</td>
<td>282.0±64.3</td>
<td>0.073</td>
</tr>
<tr>
<td>Slow-wave sleep, % of TST</td>
<td>16.3±10.0</td>
<td>19.2±10.7</td>
<td>0.260</td>
</tr>
<tr>
<td>REM sleep, % of TST</td>
<td>14.4±8.0</td>
<td>12.1±7.9</td>
<td>0.416</td>
</tr>
<tr>
<td>Supine position, % of TST</td>
<td>38.6±35.1</td>
<td>55.5±33.1</td>
<td>0.051</td>
</tr>
<tr>
<td>AHI, no/hr of sleep</td>
<td>25.3±20.0</td>
<td>17.5±19.9</td>
<td>0.123</td>
</tr>
<tr>
<td>Obstructive, %</td>
<td>94.6 [29.5]</td>
<td>96.8 [16.4]</td>
<td>0.241</td>
</tr>
<tr>
<td>Mean SaO2, %</td>
<td>94.2±2.5</td>
<td>95.0±2.4</td>
<td>0.237</td>
</tr>
<tr>
<td>Minimum SaO2, %</td>
<td>82.6±9.3</td>
<td>84.4±6.2</td>
<td>0.879</td>
</tr>
<tr>
<td>Arousal index, no/hr of sleep</td>
<td>32.1±17.0</td>
<td>25.9±15.7</td>
<td>0.135</td>
</tr>
<tr>
<td>Leg edema scale 2+ and 3+, n (%)</td>
<td>8 (23)</td>
<td>10 (33)</td>
<td>0.411</td>
</tr>
<tr>
<td>Overnight change in body weight, kg</td>
<td>-0.7±0.5</td>
<td>-0.6±0.4</td>
<td>0.698</td>
</tr>
<tr>
<td>Overnight change in body weight, %</td>
<td>-0.7±0.5</td>
<td>-0.8±0.5</td>
<td>0.519</td>
</tr>
<tr>
<td>Overnight change in calf circumference, cm</td>
<td>-1.2±0.7</td>
<td>-1.3±0.8</td>
<td>0.420</td>
</tr>
<tr>
<td>ΔNC, cm</td>
<td>0.9±0.8</td>
<td>0.1±0.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ΔNC, %</td>
<td>2.0±1.7</td>
<td>0.3±1.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ΔLFV, ml</td>
<td>-130.9±90.0</td>
<td>-180±131.8</td>
<td>0.081</td>
</tr>
</tbody>
</table>
Table 3. Univariate analysis between AHI and independent variables other than ΔLFV.

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th></th>
<th>Women</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r</td>
<td>r²</td>
<td>P</td>
<td>r</td>
<td>r²</td>
<td>P</td>
</tr>
<tr>
<td>Age</td>
<td>-0.204</td>
<td>0.042</td>
<td>0.241</td>
<td>0.106</td>
<td>0.011</td>
<td>0.576</td>
</tr>
<tr>
<td>Height</td>
<td>0.247</td>
<td>0.061</td>
<td>0.152</td>
<td>-0.177</td>
<td>0.031</td>
<td>0.349</td>
</tr>
<tr>
<td>BMI</td>
<td>0.421</td>
<td>0.177</td>
<td>0.012</td>
<td>0.227</td>
<td>0.052</td>
<td>0.227</td>
</tr>
<tr>
<td>%IBW</td>
<td>0.419</td>
<td>0.176</td>
<td>0.012</td>
<td>0.249</td>
<td>0.062</td>
<td>0.184</td>
</tr>
<tr>
<td>NC before sleep</td>
<td>0.248</td>
<td>0.062</td>
<td>0.151</td>
<td>0.126</td>
<td>0.016</td>
<td>0.508</td>
</tr>
<tr>
<td>NYHA class</td>
<td>0.385</td>
<td>0.148</td>
<td>0.023</td>
<td>0.011</td>
<td>0.001</td>
<td>0.955</td>
</tr>
<tr>
<td>LVEF</td>
<td>-0.200</td>
<td>0.051</td>
<td>0.250</td>
<td>-0.034</td>
<td>0.001</td>
<td>0.858</td>
</tr>
<tr>
<td>eGFR</td>
<td>-0.207</td>
<td>0.043</td>
<td>0.232</td>
<td>-0.032</td>
<td>0.001</td>
<td>0.868</td>
</tr>
<tr>
<td>NT-proBNP</td>
<td>0.208</td>
<td>0.043</td>
<td>0.230</td>
<td>0.039</td>
<td>0.002</td>
<td>0.838</td>
</tr>
<tr>
<td>DASI</td>
<td>-0.365</td>
<td>0.133</td>
<td>0.031</td>
<td>0.190</td>
<td>0.036</td>
<td>0.316</td>
</tr>
<tr>
<td>Sitting time</td>
<td>0.357</td>
<td>0.127</td>
<td>0.035</td>
<td>0.277</td>
<td>0.077</td>
<td>0.138</td>
</tr>
<tr>
<td>Leg edema scale</td>
<td>0.568</td>
<td>0.323</td>
<td>&lt;0.001</td>
<td>0.183</td>
<td>0.033</td>
<td>0.333</td>
</tr>
<tr>
<td>Percentage of time spent in supine position</td>
<td>0.113</td>
<td>0.013</td>
<td>0.518</td>
<td>0.348</td>
<td>0.121</td>
<td>0.060</td>
</tr>
<tr>
<td>Change in calf circumference</td>
<td>-0.516</td>
<td>0.266</td>
<td>0.002</td>
<td>-0.184</td>
<td>0.034</td>
<td>0.331</td>
</tr>
<tr>
<td>ΔANC</td>
<td>0.601</td>
<td>0.361</td>
<td>&lt;0.001</td>
<td>0.325</td>
<td>0.106</td>
<td>0.080</td>
</tr>
</tbody>
</table>
Table 4. Univariate analysis of factors related to Δ LFV.

