Research Article

The gender difference of utilization of cardiac implantable electronic device in China: data from Arrhythmia Interventional Therapy Data Registry

Ruo-Han CHEN1, Ke-Ping CHEN1, Wei HUA1, Jing XU2, Lin CHEN3, Yang-Gang SU4, Xi SU5, Jian-Gang ZOU6, Ji YAN7, Jing-Feng WANG8, Bao-Peng TANG9, Mei-Xiang XIANG10, Shu ZHANG1

1Center of Arrhythmia, Fuwai Hospital, Chinese Academy of Medical Sciences, Peking union Medical College, Beijing, China
2Department of Cardiology, Tian Jing Chest Hospital, Tianjing, China
3Department of Cardiology, FuJian Provincial Hospital, Fuzhou, China
4Department of Cardiology, ZhongShan Hospital, FuDang University, Shanghai, China
5Department of Cardiology, WuHan Asia Cardiology Hospital, Wuhan, China
6Department of Cardiology, the First Affiliated Hospital of Nanjing Medical University, NanJing, China
7Department of Cardiology, AnHui Provincial Hospital, Hefei, China
8Department of Cardiology, the First Affiliated Hospital of XinJiang Medical University, Urumichi, China
9Department of Cardiology, the Second Affiliated Hospital of ZheJiang University of School of Medical, Hangzhou, China

Abstract

Background Cardiac implantable electronic devices (CIEDs) greatly improve survival and life quality of patients. However, there are gender differences regarding both the utilization and benefit of these devices. In this prospective CIED registry, we aim to appraise the gender differences in CIED utilization in China. Methods Twenty centers from 14 provinces in China were included in our registry study. All patients who underwent a CIED implantation in these twenty centers between Jan 2015 and Dec 2016 were included. Results A total of 8570 patients were enrolled in the baseline cohort, including 7203 pacemaker, 664 implantable cardiac defibrillators (ICD) implants and 703 cardiac resynchronization therapy device (CRT/D). Totally, 4117 (48.0%) CIED patients were female, and more than 59% pacemaker patients were female, but women account only one third of ICD or CRT/D implantation in this registry. There were significant differences between genders at pacemaker and ICD indications. Female was more likely received a pacemaker due to sick sinus syndrome (SSS) (63.9% vs. 51.0%, P < 0.001). Female patients receiving an ICD were more likely due to cardiac ion channel disease (29.2% vs. 4.2%, P < 0.001). The percentage of utilization of dual-chamber pacemaker in female patients was significantly higher than male (85.3% vs. 81.1%, P < 0.001). But male patients were more likely received a cardiac resynchronization therapy devices with defibrillator than female (56.5% vs. 41.9%, P = 0.001). In pacemaker patient, male was more likely to have structure heart disease (31.3% vs. 28.0%, P = 0.002). In ICD patient, male patients were more likely to have ischemic heart disease (48.2% vs. 29.2%, P < 0.001). The mean age of women at the time of CRT/D implantation was older than men (P = 0.014). Nonischemic cardiomyopathy (70.9%) was the most common etiology in the patients who underwent the treatment of CRT/D, no matter male or female. Conclusions In real-world setting, female do have different epidemiology, pathophysiology and clinical presentation of many cardiac rhythm disorders when compared with male, and all these factors may affect the utilization of CIED implantation. But it also possibility that cultural and socioeconomic features may play a role in this apparent discrimination.

Keywords: Cardiac implantable electronic devices; Gender; Registry

1 Background

The use of cardiac implantable electronic devices (CIEDs) has greatly increased in the past ten years in China, as techniques advance and age of the population increased. The professional societies have issued several guidelines for CIED. However, these guidelines have often been derived from large clinic trials which enrolled predominantly males. Whether or not they are also suitable for the female patients is unknown as the gender differences in heart rhythm diseases and CIEDs usage have been increasingly recognized. Post-hoc meta-analysis indicated that women with mild heart failure (HF), left bundle branch block (LBBB), and a QRS duration of 130–149 ms benefited more from cardiac implantation. However, these guidelines have often been derived from large clinic trials which enrolled predominantly males. Whether or not they are also suitable for the female patients is unknown as the gender differences in heart rhythm diseases and CIEDs usage have been increasingly recognized.

Correspondence to: Ke-Ping CHEN, MD, PhD, Center of Arrhythmia Diagnosis and Treatment, Fuwai Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100037, China. E-mail: chenkeping@263.net

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resynchronization therapy (CRT) than men with similar ECG and clinical findings. On the other hand, it has become evident that female is associated with an increased risk of acute complications during primary cardiac device implantation, irrespective of age or type of device implanted. However, very little is known about the gender effects on CIED used in China. The purposed of the current registry study was to systematically evaluate the effects of gender variations on CIED implantation.

