Nocturia independently predicts left ventricular hypertrophy and left atrial enlargement among patients with cardiac symptoms

Kuo-Wei Kao¹, Weiming Cheng²,³,⁴,⁵, Ching-Ju Wu⁶ & Yu-Hua Fan⁴,⁷

Nocturia can be caused by urological disorders and systemic diseases, including heart diseases. We aimed to investigate the relationship between nocturia and structural abnormalities on echocardiography. Adult patients who underwent echocardiography for cardiac symptoms or heart murmur or had a history of structural heart disease were included. The voiding times during sleep hours were collected prospectively. Univariate and multivariate analyses were performed to evaluate the predictive value of bothersome nocturia (nocturia ≥ 2) on echocardiographic abnormalities. Of 299 patients, 182 (60.9%) reported bothersome nocturia. In patients aged ≥ 65 years, hypertension and left atrial enlargement (LAE) were associated with higher occurrences of bothersome nocturia. On multivariate analysis, bothersome nocturia was a predictive factor of LAE (odds ratio [OR] 2.453, 95% confidence interval [CI] 1.363–4.416,  p = 0.003). Moreover, bothersome nocturia could predict both LAE and left ventricular hypertrophy (LVMH) (OR 2.285, 95% CI 1.151–4.536,  p = 0.018; OR 2.056, 95% CI 1.025–4.124,  p = 0.043) in the elderly. Older age, hypertension, and LAE were risk factors for bothersome nocturia. Moreover, bothersome nocturia was predictive of LAE and LVMH in the elderly. Patients with bothersome nocturia without other significant lower urinary tract symptoms should be referred to cardiologists.

Nocturia is the most common and troublesome lower urinary tract symptom (LUTS)¹. Nocturia prevalence ranges from 11 to 35.2% in young men and 20.4% to 43.9% in young women. Moreover, the prevalence is between 68.9 and 93% in the elderly population². Nocturia is associated with poor quality of life and increased morbidity³. Furthermore, nocturia is strongly associated with depression⁴ and leads to a higher risk of incident falls in the elderly⁵. In addition to urological disorders, nocturia is also caused by systemic diseases⁶. Previous studies have reported that heart failure and uncontrolled hypertension were responsible for clinically significant nocturia⁷. Other cardiac diseases may also contribute to nocturia. One study revealed that electrocardiographic evidence of left ventricular hypertrophy (LVH) and left atrial enlargement (LAE) were significantly associated with nocturia⁸. However, to the best of our knowledge, no studies have so far thoroughly evaluated the association between structural cardiac abnormalities and nocturia. We, thus, investigated the relationship between nocturia and structural abnormalities on cardiac sonography.

Materials and methods
The study was approved by the Institutional Review Board of Taipei City Hospital (approval number: TCH-IRB-11002002) and performed in accordance with the guidelines of the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from all patients.

¹Division of Urology, Department of Surgery, Taipei City Hospital, Renai Branch, Taipei, Taiwan. ²Division of Urology, Department of Surgery, Taipei City Hospital, Zhongxiao Branch, Taipei, Taiwan. ³Institute of Biopharmaceutical Science, College of Life Science, National Yang Ming Chiao Tung University, Taipei, Taiwan. ⁴Department of Urology, College of Medicine, National Yang Ming Chiao Tung University, Taipei, Taiwan. ⁵Program in Molecular Medicine, College of Life Sciences, National Yang Ming Chiao Tung University, Taipei, Taiwan. ⁶Division of Cardiology, Department of Medicine, Taipei City Hospital, Zhongxiao Branch, Taipei, Taiwan. ⁷Department of Urology, Taipei Veterans General Hospital, Taipei, Taiwan. *email: yhfan2@gmail.com
We prospectively included adult patients from the cardiology outpatient department who underwent cardiac sonography between June 1, 2021, and July 31, 2021. Cardiac sonography was undertaken for clinical symptoms like chest pain or tightness, physical examination with heart murmur, or follow-up of structural heart disease. Patients with urinary tract infection, neurogenic bladder, or a prior history of lower urinary tract or pelvic surgery were excluded. Before the echocardiographic examination, nocturia was assessed using Question 7 of the International Prostate Symptom Score (IPSS) questionnaire “How many times did you typically get up at night to urinate?”. The patients’ basic data included age, body mass index (BMI), and presence of comorbidities, such as diabetes mellitus, hypertension, heart failure and cardiomyopathy. Elderly patients were defined as those aged ≥65 years. BMI ≥25 kg/m² was defined as obesity in the Asian population. The 2018 International Continence Society (ICS) defines nocturia as waking for passing urine during the main sleep hours. Previous literature showed that the majority of people report being troubled when the number of nocturia episodes is ≥2 and that over two voids per night is associated with impaired health-related quality of life. Therefore, we classified the participants into two groups based on the number of nocturia episodes: bothersome nocturia (nocturia ≥2) vs non-bothersome nocturia (nocturia ≤1).