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th></th>
<th></th>
<th>Women</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r</td>
<td>r²</td>
<td>P</td>
<td>r</td>
<td>r²</td>
<td>P</td>
</tr>
<tr>
<td>Age</td>
<td>-0.009</td>
<td>0.001</td>
<td>0.958</td>
<td>-0.353</td>
<td>0.125</td>
<td>0.056</td>
</tr>
<tr>
<td>Height</td>
<td>-0.075</td>
<td>0.006</td>
<td>0.668</td>
<td>-0.040</td>
<td>0.002</td>
<td>0.832</td>
</tr>
<tr>
<td>BMI</td>
<td>-0.269</td>
<td>0.072</td>
<td>0.118</td>
<td>-0.582</td>
<td>0.339</td>
<td>0.001</td>
</tr>
<tr>
<td>%IBW</td>
<td>-0.242</td>
<td>0.059</td>
<td>0.162</td>
<td>-0.566</td>
<td>0.320</td>
<td>0.001</td>
</tr>
<tr>
<td>NYHA class</td>
<td>-0.460</td>
<td>0.212</td>
<td>0.005</td>
<td>-0.488</td>
<td>0.238</td>
<td>0.006</td>
</tr>
<tr>
<td>LVEF</td>
<td>0.123</td>
<td>0.015</td>
<td>0.482</td>
<td>-0.112</td>
<td>0.013</td>
<td>0.555</td>
</tr>
<tr>
<td>eGFR</td>
<td>0.459</td>
<td>0.211</td>
<td>0.006</td>
<td>0.279</td>
<td>0.078</td>
<td>0.135</td>
</tr>
<tr>
<td>NT-proBNP</td>
<td>-0.462</td>
<td>0.213</td>
<td>0.005</td>
<td>-0.012</td>
<td>0.001</td>
<td>0.950</td>
</tr>
<tr>
<td>DASI</td>
<td>0.591</td>
<td>0.349</td>
<td>&lt;0.001</td>
<td>0.478</td>
<td>0.228</td>
<td>0.008</td>
</tr>
<tr>
<td>Sitting time</td>
<td>-0.541</td>
<td>0.293</td>
<td>&lt;0.001</td>
<td>-0.617</td>
<td>0.381</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Leg edema scale</td>
<td>-0.605</td>
<td>0.366</td>
<td>&lt;0.001</td>
<td>-0.723</td>
<td>0.523</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Figure Legends

**Figure 1.** In men (A), there was an inverse relationship between overnight change in neck circumference and ΔLFV. However, in women (B), this relationship was not significant.

**Figure 2.** In men (A), there was inverse relationship between ΔLFV and AHI. In contrast, in women (B), this relationship was a not significant.
Men (n=35)

\[ r = -0.755 \]
\[ r^2 = 0.570 \]
\[ P < 0.001 \]
Women (n=30)

$r = -0.200$

$r^2 = 0.040$

$P = 0.289$
Men (n=35)

\[ r = -0.765 \]
\[ r^2 = 0.5845 \]
\[ P < 0.001 \]
Women (n=30)

-20
0
20
40
60
80
100
AHI (events/hr sleep)

-700
-600
-500
-400
-300
-200
-100
0
100
ΔLFV (ml)

$r = -0.059$

$r^2 = 0.003$

$P = 0.755$
Differing Relationship of Nocturnal Fluid Shifts to Sleep Apnea in Men and Women with Heart Failure
Takatoshi Kasai, Shveta S. Motwani, Dai Yumino, Susanna Mak, Gary E. Newton and T. Douglas Bradley

Circ Heart Fail. published online June 7, 2012;
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