2 Methods

2.1 Data sources

Data was from National Arrhythmic Intervention Therapy Registry, which is based on a unified database developed by the national cardiovascular disease center. Information consists of implantation and follow-up data of CIED. Collected data are regularly checked for internal consistency by the Registry administrator, and online statistics are updated on a daily basis.

This registry is sponsored by Key Projects in the National Science & Technology Pillar Program during the Twelfth Five-year Plan Period (2011BAII 1802). The registry is intended to identify the gender difference in CIED usage in nowadays China.

2.2 Study population

Twenty centers from 14 provinces whose CIED implantation amount were among the top 20 in 2014 in China have contributed to this registry study. All patients implanted with a CIED including pacemaker, implantable cardiac defibrillators (ICD) and cardiac resynchronization therapy device (CRT/D) in above centers between Jan 2015 and Dec 2016 were included. Informed consent for data entry was required by the ethics committee of each participating hospital.

2.3 Baseline data collection

Individual patient data are collected and the following variables are monitored in the registry: number of CIEDs, including pacemakers, ICDs and CRT/D, implanted or replaced per center, patient demographics (i.e., age and gender), clinical indications, underlying structure heart disease, etiology of cardiomyopathy, New York Heart Association (NYHA) classification, prophylactic therapy of sudden cardiac death (SCD), ultrasound data, perioperative and postoperative complications (including infection, pneumothorax, perforation, hematoma and dislodgment), and technical information on generators and leads (manufacturer, model, lead parameters). Information regarding insurance type was also reported.

2.4 Data analysis

Categorical variables are reported as number and percentages, the continuous variables as mean values and standard deviations. Groups were compared with the chi-square test for discrete variables and the Mann-Whitney U test for continuous variables with non-normal distributions. All statistical tests were 2-sided, and a P value less than 0.05 were considered as statistically significant.

3 Results

A total of 8570 patients were enrolled in the baseline cohort, including 7203 pacemaker, 664 ICD implants and 703 CRT/D. 4117 (49.0%) patients were female.

3.1 Pacemaker

The mean age of the pacemaker patients was 68.0 ± 13.0 years, 3695 were female (51.3%), and 3508 were male (48.7%). The mean age of female patients at the time of implantation was 67.5 ± 12.8 years, and male was 68.3 ± 13.6 years (P = 0.021). There were significant differences between genders at pacing indications: atrioventricular block (AVB) and permanent atrial fibrillation were less prevalent (40.3% vs. 30.1%, 13.5% vs. 9.1%, P < 0.001) and sick sinus syndrome was more prevalent (63.9% vs. 51.0%, P < 0.001) in female than male. Likewise, underlying structural heart disease was less frequent among female (28.0% vs. 31.3%, P = 0.002). Females received significantly more dual-chamber pacemaker than male (85.3% vs. 81.1%, P < 0.001), while male received more remote monitoring devices (5.5% vs. 3.0%, P < 0.001). The percentage of rate adaptive pacemaker usage was high in whole population, 78.8% and 77.6% in male and female patients, respectively (P = 0.231) (Table 1).

3.2 ICD

A total of 664 patients were included in the baseline cohort, of whom 180 (27.1%) was female. The mean age was 56.8 ± 14.2 years and 55.6 ± 16.6 years for male and female (P = 0.43). Totally, 65.5% patients implanted ICD due to secondary prevention of SCD, 64.1% and 69.1% for male and female patients, respectively (P = 0.43). Totally, 65.5% patients implanted ICD due to secondary prevention of SCD, 64.1% and 69.1% for male and female patients, respectively (P = 0.285). As far as the type of ICD is concerned, 70.5% male and 67.2% female implanted a single-chamber ICD, there was no significant difference between genders (P = 0.448). Compared with male patients, female patients suffered ventricular tachycardia (VT) or ventricular fibrillation (VF) more likely due to car-
diac ion channel disease (29.2% vs. 4.2%, P < 0.001), less likely to have ischemic heart disease (29.2% vs. 48.2%, P < 0.001). Female patients do had better heart function, including smaller left ventricular end diastolic dimension (LVEDD), better left ventricular ejection friction (LVEF) and higher percentage of NYHA I grade (Table 2).

3.3 CRT/D

Among 703 CRT/D patients, 242 were female (34.4%), and 461 were male (65.6%). The mean age of female patients at the time of implantation was 63.3 ± 9.2 years, male was 61.2 ± 11.3 years (P = 0.014). Non-ischemic cardiomyopathy (70.9%) was the most common etiology that underlying the treatment of CRT/D, no matter male or female (69.1% vs. 74.3%, P = 0.328). There was no significant difference between male and female patients in QRS duration [166.2 ± 36.1 vs. 162.6 ± 30.0 ms, P = 0.198], NYHA heart function grade (P = 0.645) and LVEF (34.7% ± 11.3% vs. 36.5% ± 11.7%, P = 0.083), but LVEDD was small in female than in male (63.7 ± 11.1 vs. 69.0 ± 11.2 mm, P < 0.001). More male patients received CRTD therapy than female (56.5% vs. 41.9%, P = 0.001). The usage of beta-blockers, ACEI/ARB and Aldactone in CRT/D patients were 53.6%, 69% and 88.1%, there was no significant different between genders. Male were more likely prescribed Statins (Table 3).

