According to the ruling of the Medical Sciences Publications Commission No. 14313-80/10/1 and 36914-85/2/10 signed by the Minister of Health and Medical Education and the Head of the Medical Sciences Publications Commission of the Islamic Republic of Iran, this journal has been granted accreditation as a scientific-research journal.

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EDITORIAL

In the Name of God, the Most Beneficent, the Most Merciful

Dear colleagues and friends,

We are delighted to present to you Volume 20, Number 2 (2019) issue of the *Iranian Heart Journal*, which contains some interesting new studies and case reports in the domains of cardiovascular medicine and surgery from our colleagues across Iran.

*The Iranian Heart Journal* is indexed in the Scientific Information Database ([WWW.SID.IR](http://WWW.SID.IR)), IMEMR, Index Copernicus, Scopus, and CINAHL, thereby facilitating access to published literature. There is no doubt, however, that our journal needs your opinions, ideas, and constructive criticism in order to accomplish its main objective of disseminating cutting-edge medical knowledge.

As ever before, we continue to look forward to receiving your latest research and cases.

Yours truly,

*A. Hussein Tabatabaei, MD* 
Editor-in-Chief,  
*Iranian Heart Journal*

*F. Noohi, MD*  
Chairman,  
*Iranian Heart Journal*
<table>
<thead>
<tr>
<th>ORIGINAL ARTICLES: CLINICAL SCIENCE</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effects of Adding Papaverine for the Local Anesthesia of the Access Site</td>
<td>6-12</td>
</tr>
<tr>
<td>for Cardiac Catheterization</td>
<td></td>
</tr>
<tr>
<td>Amirhossein Yazdi; Ali Zahed Mehr; Ehsan Khalilipur</td>
<td></td>
</tr>
<tr>
<td>Evaluation of Gender Differences in Response to Cardiac Resynchronization</td>
<td>13-20</td>
</tr>
<tr>
<td>Therapy in a Single Heart Center</td>
<td></td>
</tr>
<tr>
<td>Shabnam Madadi; Leili Mohimi; Majid Haghjoo; Amir Farjam Fazelifar;</td>
<td></td>
</tr>
<tr>
<td>Abolfath Alizadeh; Zahra Emkanjo</td>
<td></td>
</tr>
<tr>
<td>Malnutrition and Nosocomial Infection After Pediatric Cardiac Surgery</td>
<td>21-27</td>
</tr>
<tr>
<td>Maryam Aryafar; Masoumeh Rostami; Behshid Ghadrdoost</td>
<td></td>
</tr>
<tr>
<td>Prevalence of Hepatitis C Virus Infection Among Patients With Cardiovascular Disorders in a University Hospital in Iran from March 2015 to September 2016</td>
<td>28-31</td>
</tr>
<tr>
<td>Hadi Khalaj; Kambiz Mozaffari; Nozar Givtag; Abbas Zavvarei; Nejat Mahdie</td>
<td></td>
</tr>
<tr>
<td>Evaluation of the Effects of Prazosin on Resistant Diastolic Hypertension</td>
<td>32-39</td>
</tr>
<tr>
<td>With a Focus on Sex Difference</td>
<td></td>
</tr>
<tr>
<td>Hakimeh Saadatifar; Fahimeh Khoshhal Dehdar; Maryam Moshkani Farahani;</td>
<td></td>
</tr>
<tr>
<td>Mahmoud Salesi; Samira Saadatifar</td>
<td></td>
</tr>
<tr>
<td>Evaluation of Cardiac Magnetic Resonance Imaging in Heart Failure Patients</td>
<td>40-46</td>
</tr>
<tr>
<td>Suspected of Hypertensive Cardiomyopathy in Rajaie Cardiovascular, Medical,</td>
<td></td>
</tr>
<tr>
<td>and Research Center Between 2015 and 2017</td>
<td></td>
</tr>
<tr>
<td>Sepideh Taghavi; Zahra Alizadeh Sani; Mohammad Kasaii; Mohammad Keshavarz;</td>
<td></td>
</tr>
<tr>
<td>Nasim Naderi; Ahmad Amin; Maryam Chenaghilou; Mahbobeh Abshirini; Farane</td>
<td></td>
</tr>
<tr>
<td>Loghmani</td>
<td></td>
</tr>
<tr>
<td>Impact of Hypertension on the Phase Analysis Parameters of Gated Single-Photon Emission Computed Tomography Myocardial Perfusion Imaging</td>
<td>47-55</td>
</tr>
<tr>
<td>Nahid Yaghoobi; Zahra Jamshidi Araghi; Hadi Malek; Hasan Firoozabadi;</td>
<td></td>
</tr>
<tr>
<td>Fereydoon Rastgou; Hooman Bakhshande; Ahmad Bitarafan Rajabi</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal Complications After Cardiac Surgery</td>
<td>56-61</td>
</tr>
<tr>
<td>Mohamad Golitaleb; Farzaneh Golaghaie; Masomeh Sadat mousavi; Mehdi Harorani; Homan Bakhshande Abkenar; Mehrdad Haghazali; Arshideh Mashayekh</td>
<td></td>
</tr>
</tbody>
</table>
### CONTENTS:

#### ORIGINAL ARTICLES: CLINICAL SCIENCE

- **Diagnostic Myocardial Perfusion Imaging to Detect the Anatomical Location of Coronary Artery Disease Compared With Invasive Coronary Angiography**
  Ramin Eskandari; KhaterEH Azarpira; Borzou Rashidi; Sepideh Emami; Maryam Mehrpouya; Kamal Khademvatani; Yousef Rezaei
  
  62-68

- **Comparison of the Results of Left Ventricular Epicardial and Endocardial Pacing Through the Coronary Sinus in Patients With Triple-Chamber Pacing**
  Aboalfath Alizadeh; Ehsan Ghouchian; Sajad Naderi; Mohammadesmaeil Zanganehfar; Ali Ghasemi; Najand Salek; Sara Baramaki
  
  69-74

- **Impact of Obstructive Sleep Apnea on Cardiac Troponin I: Comparisons of the Effects of Nasal O2 and Positive Airway Pressure on this Biomarker**
  Atoosa Mostafavi; Khosro Sadeghniiat-Haghighi; Seyed Abdol Hussein Tabatabaei
  
  75-80

#### CASE REPORT

- **Multiple Ruptured Chordae in an Amphetamine-Addicted Woman: A Rare Manifestation of Illicit Drugs**
  Azin Alizadehasl; Behshid Ghadrdoost; Ahmad Amin; Mohaddeseh Behjati
  
  81-84

#### INSTRUCTIONS FOR AUTHORS

  85-87

#### FORTHCOMING MEETINGS

  88-92

#### SUBSCRIPTION FORM

  93-94
Original Article

Effects of Adding Papaverine for the Local Anesthesia of the Access Site in the Transradial Approach for Cardiac Catheterization

Amirhossein Yazdi¹, MD; Ali Zahed Mehr², MD; Ehsan Khalilipur*³, MD

ABSTRACT

Background: Transradial coronary arteriography has been developed as the first method of choice for interventional procedures in many centers, and its feasibility and safety contribute to its popularity. Gaining access is the main step in radial artery arteriography. We sought to evaluate the efficacy of the preprocedural administration of papaverine in diminishing arteriography complications.

Methods: A total of 120 patients were enrolled in the present study. The study population was divided into 2 equal groups of 60 patients. One group was catheterized with the preprocedural administration of papaverine, and the other group was administered traditional TNG. The groups were thereafter compared in terms of the administration of papaverine versus traditional TNG.

Results: No significant difference was observed between the 2 groups concerning failure to gain radial access. There was a significant difference in the time to gain access (P=0.016) and in the number of tries to gain access (P=0.007) between the study groups, and both of these values were lower in the papaverine group. Subgroup analysis revealed that the time to gain access was significantly lower in the male patients (P=0.035), younger patients (P=0.008), and smokers (P=0.043). There was also a significant difference in favor of the papaverine administration with respect to the operator’s experience in the low-volume operators. Additionally, a shorter procedure time was observed in the papaverine group, which was more meaningful in the nondiabetic and nonhypertensive cases.

Conclusions: The preprocedural administration of papaverine in radial artery angiography confers benefits and could, thus, be a suitable substitution for traditional TNG with a view to diminishing the undesirable consequences of radial artery catheterization. (Iranian Heart Journal 2019; 20(2): 6-12)

KEYWORDS: Radial artery catheterization, Papaverine, TNG, Vascular side effects

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The safety and feasibility of the transradial approach for cardiac catheterization and intervention have been well established. Successful access to the radial artery needs experienced operators, and the traditional method of obtaining access by palpation is widely deemed a trial and error process. An unsuccessful attempt at accessing the radial artery can cause radial artery spasm.1 The range of successful first-attempt radial access with palpation guidance differs from 13.8% to 68.6%, which can even be further complicated in some patients such as female patients, hypotensive patients, and obese patients. These cases often necessitate multiple tries, thereby causing more vascular complications.2

If there are spasm and hematoma in the radial artery, femoral access may be preferred; the latter, however, fails to deliver the benefits of the transradial approach. Crossover to femoral access and the transradial approach failure most often occur due to insufficient puncture in 57% and radial spasm in 17% of cases.3

Previous research suggests that any intervention capable of improving the palpation and localization of the radial puncture site may reduce the failure rate by more than 70%. Accordingly, we hypothesized that the use of a vasodilator agent could augment the accuracy of identifying the radial pulse access site and, thus, improve the success rate. We chose papaverine because of its unique features inasmuch as it is a non-selective phosphodiesterase inhibitor obtained from opium “poppy”. It has been previously demonstrated that papaverine can increase cGMP and cAMP in smooth muscles.4 Intraluminal papaverine is frequently used for the prevention of spasm before coronary revascularization via the radial artery approach.5

A comparative study of the vasodilatory reactions of the radial artery to different agents showed that papaverine was as effective as nitroglycerine.6 It has also been previously reported that papaverine administration can relieve severe radial artery spasm induced by a trapped intraluminal guide-wire whenever intra-arterial verapamil and nitrates fail.7 Catecholamine release due to stress or a reduced cardiac function can intensify the radial artery spasm. Nitroglycerin in an anti-spasmolytic cocktail has a short half-life, and other agents such as calcium-channel blockers are not safe in many cardiac conditions. In contrast, papaverine has a longer half-life (about 100 min), and an in vitro study showed its effectiveness in vasoconstriction prevention mediated by intrinsic epinephrine or dopamine.8

Since the majority of coronary angiographies and interventions end before 100 minutes, papaverine can be used to lessen the radial artery spasm during the whole procedure. Papaverine is used via the subcutaneous route before the evaluation of microangiopathy in diabetic patients and increasing vascular transmural pressure in generalized scleroderma.9

No interaction has been reported for the combination of papaverine and lidocaine, and it is used (up to 300 mg) in intra-arterial infusions in cerebral vasospasm with no adverse effects.10,11

METHODS

This study was a randomized double-blinded parallel-group clinical trial. The study protocol was approved by the Research Department and the Ethics Committee of Iran University of Medical Sciences, Tehran, Iran.

Patients were enrolled from among those who were clinically indicated for diagnostic or interventional coronary artery catheterization in Rajae Cardiovascular, Medical, and Research Center; and they were selected based on our inclusion/exclusion criteria (Table 1). Written informed consent was obtained from the entire study population. The inclusion criteria were comprised of clinical candidacy for the transradial access and provision of written
informed consent; and the exclusion criteria consisted of atrioventricular blocks, any QRS prolongation >120 ms, Parkinson’s disease (using levodopa), prolonged QT intervals, breastfeeding, pregnancy, known hepatic dysfunction, type C or D response in the Barbeau test, and anatomical anomalies of the radial or brachial arteries necessitating crossover to femoral access.

**Procedure**
A total of 120 patients were randomized (block randomization) to receive 2 mL of lidocaine (2%)+0.5 mL of distilled water as the control group or 2 mL of lidocaine (2%) +0.5 mL (20 mg) of papaverine (40 mg/mL) as the papaverine group. All the solutions were prepared by an experienced cath-lab operator, and both the operators and the patients were unaware of the local anesthesia allocation. The subcutaneous solutions were injected medial to the radial pulse and 2 cm proximal to the styloid process of the radius; then, the radial artery access was gained using a 6-F Prelude EASE™ Hydrophilic Sheath Introducer (Merit Medical Systems). Depending on the operator’s preference, the anterior or posterior wall puncture was selected. Next, 5000 U of intravenous unfractionated heparin was administered. (In the case of percutaneous coronary intervention, the dose was increased.) In addition, depending on the baseline blood pressure, at least 100 µg of intra-radial nitroglycerin was injected. The operator verified if there was any radial artery spasm, as identified by significant complaints of the patients or noticeable resistance while crossing the catheter. At the end of the catheterization, a TR band (Terumo Company) was used for hemostasis, and persistent hemostasis was rechecked via the reverse Barbeau test.15

**End Points**
The end points consisted of the number of tries to gain access, the time to gain access, failure to gain radial access, vascular adverse effects (eg, hematoma and spasm), and crossover to femoral access. On the announcement of the operator that the patient was ready for the commencement of the procedure, the time to gain access was measured until a successful wire insertion. The number of tries to gain access was calculated as the number of needle skin passage and observed by an aid technician. Failure to gain radial access was taken to mean that the sheath could not be inserted or no pressure could be detected. Spasm was registered by the operator as any difficulty for the catheter passage or significant pain for the patient. Hematoma was documented after the sheath removal if it was extended >2 cm. Crossover to femoral access due to severe spasm that was refractory to spasmolytic drugs and interventions was considered the second approach.

In the fellowship training program in our center, operators’ experience is graded as high-volume (>50 angiography or intervention procedures) or low-volume (<50 angiography or intervention procedures) according to the number of transradial procedures they have performed.

**Statistical Analysis**
It was calculated that 50 patients were needed in each group to conduct a meaningful statistical analysis. A further 10 patients per group were enrolled to make the statistical power more satisfactory. The categorical variables were compared using the Pearson χ² test. The continuous variables are presented as the median, and they were compared using the paired t-test or the Mann–Whitney U-test. A logistic regression model for binary variables was employed for the analysis of adverse effects, and a linear regression model was used for the continuous variables—including the time to gain access. All the statistical analyses were performed with the SPSS software. A P value <0.05 was considered statistically significant.
RESULTS

Totally, 120 patients were recruited and they were equally divided into the papaverine group and the control group. The mean age of the papaverine group was 58.12 years (minimum=38 y and maximum=82 y), and the mean age of the control group was 58.27 years (minimum=40 y and maximum=80 y). The t-test showed no significant difference in the mean age between the 2 groups (P=0.728) (Table 2).

No significant difference was observed between the study groups in terms of the number of failed attempts to gain radial access (Table 3). There were significant differences between the groups in the time to gain access (P=0.016) and in the number of tries to gain access (P=0.007), and both were lower in the papaverine group (Table 4).

Our subgroup analysis demonstrated that the time to gain access was significantly lower in the male patients (P=0.035), the younger patients (P=0.008), and the smokers (P=0.043).

There was also a significant difference in favor of the papaverine group in terms of the operator’s experience among the low-volume operators (P=0.016) (Table 5).

A significantly shorter procedure time was observed in the papaverine group, which was more meaningful in the nondiabetic and nonhypertensive cases (P=0.039 and P=0.018). As was expected, the number of tries to gain access was meaningfully lower the in same subgroups (Table 6).

Expected adverse effects were much less frequent in the papaverine group (P=0.007), and the subgroup analysis showed significantly beneficial results among the smokers (P=0.009) (Table 7).

The rate of crossover to femoral access was lower and on the edge of significance in the papaverine group (1 case in the papaverine group vs 6 patients in the control group [P=0.056]), and it was significantly lower in the male gender but not in the other subgroups (P=0.034).

<table>
<thead>
<tr>
<th>N (percent)</th>
<th>Drug</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age level</td>
<td>Saline 60(50)</td>
<td>Papaverine 60(50)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>35-50</td>
<td>44.1(15)</td>
<td>55.9(19)</td>
<td>0.028</td>
<td></td>
</tr>
<tr>
<td>50-65</td>
<td>62.7(37)</td>
<td>37.3(22)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>65-80</td>
<td>30.8(8)</td>
<td>69.2(18)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Up to 80</td>
<td>0.0(0)</td>
<td>100(1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td>Male</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>31(45.6)</td>
<td>37(54.4)</td>
<td>0.269</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>29(56.9)</td>
<td>23(44.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fellow’s experience</td>
<td>Low-volume</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>49(48.5)</td>
<td>52(51.5)</td>
<td>0.453</td>
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</tr>
<tr>
<td></td>
<td>High-volume</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>8(42.1)</td>
<td>11(57.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>39(54.9)</td>
<td>32(45.1)</td>
<td>0.194</td>
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</tr>
<tr>
<td></td>
<td>No</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>21(42.9)</td>
<td>28(57.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>20(48.8)</td>
<td>21(51.2)</td>
<td>0.847</td>
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<td></td>
<td>No</td>
<td></td>
<td></td>
<td></td>
</tr>
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<td></td>
<td>40(50.6)</td>
<td>39(49.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>20(42.6)</td>
<td>27(57.4)</td>
<td>0.190</td>
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<td></td>
<td>No</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>40(54.8)</td>
<td>33(45.2)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Table 2. Time to gain access and the number of tries to gain access in both groups. |
|-----------------------------------------------|-------------|-----------------|--------------------|
| Time to Gain Access | N | Median(QRT) | P value |
| Papaverine | 57 | 38 (29.5-71.5) | 0.016 |
| TNG | 54 | 62.5 (37.5-109) |    |
| Number of Tries to Gain Access | N | Median(QRT) | P value |
| Papaverine | 57 | 1 (1-2) | 0.007 |
| TNG | 54 | 2 (1-3) |    |
**Table 3. Time to gain access according to the operator’s experience**

<table>
<thead>
<tr>
<th>Operator</th>
<th>N</th>
<th>Median(QRT)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-volume</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Papaverine</td>
<td>49</td>
<td>39 (28.5-60.5)</td>
<td>0.016</td>
</tr>
<tr>
<td>TNG</td>
<td>43</td>
<td>79 (39-109)</td>
<td></td>
</tr>
<tr>
<td>High-volume</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Papaverine</td>
<td>8</td>
<td>36 (30.25-64.75)</td>
<td>0.545</td>
</tr>
<tr>
<td>TNG</td>
<td>11</td>
<td>45 (30-98)</td>
<td></td>
</tr>
</tbody>
</table>

**Table 4. Subgroups with a lower number of tries to gain access results**

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>P value</th>
<th>Median(QRT)</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Younger (35-50 y)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Papaverine</td>
<td>0.037</td>
<td>1 (1-2)</td>
<td>19</td>
</tr>
<tr>
<td>TNG</td>
<td></td>
<td>2 (1.5-3.5)</td>
<td>13</td>
</tr>
<tr>
<td>Male</td>
<td>0.01</td>
<td>1 (1-2)</td>
<td>35</td>
</tr>
<tr>
<td>Papaverine</td>
<td></td>
<td>2 (2-3)</td>
<td>28</td>
</tr>
<tr>
<td>TNG</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nondiabetic</td>
<td>0.02</td>
<td>1.5 (1-2)</td>
<td>36</td>
</tr>
<tr>
<td>Papaverine</td>
<td></td>
<td>2 (1.25-3.75)</td>
<td>36</td>
</tr>
<tr>
<td>TNG</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonhypertensive</td>
<td>0.017</td>
<td>2 (1-2)</td>
<td>27</td>
</tr>
<tr>
<td>Papaverine</td>
<td></td>
<td>2 (2-4.25)</td>
<td>18</td>
</tr>
<tr>
<td>TNG</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Low-volume operator</td>
<td>0.008</td>
<td>1 (1-2)</td>
<td>49</td>
</tr>
<tr>
<td>Papaverine</td>
<td></td>
<td>2 (1-3)</td>
<td>43</td>
</tr>
<tr>
<td>TNG</td>
<td></td>
<td></td>
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<tr>
<td>Smoker</td>
<td>0.037</td>
<td>1 (1-2)</td>
<td>30</td>
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<tr>
<td>Papaverine</td>
<td></td>
<td>2 (1-3)</td>
<td>36</td>
</tr>
<tr>
<td>TNG</td>
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</table>

**Table 5. Adverse effects**

<table>
<thead>
<tr>
<th>Adverse Effect</th>
<th>Papaverine</th>
<th>TNG</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number</td>
<td>50(56.8)</td>
<td>38(43.2)</td>
<td>0.070</td>
</tr>
<tr>
<td>Spasm</td>
<td>5(27.8)</td>
<td>13(72.2)</td>
<td></td>
</tr>
<tr>
<td>Hematoma</td>
<td>2(40.0)</td>
<td>3(60.0)</td>
<td></td>
</tr>
</tbody>
</table>

**DISCUSSION**

The use of the radial approach for coronary angiography and intervention is continuously on the rise, with many operators underscoring access gain as the cornerstone of a successful procedure. A lower number of tries to gain access can reduce the rate of complications, whereas multiple attempts increase the time required, patient discomfort, and the risk of arterial spasm.