Cardiac sonography was performed by a single technician and interpreted by a cardiologist. A cardiologist has validated this cardiac sonography report. All three cardiac staff were blinded to the patients’ nocturia conditions. The performance and measurements of echocardiographic parameters were based on the 2015 recommendations of chamber quantification of the American Society of Echocardiography (ASE) and the European Association of Cardiovascular Imaging (EACVI). Echocardiological parameters, including the size of the left atrium (LA), left ventricle (LV), aorta, aortic valve (AV), mitral valve (MV), tricuspid valve (TV), and pulmonary valve (PV), were measured. The aortic valve sinus diameter, interventricular septal thickness at end-diastole (IVSd), left ventricular posterior wall thickness at end-diastole (LVPWd), left ventricular internal diameter in diastole (LVIDd), and left ventricular internal diameter in systole (LVIDs) were recorded. Left ventricular systolic and diastolic function and valve regurgitation were also measured using Doppler echocardiography.

Left ventricular ejection fraction (LVEF) was calculated using the Simpson’s biplane method. In males, the normal LVEF range was 52–72%, mildly abnormal was 41–51%, moderately abnormal was 30–40%, and severely abnormal was less than 30%. In females, the normal range was 54–74%, mildly abnormal was 41–53%, moderately abnormal was 30–40%, and severely abnormal was less than 30%.

LV diastolic dysfunction (LVDD) was measured by mitral valve E velocity divided by A-wave velocity (E/A ratio) and mitral valve E velocity divided by mitral annular c’velocity (average E/e’ ratio), and the normal range was E/A ≥0.8 and E/e’ ratio < 10, grade I was E/A ≤0.8 and E/e’ ratio < 10, grade II was E/A > 0.8 to < 2 and E/e’ ratio 10–14, and grade III was E/A > 2 and E/e’ ratio > 14. Left atrial enlargement (LAE) was defined as a left atrial dimension > 40 mm. Aortic root dilation was defined as an aortic valve sinus diameter > 38 mm in men and > 36 mm in women. Left ventricular mass (LVM) was calculated using the following formula: LVM = 0.8 × [1.04 × {(LVIDd + LVPWd + IVSd)²} - (LVIDd)²] + 0.6 g². The left ventricular mass index (LVMi) was calculated by normalizing the LVM by the body surface area based on Devereux’ formula. Left ventricular hypertrophy (LVH) was defined as an increased left ventricular mass index (LVMi) (≥125 g/m² in men and ≥110 g/m² in women). Concentric LV remodeling was defined as LVMi ≤115 g/m² in men or ≤95 g/m² in women and LV relative wall thickness (RWT) > 0.42. Moderate-to-severe AV regurgitation (AR) was considered to have intermediate-to-large color flow in AR jet width, increment vena contracta width (>3 mm), and a decrease in pressure half-time (<500 ms). Moderate-to-severe TV regurgitation (TR), MV regurgitation (MR), and PV regurgitation (PR) were defined as intermediate-to-large color flows in the TR, MR, and PR jets and dense continuous wave signals of the TR, MR, and PR jets, respectively.

