

Relation Between Mitral Valve Prolapse and Erectile Dysfunction (from a Nationwide Case-Control Study)



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Some previous literature indicated an association between cardiovascular diseases and erectile dysfunction (ED). This case-control study purposed to evaluate the association between prior mitral valve prolapse (MVP) and ED using data from the Taiwan National Health Insurance Research Dataset. In this study, 48,755 patients with ED were identified as cases, and 195,020 propensity score-matched patients without ED were selected as controls. Conditional logistic regressions were conducted to evaluate the odds ratios (ORs) for previous MVP between cases and the matched controls. In all sampled patients, 4,565 (1.87%) patients had MVP before the index date. MVP was found in 1,304 (2.67%) cases and in 3,261 (1.67%) matched controls. Patients with ED had a significantly higher occurrence of MVP than the controls. In addition, after propensity score matching, a conditional logistic regression analysis showed that the OR of previous MVP for patients with ED was 1.63 (95% confidence interval [CI] 1.52 to 1.74) compared to the matched controls. The ORs of previous MVP for patients with ED aged ≤ 65 years and those >65 years were 1.68 (95% CI 1.56 to 1.81) and 1.49 (95% CI 1.30 to 1.70), respectively, compared with the matched controls. We found that patients with erectile dysfunction had significantly higher odds of previous MVP compared with matched control subjects without ED regardless of the age group. © 2019 Elsevier Inc. All rights reserved. (Am J Cardiol 2019;124:1590–1593)

Erectile dysfunction (ED) is a prevalent disease which affects up to 50% of men aged 40 to 70 years.¹ This disease is characterized by an inability to maintain and achieve a penile erection sufficient for sexual performance.^{2–4} Patients with ED usually have a poor quality of life and commonly experience anxiety and depression.⁵ ED is recognized as a multifactorial disease. Chronic inflammation and atherosclerosis are thought to play roles in the incidence and development of ED.^{6,7} Additionally, some cardiovascular risk factors, endothelial dysfunction, and subsequent abnormal nitric oxide (NO) release were demonstrated to affect erectile function. Although mitral valve prolapse (MVP) and ED may have similar risk factors and share similar pathophysiological mechanisms, such as endothelial dysfunction, oxidative stress, and inflammation, to date, no previous study has

investigated whether or not MVP is associated with ED. Consequently, this case-control study aimed to evaluate the association between MVP and ED using a large, nationwide dataset in Taiwan.

Methods

This study used data from the Taiwan National Health Insurance (NHI) Research Dataset (NHIRD) which represents over 99% of the Taiwanese population. This database includes all registration files and medical claims data for approximately 23 million enrollees under the NHI program. The NHI program in Taiwan has provided comprehensive medical services for all its residents since 1995. Recently, the NHIRD has enabled investigators to follow the medical services of patients under the Taiwan NHI program for academic purposes. This study was approved by the Institutional Review Board of Taipei Medical University (TMU-JIRB N201801029).

This case-control study included 48,755 patients with ED as cases and 195,020 patients without ED as controls. For ED cases in this retrospective study, we identified 48,884 patients who had received a first-time diagnosis of ED (ICD-9-CM code 607.84) in ambulatory care centers from 1 January 2006 to 31 December 2013. The date of the first diagnosis of ED was defined as the index date. We then excluded those patients under 40 years of age ($n = 129$) because of the low prevalence of ED in that age group. Finally, the remaining 48,755 patients with ED were recruited in this study.

As for the controls without ED, this study attempted to recruit controls from the remaining beneficiaries of the NHIRD. We first excluded all patients who had ever been diagnosed with ED or were aged <40 years. We then

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selected 4 propensity score-matched controls (n = 195,020) per case from the residual beneficiaries of the NHIRD. Propensity score matching is a common strategy to balance the unequal distribution of demographics and health status between a study group and comparison group at the baseline. For the controls, the date of their first utilization of ambulatory care during that matched year was defined as the index date. This study attempted to investigate the association between MVP and ED. Thus, those patients who had ever diagnosed with MVP (ICD-9-CM code 424.0) were identified as MVP cases. Patients who underwent presurgery or with healed mitral regurgitation were still included in this study. Additionally, this case-control study only involved patients who had received a diagnosis of MVP previous to the index date.

All analyses in this population-based study were performed using the SAS system (SAS System for Windows, vs 9.4, SAS Institute, Cary, North Carolina). This study first used the Chi-squared test to compare differences in monthly income (<NT\$15,841, 15,841 to 25,000, \geq 25,001), geographic location (northern, central, eastern, and southern Taiwan), urbanization level (5 levels, with 1 being the most urbanized and 5 being the least), hypertension, hyperlipidemia, diabetes, coronary heart disease, and alcohol abuse between patients with ED and their matched controls without ED. In addition, conditional logistic regressions were conducted to evaluate the odds ratios (ORs) for previous MVP occurrence between patients with ED and the propensity score-matched controls without ED. The conventional $p < 0.05$ was used to estimate the statistical significance in this nationwide study.