In this study for the first time we showed a significant reduction in the time to gain access and in the number of tries to gain access after adding papaverine to lidocaine ($P=0.016$ and $P=0.007$) (Table 4). The time to gain access was significantly lower in the male patients ($P=0.035$), younger patients ($P=0.008$), and the smokers ($P=0.043$).
Moreover, we observed a significant difference in favor of papaverine administration with respect to the operator’s experience among our low-volume operators ($P=0.016$) (Table 5). Our results revealed a significantly lower time with the use of papaverine in nonhypertensive cases ($P=0.039$ and $P=0.018$). Previous studies have demonstrated a higher frequency of the radial artery spasm in the female gender. Total NO-dependent vasodilation was lower in the forearm arteries for women in a previous investigation. Nagaraja et al. evaluated the effect of papaverine on the radial artery diameter and reported its efficacy in the palpability of the radial pulse.

We showed a significant reduction in the time to gain access as regards the operator’s experience among our low-volume operators. Consequently, papaverine can be practically used in the radial approach in training centers and fellowship programs.

A lower number of tries to gain access reduces vascular complications and alleviates patient discomfort.

In the current study, overall adverse effects were much less frequent in the papaverine group ($P=0.007$) and our subgroup analysis showed significant results in the smokers ($P=0.009$) but not according to other variables and the operator’s experience (Table 7). The rate of crossover to femoral access was lower and on the edge of significance in our papaverine group (1 case in the papaverine group vs 6 cases in the control group [$P=0.056$]).

**CONCLUSIONS**

The addition of papaverine for subcutaneous anesthesia can reduce the time to gain access, access site adverse effects, severe spasm, and crossover to femoral access. It can, therefore, have a beneficial effect on the procedure length, patient comfort, procedural success, and femoral access-related complications.

**REFERENCES**


Original Article

Evaluation of Gender Differences in Response to Cardiac Resynchronization Therapy in a Single Heart Center

Shabnam Madadi¹, MD; Leili Mohimi², MD; Majid Haghjoo¹, MD; Amir Farjam Fazelifar¹, MD; Abolfath Alizadeh¹, MD; Zahra Emkanjoo¹*, MD

ABSTRACT

Background: Cardiac resynchronization therapy (CRT) has a beneficial effect on clinical symptoms, exercise capacity, and systolic left ventricular (LV) performance in patients with heart failure. The objective of the current study was to evaluate whether a gender difference exists in response to CRT according to clinical indices.

Methods: Totally, 229 consecutive patients with end-stage heart failure (LV ejection fraction ≤35%), QRS duration >120 ms, and left bundle branch block configuration underwent CRT. At baseline and 6 months post-CRT, clinical and echocardiographic parameters were evaluated and followed-up was obtained for up to 6 months. The clinical alterations after CRT implantation were compared between the men and the women.

Results: The study population consisted of 229 patients [129 (56.3%) male and 100 (43.7%) female; mean age=62.90±12.97 y, and age range=9–24]. No significant difference between the men and the women regarding age was found [men=62.13±14.26 y and women=63.89±11.12 y (P=0.3)]. The mean of the QRS width after CRT implantation in the men and the women was 147.50±23.09 and 145±18.45 ms, respectively, and the difference between the 2 groups was significant (P=0.001). There was no significant relationship between sex and hospitalization (P=0.09). At 6 months’ follow-up, LV ejection fraction in the men and the women was 18.56±6.18 and 20.78±8.96, respectively (P=0.1).

Conclusions: At 6 months’ follow-up, most of the patients had a normal sinus rhythm. Most of the deaths were seen in the males. The men had a slightly greater QRS width after CRT implantation in than the women. The chief reasons for hospitalization and mortality were shock and heart failure decompensation. LV ejection fraction before and after CRT was significantly greater in the female patients than in their male counterparts; however, the difference was significant before the implantation. (Iranian Heart Journal 2019; 20(2):13-20)

KEYWORDS: Cardiac resynchronization therapy; CRT, QRS duration, Gender, Heart failure, Ejection fraction, Left ventricle, Cardiomyopathy

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Cardiac resynchronization therapy (CRT) is currently considered a major advance in the treatment of patients with drug-refractory heart failure (HF). Recently, several major randomized trials have shown the beneficial effects of CRT on clinical symptoms, exercise capacity, and left ventricular (LV) systolic function.1-4 It was demonstrated in the CARE-HF trial that CRT also increased survival as compared to optimized medical therapy, and this was accompanied by a significant reduction in the number of rehospitalizations for heart failure.4 Further, cardiac resynchronization therapy with defibrillator (CRT-D) is also an approved treatment for patients with advanced stages of HF in the setting of a widened QRS, and this therapy leads to a reduction in symptoms, an improvement in functional capacity, and a decrease in hospitalization and mortality.5 It is unknown whether a gender-related difference in response to CRT exists. This is an essential issue as numerous studies have pointed out gender differences in the presentation of coronary artery disease (CAD) and differences in response to therapy.6-8 Accordingly, the objective of the present study was to determine whether a gender difference exists in response to CRT. According to some studies, CRT in patients with HF and with a prolonged QRS duration imparts survival benefits.9 Nevertheless, a significant absence of response (30%-40%) among treated patients indicates that the selection criteria require refinement.10 Clinical experience recommends that some patients with a QRS duration of 150 ms may respond and not all patients with a QRS duration of 150 ms benefit, indicating that CRT prescription according to the QRS duration dichotomization may be a blunt selection tool. Supplementary influences on the effects of CRT include ischemic disease, and, controversially, gender.11-13

CRT trials have assessed differing proportions of patients with these comorbidities, always with women as a minority. Later, several questions persist.14 The recently reported randomized MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy) trial demonstrated that patients treated with CRT-D with New York Heart Association (NYHA) functional class I and II, HF symptoms, a left ventricular ejection fraction (LVEF) of 0.30, and a QRS of 130 ms had a 34% reduction in the risk of HF or death, whichever came first, when compared with patients treated with an implantable cardioverter-defibrillator (ICD).

**METHODS**

Totally 229 cases with CRT implantation (NYHA III-IV), QRS>120 ms, and resistance to drug treatment during the preceding 3 years underwent CRT implantation in our tertiary care center. The patients’ data were extracted from documents, and the patients were followed up through telephone contacts and a comprehensive questionnaire. Variables and clinical characteristic were included in the questionnaire—including the underlying heart disease (ischemic cardiomyopathy [ICMP] and non-ischemic cardiomyopathy [NICMP]), the NYHA class before and after CRT implantation, echocardiographic data before implantation and 6 months thereafter (defined as LVEF, left ventricular end-diastolic volume [LVEDV], and left ventricular end-systolic volume [LVESV]), and finally the data of CRT implantation and the duration of having it. The patients’ status (death or alive), the cause of death (heart failure, arrhythmias, and others), the number of the hospitalization after implantation due to HF, arrhythmias, shock, the percentage of biventricular pacing (loss of CRT, the dislocation of the lead, infection, arrhythmias, and high thresholds), the kind of CRT (CRT-D and CRT-P), patients’ rhythm 6 months after implantation (normal sinus rhythm, atrial fibrillation, and AT), the QRS width, and the location of the coronary sinus...
(lateral, posterior, and anterolateral) were all recorded. The following selection criteria for CRT were applied: moderate-to-severe HF (NYHA class III or IV), LVEF=35%, and QRS duration >120 ms with a left bundle branch block configuration. Patients with a recent myocardial infarction (<3 mon) or decompensated HF were excluded.

Before pacemaker implantation, clinical status was assessed and 2D echocardiography was performed to assess LV volumes and LVEF. Next, tissue Doppler imaging was performed to evaluate LV dyssynchrony. LV dyssynchrony was reassessed immediately after implantation. Clinical status, LVEF, and LV volumes were reassessed at 6 months’ follow-up.

**Clinical Evaluation**

The evaluation of clinical status included an assessment of the NYHA functional class, quality-of-life score (using the Minnesota Living with Heart Failure questionnaire), and the evaluation of exercise capacity using the 6-minute corridor-walk test. Patients with an improvement of at least 1 NYHA functional class at 6 months’ follow-up were classified as responders. In addition, a long-term follow-up was performed by chart reviews, telephone contacts, and outpatient visits. Events were classified as death or heart transplantation. Follow-up data were acquired for up to 5 years.

**Statistical Analysis**

The continuous and categorical variables are presented as mean±standard deviation and percentages. The Student t-test was used to compare the quantitative variables, and the χ² test was applied to compare the categorical variables. The SPSS software, version 18.0 (Chicago, USA), was used for all the statistical analyses. The nonparametric test was employed to compare the relationship between the nonparametric variables with normal distributions and the other variables. Additionally, the nonparametric test was used to measure the NYHA functional class before and after CRT or to measure the pattern of the change. The Man–Whitney U-test was utilized to measure and to compare the QRT interval differences between the 2 groups.

**RESULTS**

Totally 229 patients were enrolled [129 (56.3%) male and 100 (43.7%) female; mean age=62.90±12.97 y, and age range=9–24]. The demographic and clinical baseline characteristics are depicted in Table 1. In the present study, hypertrophic cardiomyopathy, valvular heart disease, dilated cardiomyopathy (DCM), ICM, and ICMP were seen in 1 (5%), 1 (5%), 103 (48.4%), and 108 (50.7%) patients, respectively. According to Table 1, LVEDV, LVESV before CRT implantation, and LVEF were 179.60±73.68 mL (range=42–400), 125.58±105.86 mL (range=5.20–489), and 18.75±6.58% (range=5–35), respectively. The prevalence of the NYHA functional class before and after CRT implantation is shown in Table 2. Out of the 206 cases, 185 (88.6%) cases were alive and the most relevant causes of mortality were HF decompensation and arrhythmias: 15 (62.5%), 7 (29.2%), and 2 (8.3%), respectively. At 6 months’ follow-up, normal sinus rhythms and then atrial fibrillation were seen, respectively, in 190 (88%) and 26 (12%) of the patients.

Out of the 216 CRT-implanted cases, 165 (88.7%) were CRT-D and 21 cases (11.3%) were CRT-P. Out of the 222 cases with coronary sinus locations, the most relevant site was anterolateral in 71 (32%) patients and then MCV in 1 (5%) case and PLV in 1 (5%) case (Table 2). The hospitalization duration was 1.62±1.23 days (range=1–6 d).

The most frequent reasons for hospitalization in the patients were decompensation of HF, arrhythmias, and appropriate or successful and inappropriate or unsuccessful shock, which were respectively seen in 40 (69%), 2 (3.4%), 6 (10.3%), 8 (13.8%), and 2 (3.4%) patients.
QRS mean width was 21.10±148.60 ms (range=100–200).
Eighty-four (68.1%) female patients had DCM, whereas 39 (3.8%) men had DCM. Moreover, 30 (31.9%) of the women had ICMP, while 78 (65.5%) of the men had ICMP. The alterations in the NYHA functional class before and after CRT were measured, and no significant association was found (0.4% and 0.9%, respectively, P<0.05).
Regarding the association between sex and the NYHA classification before CRT implantation, the result revealed that out of the 73 women and the 80 men, 2 (2.7%) females and 6 (7.5%) males had the NYHA functional class I and 53 (72.6%) of the females and 48 (60%) of the males had the NYHA functional class II. Sixteen (21.9%) of the females had functional class III, while 24 (30%) of the males had functional class III. Two (2.8%) of the women and 2 (2.5%) of the men were found to have functional class IV; however, no significant association was found between the males and the females regarding the NYHA functional class (P=0.4).
DCM was mostly seen in the females, while ICMP was predominantly seen in the males. In 64 (68.1%) of the females, DCM; and in 78 (65.6%) of the men, ICMP was seen.
Before CRT implantation, 53 (72.6), of the women and 48 (60%) of the men had the NYHA classification II, while 16 (21.9%) of the women and 24 (30%) of the men were found to have the NYHA functional class III; no relationship was found between the 2 groups regarding the NYHA functional class (P=0.4).
The mean (SD) LVEDV in the men and the women was, respectively, 191.20±75.87 and 177.29±71.55 mL; nonetheless, no significant association between the 2 groups regarding LVEDV was seen (P=0.4). LVEF before CRT implantation in the men and the women was 17.73±6.31% and 20.05±6.71%, respectively, and the difference between the 2 groups regarding LVEF was significant (P=0.01) (Table 3).
At 6 months’ follow-up, the mean (SD) LVEF in the men and the women was 18.56±6.18 and 20.78±8.96, correspondingly. No significant association between the 2 groups regarding LVEF at 6 months’ follow-up was found (P=0.1). Biventricular pacing in the men and the women was 92.07±10.58 and 92.97±10.58; nonetheless, no significant association between the 2 groups concerning biventricular pacing was found (P=0.4) (Table 3). The mean age between the men and the women was measured, and it showed no significant difference between the 2 groups [men=62.13±14.26 vs women=63.89±11.12; (P=0.3)].
There was no significant association between sex and hospitalization (P=0.09); in most of the cases, the reason for hospitalization was the presence of comorbidities other than inappropriate or appropriate shock.
There was no significant association between the mortality rate and sex (P=0.4). Most of the deaths were seen in the males (18 [15.3%]), although the result was not statistically significant (P=0.05). Eighty-three (93.4%) of the women were alive. The differences of the QRS interval after CRT implantation in the men and the women were, respectively, 23.09±147.50 ms and 18.45±145 ms and the difference between the 2 groups regarding the QRS width was significant (P=0.001). There was no significant difference vis-à-vis the mean (SD) of LVEF before and after CRT implantation between the male and female patients (0.60±5.15 vs 0.26±6.03; P=0.7).
Ninety (91.8%) women and 75 (85.2%) men had CRT-D, which showed that the most frequent kind of CRT implanted was CRT-D, although statistically no significant difference was found (P=0.08).

**DISCUSSION**

A previous study evaluated 137 men and 36 women with HF after the implantation of CRT and showed significantly improved echocardiographic parameters in both groups at
2 years’ follow-up. The response to CRT in both men and women was similar, and no significant difference was seen regarding sex in response to CRT and long-term survival.\textsuperscript{15} In the MADIT CRT study, the response to CRT was improved in women in contrast to men.\textsuperscript{16} In another study on 212 patients with HF, NICMP, and left bundle branch block, the response to CRT at 2 years’ follow-up was 71\%, which was higher in women than in men (84\% vs 58\%). In addition, the response to CRT when the QRS width was smaller was higher in men. (When the QRS width was <150 ms, a response of 86\% vs 36\% was expected; and the QRS width was >150 ms, this rate was expected to be 83\% vs 69\%).\textsuperscript{17} After CRT implantation, the 1-year survival rate was 91\%, the 5-year survival rate was 63\%, and the 10-year survival rate was 39\%; however, total death in women in comparison to men was low. The female gender was defined as the independent predictor factor for the total mortality rate.\textsuperscript{18} Our study confirmed that there is a significant association between sex and LVEF (P<0.05). The mortality rate was greater in our male patients than in our female patients (P<0.05). LVEF alterations between the 2 groups were nearly the same (P>0.05).

We detected DCM in 68.1\% of the female and ICMP in 65.6\% of the male patients. Additionally, 31.9\% of the females had ICMP, while 65.5\% of the men had ICMP (P<0.001). According to a substudy from the MADIT-CRT trial, women accounted for 25\% of the study population. While the men received significant benefits from CRT-D therapy, the women had significantly better consequences with CRT-D therapy than the men for death or HF, for HF only, and for death at any time. The women had a significant (72\%) reduction in all-cause mortality in the total population, with even larger diminishations in mortality for those with QRS=150 ms.\textsuperscript{15} In a European cohort of the REVERSE (Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction) trial involving 162 patients with the NYHA functional class I and II and HF, LVEF was 0.35 and QRS was 120 ms, and practically 20\% of the subjects were female. In addition, the clinical composite end point of deteriorated HF was reduced to a comparable degree with CRT therapy in the women and men.\textsuperscript{19} According to some studies on HF, women—especially those with non-ischemic heart disease—have an overall survival advantage.\textsuperscript{20} Research has also shown that women achieve greater reductions in left conduction disturbances and greater cardiac dyssynchrony than men, which might explain why women were more responsive to CRT than men in our investigation. It is commonly believed that in subjects without heart disease, women have—on average—QRS durations that are approximately 10 ms shorter than those in men.\textsuperscript{21} Overall, in subjects with HF, a prolongation of QRS=120 ms occurs in 14\% to 47\% of patients.\textsuperscript{22} In the MADIT-CRT trial, for any given QRS duration=130 ms, women might have—on a relative basis—more conduction disturbances and greater cardiac dyssynchrony than men, and this might clarify why women were more responsive to CRT than men in those trials.\textsuperscript{15} Likewise, in our investigation, the mean of the QRS width after CRT implantation in the men was approximately more than the QRS width in the women (147.50±23.09 vs 145±18.45; P=0.001). In the COMPANION (Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure) trial, women made up 33\% of the study population. These female patients had a 56\% reduction in the risk of sudden cardiac death with CRT-D compared with optimal pharmacologic therapy, and the female sex was associated with reduced risks in conjunction with CRT-D therapy.\textsuperscript{23} The results of that study are in accordance with our results, showing that most of the deaths were seen in males (15.3\%), although this result...
was not statistically significant \((P=0.05)\). Of all the female patients, 93.4% survived. The mean QRS width after CRT implantation was 147.50±23.09 in the men and 145±18.45 in the women; the difference between the 2 groups regarding the QRS width was significant \((P=0.001)\).