Statistical analyses were performed using IBM SPSS Statistics for Macintosh, ver. 24 (IBM Corp., Armonk, NY, USA). Pearson’s chi-square test was used to analyze factors associated with bothersome nocturia. Univariate and multivariate analyses were performed with logistic regression to evaluate the predictive value of bothersome nocturia on echocardiographic abnormalities after adjusting for sex, age, obesity, hypertension, diabetes mellitus, diuretic use and heart disease. Statistical significance was set at p < 0.05.

Results
A total of 299 patients aged between 20 and 95 years were included in the study, of whom 134 (44.8%) were men and 165 (55.2%) were women. Elderly patients accounted for 70.6%, while patients with obesity accounted for 50.8%. Hypertension was found in 226 (75.6%) patients, and 4 (1.3%) patients had a history of heart diseases, including three with heart failure and one with cardiomyopathy. Bothersome nocturia was reported in 182 patients (60.9%). Regarding echocardiographic abnormalities, 27 (9%) had abnormal LVEF, 10 (3.3%) had grade II-III LV diastolic dysfunction, 109 (36.5%) had LAE, and 85 (28.4%) patients had LVH (Table 1).

Among all patients, those older than 65 years of age were found to have higher occurrences of bothersome nocturia (69.2% vs. 40.9%, p < 0.001). Patients with hypertension (64.2% vs. 50.7%, p = 0.040) and LAE (73.4% vs. 53.7%, p = 0.001) also had higher occurrences of bothersome nocturia. Additionally, there was a tendency for patients with LVH to have higher occurrences of bothersome nocturia with a borderline significance (69.4% vs. 75.5%, p = 0.056) (Table 2).

In elderly patients, the prevalence of bothersome nocturia was not associated with increasing age and the presence of hypertension. Similarly, patients with LAE had higher occurrences of bothersome nocturia (77.9% vs. 63.2%, p = 0.024), and those with LVH tended to have higher occurrences of bothersome nocturia with a borderline significance (77.5% vs. 65.0%, p = 0.064). Furthermore, the prevalence of bothersome nocturia was lower in obese patients compared with that in non-obese patients (58.1% vs. 75.7%, p = 0.038) (Table 2).