Results

This population-based case-control study recruited 48,755 patients with ED as cases and 195,020 propensity score-matched patients without ED as controls. The mean ages of the cases and their matched controls were both 55 ± 9.7 years ($p > 0.999$). Demographic characteristics and co-morbidities of patients with and those without ED are presented in Table 1. After matching for the propensity score, there were no significant differences in monthly income, geographic region, urbanization level, hypertension, hyperlipidemia, diabetes, coronary heart disease, or alcohol abuse between patients with ED and matched controls without ED (all $p > 0.999$).

Table 2 first shows the prevalence of MVP in sampled patients. It reveals that 4,565 (1.87%) in all sampled patients had MVP before the index date. MVP was found in 1,304 (2.67%) cases and in 3,261 (1.67%) matched controls ($p < 0.001$). Patients with ED had a significantly higher occurrence of MVP than the controls. In addition, after propensity score matching, a conditional logistic regression analysis showed that the OR of previous MVP for cases was 1.63 (95% confidence interval 1.52 to 1.74) compared with the matched controls.

Additionally, Table 3 shows the prevalence, ORs, and 95% confidence interval for MVP occurrence in sampled patients according to age group. This study found that ED was associated with previous MVP in patients aged ≤ 65 years and those > 65 years. The OR of previous MVP in patients with ED aged ≤ 65 years was 1.68 compared with the controls. Furthermore, the OR of previous MVP in

Table 1

Demographic characteristics and comorbidities of patients with erectile dysfunction and controls in Taiwan (n = 243,775)

Variable	Patients with erectile dysfunction (n = 48,755)	Controls (n = 195,020)	p Value
Age group (years)			>0.999
40 to 50	17,700 (36.3%)	70,800 (36.3%)	
51 to 60	18,288 (37.5%)	73,152 (37.5%)	
61 to 70	9082 (18.6%)	36,328 (18.6%)	
71 to 80	3091 (6.3%)	12,364 (6.3%)	
>80	594 (1.2%)	2376 (1.2%)	
Monthly income			>0.999
\leq NT\$15,840	10,522 (21.6%)	42,088 (21.6%)	
NT\$15,841 to 25,000	14,596 (29.9%)	58,384 (29.9%)	
\geq NT\$25,001	23,637 (48.5%)	94,548 (48.5%)	
Geographic region			>0.999
Northern	26,424 (54.2%)	105,696 (54.2%)	
Central	10,803 (22.2%)	43,212 (22.2%)	
Southern	11,093 (22.8%)	44,372 (22.8%)	
Eastern	435 (0.9%)	1740 (0.9%)	
Urbanization level			>0.999
1 (most urbanized)	16,383 (33.6%)	65,532 (33.6%)	
2	14,607 (30.0%)	58,428 (30.0%)	
3	7110 (14.6%)	28,440 (14.6%)	
4	5666 (11.6%)	22,664 (11.6%)	
5 (least urbanized)	4989 (10.2%)	19,956 (10.2%)	
Comorbidities			
Hypertension	16,816 (34.5%)	67,264 (34.5%)	>0.999
Hyperlipidemia	10,807 (22.2%)	43,228 (22.2%)	>0.999
Diabetes mellitus	8882 (18.2%)	35,528 (18.2%)	>0.999
Coronary heart disease	3663 (7.5%)	14,652 (7.5%)	>0.999
Alcohol abuse	27 (0.1%)	108 (0.1%)	>0.999

The average exchange rate in 2012 was US\$1 \approx New Taiwan (NT) \$30.

patients with ED aged > 65 years was 1.49 higher than the matched controls.

Discussion

This case-control study observed that patients with ED were likely to have had previous MVP than those propensity score matched-controls without ED regardless of the age group. Previous research showed that cardiovascular diseases and certain risk factors were related to the occurrence and development of ED.^{6,8-11} Nevertheless, even if MVP is a common cardiac disease worldwide and both ED and MVP share similar pathophysiology, no epidemiological studies have attempted to ascertain the association between previous MVP and ED.

This study found a positive association between previous MVP and ED. This observation is consistent with many previous studies that attempted to explore relations between cardiovascular risk factors and ED.¹²⁻¹⁵ For instance, one cross-sectional study which included 2,126 males in the National Health and Nutrition Examination Survey found that patients with ED had a greater prevalence of cardiovascular risk factors, hypercholesterolemia, cardiovascular disease, etc. compared with those males without ED.¹² Another study in Europe also reported that cardiac problems and circulatory problems were associated with ED.¹³ However, to date, the genuine association between previous MVP and ED is still unclear.