**CONCLUSIONS**

Totally, the women in the present study obtained significantly greater reductions in death or HF (whichever came first), HF alone, and all-cause mortality with CRT-D therapy than did the men. This finding is most probably due to the fact that these more favorable results for women were associated with consistently greater echocardiographic evidence of reverse cardiac remodeling in women than in men. At 6 months’ follow-up, most of the patients had a normal sinus rhythm. Most of the deaths were seen in the males. The men had slightly greater QRS widths after CRT implantation than did their female counterparts. LVEF before and after CRT was significantly greater in the females than in the males; the difference, however, was significant before the implantation.

| Table 1. Baseline characteristics of the study population |
|----------------|----------------|----------------|
|                | Men \[N=206\] | Women          | \(P\) value   |
| Age (y)        | 62.13±14      | 63.89±11.04    | 0.3           |
| NYHA class     |               |                | 0.4           |
| I              | 6(7.5%)       | 2(2.7%)        |               |
| II             | 53(72.6%)     | 48(60%)        |               |
| III            | 24(30%)       | 16(21.9%)      |               |
| IV             | 2(2.5%)       | 2(2.5%)        |               |
| QRS (male, female) ms | 147 | 145 | 0.4 |
| Left ventricular ejection fraction | 17.7±6.31 | 20±8.7 | 0.1 |
| Left ventricular end-diastolic volume | 181.2±75 | 177.29±71 | 0.3 |
| Type of cardiomyopathy (male, female) |          |                | \(P<0.001\) |
| hypertrophic cardiomyopathy | 1(0.8%) | 0 | |
| valvular heart disease | 1(0.8%) | 0 | |
| dilated cardiomyopathy | 39(3.8%) | 64(68%) | |
| ischemic cardiomyopathy | 78(65.5%) | 30(31.9%) | |

| Table 2. Prevalence of the clinical data |
|----------------|----------------|----------------|
| Variables                  | N (percent)     |
| Arrhythmia                 | normal sinus rhythm atrial fibrillation | 190(88%) 28(12%) |
| Coronary sinus location of the lead | anterolateral | 71(32%) |
| Reason for hospitalization | MCV PLV other reason | 1(5%) 1(5%) 40(69%) |
| heart failure               | 8(13.8%)        |
| appropriate shock           | 6(10.3%)        |
| inappropriate shock         | 2(3.4%)         |
| arrhythmia                  | 2(3.4%)         |

| Table 3. LVEF alterations before and after CRT implantation |
|----------------|----------------|----------------|
| Before CRT     | LVEF (Females) | LVEF (Males)  | \(P\) value |
| 20.05±6.71     |                | 20.78±8.96    | 0.01        |
| After CRT      | 17.73±6.31     | 18.56±6.18    | 0.1         |

CRT, Cardiac resynchronization therapy; LVEF, Left ventricular ejection fraction \(P<0.05\) was considered to be the level of significance.
Table 4. Patients’ outcome after CRT implantation

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Male</th>
<th>Female</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CS lead location lateral</td>
<td>51(41.5%)</td>
<td>46(46.5%)</td>
<td>0.7</td>
</tr>
<tr>
<td>CRT-D</td>
<td>90(91.8%)</td>
<td>75(85.2%)</td>
<td>0.08</td>
</tr>
<tr>
<td>QRS width (ms)</td>
<td>147.50±23.09</td>
<td>145±18.45</td>
<td>0.001</td>
</tr>
<tr>
<td>Death</td>
<td>18(15.3%)</td>
<td>83(93.4%)</td>
<td>0.05</td>
</tr>
<tr>
<td>Mortality rate Other reason (%)</td>
<td>10(55.6%)</td>
<td>5(83.3%)</td>
<td>0.4</td>
</tr>
<tr>
<td>AF (%)</td>
<td>6(33.3%)</td>
<td>1(16.7%)</td>
<td></td>
</tr>
<tr>
<td>BVP (%)</td>
<td>92.07±10.58</td>
<td>92.97±10.58</td>
<td>0.4</td>
</tr>
</tbody>
</table>

CS, Coronary sinus; CRT, Cardiac resynchronization therapy; AF, Atrial fibrillation; BVP, Biventricular pacing
P<0.05 was considered to be the level of significance.

Table 5. Clinical and demographic data comparison between the males and females

<table>
<thead>
<tr>
<th></th>
<th>Male/Female</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>Male</td>
<td>62.13±14.24 63.89±11.12</td>
</tr>
<tr>
<td></td>
<td>female</td>
<td></td>
</tr>
<tr>
<td>LVEDV (mL)</td>
<td>male</td>
<td>181.20±75.87 177.29±71.55</td>
</tr>
<tr>
<td></td>
<td>female</td>
<td></td>
</tr>
<tr>
<td>BVP (%)</td>
<td>Male</td>
<td>92.07±16.20 92.97±10.58</td>
</tr>
<tr>
<td></td>
<td>female</td>
<td></td>
</tr>
<tr>
<td>QRS (ms)</td>
<td>male</td>
<td>147.50±23.09 145.51±18.45</td>
</tr>
<tr>
<td></td>
<td>female</td>
<td></td>
</tr>
</tbody>
</table>

BVP, Biventricular pacing; LVEDV, Left ventricular end-diastolic volume
P<0.05 was considered to be the level of significance.

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Original Article

Malnutrition and Nosocomial Infection After Pediatric Cardiac Surgery

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ABSTRACT

Background: Malnutrition is common among children with cardiovascular diseases. A few studies have been conducted on the relationship between malnutrition and the incidence of postoperative infections among these children. This study sought to evaluate the relationship between malnutrition and nosocomial infections in pediatric patients undergoing cardiac surgery.

Methods: Totally, 129 children <15 years old who developed nosocomial infections after cardiac surgery were enrolled. According to weight for age, weight for height, and height for age, malnutrition was defined as mild, moderate, and severe. The association between some blood factors such as hemoglobin and hematocrit and malnutrition was also investigated.

Results: The prevalence of mild, moderate, and severe malnutrition based on weight for age was 19.5% (n=23), 16.9% (n=20), and 32.2% (n=38), respectively; according to height for age was 15.4% (n=19), 13.8% (n=17), and 20.3% (n=25), respectively; and according to weight for height was 19.4% (n=24), 18.5% (n=23), and 31.5% (n=39), respectively. Pneumonia was significantly associated with moderate and severe malnutrition (P=0.006). Among biochemical indices, only hemoglobin (P=0.007) and hematocrit (P=0.01) were associated with malnutrition in these children.

Conclusions: Pneumonia and anemia are associated with malnutrition in children undergoing cardiac surgery and it is necessary to resolve malnutrition before therapeutic processes. (Iranian Heart Journal 2019; 20(2): 21-27)

KEYWORDS: Malnutrition, Nosocomial infection, Pediatric, Cardiac surgery

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Nosocomial infections occur 48–72 hours after hospitalization and the symptoms appear in the hospital or after discharge. Generally, the prevalence of these infections depends on several factors such as the severity of the underlying diseases such as the immune system deficiency.¹ Nosocomial infections in pediatric patients are also the most important cause of comorbidity and mortality, leading to increased costs and
prolonged periods of hospitalization. This problem is more serious among infants, preterm infants, and children with congenital anomalies.\(^1\)

In this regard, malnutrition independently increases hospital mortality resulting from infection, pressure ulcers, and delayed wound healing, and all of these prolong the hospitalization period and the mortality rate of patients. Nutrition and infection greatly affect each other. Numerous studies confirm that the incidence of infection—nosocomial infections in particular—is among the problems resulting from malnutrition.\(^1,2\)

On the other hand, some of the risk factors of nosocomial infections are malnutrition, diabetes, and obesity. The nutritional deficiencies result in weak immune system performance and susceptibility to infections.\(^1,2\)

The nutritional status of patients is evaluated by various variables such as the amount of consumed food, body weight, weight loss, anthropometric data, liver proteins, and body mass analysis. The early diagnosis of malnutrition as an independent indicator and risk factor for the incidence of infection, in tandem with screening and the early diagnosis of patients at risk, is an appropriate way to reduce the high incidence of nosocomial infections.\(^2\)

Malnutrition is common in children with congenital heart diseases. This is due to inadequate nutrition, increased need for energy, intestinal malabsorption, and reduced splanchnic blood flow.\(^3\)

Inadequate nutrition is defined as low weight for age, which is associated with the increased rate of mortality in children and the incidence of many infections.\(^4\) Some studies have reported that malnutrition defined as low weight for age or low serum albumin levels is associated with increased mortality and postoperative infections in children with cardiovascular diseases.\(^5,6\)

A few studies have been performed on the relationship between nutrition status and the outcome of surgery, particularly the incidence of nosocomial infections in children with cardiovascular diseases. Therefore, in this study, the relationship between nutrition status and the incidence of nosocomial infections in children <15 years old and cardiovascular diseases was investigated.

**METHODS**

In this cross-sectional study, the height (cm), weight (kg), and age of 129 children <15 years old with congenital heart diseases undergoing surgery at Rajaie Cardiovascular, Medical, and Research Center in 2015, who developed nosocomial infections during ICU stay, were recorded.

The weight of the children was measured using a Seca (model 334) portable electronic scale (error rate <5 g), and Seca (model 786) mechanical column scale (error rate=0.5 kg). Their height was measured using the Seca (model 217 and model 207) stadiometer (error rate=1 mm) by a trained nurse.

The malnutrition degree in the children was determined by comparing weight for age, height for age, and weight for height of the children with the World Health Organization’s standard tables, and the malnutrition level was assessed in 3 groups of mild (-1.1 to -2.0 SD), moderate (-2.1 to -3.0 SD), and severe (<-3 SD).\(^7\)

The biochemical data of these children were checked on the first day of hospitalization—including Hg, Hct, serum albumin, and total protein. Albumin and total protein were measured by calorimetric, hemoglobin was measured by cyanmethemoglobin methods, and hematocrit was assessed based on hemoglobin.

The diagnosis of nosocomial infections was based on the Iranian Guideline to Nosocomial Infection Care System. For the diagnosis of clinical sepsis, the patient should have at least one of the following symptoms not resulted from another known cause: fever (temperature >38°C), hypotension (systolic pressure< 90 mm Hg), or oliguria (<20 cm\(^3\)/h) and no blood
culture or no organism or antigen found in the blood, or no obvious infection in another location. Any of the following symptoms represents pneumonia: 1) dullness in the clinical examination, 2) radiography of the patient’s chest and cavity or pleural effusion, and 3) maximum age of 1 having at least 2 of the following symptoms: apnea, tachycardia, bradycardia, wheezing, coughing, or rhonchi.

**Diagnosis of the urinary tract infection**
The patient should have at least one of the following symptoms: temperature >38°C, frequent urination, dysuria, excessive suprapubic pain with local touch, and positive culture with $10^5 \leq$ microorganisms per cm$^3$ of urine provided, in which no more than 2 organisms are grown.

**Diagnosis of surgical site infection**
The surface infection of the surgical site should have the following characteristics: infection has occurred within 30 days after the surgery and only affected the skin and subcutaneous tissue, with at least one of the following symptoms: 1) purulent discharge from surface incision, 2) organism aseptically separated from the liquid or tissue of the surface incision, and 3) the presence of at least one of these symptoms: pain, local swelling, redness, or heat, and the wound having been intentionally opened by the doctor.

This study was approved by our institutional review board according to the Helsinki Declaration of the World Medical Association (2000).

**Statistical Analysis**
The statistical analyses were performed with the SPSS software, version 15, for Windows (SPSS Inc, Chicago, Illinois). The mean, the standard deviation (SD), and frequencies were used for the descriptive analysis. For the evaluation of the distribution of data, the one-sample Kolmogorov–Smirnov test was used. The mean variables between the 2 groups were tested using an independent $t$-test or the Mann–Whitney $U$-test. A multivariate analysis was used to test the variables that could predict postoperative nosocomial infections.

**RESULTS**
In total, 129 children with congenital heart diseases who underwent open-heart surgery were enrolled. The mean age of all the children was $20.78 \pm 38.82$ months, ranging from newborn to 15 years old. Girls accounted for 44.2% of all the patients. The distribution of congenital heart diseases in the children is shown in Table 1.

<table>
<thead>
<tr>
<th>Congenital Heart Disease</th>
<th>N(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tetralogy of fallot</td>
<td>25(19.37)</td>
</tr>
<tr>
<td>Transposition of great arteries</td>
<td>24(18.6)</td>
</tr>
<tr>
<td>Ventricular septal defect</td>
<td>46(35.65)</td>
</tr>
<tr>
<td>Single ventricle</td>
<td>4(3.1)</td>
</tr>
<tr>
<td>Complete A-V canal defects</td>
<td>9(6.97)</td>
</tr>
<tr>
<td>Arterial septal defect</td>
<td>20(15.5)</td>
</tr>
<tr>
<td>Coarctation of the aorta</td>
<td>4(3.1)</td>
</tr>
<tr>
<td>Double-outlet right ventricle</td>
<td>5(3.87)</td>
</tr>
<tr>
<td>Pulmonary atresia</td>
<td>5(3.87)</td>
</tr>
<tr>
<td>Patent ductus arteriosus</td>
<td>26(20.15)</td>
</tr>
</tbody>
</table>

All the included patients had documented significant postoperative infections—including bacteremia, sepsis, mediastinitis, urinary tract infections, and pneumonia—which were defined as culture-positive endotracheal tube aspirate with chest radiograph changes consistent with pneumonia and significant pleural effusions requiring the insertion of new chest tubes, positive urinary, and blood culture.

**Distribution of nosocomial infections**
As is shown in Table 2, among all the patients, 4 kinds of nosocomial infections were detected: surgical site infection, the bloodstream infection, the urinary tract infection, and pneumonia. Among all the isolates, pneumonia was the most prevalent pathogen (92, 71.3%).
Table 2. Nosocomial infection distribution

<table>
<thead>
<tr>
<th>Nosocomial Infections</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bloodstream infection</td>
<td>67(51)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>92(71)</td>
</tr>
<tr>
<td>Surgical site infection</td>
<td>7(5.4)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>4(3.1)</td>
</tr>
</tbody>
</table>

Nutritional status

Based on the z score, the prevalence of moderate and severe malnutrition according to height for age, weight for age, and weight for height was 20.3%, 32.3%, and 31.2%, respectively. Nutrition status based on the z score is shown in Table 3.

Table 3. Severity of malnutrition based on the z score

<table>
<thead>
<tr>
<th>Severity of Malnutrition</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malnutrition based on WA</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>37(31.4)</td>
</tr>
<tr>
<td>Mild</td>
<td>23(19.5)</td>
</tr>
<tr>
<td>Moderate</td>
<td>20(16.9)</td>
</tr>
<tr>
<td>Severe</td>
<td>38(32.2)</td>
</tr>
<tr>
<td>Malnutrition based on HA</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>62(50.4)</td>
</tr>
<tr>
<td>Mild</td>
<td>19(15.4)</td>
</tr>
<tr>
<td>Moderate</td>
<td>17(13.8)</td>
</tr>
<tr>
<td>Severe</td>
<td>25(20.3)</td>
</tr>
<tr>
<td>Malnutrition based on WH</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>38(30.6)</td>
</tr>
<tr>
<td>Mild</td>
<td>24(19.4)</td>
</tr>
<tr>
<td>Moderate</td>
<td>23(18.5)</td>
</tr>
<tr>
<td>Severe</td>
<td>39(31.5)</td>
</tr>
</tbody>
</table>

WA, Weight for age; HA, Height for age; WH, Weight for height

All the patients were divided into 2 groups: with malnutrition and without malnutrition, based on the z score. The patients with moderate and severe malnutrition were considered to be malnourished.

There was a significant relationship between malnutrition severity and pneumonia ($P=0.006$). Pneumonia diagnosis occurred more frequently in the patients with severe and moderate malnutrition according to weight for age, weight for height, and height for age scores ($P=0.007$, $P=0.036$, and $P=0.01$, respectively).

Laboratory findings

The association between some laboratory parameters and malnutrition is presented in Table 4. In a group composed of children with malnutrition, hemoglobin (Hb) and hematocrit (Hct) were significantly less than that in the children without malnutrition (Hb: 13.06±2.70 vs 14.74±2.84; $P=0.007$ and Hct: 39.06±7.96 vs 43.76±8.46; $P=0.01$). The other biochemical parameters had no association with malnutrition ($P>0.05$).

Multivariable analysis

Multivariable modeling is shown in Table 5. After the adjustment of the variables, the multivariable modeling revealed that the only factor associated with malnutrition was hemoglobin ($P=0.008$). No other laboratory factors were associated with malnutrition.