On multivariate analysis, in addition to age, sex, obesity, hypertension, diabetes mellitus, use of diuretics and heart disease, we also adjusted for LVH in the evaluation of the predictive value of bothersome nocturia on LAE.
|                      | Patients (N=299) |
|----------------------|-----------------|
|                      | Number | Percentage (%) |
| **Age**              |        |                |
| < 65 years           |     88  | 29.4           |
| ≥ 65 years           |    211  | 70.6           |
| **Sex**              |        |                |
| Male                 |   134  | 44.8           |
| Female               |    165  | 55.2           |
| **BMI**              |        |                |
| < 25                 |    147  | 49.2           |
| ≥ 25                 |    152  | 50.8           |
| **Bothersome nocturia** |    |                |
| Yes                  |    182  | 60.9           |
| No                   |    117  | 39.1           |
| **Hypertension history** |    |                |
| Yes                  |    226  | 75.6           |
| No                   |     73  | 24.4           |
| **Heart disease history** |    |                |
| Yes                  |       4  | 1.3            |
| No                   |    299  | 98.7           |
| **Diuretic usage**   |        |                |
| Yes                  |      17 | 5.7            |
| No                   |   282  | 94.3           |
| **Diabetes mellitus** |        |                |
| Yes                  |    93   | 31.1           |
| No                   |   206   | 68.9           |
| **Aortic root dilation** |     |                |
| Yes                  |     24  | 8              |
| No                   |   275   | 92             |
| **Left atrial enlargement** |     |                |
| Yes                  |     109 | 36.5           |
| No                   |   190   | 63.5           |
| **Left ventricle hypertrophy** |     |                |
| Yes                  |     85  | 28.4           |
| No                   |   214   | 71.6           |
| **Concentric remodeling** |    |                |
| Yes                  |   122   | 40.8           |
| No                   |   177   | 59.2           |
| **Moderate-to-severe AR** |     |                |
| Yes                  |     62  | 20.7           |
| No                   |   237   | 79.3           |
| **Moderate-to-severe TR** |     |                |
| Yes                  |    107  | 35.8           |
| No                   |    192  | 64.2           |
| **Moderate-to-severe MR** |     |                |
| Yes                  |     79  | 26.4           |
| No                   |   220   | 73.6           |
| **Moderate-to-severe PR** |     |                |
| Yes                  |     59  | 19.7           |
| No                   |   240   | 80.3           |
| **Left ventricular ejection fraction** |     |                |
| Abnormal             |      27 | 9              |
| Normal               |   272   | 91             |
| **Left ventricular diastolic dysfunction** |     |                |
| Grade II to III      |     10  | 3.3            |
| Normal or grade 1    |    289  | 96.7           |
| **Stenotic valvular disorder** |     |                |
| Continued            |        |                |
Our study had several limitations. First, we included patients from the cardiology department rather than the general population. The association between bothersome nocturia and echocardiographic abnormalities, especially in those without obvious cardiac symptoms, may be underestimated. Second, although this was a prospective study, we did not analyze the effects of antihypertensive drugs other than diuretics on nocturia. Third, we did not perform prostate ultrasonography to evaluate the size of the prostate gland in male participants, which may also have an impact on the severity of nocturia. Fourth, we did not follow-up with the patients in a cross-sectional study to evaluate the association between nocturia and echocardiographic abnormalities. Fifth,
|                          | All (N = 299) | Elderly patients (N = 211) |
|--------------------------|---------------|---------------------------|
|                          | Non-bothersome nocturia, N(%) | Bothersome nocturia, N(%) | p-value | Non-bothersome Nocturia, N (%) | Bothersome Nocturia, N (%) | p-value |
| **Age ≥ 65**             |               |                           |         |                               |                           |         |
| No                       | 52 (59.1%)    | 36 (40.9%)                | < 0.001 | 52 (33.5%)                    | 103 (66.5%)               | 0.151   |
| Yes                      | 65 (30.8%)    | 146 (69.2%)               |         | 13 (23.2%)                    | 43 (76.8%)                |         |
| **Age ≥ 80**             |               |                           |         |                               |                           |         |
| No                       |               |                           |         |                               |                           |         |
| Yes                      |               |                           |         |                               |                           |         |
| **Sex**                  |               |                           |         |                               |                           |         |
| Male                     | 52 (38.8%)    | 82 (61.2%)                | 0.917   | 24 (27.0%)                    | 65 (73.0%)                | 0.302   |
| Female                   | 65 (39.4%)    | 100 (60.6%)               |         | 41 (33.6%)                    | 81 (66.4%)                |         |
| **Obesity**              |               |                           |         |                               |                           |         |
| No                       | 53 (36.1%)    | 94 (63.9%)                | 0.284   | 26 (24.3%)                    | 81 (75.7%)                | 0.038   |