Table 2. The characteristics of pacemaker patient.

|                | Male, n = 3508 | Female, n = 3695 | P value |
|----------------|---------------|-----------------|---------|
| Pacing indication |               |                 |         |
| SSS            | 1790 (51.0%)  | 2360 (63.9%)    | 0.000   |
| AVB            | 1414 (40.3%)  | 1111 (30.1%)    | 0.000   |
| Chronic AF     | 475 (13.5%)   | 337 (9.1%)      | 0.000   |
| Other          | 48 (1.4%)     | 58 (1.6%)       | 0.495   |
| Structural heart disease | 1098 (31.3%) | 1034 (28.0%) | 0.002   |
| Type of PM     |               |                 | 0.000   |
| Single-chamber  | 663 (18.9%)   | 544 (14.7%)     |         |
| Dual-chamber    | 2845 (81.1%)  | 3151 (85.3%)    |         |
| Rate adaptive PM | 2764 (78.8%) | 2868 (77.6%)    | 0.231   |
| Remote monitor PM | 193     | 110             | 0.000   |

Data are presented as mean ± SD or n (%). AF: atrial fibrillation; AVB: atrial ventricular block; PM: pacemaker; SSS: sick sinus syndrome.

Table 3. The characteristics of CRT/D patient.

|                | Male, n = 461 | Female, n = 242 | P value |
|----------------|---------------|-----------------|---------|
| Mean age, yrs  | 61.2 ± 11.3   | 63.3 ± 9.2      | 0.014   |
| Etiology       |               |                 | 0.326   |
| Ischemia cardiomyopathy | 142 (30.9%) | 62 (25.7%)      |         |
| Non-ischemia cardiomyopathy | 318 (69.1%) | 179 (74.3%)    |         |
| QRS duration, ms | 166.2 ± 36.1 | 162.6 ± 30.0    | 0.198   |
| LVEDD, mm      | 69.0 ± 11.2   | 63.8 ± 11.1     | 0.000   |
| LVEF           | 34.7% ± 11.3% | 36.5% ± 11.7%   | 0.083   |
| NYHA class     |               |                 | 0.645   |
| I              | 22 (4.8%)     | 10 (4.1%)       | 0.849   |
| II             | 103 (22.3%)   | 55 (22.8%)      | 0.924   |
| III            | 295 (64.0%)   | 158 (65.6%)     | 0.740   |
| IV             | 41 (8.9%)     | 18 (7.5%)       | 0.569   |
| CRT type       |               |                 | 0.001   |
| CRT/P          | 199 (43.5%)   | 140 (58.1%)     |         |
| CRT/D          | 258 (56.5%)   | 101 (41.9%)     |         |
| Medications    |               |                 | 0.144   |
| Beta-blockers  | 164 (55.0%)   | 89 (51.1%)      | 0.188   |
| ACEI/ARB       | 213 (71.5%)   | 113 (64.9%)     | 0.105   |
| Aldactone      | 259 (86.9%)   | 157 (90.2%)     | 0.084   |
| Diuretics      | 254 (85.2%)   | 151 (86.8%)     | 0.162   |
| Digoxin        | 174 (58.4%)   | 94 (54.0%)      | 0.252   |
| Statin         | 56 (18.8%)    | 18 (10.3%)      | 0.038   |

Data are presented as mean ± SD or n (%). ACEI: angiotensin-converting enzyme inhibitors; ARB: angiotensin receptor blocker; CRT: cardiac resynchronization therapy; CRT/D: cardiac resynchronization therapy-defibrillator; CRT/P: cardiac resynchronization therapy-pacemaker; LVEDD: left ventricular end diastolic diameter; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association.
4 Discussion

Our data showed there was large difference between genders in CIEDs utilization, including underlying heart disease, implantation indication and device choices. These phenomena, some could be explained by the gender difference of eletrophysiological properties, some is more complicated, cultural and socioeconomic features may also play a role in this apparent discrimination.

4.1 Pacemaker

Our data showed significant differences for pacemaker indication and device selection between both genders. Concerning pacing indications, females have a lower incidence of atrioventricular block and higher incidence of sinus node dysfunction as primary pacing indication, compared with males. This distribution can be found in previous studies as well.[2-4] The underlying mechanism is unclear. This gender disparity could be explained to some extent by the effects of sex hormones on autonomic tone modification and on the electrophysiological properties of the myocardial cell.