Table 4. Association between laboratory findings and malnutrition

<table>
<thead>
<tr>
<th></th>
<th>Without Malnutrition</th>
<th>With Malnutrition</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb (mg/dL)</td>
<td>14.74±2.84</td>
<td>13.06±2.70</td>
<td>0.007</td>
</tr>
<tr>
<td>Hct (mg/dL)</td>
<td>43.76±8.46</td>
<td>39.06±7.96</td>
<td>0.01</td>
</tr>
<tr>
<td>K</td>
<td>4.32±0.53</td>
<td>4.43±0.52</td>
<td>0.33</td>
</tr>
<tr>
<td>Ca</td>
<td>8.90±0.98</td>
<td>8.80±0.85</td>
<td>0.63</td>
</tr>
<tr>
<td>P</td>
<td>5.45±1.44</td>
<td>4.83±1.46</td>
<td>0.10</td>
</tr>
<tr>
<td>Na</td>
<td>137.27±5.23</td>
<td>135.91±10.61</td>
<td>0.92</td>
</tr>
<tr>
<td>Ca ion</td>
<td>1.66±0.41</td>
<td>1.71±0.46</td>
<td>0.62</td>
</tr>
<tr>
<td>Mg</td>
<td>1.92±0.37</td>
<td>1.83±0.39</td>
<td>0.26</td>
</tr>
<tr>
<td>FBS</td>
<td>93.51±14.43</td>
<td>87.93±21.63</td>
<td>0.08</td>
</tr>
<tr>
<td>D3</td>
<td>19.92±9.79</td>
<td>26.81±25.06</td>
<td>0.77</td>
</tr>
<tr>
<td>Albumin</td>
<td>34.95±7.76</td>
<td>35.27±7.45</td>
<td>0.75</td>
</tr>
<tr>
<td>Total protein</td>
<td>52.50±10.21</td>
<td>55.09±11.37</td>
<td>0.37</td>
</tr>
</tbody>
</table>
DISCUSSION

Malnutrition is one of the causes of the immune system deficiency and sensitivity to infections in humans. Severe protein-energy malnutrition in children is defined as a weight for age <70% the ideal value, or presence of edema in the Marasmus and Kwashiorkor conditions. Severe protein-energy malnutrition in children and infants causes thymus atrophy, reduced numbers of cells, and reduced antibody response to polysaccharide antigens of capsular bacteria such as Streptococcus pneumonia. The epithelial defense system is also disturbed for intestinal mucous structural changes and reduces the IgA secretion. Nutritional deficiency impairs the immune system competence and increases the frequency and severity of infection; in addition, it reduces muscle mass, physical energy, postoperative recovery, and wound healing. The association between the nutritional status and the immune system has been a research subject for several decades and numerous studies have shown that the protein-calorie malnutrition causes damage to the immune system, including cellular immunity and the secretion of immunoglobulin A. The protein-calorie malnutrition is one of the most important secondary causes of the immune system deficiency in the world. Several mechanisms have been proposed to explain the relationship between malnutrition and susceptibility to infectious diseases. For example, it causes a disorder in the normal development of the immune system. Stimulating the immune system by infection increases the demand for energy and results in a defective nutritional cycle and increased susceptibility to the infection. This infection by itself leads to a loss of protein, energy, minerals, and vitamin reserves of the body. During the immune response, energy consumption is increased, while food intake is decreased in the body of the infected person. Metabolic responses to infections include hypermetabolism, negative nitrogen balance, increased gluconeogenesis, and increased fat oxidation; such responses occur by the secretion of hormones, cytokines, and other proinflammatory mediators. In this study, the prevalence of malnutrition in the children was evaluated according to weight for age, weight for height, and height for age. The results showed that incidence of mild, moderate, and severe malnutrition, according to weight for age was 19.5% (n=23), 16.9% (n=20), and 32.2% (n=38); according to height for age was 15.4% (n=19), 13.8% (n=17), 20.3% (n=25); and according to weight for height was 19.4% (n=24), 18.5% (n=23), and 31.5% (n=39), respectively. Mehrizi and Drash reported that the prevalence of acute malnutrition and chronic malnutrition in their study was 55% and 52% in children, respectively. In Turkey, the incidence of acute malnutrition and chronic malnutrition was 65% and 42%, respectively, in children with congenital heart diseases. Because children with malnutrition are at risk for infectious diseases, in this work, the relationship between 4 types of infections (urinary tract, blood, surgical site, and pneumonia) was evaluated with malnutrition in children and the results demonstrated that pneumonia generally had a significant...
association with moderate and severe malnutrition ($P=0.006$). Additionally, there was a significant relationship with pneumonia according to weight for age ($P=0.007$), height for age ($P=0.01$), and weight for height ($P=0.036$).

Anderson et al\textsuperscript{12} showed that malnutrition, according to weight for age, in 19\% of their patients with single ventricle (age=18–72 mon) was below -2 SD and these children were more susceptible to postoperative infection ($P=0.006$). Moreover, the only predictive factor for a prolonged hospital stay was the development of nosocomial infections in these children.

In another research performed in 2004, the prevalence of surgical site infection in children undergoing cardiac surgery was estimated at approximately 3.4\% and the risk factor of such an infection was the duration of surgery in these children.\textsuperscript{13}

In the present study, the relationship between some biochemical factors such as hemoglobin, hematocrit, albumin, and total protein was also investigated with the incidence of infection. In the studied biochemical indicators, only hemoglobin ($P=0.007$) and hematocrit ($P=0.01$) were significantly associated with malnutrition in these children.

The relationship between anemia and pneumonia was specified in 1925. In a study conducted in 2014, malnutrition and anemia were introduced as pneumonia risk factors.\textsuperscript{14} The blood hemoglobin level is the most reliable anemia index among all individuals. Anemia is one of the major problems of society, which can affect any individual at any stage of life, but its prevalence is higher among women and children. Anemia is also proposed as one of the risk factors of lower respiratory tract infection among children.\textsuperscript{15-16} Iron is an essential nutrient for both humans and microbes. There are many assumptions about increased susceptibility to infectious diseases as the result of iron deficiency and iron deficiency anemia.\textsuperscript{15-17}

Cellular and humoral immunity is disturbed by iron deficiency anemia. For example, the phagocytic activity of monocytes is reduced in patients with iron deficiency anemia and bacteria-killing enzymes are not generated sufficiently in the individual with iron deficiency anemia. The generation of interleukin in children with iron deficiency anemia is also disturbed. Iron is required for the proliferation of high-speed tissues such as intestinal epithelial surface, which is among the protective organs against infections.\textsuperscript{16}

According to the results of the current research, since pneumonia and anemia are associated with malnutrition in children undergoing cardiac surgery, it is necessary to resolve them before therapeutic processes. Thus, it is recommended that these children be evaluated in terms of nutrition before undergoing therapeutic processes and the possible deficiencies be compensated for using nutritional supplements, proper nutrition techniques, increasing calorie intake, modifying the nutrition pattern, and using suitable nutritional supplements.

\textbf{Conflict of Interest:} There was no conflict of interest.

\textbf{REFERENCES}


Prevalence of HCV Infection Among Patients With Cardiovascular Disorders in Iran From March 2015 to September 2016

Hadi Khalaj¹, MS; Kambiz Mozaffari¹, MD; Nozar Givtag¹, PhD; Abbas Zavvarei¹, PhD; Nejat Mahdieh*, PhD

ABSTRACT

Background: Hepatitis C virus (HCV) infection is prevalent and potentially fatal in patients with cirrhosis and hepatocellular carcinoma. The main routes of transmission are via sharing syringes, blood products, and sexual contact. We sought to determine the incidence of HCV infection among patients with cardiovascular diseases (CVDs) in an 18-month period.

Methods: During a period of 18 months, 39450 patients with CVDs underwent HCV Ab measurement via the ELISA technique. Hbs Ag was also checked among HCV-positive cases in Rajaie Cardiovascular, Medical, and Research Center in Tehran, Iran from 2015 to 2016.

Results: The patients were aged between 4 months and 97 years. In 72 out of the 39450 patients (0.18%), HCV Ab was positive and 2 out of the 72 patients (2.7%) were also positive for HBs Ag.

Conclusions: The prevalence of HCV infection in patients affected by CVDs in a single referral center in Iran may be lower than that in other groups. (Iranian Heart Journal 2019; 20(2): 28-31)

KEYWORDS: HCV Ab, CVD, HCV infection

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Patients with cardiovascular diseases (CVDs) presenting to referral centers may also have comorbidities such as hepatitis C virus (HCV) infection and could, as such, spread their infection to healthcare workers and other patients. Thus, these patients’ infectivity status should be checked through serological methods; for instance, the ELISA method is drawn upon to determine patients’ HCV Ab levels. HCV infection is a global health problem with prevalence rates ranging from 0.1% to 12% in different countries.¹,² According to the World Health Organization, up to 3% of the world’s
population (ie, 170 million) has HCV infection. In other words, 2 million Iranian individuals are affected by this virus.

HCV infection is transmitted via such various routes as blood transfusion, sexual contact, and sharing needles. Indeed, contaminated needles and drug abuse are the major risk factors for HCV infection in Egypt and in Iran drug abuse is the main source of infection. Healthy blood donors are at different risk rates in various geographical regions. For instance, the prevalence of infection among these individuals is 0.01–0.02% in northern Europe and 1–1.5% in southern Europe, whereas this frequency is up to 6.5% in some parts of Africa. In addition, approximately 50–100% of intravenous drug abusers are affected by HCV the world over. Iran is located in the Middle East in a position akin to a bridge between the Indian Subcontinent, the Arabian Peninsula, Middle Asia, and Europe. There are many heterogeneous factors that constitute the etiologies of HCV infection in Iran and this scenario is liable to complication by mass immigration from Afghanistan and Iraq, frequent travels through Iran’s western borders to Turkey, and illegal drug trafficking from Iran’s eastern borders to Pakistan and Afghanistan, all of which have affected the epidemiology of HCV infection.

The groups at high risk for HCV infection include hemophiliacs, hemodialysis patients, infants born to mothers with HCV infection, and promiscuous individuals.

**METHODS**

The information obtained regarding the patients’ HCV infection status was retrieved through the hospital information system (HIS), and quality control and instrument calibration were performed before the analytical phase on a daily basis. This retrospective study was performed between 2015 and 2016 on 39450 patients with CVDs in Rajaie Cardiovascular, Medical, and Research Center, Tehran, Iran. From the entire study population, 5 mL of peripheral blood was obtained in a plain tube with an activator. The blood samples were used to determine, HCV Ab via the Enzyme-Linked Immunosorbent Assay (ELISA) method (Dia Pro Italy).

HCV antibodies were checked using the ELISA 192 Test Dia Pro System. All seropositive cases were checked using a secondary ELISA Kit (Dia Pro Italy), and HBs Ag was detected in these individuals as well. All the stages were performed according to the manufacturer’s manual.

**RESULTS**

The prevalence of HCV Ab among the patients was 1.8 per thousand (0.18%). Sixteen of the 39450 (0.04%) patients were female. The range of the patients’ age was between 4 months and 97 years. The distribution of the patients’ age and sex is shown in Figure 1. There were 72 seropositive cases; all these 72 HCV-positive patients were checked for co-infection of HBV Ag with the aid of the ELISA method. Two of these 72 patients also had HBs Ag in their sera. Accordingly, the prevalence of co-infection of HCV and HBV was 2/39450 among the patients. In the age range of 40–60 years, most of the cases were male (23 males vs 6 females) (Fig. 1), presumably because they were more likely to have been exposed to risk factors.

**DISCUSSION**

HCV infection is a cause of death and morbidity. Here, we report the HCV Ab results of 39450 patients with CVDs referring to Rajaie Cardiovascular, Medical, and Research Center, Tehran, Iran.

The overall prevalence of HCV Ab was 0.18% among our patients. A wide range of prevalence rates has been reported for HCV Ab in various regions of the world.
HCV affects 1% in the United Kingdom, while this prevalence is between 0.42% and 0.84% in Germany.\textsuperscript{11,12} Our study showed a low frequency of HCV infection in comparison to that in other populations. Other research groups have published similar prevalence rates for HCV infection in Iran. For example, Ahmadi et al\textsuperscript{13} studied 1654 cases using ELISA testing for HCV Ab and reported that the overall prevalence of HCV seropositivity was 0.42%. A systematic review of the published reports on the prevalence of HCV infection in Iranian populations showed that the frequency of HCV infection was 0.16%, varying from 0 in Khuzestan to 1.3% in Guilan.\textsuperscript{14} The HCV prevalence varies in different populations of Iran. In the present study, we focused on patients with CVDs referring to a tertiary referral center. This is the first study on a large number of patients suffering from CVDs in Iran. They are many factors that could affect the prevalence of HCV in Iran. The prevalence of HCV may have been decreased by a nationwide blood safety program in recent years, and traditional customs may have also contributed to the reduction in the frequency of HCV infection.

**Figure 1.** Age and sex distribution of HCV Ab positivity in patients referring to Rajaie Cardiovascular, Medical, and Research Center

**Figure 2.** Age distribution of HCV Ab positivity in patients referring to Rajaie Cardiovascular, Medical, and Research Center

**Acknowledgments**

We herewith thank all the staff of Central and Cardiogenetic Research Laboratories, Rajaie Cardiovascular, Medical, and Research Center.

**Conflict of Interest**

None.
Prevalence of HCV Infection Among Patients With Cardiovascular Disorders in Iran From March 2015 to September 2016

REFERENCES


Original Article

Evaluation of the Effects of Prazosin on Resistant Diastolic Hypertension With a Focus on Sex Difference

Hakimeh Saadatifar¹, MD; Fahimeh Khoshhal Dehdar¹, MD; Maryam Moshkani Farahani², MD; Mahmoud Salesi³, PhD; Samira Saadatifar¹, PhD

ABSTRACT

Background: Despite all the focus on systolic blood pressure (SBP), few studies exist on high diastolic blood pressure (DBP) treatment between the different genders. In this study, we investigated the effects of prazosin as an additional treatment for refractory DBP.

Methods: Totally, 75 nonblack adults were enrolled in this study with primary hypertension and DBP >100 mm Hg as isolated diastolic hypertension or systolic-diastolic hypertension. All the patients were treated with 1 or more drugs from the 5 major antihypertensive group drugs (ACE-I, ARB, diuretic, Ca-channel blockers, and beta-blockers). If hypertension did not respond to these drugs, prazosin was added at a mean dose of 1–2 mg (1.6 mg) daily.

Result: Many of the patients needed additional low doses of prazosin for the control of DBP. The response of the females was significantly better than that of the males to the 5 major antihypertensive drugs (P=0.001). This study showed that the 5 major drug groups, albeit conferring good SBP control (25.8% reduction in SBP), in the majority of the patients only caused a 10% decrease in DBP. However, prazosin led to a 21.8% decrease in DBP and a 9.5% decrease in SBP. Consequently, prazosin could be an effective drug in controlling resistant DBP with minimal side effects.

Conclusions: Low-dose prazosin as an additional drug to other major antihypertensive drugs with minor and transient complications can be reliably effective in reducing resistant DBP. (Iranian Heart Journal 2019; 20(2): 32-39)

KEYWORDS: Resistant, HTN-diastolic, HTN-systolic

Prazosin is an antihypertensive drug used in the second line according to the guideline (JNC 8)¹ if hypertension does not respond to other first-line drug groups (calcium-channel blockers, angiotensin-converting enzyme inhibitors [ACEIs], angiotensin receptor blocking agent [ARBs], diuretics, and beta-blockers). For all the attention hitherto paid to systolic blood pressure (SBP), there is a dearth of data on the treatment
of high diastolic blood pressure (DBP) in the different genders. Additionally, no specific studies have evaluated uncontrolled idiopathic diastolic hypertension in patients with a normal renal function. Accordingly, we sought to study the effects of adding low-dose prazosin to other hypertensive drugs in the management of diastolic hypertension (DBP>100 mm Hg) not responding well to other antihypertensive drugs. We also compared the effects of prazosin in resistant DBP between male and female patients.

**METHODS**

Seventy-five nonblack nonalcoholic Iranian patients (27–70 years old) with primary hypertension and DBP> 100 mm Hg (isolated diastolic hypertension or systolic-diastolic hypertension) were studied. Patients with secondary hypertension due to renal failure, nephropathy or other organ failure were excluded from this study. All the patients were visited in our outpatient clinic for uncontrolled hypertension during a 1-year period (2016–2017).

Blood pressure (BP) was recorded by a single investigator with a manual mercury sphygmomanometer on the right arm with cuff inflation in the sitting position after 10 minutes of rest. The mean blood pressure of at least 2 measurements on 2 separate observations was recorded in mm Hg. None of the patients was on antihypertensive therapy in the preceding 6 months. All the patients maintained their ordinary diet and exercise program throughout this study.

The mean BP was calculated as (2×DBP+1×SBP)/3. Height and body weight were used to calculate the body mass index (BMI) (weight [kg] / height² [m]). Statistical analysis was done using the χ² test or the Fisher exact test and the Mann–Whitney test. A P value <0.05 was considered significant.

Strategy B or C for antihypertensive drugs according to the JNC 8 was used1: (B strategy: Start 1 drug and then add a second drug before achieving the maximum dose of the initial drug.) and (C strategy: Begin with 2 drugs at the same time either as 2 separate pills or as a single pill combination.)

These drugs (diuretics, beta-blockers, ACEIs, ARBs, and Ca-channel blockers) were started in the first visit orally and their dose was increased gradually to control hypertension. SBP reached the target level (<140 mm Hg) in all the patients, but diastolic hypertension did not reach the target level (<90 mm Hg) in 50 patients and only 25 patients achieved the target DBP with these 5 first-line drugs.

The patients were visited at the intervals of 1 to 2 weeks. In the patients with uncontrolled diastolic hypertension after 1 month, low-dose oral prazosin was added to the other antihypertensive drugs.

In this study, information about the side effects of prazosin was given to the patients, especially first-dose postural hypotension. Almost all the patients received a diuretic for the control of SBP.

All the patients received 1 or more of the following antihypertensive drugs (5 major classes) to control systolic hypertension: hydrochlorothiazide, furosemide, atenolol, metoprolol, propranolol, captopril, enalapril, losartan, losartan-H (losartan 50 mg–12.5 mg hydrochlorothiazide), spironolacton, valsartan, and amlodipine.

After 1 month, prazosin was started in 50 patients with uncontrolled DBP at a dose of 0.5 mg at night. The patients were visited 3 days after starting prazosin to detect orthostatic hypotension (a fall of 10 mm Hg in SBP 3–5 minutes after a person assumes a standing position from a lying position). If DBP was not controlled, the dose of prazosin was increased gradually every 1 or 2 weeks. The dose of prazosin was 0.5–5 mg once or twice daily (0.5–10 mg, mean=1–2 mg [1.6 mg/d]). Prazosin was used in this study to lower
DBP to below 90 mm Hg and the other first-line drugs were also continued without any change in their dosage.

**RESULTS**

Table 1 shows the patients’ baseline characteristics according to response to hypertension treatment with the 5 major antihypertensive drugs.

According to Table 3, the response of the female patients to the 5 major antihypertensive drugs was better than that of the male patients ($P=0.001$), but no difference was detected based on their age differences and, overall, the response in the overweight patients was lower than that among the patients with normal weights ($P=0.07$).

### Table 1. Baseline characteristics according to response to hypertension treatment with the 5 major antihypertensive drugs

<table>
<thead>
<tr>
<th>Variable</th>
<th>Response to Treatment</th>
<th>Total</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>25(33.3%)</td>
<td>50(66.7%)</td>
<td>75(100%)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>14(60.9%)</td>
<td>9(39.1%)</td>
<td>23(30.7%)</td>
</tr>
<tr>
<td>Male</td>
<td>11(21.2%)</td>
<td>41(78.8%)</td>
<td>52(69.3%)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50</td>
<td>50.3 ± 8.8</td>
<td>52.6 ± 9.5</td>
<td>51.8 ± 5.8</td>
</tr>
<tr>
<td>≥50</td>
<td>10(32.3%)</td>
<td>21(67.7%)</td>
<td>31(41.3%)</td>
</tr>
<tr>
<td>51-55</td>
<td>9(45%)</td>
<td>11(55%)</td>
<td>20(26.7%)</td>
</tr>
<tr>
<td>≥56</td>
<td>6(25%)</td>
<td>18(75%)</td>
<td>24(32%)</td>
</tr>
<tr>
<td>BMI</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Normal</td>
<td>3(50%)</td>
<td>3(50%)</td>
<td>6(8%)</td>
</tr>
<tr>
<td>Overweight</td>
<td>9(22.5%)</td>
<td>31(77.5%)</td>
<td>40(53.3%)</td>
</tr>
<tr>
<td>Obesity</td>
<td>13(44.8%)</td>
<td>16(55.2%)</td>
<td>29(38.7%)</td>
</tr>
</tbody>
</table>

† $χ^2$ Test or the Fisher exact test, ‡ Mann–Whitney test

In Table 2, the BP changes before and after the addition of prazosin according to age, sex, and the BMI are presented. The SBP changes had a significant correlation with age and the 5 antihypertensive drugs. The older patients had a better response to the 5 antihypertensive drugs and the mean BP change was significant in the female patients ($P=0.032$).