| Yes                      | 64 (42.1%)    | 88 (57.9%)                |         | 39 (41.9%)                    | 54 (58.1%)                |         |
| **Hypertension history** |               |                           |         |                               |                           |         |
| No                       | 36 (49.3%)    | 37 (50.7%)                | 0.040   | 14 (32.6%)                    | 29 (67.4%)                | 0.780   |
| Yes                      | 81 (35.8%)    | 145 (64.2%)               |         | 51 (30.4%)                    | 117 (69.6%)               |         |
| **Diuretic use**         |               |                           |         |                               |                           |         |
| No                       | 110 (39.0%)   | 172 (61.0%)               | 0.859   | 62 (31.2%)                    | 137 (68.8%)               | 0.759   |
| Yes                      | 71 (41.2%)    | 10 (58.8%)                |         | 21 (50.0%)                    | 16 (50.0%)                |         |
| **Diabetes mellitus history** |             |                           |         |                               |                           |         |
| No                       | 87 (42.2%)    | 119 (57.8%)               | 0.102   | 47 (32.6%)                    | 97 (67.4%)                | 0.398   |
| Yes                      | 30 (25.6%)    | 63 (34.6%)                |         | 18 (26.9%)                    | 49 (73.1%)                |         |
| **Aortic root dilatation** |             |                           |         |                               |                           |         |
| No                       | 104 (37.8%)   | 102 (62.2%)               | 0.116   | 56 (29.0%)                    | 137 (71.0%)               | 0.106   |
| Yes                      | 13 (54.2%)    | 11 (45.8%)                |         | 7 (50.0%)                     | 9 (50.0%)                 |         |
| **Left atrial enlargement** |             |                           |         |                               |                           |         |
| No                       | 88 (46.3%)    | 102 (53.7%)               | 0.001   | 46 (36.8%)                    | 79 (63.2%)                | 0.024   |
| Yes                      | 29 (26.6%)    | 80 (73.4%)                |         | 19 (22.1%)                    | 67 (77.9%)                |         |
| **Left ventricle hypertrophy** |           |                           |         |                               |                           |         |
| No                       | 91 (42.5%)    | 123 (57.5%)               | 0.056   | 49 (35.0%)                    | 91 (65.0%)                | 0.064   |
| Yes                      | 26 (30.6%)    | 59 (69.4%)                |         | 16 (22.5%)                    | 55 (77.5%)                |         |
| **Concentric remodeling** |             |                           |         |                               |                           |         |
| No                       | 74 (41.8%)    | 103 (58.2%)               | 0.253   | 35 (30.7%)                    | 79 (69.3%)                | 0.972   |
| Yes                      | 43 (35.2%)    | 79 (64.8%)                |         | 30 (30.9%)                    | 67 (69.1%)                |         |
| **Moderate-to-severe AR** |             |                           |         |                               |                           |         |
| No                       | 97 (40.9%)    | 140 (59.1%)               | 0.213   | 52 (32.1%)                    | 110 (67.9%)               | 0.459   |
| Yes                      | 20 (32.3%)    | 42 (67.7%)                |         | 13 (26.5%)                    | 36 (73.5%)                |         |
| **Moderate-to-severe TR** |             |                           |         |                               |                           |         |
| No                       | 74 (38.5%)    | 118 (61.5%)               | 0.780   | 36 (28.1%)                    | 92 (71.9%)                | 0.295   |
| Yes                      | 43 (40.2%)    | 64 (59.8%)                |         | 29 (34.9%)                    | 54 (65.1%)                |         |
| **Moderate-to-severe MR** |             |                           |         |                               |                           |         |
| No                       | 89 (40.5%)    | 131 (59.5%)               | 0.434   | 46 (30.7%)                    | 104 (69.3%)               | 0.945   |
| Yes                      | 28 (35.4%)    | 51 (64.6%)                |         | 19 (31.1%)                    | 42 (68.9%)                |         |
| **Moderate-to-severe PR** |             |                           |         |                               |                           |         |
| No                       | 91 (37.9%)    | 149 (62.1%)               | 0.386   | 49 (29.7%)                    | 116 (70.3%)               | 0.509   |
| Yes                      | 26 (44.1%)    | 33 (55.9%)                |         | 16 (34.8%)                    | 30 (65.2%)                |         |
| **LV ejection fraction** |             |                           |         |                               |                           |         |
| Normal                   | 108 (39.7%)   | 164 (60.3%)               | 0.518   | 63 (32.1%)                    | 133 (67.9%)               | 0.156   |
| Abnormal                 | 9 (33.3%)     | 18 (66.7%)                |         | 2 (13.3%)                     | 13 (86.7%)                |         |
| **LV diastolic dysfunction** |           |                           |         |                               |                           |         |
| Normal or grade I        | 114 (39.4%)   | 175 (60.6%)               | 0.745   | 62 (30.8%)                    | 139 (69.2%)               | 1.000   |
| Grade II to III          | 3 (30.0%)     | 7 (70.0%)                 |         | 3 (30.0%)                     | 7 (70.0%)                 |         |