Many clinic trials have shown that the DDD (dual-chamber pacing) is better than VVI (single-chamber ventricular pacing) in reducing the HF and atrial fibrillation events. Rate adaptive pacing could increase the pacing rate according to metabolism, it is more physiological. Nowadays, more than 80% patients underwent a dual-chamber pacemaker implantation, more than 75% devices has rate adaptive function in China. In our study, more women were implanted a dual-chamber pacemakers, this may be because the lower percentage of persistent AF in women in this registry. But no sex difference in the selection of rate adaptive pacemaker was demonstrated in this study.

4.2 ICDs

ICDs reduce mortality in patients resuscitated from malignant ventricular arrhythmias.[5,6] There is also evidence that these devices are useful for the primary prevention of SCD in patients with reduced LVEF.[7-9] In our study, more than two thirds patients implanted an ICD due to secondary prevention, no significant difference between male and female.

In our study, women were less prone to ventricular arrhythmias except ion channel disease including long-QT syndrome and Idiopathic ventricular fibrillation. Men were more likely implanted ICD due to ischemia cardiomyopathy. Women have better heart function than men, the percentage of NYHA I grade was higher and LVEDD and LVEF were better in women than in men. These were similar as the previous researches. In both congenital[10] and acquired[11]LQTS, a female predominance has been reported. Furthermore, among patients with LQTS, female gender is well recognized as an independent risk factor for sudden cardiac death, irrespective of the presence of underlying CAD, electrolyte imbalance, level of QTc at baseline, or prescribed medications.[12] In idiopathic VT, it has been reported that a higher prevalence of life-threatening arrhythmias in women, such as VF.[13] But in patients of coronary artery disease, VT or VF is less inducible in women despite similar ejection fractions, number of diseased coronary arteries and history of myocardial infarction.[14] These founding could not be merely explained by the gender differences in SCD substrates and mechanisms. The gender difference in susceptibility to ventricular arrhythmia under difference pathophysiological situation may also play a role.

4.3 CRT/D

Our study found that the only 34.4% patients implanted CRT/D were female. Meanwhile, the percentage of CRT/D was much less in female than in male. Clinical trials and observational studies also demonstrate a significant gender disparity in utilization of CRT: less than one-third of CRT device recipients are women.[15-18] Data regarding gender-related differences in outcomes after CRT demonstrate women seem have a greater clinical benefit from CRT than men.[19,20] Although nonischemic HF is more frequent in women, which is associated with a better prognosis.[21] The mechanisms behind the more favorable response of women to CRT could not be merely explained by the influence HF etiology on prognosis, cause these gender differences persist even when comparing nonischemic female and male subgroup.[20,21] In our study, nonischemic cardiomyopathy was the most common etiology among the patient underlying CRT/D treatment, no matter male or female. But the percentage of ischemic cardiomyopathy is higher in male than in female, this may be could explained why the Statin prescription is more common in male than in female in this study.

4.4 Gender difference in utilization

Despite expanding indications and a clear survival benefit in patients at risk, the gender disparities in the CIEDs’ utilization remain. Our study showed the ratio between male and female in pacemaker patient is about 1:1, but female is three times less likely to receive a CRT/D compared with men. Previously study showed female made up > 50% of patients with HF,[22] and had a greater clinical benefit from CRT/D than men,[23,24] but female patients account only one third of CRT/D implantation no matter in clinic trials but also in the real-world registry. Why are women less likely to receive a more sophisticated device? A longer time to diagnosis, later referral for invasive procedures, difficulty access to specialized implanting physicians also may be partly...
responsible for these phenomena. A selection bias by implanting physicians due to somewhat the smaller body size with a more challenging implantation in female may also play a role. Additionally, women may be more reluctant to a device therapy at all, when compared with men.

This study lies in the source of the data that were obtained through the National Arrhythmic Interventional Therapy Data Registry, evaluating a large cohort of patients taken from the real world of clinical practice, and not from trials that collect patients who fulfill only selected criteria. Our study found out the gender difference in CIED clinic usage in China. Female share the same opportunity in routinely pacing for bradycardia, but there is great discrimination in sophisticated device for the treatment of SCD and HF. Gender exerts a profound influence on the epidemiology, pathophysiology and clinical presentation of many cardiac rhythm disorders, and all these factors may affect the outcome of invasive electrophysiological procedures. But it also possibility can’t be ruled out that cultural and socioeconomic features may play a role in this apparent discrimination.

4.5 Limitations

The study was conceived as a descriptive report of data collected by the Chinese National arrhythmia interventional therapy data registry system. A systematic analysis of factors potentially influencing global and regional implantation rates was out of the aim of this report and needs to be investigated further.

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