After the addition of prazosin, although the DBP changes were not significant between sex, age, and the BMI, the drug was able to decrease DBP, especially in the men. The SBP changes in high BMI was significant with prazosin ($P=0.013$).

Table 2 and Figure 1 compare the changes in BP between the baseline characteristics of the patients.

### Side effects of prazosin in the study population

Six patients had orthostatic hypotension following the administration of the first doses, which was resolved after continuing the drug. Two patients suffered syncopal attacks after the first dose with no major trauma, which was resolved after continuing the drug. Five patients had palpitation, which required the addition of a beta-blocker (propranolol or metoral). Two patients reported headaches after the first doses. One patient reported vertigo with prazosin therapy, which was resolved after continuing the treatment. Two patients discontinued prazosin due to fatigue 2 months after it was started. One neurotic female patient discontinued prazosin after 2 months due to nasal congestion and impaired taste sensation but her DBP remained controlled.
### Table 2. Comparisons of the changes in blood pressure between the baseline characteristics

<table>
<thead>
<tr>
<th>BP</th>
<th>Factor</th>
<th>Group</th>
<th>Before</th>
<th>After</th>
<th>Change</th>
<th>P value</th>
<th>After</th>
<th>Change</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>DBP</td>
<td>Gender</td>
<td>Male</td>
<td>115.6±10.8</td>
<td>99.0±10.2</td>
<td>-16.6±11.1</td>
<td>.134‡</td>
<td>80.7±5.6</td>
<td>-22.4±7.5</td>
<td>.843‡</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td></td>
<td>114.7±11.6</td>
<td>91.9±11.9</td>
<td>-22.8±15.1</td>
<td></td>
<td>79.4±6.8</td>
<td>-24.4±11.8</td>
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<tr>
<td></td>
<td>Age</td>
<td>≤50</td>
<td>117.5±12.1</td>
<td>98.2±12.4</td>
<td>-19.3±10.5</td>
<td>.227†</td>
<td>80.7±5.9</td>
<td>-24.0±9.9</td>
<td>.755†</td>
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<td>116.0±12.3</td>
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<td>-21.5±16.4</td>
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<td>82.2±3.4</td>
<td>-20.9±8.0</td>
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<tr>
<td></td>
<td></td>
<td>≥56</td>
<td>112.0±7.2</td>
<td>97.0±9.3</td>
<td>-15.0±11.4</td>
<td></td>
<td>79.1±6.7</td>
<td>-22.5±6.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>BMI</td>
<td>Normal</td>
<td>115.0±10.4</td>
<td>91.6±9.8</td>
<td>-23.3±16.3</td>
<td>.397†</td>
<td>76.6±10.4</td>
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<td>.632†</td>
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<td>Overweight</td>
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<td>-17.1±13.2</td>
<td></td>
<td>80.5±5.2</td>
<td>-21.7±7.2</td>
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<tr>
<td></td>
<td></td>
<td>Obesity</td>
<td>115.8±12.6</td>
<td>96.3±13.1</td>
<td>-19.4±11.1</td>
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<td>81.2±6.2</td>
<td>-24.7±10.1</td>
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<td>Total</td>
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<td></td>
<td>80.5±5.8</td>
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<tr>
<td>SBP</td>
<td>Gender</td>
<td>Male</td>
<td>179.4±23.8</td>
<td>133.2±8.8</td>
<td>-46.1±20.1</td>
<td>.110‡</td>
<td>123.0±4.4</td>
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<tr>
<td></td>
<td>Female</td>
<td></td>
<td>181.3±22.6</td>
<td>128.0±10.0</td>
<td>-53.2±18.8</td>
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<td>120.0±7.1</td>
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<td>Age</td>
<td>≤50</td>
<td>171.6±21.4</td>
<td>130.6±8.6</td>
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<td>182.0±21.4</td>
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<td></td>
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<td>≥56</td>
<td>189.1±24.3</td>
<td>134.1±9.1</td>
<td>-55.0±20.3</td>
<td></td>
<td>123.9±4.7</td>
<td>-13.0±7.3</td>
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<tr>
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<td>BMI</td>
<td>Normal</td>
<td>176.6±27.3</td>
<td>125.8±12.8</td>
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<td>.678†</td>
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<td>.013†</td>
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<td>Overweight</td>
<td>177.2±23.2</td>
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<td>-46.3±18.9</td>
<td></td>
<td>122.2±4.0</td>
<td>-10.9±6.9</td>
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<tr>
<td></td>
<td></td>
<td>Obesity</td>
<td>184.2±22.9</td>
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<td>-50.5±20.5</td>
<td></td>
<td>122.5±6.8</td>
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<td>Total</td>
<td>180.0±23.3</td>
<td>131.6±9.4</td>
<td>-48.3±19.8</td>
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</tr>
<tr>
<td>Mean BP</td>
<td>Gender</td>
<td>Male</td>
<td>136.9±10.9</td>
<td>110.4±8.6</td>
<td>-26.4±10.2</td>
<td>.032‡</td>
<td>94.8±4.4</td>
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<tr>
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<td>Female</td>
<td></td>
<td>136.9±10.8</td>
<td>103.9±10.8</td>
<td>-32.9±12.5</td>
<td></td>
<td>92.9±6.3</td>
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<tr>
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<td>Age</td>
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<td>51-55</td>
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<td>106.4±10.5</td>
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<td></td>
<td>95.9±2.5</td>
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<td>≥56</td>
<td>137.7±9.6</td>
<td>109.4±8.2</td>
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<td>94.1±5.3</td>
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</tr>
<tr>
<td></td>
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<td>135.5±10.2</td>
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<td>94.4±3.8</td>
<td>-18.1±5.5</td>
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<tr>
<td></td>
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<td>138.7±12.1</td>
<td>108.9±11.1</td>
<td>-29.8±10.9</td>
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<td>95.0±5.9</td>
<td>-22.5±8.2</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>Total</td>
<td>136.9±10.8</td>
<td>108.4±9.7</td>
<td>-28.4±11.3</td>
<td></td>
<td>94.5±4.8</td>
<td>-19.6±6.7</td>
<td></td>
</tr>
</tbody>
</table>

DBP, Diastolic blood pressure; SBP, Systolic blood pressure; BMI, Body mass index

‡ Mann–Whitney test, † Kruskal–Wallis test, * only patients treated with prazosin

---

**Figure 1.** Changes in blood pressure (BP) according to response to hypertension treatment with the 5 major antihypertensive drugs and after prazosin therapy (BP3)
**DISCUSSION**

In our study, among different antihypertensive treatments, prazosin—a selective alpha receptor antagonist—effectively controlled resistant DBP, especially in male patients, while other antihypertensive agents usually controlled SBP. Previous studies have shown that prazosin decreases DBP and SBP by 10–14%. In our study, prazosin led to a 21.8% decrease in DBP and a 9.5% decrease in SBP. Therefore, we achieved a DBP <90 mm Hg with prazosin with no side effects at 12 months’ follow-up.

The effects of single or combination therapy with prazosin on controlling hypertension have been shown for decades; however, the effects of single therapy are less than those of combination therapy. Moreover, single therapy is mainly effective in mild-to-moderate hypertension.

In previous studies, besides prazosin, adding other alpha-blockers like doxazosin to other antihypertensive drugs resulted in the optimal control of BP in patients with resistant hypertension defined as failure of BP control despite treatment with 3 drugs, including diuretics.

Many studies have shown the favorable metabolic effects of alpha-blockers in antihypertensive regimens. In a study by Takao Saruta, prazosin increased HDL-cholesterol, inhibited the elevations of total cholesterol, and decreased triglycerides when administered in low doses in hypertensive patients.

A study showed that alpha (1)-adrenoceptor antagonists like doxazosin were useful in hypertensive patients who had hyperlipidemia, benign prostatic hyperplasia, pheochromocytoma, and hypertensive chronic cerebral infarction. It has also been reported that prazosin with its vasodilatory effects is useful in severe congestive heart failure through inducing a sustained decrease in both cardiac preload and impedance.

According to a previous study, adding 4 mg of extended-release doxazosin at night to multi-drug antihypertensive therapy improves cardiovascular autonomic control, increases heart-rate variability, controls SBP and DBP, and decreases pulse pressure. Frans et al reported the effects of prazosin on the regression of ventricular hypertrophy, which is effective in the prognosis of hypertensive patients, as compared with hydralazine.

The effects of prazosin on controlling BP in chronic renal failure and kidney transplantation patients have been well established. Furthermore, a group of patients with hypertension who use 2 or more drugs like diuretics or ACE inhibitors for hypertension control gradually develop some degrees of mild renal insufficiency, which highlights the importance of prazosin. The focus of our study was on high grades of resistant diastolic hypertension (≥110 mm Hg) in patients without renal or other organs failure. The SBP of all the patients was controlled with treatment regimens recommended in relevant guidelines, while their DBP was not controlled in 50 out of 75 patients.

In a study by Han et al, beta-blockers and ACE inhibitors were effective in controlling isolated diastolic hypertension and thiazide and calcium-channel blocker were effective in systolic/diastolic hypertension; nonetheless, in our study, DBP was not controlled in the majority of the patients (50 from 70) with these major first-line drugs.

A previous study showed that alpha-adrenoceptor blockade with prazosin reversed cardiac remodeling and ameliorated subcellular defects in heart failure due to myocardial infarction.

Further, previous studies have shown that it is easier to control DBP than SBP. In our study, DBP was not controlled with major antihypertensive drugs in 50 of 75 patients, in whom prazosin was used, despite SBP control. The reason for the difference could be that the
patients mostly had diastolic hypertension >110 mm Hg and only 6 out of 50 patients had DBP <110 mm Hg, whereas in previous studies, DBP was mainly less than these values. In our study, it was much harder to control high-grade diastolic hypertension than systolic hypertension in men and it was easier to achieve better control in women. In this study, patients with uncontrolled resistant diastolic hypertension were mostly men. This finding can be explained by the hormonal effects of androgen in men and the known effects of this hormone on activating the renin-angiotensin system and the subsequent increase in vascular resistance.\textsuperscript{18,19} Prazosin decreases vascular resistance as an alpha-blocker. The patients whose DBP was controlled without prazosin were mostly women, and the reason could be the hormonal effect and more stress in women.

In our study, adding low-dose prazosin to other antihypertensive regimens caused a reduction in DBP to the target level. Prazosin was administered at a mean dose of 1–2 mg (1.6 mg) daily in our study, starting from a dose of 0.5 mg oral at bedtime that increased gradually to 0.5–10 mg daily.

First-dose phenomenon with prazosin, which means orthostatic hypotension or syncope following the administration of the first dose of prazosin, has been reported in previous clinical studies mostly with higher doses and in combination with other antihypertensive drugs. We used low-dose prazosin in this study. Low-dose prazosin was started at night with no major side effects, especially syncope and orthostatic hypotension.

Of 50 patients that received prazosin, 6 had orthostatic hypotension following the first doses, which was resolved after continuing the drug. Two patients suffered syncopal attacks with the first dose with no major trauma, which was resolved after continuing the drug. Five patients, who were mostly young (<45 years of age), had palpitation, which required the addition of a beta-blocker (propranolol or metoral). Two patients reported headaches in the first doses. One patient reported vertigo with prazosin therapy, which was resolved after continuing the therapy. Two patients discontinued prazosin due to fatigue 2 months after it was started; DBP in these patients increased. One neurotic female patient discontinued prazosin after 2 months due to nasal congestion and impaired taste sensation but her DBP remained controlled.

In our study, if a patient discontinued prazosin, DBP increased during the 12-month follow-up. The only exception was the neurotic woman, in whom DBP did not increase after discontinuing prazosin. We had no cases of fluid retention as a side effect of prazosin.

Orthostatic hypotension is the most common side effect of prazosin that is mainly observed following the administration of the first dose of this drug. The following hints reduce the likelihood of its occurrence: using low-dose prazosin, taking the first dose just before sleeping, attention to the simultaneous use of diuretics, no sildenafil administration, and using prazosin in the first line of treatment.\textsuperscript{20} Renal failure, bradycardia, diabetes, hyperlipidemia, hyperuricemia, bronchospasm, and erectile dysfunction, which may be seen or exacerbated with other antihypertensive agents, are rare with prazosin.\textsuperscript{21} Prazosin is, therefore, considered a safe option in this situation.

Since DBP is directly associated with vascular resistance and inversely associated with pulse pressure, prazosin and other selective alpha-blockers like terazosin have an important role in the prognosis of cardiovascular and hypertensive patients through decreasing the vascular resistance and increasing pulse pressure.\textsuperscript{18}

Careful control of BP is very important in decreasing cardiovascular mortality and most hypertensive patients need 2 or more drugs to control their blood pressure.\textsuperscript{22} Thus, it is important to select drug combinations with minimal side effects to control DBP. Men have higher BP than do women at the same age due to the blunting of the pressure-natriuresis...
relationship, high androgen and renin-angiotensin system; nonetheless, post menopause, women mostly have higher BP than do men mostly due to the loss of estrogen.  

**CONCLUSIONS**

In our study, prazosin was an effective drug in controlling resistant DBP with minimal side effects besides other antihypertensive regimens, especially in male patients. More attention should be paid to adding this drug to the main antihypertensive drugs in the first line of treatment of high-grade diastolic hypertension in special groups of patients like those with metabolic disorders, hyperglycemia, hyperlipidemia, benign prostatic hyperplasia, and erectile dysfunction, as well as patients with cardiac failure, bradyarrhythmia, renal failure, and renal transplantation.

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**Conflict of Interest:** No conflicting relationship exists for any author.

**Disclosure:** The authors report no conflict of interest. The authors alone are responsible for the content and writing of the paper.

**REFERENCES**


Original Article

Evaluation of Cardiac Magnetic Resonance Imaging in Heart Failure Patients Suspected of Hypertensive Cardiomyopathy in Rajaie Cardiovascular, Medical, and Research Center Between 2015 and 2017

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ABSTRACT

Background: Chronic hypertension is one of the most important threats to public health in that it could cause structural and functional myocardial dysfunction, leading to myocardial hypertrophy and fibrosis. The early detection of cardiac remodeling due to hypertension has curative and preventive advantages; in this regard, cardiac magnetic resonance imaging (CMR) is a helpful modality.

Methods: In this cross-sectional descriptive study, 20 patients with heart failure and no other risk factors, except hypertension, who were referred to the Heart Failure Clinic of Rajaie Cardiovascular, Medical, and research Center between 2015 and 2017 were evaluated with CMR. The left ventricular mass index (LVMI) was normal in 55% and increased in 45% of the patients, and the left ventricular myocardial thickness (LVMT) was normal in 25% and increased in 75%. Twenty-five percent of the patients had normal LVMI and LVMT. Concentric remodeling was observed in 30% of the patients and 45% had concentric hypertrophy. All the patients had an increased LV end-systolic volume index. LV noncompaction without a specific fibrosis pattern was detected in 25% of the patients. Twenty-five percent of the patients had a scattered pattern, possibly due to diffuse interstitial fibrosis.

Conclusions: In this study, most of the patients with hypertensive cardiomyopathy were in the normal LVMI/LVMT or cardiac remodeling group and all of them had an increased LV end-systolic volume index. Both of these findings are suggestive of increased wall stress, which could lead to heart failure with a reduced ejection fraction and its progression. (Iranian Heart Journal 2019; 20(2): 40-46)

KEYWORDS: Hypertension, Cardiomyopathy, CMR (cardiovascular magnetic resonance)

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Hypertension is one of the important problems of public health in that it affects about 50% of patients who suffer from stroke or ischemic heart disease. Chronically elevated blood pressure could cause structural and functional myocardial disturbances. Left ventricular (LV) hypertrophy, a normal response to increased afterload, is commonly seen in hypertensive patients. Increased hypertension can lead to myocardial interstitial fibrosis, a relevant factor in LV hypertrophy and diastolic dysfunction.

Hypertensive cardiomyopathy is a structural heart disease and generally has an association with LV concentric hypertrophy as well as with systolic and diastolic dysfunction in patients with chronic hypertension. This disease could appear in the absence of other situations which could cause functional myocardial impairment and hypertrophy. Chronic increased blood pressure could cause myocardial functional and structural disturbances, leading to ischemia, fibrosis, and hypertrophy. Hypertensive cardiomyopathy usually causes relaxation impairment instead of contraction disorders. The patients are usually asymptomatic at rest, but their LV has no compliance for receiving the returned blood; consequently, it cannot eject enough cardiac output, causing exertional intolerance. The important point is that LV hypertrophy itself is a risk factor for morbidity and mortality, so the early detection of ventricular hypertrophy in hypertensive patients is crucial for better treatment. In addition to pathological findings, echocardiography and cardiac magnetic resonance imaging (CMR) are the ideal tools in hypertensive cardiomyopathy. Echocardiographic findings are helpful in the diagnosis of hypertensive cardiomyopathy and in its discrimination from other cardiomyopathies, including asymmetric left septum hypertrophy, which is commonly seen in hypertrophic cardiomyopathy and is highly characteristic of it; however, in LV hypertrophy due to hypertension or hypertensive cardiomyopathy, concentric LV hypertrophy is observed. Other studies have shown that although 13–31% of patients with hypertensive cardiomyopathy have symmetric hypertrophy, 4–47% of these patients have asymmetric septum hypertrophy. In this regard, echocardiographic findings themselves are not reliable for a definite diagnosis. Pathological evaluations are useful in the differential diagnosis of hypertensive cardiomyopathy. Invasive biopsy is a helpful tool for the specific diagnosis of hypertensive cardiomyopathy. Pathology is a powerful method; be that as it may, not only is biopsy an invasive procedure with its additional risks but also different studies have reported diverse histological findings.

CMR is capable of revealing data on the heart’s 3D anatomy, function, histological characteristics, and valvular diseases, as well as the perfusion of epicardial coronary arteries without ionized radiation. Myocardial fibrosis could be evaluated through gadolinium injection (an extracellular factor that accumulates in the regions of fibrosis and edema). Delayed gadolinium enhancement can detect infarction and fibrosis zones. The pattern and amount of late gadolinium enhancement are effective in the discrimination of hypertrophic cardiomyopathy from hypertensive cardiomyopathy. The evaluation of the LV mass and wall thickness with CMR has higher accuracy than that with echocardiography and is especially useful in detecting minor changes in the ventricular mass over time and after treatment. Additionally, it is useful as an independent prognostic factor in predicting cardiovascular mortality.