Table 2. Difference in the prevalence of bothersome nocturia among all patients and elderly patients (≥ 65 years). AR aortic valve regurgitation; TR tricuspid valve regurgitation; MR mitral valve regurgitation; PR pulmonary valve regurgitation; LV Left ventricular.
we evaluated LA size using conventional M-mode LA dimension rather than LA volume. Measurement of LA size using conventional M-mode LA dimension is simple and convenient but not reliably accurate, given that the LA is not a symmetrically shaped three-dimensional structure. It is unknown whether treatment of structural heart diseases, such as LAE or LVH, could also improve the severity of nocturia. Nevertheless, the results of this study have important implications. Our results suggest that urologists should refer patients with bothersome nocturia without other significant LUTS to cardiologists to evaluate the presence of structural heart disease, which may be potentially critical to patients.

**Conclusion**

Older age, hypertension, and echocardiographic evidence of LAE are associated with a higher incidence of bothersome nocturia. Furthermore, bothersome nocturia could predict structural heart diseases, including LAE and LVH, in the elderly. Referral to cardiologists should be considered for patients with bothersome nocturia.

**Data availability**

Data utilized in our study are available from the Taipei City Hospital. Based on the “Personal Information Protection Act” in Taiwan, data cannot be made publicly available due to legal restrictions imposed by the government of Taiwan. Requests for data can be sent as a formal proposal to the Institutional Review Board of Taipei City Hospital.

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### Table 3. Multivariate analysis to investigate the predictive value of bothersome nocturia on various echocardiographic abnormalities in all patients and in the elderly (≥65 years) patient groups. AR aortic valve regurgitation; TR tricuspid valve regurgitation; MR mitral valve regurgitation; PR pulmonary valve regurgitation. *Besides adjustment with patients’ age, sex, obesity, hypertension, diabetes mellitus, diuretic use, and, heart disease in other echocardiographic abnormalities, left ventricle hypertrophy was also added to adjust for left atrial enlargement. Significant Values are in bold.*

| Structural heart diseases          | All patients | Elderly patients |
|-----------------------------------|--------------|-----------------|
| Left atrial enlargement           | 2.453 *      | 1.363           |
| Left ventricle hypertrophy        | 1.609        | 0.882           |
| Moderate-to-severe AR             | 1.309        | 0.696           |
| Moderate-to-severe TR             | 0.846        | 0.495           |
| Moderate-to-severe MR             | 1.211        | 0.677           |
| Moderate-to-severe PR             | 0.68         | 0.359           |

| Odds ratio of bothersome nocturia | 95% CI     | p-value | Odds ratio of bothersome nocturia | 95% CI     | p-value |
|-----------------------------------|------------|---------|-----------------------------------|------------|---------|
| Left atrial enlargement           | 2.285 *    | 0.003   | 2.190                            | 0.018      |
| Left ventricle hypertrophy        | 2.056      | 0.121   | 1.900                            | 0.043      |
| Moderate-to-severe AR             | 1.190      | 0.404   | 0.56                             | 0.651      |
| Moderate-to-severe TR             | 0.597      | 0.541   | 0.313                            | 0.119      |
| Moderate-to-severe MR             | 0.943      | 0.519   | 0.478                            | 0.866      |
| Moderate-to-severe PR             | 0.693      | 0.236   | 0.333                            | 0.326      |

| All patients Elderly patients     |            |         | All patients Elderly patients    |            |         |
|-----------------------------------|------------|---------|-----------------------------------|------------|---------|
| Odds ratio of bothersome nocturia |            |         | Odds ratio of bothersome nocturia |            |         |
| Left atrial enlargement           |            |         | 2.285 *                          |            | 0.003   |
| Left ventricle hypertrophy        |            |         | 2.056                            |            | 0.121   |
| Moderate-to-severe AR             |            |         | 1.190                            |            | 0.404   |
| Moderate-to-severe TR             |            |         | 0.597                            |            | 0.541   |
| Moderate-to-severe MR             |            |         | 0.943                            |            | 0.519   |
| Moderate-to-severe PR             |            |         | 0.693                            |            | 0.236   |

Odds ratio of bothersome nocturia 95% CI p-value
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Author contributions
K.W.K. and Y.H.F. conceived and designed the study; C.J.W. and Y.H.F. directed the study including data analysis and interpretation; W.M.C. performed statistical analysis; K.W.K. and W.M.C. wrote the manuscript; Y.H.F. revised it critically for important intellectual content. All authors reviewed the results and approved the final version of the manuscript.

Competing interests
The authors declare no competing interests.

Additional information
Correspondence and requests for materials should be addressed to Y.-H.F.

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