Table 2
Prevalence, odds ratios (ORs), and 95% confidence intervals (CIs) for mitral valve prolapse

Variable	Total (n = 243,775)	Patients with erectile dysfunction (n = 48,755)	Controls (n = 195,020)
Mitral valve prolapse occurrence			
Yes	4565 (1.87%)	1304 (2.67%)	3261 (1.67%)
No	239,210 (98.13%)	47,451 (97.33%)	191,759 (98.33%)
OR (95% CI)		1.63* (1.52~1.74)	1.00

* p < 0.001.

Table 3
Prevalence, odds ratios (ORs), and 95% confidence intervals (CIs) for mitral valve prolapse occurrence among sampled patients according to age group

Variable	≤65 years (n = 204,280)		>65 years (n = 39,495)	
	Patients with erectile dysfunction (n = 40,856)	Controls (n = 163,424)	Patients with erectile dysfunction (n = 7,899)	Control group (n = 31,596)
Mitral valve prolapse occurrence				
Yes	989 (2.4%)	2397 (1.5%)	315 (4.0%)	864 (2.7%)
No	39,867 (97.6%)	161,027 (98.5%)	7584 (96.0%)	30,732 (97.3%)
OR (95% CI)	1.68* (1.56~1.81)	1.00	1.49* (1.30~1.70)	1.00

* p < 0.001.

The connection between previous MVP and ED in this study might be related to their pathophysiological mechanisms. Recently, many investigators recognized that some biological pathways and vascular pathogenesis play important roles in the occurrence and development of ED.^{5,7,10,16–18} First, previous studies previously demonstrated the role of endothelial dysfunction in ED physiology.¹⁶ In general, chronic inflammation and abnormal oxidative stress can both lead to the impairment of endothelial function.¹⁰ The reduced production of NO due to endothelial dysfunction can affect the functions of smooth muscle, influence the penile arterial system, and further contribute to the incidence of ED.^{7,17} Second, previous research showed that arterial insufficiency or arterial stenosis, caused by atherosclerosis, might reduce blood flow during an erection and further contribute to the occurrence of ED.^{5,18} According to the previous literature, as for ED, the relevant data displayed a complex interplay in endothelial dysfunction, oxidative stress, inflammation, and vascular processes.¹⁴

To date, the definite pathophysiological pathway for MVP is still uncertain. However, many studies revealed that MVP might be a multifactorial disease.¹⁹ In addition, endothelial dysfunction and oxidative stress are potentially involved in the process of MVP.^{19,20} One previous study indicated that endothelial dysfunction may be associated with the early development of valve disease and regurgitation, because abnormal NO release and endothelial NO synthase expression were related to early local alterations in mitral valves.²¹ MVP is recognized as a common cardiovascular disease that can affect patients' blood flow and circulation.²² Consequently, it is plausible that MVP may be an important risk factor for ED, because these 2 diseases might share similar biological and vascular pathogenesis.

The unique strength of our study is the use of a longitudinal, nationwide database in Taiwan. First, the NHIRD is representative of the entire Taiwanese population, and this feature provided an adequate sample size and statistical power. Second, the use of this database could eliminate the potential impact of selection bias inherent in community-based studies.

Third, characteristics of the NHIRD could also avoid recall bias. Fourth, this study used propensity score matching to select patients without ED as controls. This strategy could have decreased the potential confounding effects due to demographics and some risk factors. Last, most residents in Taiwan are of Chinese Han ethnicity. Therefore, the homogeneous population used in this study could decrease the influence of ethnicity.

Nevertheless, several limitations should be considered in this study. First, we did not consider smoking status, body-mass index, physical activity, or medications in this study. These factors might affect the connection between previous MVP and ED. Second, even though the NHIRD is a nationwide database, it might not include all patients with MVP or ED in Taiwan. This is because several patients with mild symptoms of MVP or ED might not be aware of being affected by these 2 diseases. Thus, they might not immediately seek medical services. Third, the database used in this study provides no information regarding the study cohorts' perception of the MVP or ED. In addition, there was no record regarding the MVP severity and MVP types. Therefore, further studies should be carried out to investigate the relevant issues. Finally, generalization of the relevant findings to other ethnicities was not demonstrated in this study, because most patients involved in this case-control study were of Chinese ethnicity.

In conclusion, this population-based case-control study highlighted that ED was associated with previous MVP regardless of the age group.

Disclosures

The authors have no conflicts of interest to disclose.

Supplementary materials

Supplementary material associated with this article can be found in the online version at <https://doi.org/10.1016/j.amjcard.2019.08.010>.

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