In the present study, we aimed to evaluate hypertensive cardiomyopathy in patients via CMR with a view to determining specific fibrosis patterns and assessing findings on the cardiac mass, wall thickness, end-systolic and end-diastolic volumes, and the stroke volume of the LV and the right ventricle (RV).
METHODS

CMR was done in all the patients (Siemens Avanto 1.5 T, Germany). Vertical and horizontal long-axis and sagittal planes of the LV outflow tract were acquired through balanced steady-state free precision cine images (acquired voxel size=1.6x1.3x8.0 mm; 25 phases per cardiac cycle). The short-axis cines were received from the mitral valve annulus to the apex (acquired voxel size=1.6x1.3x8.0 mm; 25 phases per cardiac cycle). The analysis of the images was done by standardized protocols for the measurement of the cardiac function and volumes and the LV mass. The short-axis views were used for the manual measurement of myocardial wall thickness. The assessment of myocardial fibrosis was done via late gadolinium enhancement. The optimization of the inversion time was used for myocardial nulling.

For the analysis of the CMR data, we drew upon the Normal Values for Cardiovascular Magnetic Resonance in Adults and Children Journal.

Patients with increased ventricular thickness and normal mass were categorized as concentric remodeling and patients with increased mass and also wall thickness were grouped as concentric hypertrophy.

The LV mass index was defined as the mass indexed to the body surface area, and the LV end-diastolic volume index was defined as the LV end-diastolic volume to the body surface area.

With respect to the left ventricular mass index (LVMI), the patients were divided into 3 groups: 1) normal range (49–85 for men and 41–81 for women), 2) increased range (>85 for men and >81 for women), and 3) decreased range (<49 for men and <41 for women). The results in relation to these definitions are outlined in Table 2.

The left ventricular ejection fraction (LVEF [%]) was categorized as follows: 1) normal value (57–77 for men and women), 2) increased value (>77 for men and women), and 3) decreased value (<57 for men and women).

The left ventricular end-systolic volume index (LVESVI [mL/m²]) classification was as follows: 1) normal value (14–38 for men and 14–34 for women), 2) increased value (>38 for men and >34 for women), and 3) decreased value (<14 for both sexes).

The left ventricular myocardial thickness (LVMT [mm]) was classified as follows: 1) normal value (5.7–10.9 for men and 4.6–9 for women), 2) increased value (>10.9 for men and >9 for women), and 3) decreased value (<5.7 for men and <4.6 for women).

The left ventricular stroke volume index (LVSVI [mL/m²]) was classified as follows: 1) normal value (42–66 for men and 38–66 for women), 2) increased value (>66 for both sexes), and 3) decreased value (<42 for men and <38 for women).

The right ventricular ejection fraction (RVEF [%]) classification was as follows: 1) normal value (52–72 for men 51–71 for women), 2) increased value (>72 for men and >71 for women), and 3) decreased value (<52 for men and <51 for women).

The right ventricular end-systolic volume index (RVESVI [mL/m²]) was classified as follows: 1) normal value (19–59 for men and 12–52 for women), 2) increased value (>59 for men and >52 for women), and 3) decreased value (<19 for men and <12 for women).

The right ventricular end-diastolic volume index (RVEDVI [mL/m²]) was classified as follows: 1) normal value (61–121 for men and 48–112 for women), 2) increased value (>121 for men and >112 for women), and 3) decreased value (<61 for men and <48 for women).

The right ventricular stroke volume index (RVSVI [mL/m²]) classification was as follows: 1) normal value (41–73 for men 35–71 for women), 2) increased value (>73 for men and >71 for women), and 3) decreased value (<41 for men and <35 for women).
RESULTS

The demographic characteristics of the study population are summarized in Table 1. The LVMI, LVEDVI, LVEF, LVESVI, LVMT, and LVSVI findings of the patients are outlined in Table 2. Additionally, the RVEF, RVESVI, RVEDVI, and RVSVI data are shown in Table 3.

The CMR evaluation of our patients with hypertensive cardiomyopathy showed LV noncompaction features in 25%. Furthermore, 25% of the patients had nonspecific scattered patterns during the fibrosis assessment.

Table 1. Demographic characteristics of the patients

<table>
<thead>
<tr>
<th></th>
<th>Number / median</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>50</td>
</tr>
<tr>
<td>Weight</td>
<td>80</td>
</tr>
<tr>
<td>Height</td>
<td>174</td>
</tr>
<tr>
<td>Male</td>
<td>n=16(80%)</td>
</tr>
<tr>
<td>Female</td>
<td>n=4(20%)</td>
</tr>
</tbody>
</table>

DISCUSSION

Chronically elevated blood pressure is one of the most important agents of public health problems that could cause myocardial structural and functional disorders and lead to the fibrosis and hypertrophy of the myocardium. Hypertensive cardiomyopathy is a structural heart disease that occurs in patients with longstanding increased blood pressure in the absence of diseases which could cause cardiac dysfunction and myocardial hypertrophy. LV hypertrophy and remodeling occurs commonly in hypertensive patients in response to increased afterload. Increased blood pressure leads to myocardial interstitial fibrosis, which is associated with LV hypertrophy and diastolic dysfunction. LV remodeling and hypertrophy in hypertensive cardiomyopathy patients is an accommodative response to increased afterload in the background of elevated blood pressure which is interpretable by the Laplace Law.

LV hypertrophy and remodeling occurs commonly in hypertensive patients in response to increased afterload. Increased blood pressure leads to myocardial interstitial fibrosis, which is associated with LV hypertrophy and diastolic dysfunction. On the other hand, an increased blood volume leads to an increased radius in the cardiac chambers and finally causes eccentric hypertrophy. Velagaleti on the basis of data from Framingham study suggested that eccentric hypertrophy as well as concentric hypertrophy eventually leads to heart failure with a reduced or preserved EF.

Twenty-five percent of the patients had normal LVMI and LVMT. Concentric remodeling was observed in 30% of the patients, and 45% had concentric hypertrophy. All the patients had an increased LVESVI.

Table 2. Frequency of the normal and abnormal findings in the left side

<table>
<thead>
<tr>
<th></th>
<th>LVMI</th>
<th>LVEDVI</th>
<th>LVEF</th>
<th>LVESVI</th>
<th>LVMT</th>
<th>LVSVI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>n=11(55%)</td>
<td>n=7(45%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased</td>
<td>n=9(45%)</td>
<td>n=13(65%)</td>
<td></td>
<td>n=20(100%)</td>
<td>n=15(75%)</td>
<td>n=4(20%)</td>
</tr>
<tr>
<td>Decreased</td>
<td>n=20(100%)</td>
<td></td>
<td></td>
<td>n=16(80%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 3. Frequency of the normal and abnormal findings in the right side

<table>
<thead>
<tr>
<th></th>
<th>RVEF</th>
<th>RVESVI</th>
<th>RVEDVI</th>
<th>RVSVI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>n=3(15%)</td>
<td>n=16(80%)</td>
<td>n=12(60%)</td>
<td>n=4(20%)</td>
</tr>
<tr>
<td>Increased</td>
<td>n=4(20%)</td>
<td>n=6(30%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased</td>
<td>n=17(85%)</td>
<td>n=6(30%)</td>
<td></td>
<td>n=16(80%)</td>
</tr>
</tbody>
</table>
detection in early stages to prevent the exacerbation of the disease by treatment in early stages.\textsuperscript{22}

CMR has a pivotal role in the detection and follow-up of these patients. It is a gold-standard method for measuring the EF, mass, and volume of the LV or the RV. CMR using Gadolinium could be effective in describing the myocardial texture, the existence of fibrosis, viability assessment, and also the diagnosis of diverse cardiomyopathies.\textsuperscript{22}

Elevated blood pressure can be a substrate for cardiac remodeling, the early detection of which is of utmost importance for the commencement of treatment and the prevention of heart failure progression, and CMR in this regard is helpful.\textsuperscript{22}

In this cross-sectional descriptive study, 20 patients with EF<40% who had no other risk factors for heart failure except hypertension were evaluated by CMR. Sixteen (80%) patients were male and 4 (20%) were female, and the median age of the study population was 50 years.

In their study, Ganau and colleagues\textsuperscript{17} reported that the LVMI and LV thickness were normal in about 52% of their hypertensive patients. In addition, 13 patients had increased wall thickness with normal mass (concentric remodeling), 27 had increased mass with normal wall thickness (eccentric hypertrophy), and 8% had increased mass and wall thickness (concentric hypertrophy).

Cuspidi and his colleagues\textsuperscript{18} in their study found a low prevalence of concentric hypertrophy in comparison with the eccentric type in hypertensive patients, but the concentric type could predispose to adverse complications as well as eccentric hypertrophy.

CMR findings in our study showed normal LVMI in 55% of the patients and increased values in 45%. The LVMI and LV thickness were normal in 25% of the patients, 13% had increased wall thickness with normal mass (concentric remodeling), and 45% had increased mass in addition to wall thickness (concentric hypertrophy). According to these findings, the majority of the patients were in the cardiac remodeling and normal group and all the patients had increased LVESVI. Probably, one of the causes of cardiomyopathy in these patients is increased wall stress, leading to cardiomyopathy and its progression.

The prevalence of LV hypertrophy is different according to the various stages of hypertension and varies between 20% in mild hypertension and 100% in severe hypertension.\textsuperscript{19} In a study conducted by Cuspidi and his colleagues\textsuperscript{17} based on echocardiographic data on 37 700 individuals, the prevalence of LV hypertrophy was 19–48% in patients with untreated hypertension and 58–77% in high-risk hypertensive ones.

The LVMT was normal in 25% and increased in 75% in our study. Wall thickness in the majority of the patients was in the normal or mildly increased range; therefore, this mild hypertrophy may have been associated with the increased LVESVI in all the patients, leading to elevated wall stress and predisposition to a reduction in the EF.

The late gadolinium enhancement pattern could be a new method for the risk stratification of patients with hypertensive cardiomyopathy. Given the relationship between fibrosis and diastolic dysfunction, it could be useful in the diagnosis of patients with hypertensive cardiomyopathy who are at risk of diastolic heart failure.\textsuperscript{19}

Fifty percent of patients with elevated blood pressure had late gadolinium enhancement without specific patterns and most of them had focal non-subendocardial distributions in a study by Andersen, Rudolph and their colleagues.\textsuperscript{20,21} The assessment of fibrosis in our study showed a scattered pattern in 25% of the patients unlike specific patterns in other cardiomyopathies. LV noncompaction was seen in 25% of the patients: they may have had this disorder from the outset and its association with hypertension caused the progression of heart failure or it might have been the longstanding
hypertension which predisposed them to LV noncompaction. Precise control of hypertension is recommended, especially in patients with increased wall stress based on myocardial thickness, diameter, and volume in initial imaging and also in the presence of systemic hypertension. These patients should be visited at shorter intervals with tight control of their blood pressure. It is recommended that evaluations of hypertensive patients be in a prospective manner to define which mechanical characteristics of their heart lead to the reduced EF with a view to defining a better approach to diagnosis and treatment in these patients.

CONCLUSIONS

In our hypertensive patients with a reduced EF, increased ventricular wall thickness and mass led to a concentric hypertrophy pattern in the majority of the patients. Increased LVESVI caused elevated wall stress, injury to myocytes, and finally a reduced EF.

Abbreviations
CMR: Cardiovascular Magnetic Resonance; LV: Left Ventricle; RV: Right Ventricle; BSA: Body Surface Area; SV: Stroke Volume; EF: Ejection Fraction; CI: Cardiac Index; LVMT: Left Ventricular Myocardial Thickness; LVMI: Left ventricular Mass Index; LVESVI: Left ventricular End Systolic Volume Index; LVEDVI: Left Ventricle End Diastolic Volume Index; LVSVI: Left Ventricular Stroke Volume Index; RVEDVI: Right Ventricular End Diastolic Volume Index; RVESVI: Right Ventricular Stroke Volume Index.

Limitations
This case-series evaluation had a small sample volume. In addition, ethical issues regarding CMR performance precluded a comparison of the results with those in normal subjects.

Acknowledgments
We herewith thank Mrs. Fereshteh Hasanzadeh, the magnetic resonance imaging supervisor at Omid Hospital, for her collaboration with us in this study.

REFERENCES


Original Article

Impact of Hypertension on the Phase Analysis Parameters of Gated Single-Photon Emission Computed Tomography Myocardial Perfusion Imaging

Nahid Yaghoobi1, MD; Zahra Jamshidi Araghi1, MD; Hadi Malek1*, MD; Hasan Firoozabadi1, MD; Fereydoon Rastgou1, MD; Hooman Bakhshande1, PhD; Ahmad Bitarafan Rajabi1, PhD

ABSTRACT

Background: We sought to evaluate the association between hypertension (HTN) and left ventricular (LV) mechanical synchrony parameters derived via the phase analysis of gated single-photon emission computed tomography (GSPECT) myocardial perfusion imaging (MPI).

Methods: Ninety-nine patients with no known coronary heart disease (CHD) who underwent GSPECT MPI and had normal resting and post-stress scan with a recent normal echocardiographic examination and a positive history of HTN were recruited. The gated images were analyzed by Cedar–Sinai’s quantitative GSPECT. The global and regional LV mechanical synchrony indices—including phase histogram bandwidth (PHB), phase standard deviation (PSD), and entropy—were derived and compared with the results of the control group, which had previously been defined with the same protocol for a group of 100 patients with a low likelihood for CHD.

Results: Comparisons between the study and control groups revealed that neither global nor regional wall-based indices for PHB, PSD, and entropy were significantly different between the 2 groups ($P > 0.05$), whether or not HTN was accompanied by comorbid diabetes. Congruent with the control group, a significant difference was detected between the global LV phase parameters of the 2 genders ($P < 0.05$).

Conclusions: HTN does not intrinsically have a significant impact on the mechanical synchrony indices of GSPECT MPI. (Iranian Heart Journal 2019; 20(2): 47-55)

KEYWORDS: Hypertension, SPECT, MPI, Left ventricular dyssynchrony, Phase analysis

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Coronary heart disease (CHD) has long been established as a leading cause of morbidity and mortality among adults, and the crucial role of the conventional risk factors in the development of this disease of paramount importance has well been appreciated. Hypertension (HTN) is one of the major independent risk factors, which apart from association with obstructive coronary artery disease could impose significant adverse
effects on the cardiac structure as increased left ventricular (LV) wall thickness and mass, leading to LV hypertrophy and the deterioration of diastolic and systolic functions.\(^3\) On the other hand, some common chronic conditions such as impaired fasting glucose have been estimated to be more prevalent in adults with than in those without HTN.\(^4\) Of note, diabetes mellitus (DM), as a common comorbidity of HTN (and CHD), could itself impose the same adverse effect on the cardiac structure and function.\(^5\) Gated single-photon emission computed tomography (GSPECT) myocardial perfusion imaging (MPI) is a well-established imaging method for the evaluation of myocardial ischemia as well as for the assessment of other relevant clinical issues in patients with CHD including response to treatment, risk stratification, and myocardial viability.\(^6\) More recently, the application of the evolving technique of LV phase analysis to GSPECT MPI has made it easily applicable to evaluate global and regional LV mechanical dyssynchrony simultaneously with the assessment of the LV myocardial perfusion and function\(^6,\)\(^7\) by using different types of automated software algorithms.\(^7,\)\(^8\) In addition, compared with other imaging modalities for the assessment of LV mechanical dyssynchrony, the main advantages of the phase analysis of GSPECT MPI are widespread availability, simplicity, repeatability, high reproducibility, and automated quantification.\(^6,\)\(^9-12\)

A growing body of literature has investigated different factors which could probably exert an influence on the distribution of the LV phase indices—including the heart rate,\(^13\) the injected dose of the radiotracer,\(^8\) the type of image reconstruction,\(^14\) the acquisition orbit,\(^15\) and the presence or absence of perfusion defects in MPI.\(^9\) Accordingly, the present study was undertaken to determine whether HTN as a common comorbidity in CHD \(^2\) has any appreciable independent impact on the global and regional parameters of phase analysis by comparing the results with those of patients categorized as low risk for CHD.

To the best of our knowledge, this article is the first study to specifically evaluate the impact of HTN on the phase analysis indices of GSPECT MPI.

**METHODS**

**Patients and Study Protocol**

A group of consecutive patients with no known CHD who had been referred to our department on the basis of the cardiologists’ clinical judgment underwent MPI. The study inclusion criteria were coexistence of a positive history of HTN in the presence of normal resting and post-stress MPI in addition to a recent (within 2 months) normal echocardiography indices including a normal global left ventricular ejection fraction (LVEF\(\geq\) 50%)\(^16\) in particular and without any appreciable evidence of wall motion abnormality or valvular heart disease. A normal MPI was defined as the absence of any significant perfusion defect read by an expert nuclear medicine specialist in agreement with a summed stress score <4 and the absence of an elevated lung-to-heart uptake ratio (LHR>0.4) or transient LV dilation (>1.1 for the exercise test and >1.15 for the dipyridamole stress test). A normal gated functional study was described as a global LVEF\(\geq\)50% with a summed motion score and a summed thickening score of zero.\(^17\)

Ultimately, a total of 99 subjects met the criteria. A positive history of HTN as well as DM was defined on the basis of the patients’ medical records and documents; all the patients were under medical treatment and reasonably controlled.

The control group was composed of 100 subjects with a low pretest likelihood for CHD who had previously been evaluated for the determination of the normal ranges of global and regional phase indices provided by Malek et al.\(^17\)
**Image Acquisition and Processing**
Gated SPECT MPI was acquired according to the predefined 2-day stress (exercise or pharmacological with dipyridamole)/ rest protocol using 10–15 mCi of Tc99m-sestamibi in each phase of the study. Imaging was started 15–20 minutes following exercise and 45–60 minutes after resting injections or pharmacological stress tests. The acquisition was performed in the supine position using a dual-headed SPECT-CT camera (Symbia T2, Siemens Medical Systems) with low-energy high-resolution collimators, a window of 20% around the 140-keV Tc99m photopeak, step and shoot mode, 180° right anterior oblique to left posterior oblique arc, noncircular body-contoured orbit with 64 projections, 25 seconds per projection, 16 frames per ECG R-R cycle, and fixed temporal resolution forward-backward gating mode using a fixed acceptance window of 30%. The data were stored in a 64 × 64 matrix.

All the images were initially reviewed for quality assurance and the exclusion of those distorted by any kind of interfering factors including extracardiac or excessive sub-diaphragmatic radiotracer activity and motion artifacts. Then reconstruction was done by filtered back projection using Butterworth filtering (cutoff: 0.4, order: 5), followed by data processing with the commercially available Cedar-Sinai’s quantitative gated SPECT (QGS) software to derive LV phase indices—including phase histogram bandwidth (PHB) (the width of histogram which includes 95% of the elements in the phase distribution), phase standard deviation (PSD) (standard deviation of the phase distribution), and entropy (defined by summation of \([f_i \times \log(f_i)]/\log(n)\), in which \(f\) and \(n\) are representing frequency in the \(i^{th}\) bin and number of bins, respectively) based on the 2 modes of global whole LV and regional wall-based model, composed of 5 main ventricular walls: apex, septum, anterior, inferior, and lateral walls.

**Statistical Analysis**
The fitness of the interval data to a normal distribution was assessed using the one-sample Kolmogorov–Smirnov test. The data were described as mean ± standard deviation (SD) for the interval variables and count (%) for the categorical variables. Comparisons of the measured indices between the study groups were performed via the independent \(t\)-test (for 2 groups) and one-way analysis of variance (ANOVA), followed by the Bonferroni post-hoc test (for 3 groups). A \(P\) value ≤ 0.05 was considered to be statistically significant. The statistical analyses were conducted with IBM SPSS Statistics 22 for Windows (IBM Inc, Armonk, NY).

**RESULTS**

**Patients**
Of the total 99 patients who were enrolled in the study from October 2017 to March 2018, 66 (66.6%) were male. The patients were divided into 2 groups, consisting of patients suffering from only HTN (66.7%) and those with a positive history of HTN in conjunction with DM (33.3%). The mean duration of HTN was 6.1±6.4 years; all the patients were under medical treatment and controlled.

The demographic and baseline GSPECT data of the whole study group as well as those of the control group are summarized in Table 1.

The LV phase indices (PHB, PSD, and entropy) were derived based on global whole ventricle and regional wall-based synchrony at resting and post-stress conditions.

**Global Parameters**
As is presented in the tables, the derived values for PHB, PSD, and entropy in neither of the patient groups were significantly different from those in the control group, neither at rest (Table 2) nor at the post-stress phase \((P>0.05)\) (Table 3).

**Regional Parameters**
In the same manner, the regional wall-based synchrony parameters disclosed no significant
difference in PHB, PSD, and entropy between the 2 groups of patients and the control group in either of the rest or post-stress phase (Table 4 and Table 5, respectively).

**Sex Differences**
In agreement with the control group, all of the 3 calculated synchrony parameters were significantly different between the 2 genders of the whole study group (Table 6).

**Stress Test**
As is shown in Table 7, a comparison of the 2 types of the stress test revealed no statistically significant difference between any of the synchrony indices.

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**Table 1.** Demographic and baseline GSPECT data of the study population and the control group

<table>
<thead>
<tr>
<th>Demographic and LV Function Parameters</th>
<th>Patients LLK (N=100)</th>
<th>Patients With HTN+/−DM (N=99)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>56(56%)</td>
<td>49(49.5%)</td>
</tr>
<tr>
<td>BW (kg)</td>
<td>83.32±17.00</td>
<td>79.21±14.31</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>167.15±9.29</td>
<td>164.51±11.03</td>
</tr>
<tr>
<td>BMI (Kg/m²)</td>
<td>29.74±5.2</td>
<td>29.06±4.15</td>
</tr>
<tr>
<td>Age (y)</td>
<td>48.47±9.76</td>
<td>59.84±8.93</td>
</tr>
<tr>
<td>EDV (mL)</td>
<td>66.3±18.9</td>
<td>65.24±18.49</td>
</tr>
<tr>
<td>ESV (mL)</td>
<td>20.5±15.4</td>
<td>16.59±10.04</td>
</tr>
<tr>
<td>LVEF</td>
<td>0.74±0.87</td>
<td>0.76±0.09</td>
</tr>
<tr>
<td>Exercise stress</td>
<td>19(19%)</td>
<td>49(49.5%)</td>
</tr>
</tbody>
</table>

BW, Body weight; BMI, Body mass index; EDV, End-diastolic volume; ESV, End-systolic volume; LVEF, Left ventricular ejection fraction.

**Table 2.** Comparison of the global whole LV synchrony phase parameters at resting state between the control and the 2 study groups

<table>
<thead>
<tr>
<th>Global Whole LV Phase Parameters (Rest)</th>
<th>Control Group (N=100)</th>
<th>HTN (N=66)</th>
<th>Patients With DM &amp; HTN (N=33)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PHB</td>
<td>29.12±10.40</td>
<td>27.91±10.65</td>
<td>26.55±9.25</td>
<td>.434</td>
</tr>
<tr>
<td>PSD</td>
<td>7.07±3.17</td>
<td>6.68±2.78</td>
<td>6.42±2.85</td>
<td>.497</td>
</tr>
<tr>
<td>Entropy</td>
<td>0.33±0.75</td>
<td>0.32±0.08</td>
<td>0.32±0.08</td>
<td>.722</td>
</tr>
</tbody>
</table>

Data are presented as mean ± standard deviation, PHB and PSD in degrees, and entropy in percentages.

**Table 3.** Comparison of the global whole LV synchrony phase parameters at the post-stress phase between the control and the 2 study groups

<table>
<thead>
<tr>
<th>Global Whole LV Phase Parameters (Stress)</th>
<th>Control Group (N=100)</th>
<th>HTN (N=66)</th>
<th>Patients With DM &amp; HTN (N=33)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PHB</td>
<td>24.54±9.14</td>
<td>24.36±8.47</td>
<td>25.45±8.62</td>
<td>.837</td>
</tr>
<tr>
<td>PSD</td>
<td>5.78±2.55</td>
<td>5.84±2.20</td>
<td>6.19±2.50</td>
<td>.697</td>
</tr>
<tr>
<td>Entropy</td>
<td>.29±.07</td>
<td>.29±.080</td>
<td>.31±.07</td>
<td>.598</td>
</tr>
</tbody>
</table>

Data are presented as mean ± standard deviation, PHB and PSD in degrees, and entropy in percentages.

LV, Left ventricle; PHB, Phase histogram bandwidth; PSD, Phase standard deviation.
Table 4. Comparison of regional wall-based LV synchrony phase parameters at resting state between the control and the 2 study groups

<table>
<thead>
<tr>
<th>Regional Wall-Based Phase Parameters (Rest)</th>
<th>Control Group (N=100)</th>
<th>Patients With HTN (N=66)</th>
<th>Patients With DM &amp; HTN (N=33)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apex</td>
<td>PHB</td>
<td>13.14±4.06</td>
<td>12.00±4.07</td>
<td>13.2±4.68</td>
</tr>
<tr>
<td></td>
<td>PSD</td>
<td>2.65±1.13</td>
<td>2.41±1.26</td>
<td>2.70±1.41</td>
</tr>
<tr>
<td></td>
<td>Entropy</td>
<td>0.14±0.07</td>
<td>0.13±0.07</td>
<td>0.14±0.08</td>
</tr>
<tr>
<td>Lateral</td>
<td>PHB</td>
<td>25.80±12.43</td>
<td>24.27±12.06</td>
<td>21.45±7.35</td>
</tr>
<tr>
<td></td>
<td>PSD</td>
<td>7.09±5.08</td>
<td>6.01±3.38</td>
<td>5.24±2.41</td>
</tr>
<tr>
<td></td>
<td>Entropy</td>
<td>0.29±0.10</td>
<td>0.28±0.08</td>
<td>0.26±0.08</td>
</tr>
<tr>
<td>Inferior</td>
<td>PHB</td>
<td>23.27±9.60</td>
<td>24.09±9.26</td>
<td>22.36±8.25</td>
</tr>
<tr>
<td></td>
<td>PSD</td>
<td>5.84±3.28</td>
<td>5.78±2.80</td>
<td>5.36±2.33</td>
</tr>
<tr>
<td></td>
<td>Entropy</td>
<td>0.27±0.91</td>
<td>0.28±0.09</td>
<td>0.27±0.08</td>
</tr>
<tr>
<td>Septum</td>
<td>PHB</td>
<td>22.5±11.06</td>
<td>21.00±11.73</td>
<td>20.72±17.35</td>
</tr>
<tr>
<td></td>
<td>PSD</td>
<td>5.64±3.44</td>
<td>5.16±3.35</td>
<td>4.78±2.56</td>
</tr>
<tr>
<td></td>
<td>Entropy</td>
<td>0.26±0.09</td>
<td>0.24±0.12</td>
<td>0.24±0.10</td>
</tr>
<tr>
<td>Anterior</td>
<td>PHB</td>
<td>23.22±10.28</td>
<td>23.90±10.33</td>
<td>23.09±14.70</td>
</tr>
<tr>
<td></td>
<td>PSD</td>
<td>6.29±3.23</td>
<td>5.68±2.79</td>
<td>5.84±4.89</td>
</tr>
<tr>
<td></td>
<td>Entropy</td>
<td>0.29±0.10</td>
<td>0.28±0.10</td>
<td>0.26±0.08</td>
</tr>
</tbody>
</table>

Data are presented as mean ± standard deviation, PHB and PSD in degrees, and entropy in percentages.
LV, Left ventricle; PHB, Phase histogram bandwidth; PSD, Phase standard deviation

Table 5. Comparison of regional wall-based LV synchrony phase parameters at the post-stress phase between the control and the 2 study groups

<table>
<thead>
<tr>
<th>Regional Wall-Based Phase Parameters (Stress)</th>
<th>Control Group</th>
<th>Patients With HTN (N=66)</th>
<th>Patients With DM &amp;/or HTN (N=33)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apex</td>
<td>PHB</td>
<td>11.28±3.93</td>
<td>11.09±3.68</td>
<td>10.54±3.01</td>
</tr>
<tr>
<td></td>
<td>PSD</td>
<td>2.04±1.22</td>
<td>2.08±1.31</td>
<td>1.91±1.06</td>
</tr>
<tr>
<td></td>
<td>Entropy</td>
<td>0.10±0.07</td>
<td>0.11±0.07</td>
<td>0.09±0.06</td>
</tr>
<tr>
<td>Lateral</td>
<td>PHB</td>
<td>22.74±12.15</td>
<td>22.09±10.53</td>
<td>22.54±9.00</td>
</tr>
<tr>
<td></td>
<td>PSD</td>
<td>5.63±3.64</td>
<td>5.39±3.10</td>
<td>5.71±2.85</td>
</tr>
<tr>
<td></td>
<td>Entropy</td>
<td>0.26±0.09</td>
<td>0.26±0.09</td>
<td>0.27±0.07</td>
</tr>
<tr>
<td>Inferior</td>
<td>PHB</td>
<td>19.88±10.59</td>
<td>20.72±8.69</td>
<td>22.72±9.80</td>
</tr>
<tr>
<td></td>
<td>PSD</td>
<td>4.75±3.06</td>
<td>4.83±2.43</td>
<td>5.67±3.21</td>
</tr>
<tr>
<td></td>
<td>Entropy</td>
<td>0.24±0.08</td>
<td>0.24±0.08</td>
<td>0.27±0.10</td>
</tr>
<tr>
<td>Septum</td>
<td>PHB</td>
<td>18.24±7.76</td>
<td>19.27±9.14</td>
<td>20.36±10.81</td>
</tr>
<tr>
<td></td>
<td>PSD</td>
<td>4.23±2.39</td>
<td>4.81±2.84</td>
<td>4.84±2.96</td>
</tr>
<tr>
<td></td>
<td>Entropy</td>
<td>0.22±0.08</td>
<td>0.23±0.09</td>
<td>0.23±0.11</td>
</tr>
<tr>
<td>Anterior</td>
<td>PHB</td>
<td>20.88±7.83</td>
<td>20.81±7.45</td>
<td>19.63±5.25</td>
</tr>
<tr>
<td></td>
<td>PSD</td>
<td>5.00±2.35</td>
<td>5.02±2.16</td>
<td>4.70±1.48</td>
</tr>
<tr>
<td></td>
<td>Entropy</td>
<td>0.25±0.08</td>
<td>0.25±0.08</td>
<td>0.25±0.07</td>
</tr>
</tbody>
</table>

Data are presented as mean ± standard deviation, PHB and PSD in degrees, and entropy in percentages.
LV, Left ventricle; PHB, Phase histogram bandwidth; PSD, Phase standard deviation

Table 6. Gender-specific global synchrony parameters in the whole study population

<table>
<thead>
<tr>
<th>Global Whole LV Phase Parameters(Rest)</th>
<th>Female (N=50)</th>
<th>Male (N=49)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PHB</td>
<td>24.96±9.26</td>
<td>30.00±10.53</td>
<td>.013</td>
</tr>
<tr>
<td>PSD</td>
<td>5.88±2.43</td>
<td>7.33±2.97</td>
<td>.010</td>
</tr>
<tr>
<td>Entropy</td>
<td>0.30±0.07</td>
<td>0.34±0.08</td>
<td>.009</td>
</tr>
</tbody>
</table>

Data are presented as mean ± standard deviation, PHB and PSD in degrees, and entropy in percentages.
LV, Left ventricle; PHB, Phase histogram bandwidth; PSD, Phase standard deviation
Impact of Hypertension on Phase Analysis

Table 7. Comparison of the global LV synchrony parameters at the post-stress phase between the exercise and pharmacological tests

<table>
<thead>
<tr>
<th>Global Whole LV Phase Parameters</th>
<th>Pharmacologic Stress Test (N=50)</th>
<th>Exercise Test (N=49)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PHB</td>
<td>Stress 23.88±7.42</td>
<td>25.59±9.46</td>
<td>0.319</td>
</tr>
<tr>
<td></td>
<td>Rest 26.40±9.99</td>
<td>28.53±10.35</td>
<td>0.300</td>
</tr>
<tr>
<td>PSD</td>
<td>Stress 5.77±2.01</td>
<td>6.15±2.56</td>
<td>0.403</td>
</tr>
<tr>
<td></td>
<td>Rest 6.16±2.66</td>
<td>7.04±2.87</td>
<td>0.119</td>
</tr>
<tr>
<td>Entropy</td>
<td>Stress 0.30±0.07</td>
<td>0.30±0.08</td>
<td>0.956</td>
</tr>
<tr>
<td></td>
<td>Rest 0.31±0.08</td>
<td>0.34±0.07</td>
<td>0.072</td>
</tr>
</tbody>
</table>

Data are presented as mean ± standard deviation, PHB and PSD in degrees, and entropy in percentages. LV, Left ventricle; PHB, Phase histogram bandwidth; PSD, Phase standard deviation.

DISCUSSION

To the best of our knowledge, this article is the first study to specifically evaluate the impact of HTN on the phase analysis indices (PHB, PSD, and entropy) of GSPECT MPI. Compared with the control group, composed of subjects categorized as a low pretest likelihood for CHD with normal ECG, normal LVEF, and negative MPI, we found no significant differences between the mechanical synchrony parameters in the study group, composed of patients suffering from HTN alone or HTN and DM together.

Gated SPECT MPI, which is widely used for the evaluation of CHD, is a validated accurate method to assess mechanical dyssynchrony in conjunction with the assessment of myocardial perfusion and the LV function in a single study. A considerable body of literature has addressed the influence of various technical issues on the relationship between certain preclinical states and the phase analysis parameters of GSPECT MPI. Among the technical factors, the method of image reconstruction and the type of camera represented no influence on the calculated parameters, while the total accumulated count or noise has shown significant effects on the indices in question. On the other hand, investigations on the administered dose of the radiotracer on the phase analysis results are still controversial. In terms of the patients’ demographic data and clinical status, gender as well as the post-stress and resting state of the patients during image acquisition has shown a significant impact on the phase analysis indices; whereas, age and the pattern of perfusion abnormality have demonstrated no influence on mechanical dyssynchrony parameters.

HTN, as a major conventional risk factor and a common comorbidity of CHD, is well known for its adverse effects not only on coronary arteries and myocardial perfusion but also on the cardiac structure and function, which may lead to LV hypertrophy and heart failure. It may also induce subendocardial ischemia and could be hypothesized as a potentially influential factor on LV mechanical dyssynchrony and on the indices derived by GSPECT MPI. In addition, DM has been introduced as a common comorbidity for either CHD or HTN with similar adverse effects on the cardiac structure, perfusion, and function with the same potential impact on LV mechanical dyssynchrony.

Precedent for our study, Hämäläinen et al reported a normal range of phase analysis parameters in a group of subjects wherein hypertensive patients without any history of cardiovascular problems were enrolled and then subanalyzed. In terms of LV phase analysis indices, no statistically significant difference was noted between the subjects without and the patients with risk factors in their subanalysis.
In keeping with this observation, Samad et al provided information about dyssynchrony in patients with LV dysfunction in which patients with a positive history of DM and HTN were analyzed as subgroups. The study revealed an association between HTN and an increase in PSD by a univariate model, even though it was not confirmed by a multivariate analysis. DM, nevertheless, manifested no appreciable influence on the phase analysis parameters in comparison with those of the others without this comorbid condition. Guillermo et al also found no significant association in their pilot study subanalysis between cardiovascular risk factors and LV phase indices. We provided data which might rule out the association between HTN and mechanical dyssynchrony. Our study also confirmed that the LV phase parameters are significantly influenced by gender. It could also be stated that the different methods of the stress test (ie, exercise and dipyridamole tests) do not have a significant impact on the phase indices derived from GSPECT MPI, which was in contrast with the results of the control group.

**Limitations**

The present study has all the same limitations of a single tertiary center study with a limited number of patients. Our study should be considered a hypothesis-generating study. We did not classify the hypertensive patients based on the duration or severity of their disease or the type of medical treatment; as a result, a larger study population of patients suffering from HTN having different degrees of adverse impact on the cardiac structure and function might be needed to confirm the results. Moreover, for ethical reasons, the control group was not recruited from normal volunteer subjects.

**New Knowledge Gained**

There seems to be no direct association between HTN and LV mechanical synchrony.

**CONCLUSIONS**

HTN does not intrinsically have a significant impact on the mechanical synchrony indices of GSPECT MPI. It could be concluded that in the presence of this cardinal risk factor, whether or not accompanied by DM, the phase analysis data of the patients with or suspected of CHD could independently be interpreted as the direct effect of the coronary epicardial disease not influenced by this comorbid state.

**Conflict of Interest:** None.

**REFERENCES**


Impact of Hypertension on Phase Analysis

Yaghoobi et al


Original Article

Gastrointestinal Complications After Cardiac Surgery

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ABSTRACT

Background: Gastrointestinal (GI) complications occur after 0.4–2.9% of cardiac surgery procedures. Although infrequent, GI complications constitute some of the most serious complications of cardiac surgery with a high associated morbidity and mortality rate of 14–63%. In this study, we aimed to determine the incidence of and the risk factors for GI complications following open-heart surgery.

Methods: In this retrospective study, 800 adult patients who underwent valvular surgery, coronary artery bypass grafting (CABG), combined procedures, aortic surgery, and the surgical correction of adult congenital heart defects in Rajaie Cardiovascular, Medical, and Research Center between April 2014 and May 2016 were studied. The clinical data on any GI complication—including its incidence, characteristics, diagnostic measures, mortality, and medical or surgical management—were retrospectively analyzed. Statistical analysis was performed using a non-paired Student t-test and the χ² test.

Results: A total of 800 patients underwent open cardiac surgery: 340 (42.5%) had CABG, 290 (36.3%) had valve surgery, 120 (15%) had combined procedures (valve surgery + CABG), 15 (1.9%) had aortic surgery, and 35 (4.3%) had congenital defect correction. Among these patients, GI complications were seen in 36 patients, with an incidence rate of 4.5%. The total mortality rate was 11.1%. Our results revealed that advanced age, a prolonged cardiopulmonary bypass time, prolonged mechanical ventilation, a history of peptic ulcer, and the use of inotropic support or intra-aortic balloon pumps were the risk factors for GI complications after cardiac surgery.

Conclusions: GI complications following cardiac surgery have a low incidence rate but high morbidity and mortality rates. Primary detection and prompt appropriate intervention are essential for the outcome of the patients. (Iranian Heart Journal 2019; 20(2): 56-61)

KEYWORDS: Gastrointestinal complications, Cardiac surgery, Complications, Cardiac surgery, Acute mesenteric ischemia, Cardiopulmonary bypass

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Gastrointestinal (GI) complications occur after 0.4–2.9% of cardiac surgery procedures.\(^1\) Although infrequent, GI complications are deemed serious complications of cardiac surgery with a high associated morbidity and mortality rate of 14–63%.\(^2,3\) The most common reported GI complications include bleeding, pancreatitis, perforated ulcer, mesenteric ischemia, ileus obstruction, cholecystitis, and diverticulitis.\(^4\) Despite the advances made in the areas of anesthesia, extracorporeal circulation, surgical techniques, perfusion technologies, and postoperative care, the rate of GI complications is still high following cardiac surgery.\(^5\) It can be a challenge to reach an early diagnosis of such complications. Unfortunately, patients with GI complications frequently present with atypical symptoms, often have severe underlying diseases, and may be unable to describe symptoms or react to examination due to mechanically ventilated sedation and analgesia. In addition, the symptoms may be overshadowed by severe cardiac and pulmonary conditions.\(^5,6,7\) There is a growing belief that splanchnic perfusion during cardiopulmonary bypass (CPB) may not be adequate for metabolic needs and, thus, contributes to the development of GI complications.\(^8\) What usually ensues is prolonged mechanical ventilation and intensive care unit (ICU) and hospital lengths of stay as well as additional invasive procedures such as surgery and endoscopy, all of which increase the cost of hospitalization.\(^9,10,11\) In this study, we aimed to determine the incidence of and the risk factors for GI complications following open-heart surgery.

**METHODS**

In this retrospective study, 800 adult patients who underwent valvular surgery, coronary artery bypass grafting (CABG), combined procedures, aortic surgery, and the surgical correction of adult congenital heart defects in Rajaie Cardiovascular, Medical, and Research Center between April 2014 and May 2016 were studied. The exclusion criteria consisted of off-pump CABG and thoracic or thoracoabdominal aortic surgery. Every operation involved the use of moderately hypothermic (28–32°C) CPB perfusion. Myocardial preservation was achieved with cold (4°C) crystalloid cardioplegia solutions and warm blood via both anterograde and retrograde techniques, supplemented with topical hypothermia in the pericardial cavity. During CPB, the hematocrit level was kept minimally at 22–25%. All the patients had a nasogastric tube placed in the operating room, and the tube remained in place for a minimum of 12 hours after the operation and longer if the patient remained intubated. They also received prophylactic intravenous antibiotics and conventional blood or liquid infusion, if necessary. In patients with a postoperative low cardiac output, inotropic drug support was required, with or without the insertion of the intra-aortic balloon pump (IABP). The routine inotropic drug support consisted of dopamine/duobafendin or amrinon/milrinone, combined with additional vasoconstrictors such as adrenalin and phenylephrine, if necessary. Postoperatively, all the patients underwent a routine prophylactic antacids treatment against ulcers with ranitidine in the ICU. A proton-channel blocker (pantoprazole) was only used in patients with a history of ulcers. Anticoagulant therapy was applied in all cases that had undergone valve(s) replacement and/or vascular prosthesis implantation. GI complications were classified as follows: GI hemorrhage, gastroduodenal perforation, paralytic ileus, acute calculus cholecystitis, acute calculus cholecystitis, and ischemic bowel disease. The clinical data on any GI complication—including its incidence, characteristics, diagnostic measures, mortality, medical or surgical management, and relative risks—were retrospectively analyzed.\(^7\) Statistical analysis was performed using a non-paired Student \(t\)-test and the \(\chi^2\) test. The
statistical analyses were performed using the SPSS software, version 21, for Windows (SPSS Inc, Chicago, IL, USA). A P value < 0.05 was considered statistically significant.

RESULTS

Out of the 800 patients, 464 (58%) were men and 336 (42%) were women at a mean age of 68±13.5 years. The mean weight was 68.6 kg, and the body mass index was 21.8. The operative procedures were comprised of CABG, isolated valve surgery, combined CABG and valve surgery, and the surgical correction of adult congenital heart defects. Totally, 411 (62.7%) patients were placed on the pump for a maximum of 100 minutes and 228 (37.3%) patients experienced it for longer than 100 minutes. The demographic and operative characteristics of all the patients are illustrated in Table 1. In addition, 495 (61.8%) patients had hypothermia over 30°C and 305 (38.2%) experienced hypothermia ≤28 °C. For all the study participants, the mean arterial pressure was 65 mm Hg during cardiac surgery. A total of 800 patients underwent open cardiac surgery: 340 (42.5%) had CABG, 290 (36.3%) had valve surgery, 120 (15%) had combined procedures (valve surgery + CABG), 15 (1.9%) had aortic surgery, and 35 (4.3%) had congenital defect correction. Among these patients, GI complications were seen in 36 patients, with an incidence rate of 4.5%. The total mortality rate was 11.1%, as opposed to 1.3% in the patients without GI complications (P<0.0001). The mortality and morbidity in the patients with and without postoperative GI complications are presented in Table 2. Nine patients needed surgical treatment, and medical handling was applied in the remaining patients. The results of the logistic regression analysis of the risk factors for GI complications after cardiac surgery are depicted in Table 3.

<table>
<thead>
<tr>
<th>Complication</th>
<th>Patients</th>
<th>Incidence</th>
<th>Laparotomies</th>
<th>Deaths</th>
<th>Mortality(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GI bleeding</td>
<td>8</td>
<td>22.2</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Paralytic ileus</td>
<td>12</td>
<td>33.3</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Acute cholecystitis</td>
<td>5</td>
<td>13.8</td>
<td>5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>4</td>
<td>11.1</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Gastroduodenal perforation</td>
<td>2</td>
<td>2.7</td>
<td>1</td>
<td>1</td>
<td>50</td>
</tr>
<tr>
<td>Ischemic bowel disease</td>
<td>2</td>
<td>5.5</td>
<td>2</td>
<td>2</td>
<td>100</td>
</tr>
<tr>
<td>Hepatic dysfunction</td>
<td>4</td>
<td>11.1</td>
<td>0</td>
<td>1</td>
<td>25</td>
</tr>
<tr>
<td>Total</td>
<td>36</td>
<td>4.5</td>
<td>9</td>
<td>4</td>
<td>11.1</td>
</tr>
</tbody>
</table>

GI, Gastrointestinal

<table>
<thead>
<tr>
<th>Without GI Complications</th>
<th>With GI Complications</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>1.3%</td>
<td>11.1%</td>
</tr>
<tr>
<td>Mean intensive care stay (d)</td>
<td>3.8±2.97</td>
<td>11.25±8.63</td>
</tr>
<tr>
<td>Mean hospital stay (d)</td>
<td>11.23±3.15</td>
<td>27.35±9.65</td>
</tr>
</tbody>
</table>

GI, Gastrointestinal

The patients with GI complications had a longer ICU stay and a higher mortality rate, while the late appearance of GI complications was associated with a prolonged hospital stay (Table 2).

According to our logistic regression analysis, advanced age, a prolonged CPB time, prolonged mechanical ventilation, a history of peptic ulcer, and the use of inotropic support or the IABP were the risk factors for GI complications after cardiac surgery (Table 3).
DISCUSSION

The pathophysiology of GI complications after cardiac surgery has yet to be fully elucidated. A low cardiac output resulting in visceral hypoperfusion and mucosal ischemia and necrosis has been implied. Surgical trauma, anticoagulation, anesthesia, CPB, and hypothermia are responsible for triggering stress responses that may ultimately lead to visceral organ injury. CPB has also been implicated in the development of micro emboli, increase in intestinal permeability, free radical production through ischemia reperfusion injury, splanchnic hypoperfusion, and gastric mucosal acidosis. Previous studies have reported that complications after cardiac surgery are relatively rare, with an incidence ranging from 0.3–2% and a high mortality rate of 11–59%. For example, the inpatient mortality rate of patients who developed ischemic bowel disease or gastroduodenal perforation was as high as 100% and 50%, respectively. In our study, the incidence of GI complications in patients undergoing cardiac surgery was 4.5% with a mortality rate of 11.1%, both of which are consistent with the existing reports. Despite improvements in perioperative care, monitoring, anesthesia, and operative techniques, the incidence and mortality of GI complications have not changed through the years. In the current study, 5 possible predictors of GI complications after cardiac surgery were identified: older age, increased durations of CPB time, prolonged mechanical ventilation, a history of peptic ulcer, and the use of inotropic support or the IABP, which chimes in with the studies by Gomez et al, Karangelis et al, Vassiliou et al, Zhang et al, Mangi et al, Rodriguez et al, Filsoufi et al, Ashfaq et al, and Gulkarov et al. Vasoconstrictor drug therapy after cardiac surgery, exclusively norepinephrine and epinephrine, has been associated with a rise in mean arterial pressure and systemic blood flow; however, it is correlated with a decline in the splanchnic flow repartition of blood flow from the splanchnic to the systemic circulation. In our study, we found a significant relationship between GI complications and a prolonged length of stay in the ICU and the hospital, which is consistent with the studies by Chaudhry et al, Yapici et al, and Rodriguez et al.

CONCLUSIONS

In conclusion, GI complications following cardiac surgery have a low incidence rate but high morbidity and mortality rates. The diagnosis of GI complications remains difficult because signs and symptoms are often subtle, or nonspecific, and this commonly leads to a delay in definitive diagnosis and treatment. Primary detection and prompt appropriate intervention are essential for the outcome of the patients.

Acknowledgements

We hereby thank all the personnel of Rajaie Cardiovascular, Medical, and Research Center.

REFERENCES


Original Article

Diagnostic Myocardial Perfusion Imaging to Detect the Anatomical Location of Coronary Artery Disease Compared With Invasive Coronary Angiography

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ABSTRACT

Background: Although invasive coronary angiography (CAG) is the gold standard for the diagnosis of coronary artery disease (CAD), myocardial perfusion imaging (MPI) is also used in suspected cases. In this study, we sought to determine the diagnostic value of MPI in the anatomical localization of CAD.

Methods: In a retrospective study, all patients with an intermediate to high probability of CAD who had positive single-photon emission computed tomography MPI and subsequently underwent CAG between January 2016 and January 2017 were evaluated.

Results: A total of 210 patients at a mean age of 60.2±10.6 years underwent MPI and CAG. Abnormal anterior segments in MPI had a positive predictive value (PPV) of 68.1% to detect a diseased left anterior descending artery (LAD), and the negative predictive value (NPV) of similar segments for a concomitant LAD and right coronary artery (RCA) involvement was the highest (90.4%). Abnormal inferior segments in MPI had PPVs of 65.1% and 47% for the LAD and the RCA, respectively. The NPV was 81.8% for a concomitant LAD and RCA involvement and it was greater than either of each alone. Among the patients with abnormal posterior segments, the RCA and the left circumflex artery (LCX) had a PPV of 66.7%, which was greater than that of a concomitant RCA and LCX involvement. The NPV for either RAC or LCX alone or both arteries together was similar.

Conclusions: MPI provides a relatively good diagnostic accuracy to detect abnormal segments matched to the involved coronary arteries in CAG. However, diagnostic accuracy was more pronounced in matching single-vessel CAD compared with double-vessel CAD. (Iranian Heart Journal 2019; 20(2): 62-68)

KEYWORDS: Coronary artery disease, Myocardial perfusion imaging, Coronary angiography

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Atherosclerosis is a multifactorial disease attributed to some conventional risk factors, and it leads to the development of coronary artery disease (CAD). The exact prevalence of CAD as the manifestation of atherosclerosis is unknown, particularly in an asymptomatic population. With the implementation of noninvasive imaging modalities such as echocardiography, computed tomography coronary angiography, myocardial perfusion imaging (MPI), positron emission tomography, and cardiovascular magnetic resonance imaging, there have been higher numbers of CAD cases among patients with suspected ischemic heart diseases.

Although invasive coronary angiography (CAG) is the gold standard for the diagnosis of CAD, the application of imaging modalities in patients with suspected acute coronary syndrome (ACS) with an inconclusive electrocardiogram and cardiac biomarkers is recommended by the guidelines. Of those imaging modalities, MPI is a widely-used and cost-effective tool which is of great diagnostic value for the evaluation of patients with known or suspected CAD, or even for the left ventricular function. Despite its good diagnostic accuracy in different studies, the sensitivity and specificity of MPI can be varied, which may be attributable to the study population. In the present study, we sought to evaluate the diagnostic value of MPI in the localization of CAD among patients with suspected CAD who had positive MPI findings and subsequently underwent invasive CAG.

**METHODS**

**Study Protocol**

In a retrospective study, all patients who had an intermediate to high probability for CAD underwent single-photon emission computed tomography (SPECT) MPI and subsequently underwent CAG between January 2016 and January 2017 were evaluated. The inclusion criteria included patients older than 18 years old with stable angina and positive MPI for the diagnosis of CAD who subsequently underwent invasive CAG. Patients with a prior myocardial infarction, a recent or recurrent ACS, valvular heart diseases, and heart failure were excluded from the study. Our local ethics committee at Iran University of Medical Sciences approved the study protocol.

**Diagnostic Modalities**

In all the patients, nuclear scanning was performed using the rest-stress protocol SPECT MPI (with technetium-99m sestamibi) along with the symptom-limited exercise test or the pharmacological stress test. Data were obtained using a Philips Forte SPECT camera (Philips Healthcare, the Netherlands), followed by making reconstructions presenting in a polar map format based on segmental territories. All patients with a positive MPI underwent invasive CAG to identify the probable lesions in the coronary arteries. All CAG procedures were undertaken based on the Judkins technique and were analyzed without knowledge of MPI results. A significant CAD was defined as at least 1 coronary artery with >50% stenosis. For each artery, the most severe stenosis was identified.

**Anatomical Territories**

The result of SPECT MPI was categorized into 3 segments as follows:

1) anterior and anteroseptal
2) inferior
3) posterior

And the result of invasive CAG was matched for each of the mentioned segments as follows:

1) left anterior descending artery (LAD), right coronary artery (RCA), alone and both together
2) LAD, RCA, alone and both together
3) RCA, left circumflex artery (LCX), alone and both together

**Statistical Analysis**

All the data were presented as mean ± SD or numbers (percentages). The diagnostic performance of MPI was also compared with that of CAG so as to identify patients with significant CAD in defined anatomical territories and its relevant coronary artery...
branch. All the analyses were performed using the SPSS statistical software for Windows, version 18.0 (Chicago, IL, SPSS Inc). Two-sided P values were calculated.

RESULTS
A total of 210 patients with abnormal MPI who subsequently underwent CAG were analyzed. The patients’ mean age was 60.2±10.6 years, and 124 patients (59%) were male. Other medical histories are summarized in Table 1. Fifty-four (25.7%) patients had normal coronary arteries without significant involvement of the arteries. The number of patients with triple-vessel, double-vessel, and single-vessel CAD was 54 (25.7%), 50 (23.8%), and 46 (21.9%), respectively. The LAD was involved the most (64.3%). The concomitant involvement of the LAD and the RCA was more frequent than other double-vessel CADs. The significant involvement of the left main CAD was detected in 6 (2.9%) patients.

The patients with the involvement of the anterior and anteroseptal walls of the heart in MPI had a positive predictive value (PPV) of 68.1% to detect a diseased LAD. The PPV of the RCA or a concomitant LAD and RCA involvement was less than that of the LAD alone. In addition, the negative predictive value (NPV) of MPI with involved anterior and anteroseptal segments was the highest (90.4%) in the patients with a concomitant significant LAD and RCA involvement (Table 2). The patients with abnormal inferior segments in MPI had PPVs of 65.1% and 47% for diseased LAD and RCA in CAG, respectively. However, the NPV was 81.8% for a concomitant LAD and RCA involvement, and it was greater than that of the LAD or RCA alone (Table 3). Among the patients with posterior wall abnormalities in MPI, the RCA and the LCX had a similar PPV (66.7%), and it was greater than that of a concomitant RCA and LCX involvement. On the other hand, the NPV for either RCA or LCX alone or both arteries together was similar (Table 3).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total patients</td>
<td>210</td>
</tr>
<tr>
<td>Age (y)</td>
<td>60.2 ± 10.6</td>
</tr>
<tr>
<td>Male gender</td>
<td>124 (59%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>120 (57.1%)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>119 (56.7%)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>93 (44.3%)</td>
</tr>
<tr>
<td>Current smoking</td>
<td>65 (31%)</td>
</tr>
<tr>
<td>Familial history of CAD</td>
<td>97 (46.2%)</td>
</tr>
<tr>
<td>Prior myocardial infarction</td>
<td>70 (33.3%)</td>
</tr>
</tbody>
</table>

Table 1. Patients’ characteristics and overall findings in the imaging evaluation

<table>
<thead>
<tr>
<th>CAG</th>
<th>MPI for the Anterior and Anteroseptal Walls</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Positive</td>
<td>58.5%</td>
<td>50.7%</td>
<td>68.1%</td>
<td>59.6%</td>
<td>0.200</td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td>37</td>
<td>38</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Positive</td>
<td>67.7%</td>
<td>54.7%</td>
<td>54.3%</td>
<td>68.1%</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td>53</td>
<td>64</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Positive</td>
<td>64%</td>
<td>45.9%</td>
<td>13.8%</td>
<td>90.4%</td>
<td>0.348</td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td>100</td>
<td>85</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2. Diagnostic performance of MPI to detect coronary arteries perfusing the anterior and anteroseptal walls of the heart
Table 3. Diagnostic performance of MPI to detect coronary arteries perfusing the inferior wall of the heart

<table>
<thead>
<tr>
<th>CAG</th>
<th>MPI for the Inferior Wall</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Positive</td>
<td>108/27</td>
<td>80%</td>
<td>22.6%</td>
<td>65.1%</td>
<td>38.6%</td>
</tr>
<tr>
<td>LAD</td>
<td>Negative</td>
<td>58/17</td>
<td></td>
<td></td>
<td></td>
<td>0.649</td>
</tr>
<tr>
<td>RCA</td>
<td>Positive</td>
<td>78/15</td>
<td>83.9%</td>
<td>24.8%</td>
<td>47%</td>
<td>65.9%</td>
</tr>
<tr>
<td>LAD and RCA</td>
<td>Positive</td>
<td>17/8</td>
<td>68%</td>
<td>19.4%</td>
<td>10.2%</td>
<td>81.8%</td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td>88/29</td>
<td></td>
<td></td>
<td></td>
<td>0.126</td>
</tr>
</tbody>
</table>

Table 4. Diagnostic performance of MPI to detect coronary arteries perfusing the posterior wall of the heart

<table>
<thead>
<tr>
<th>CAG</th>
<th>MPI for the Posterior Wall</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCA</td>
<td>Positive</td>
<td>2/81</td>
<td>2.1%</td>
<td>56%</td>
<td>66.7%</td>
<td>99.1%</td>
</tr>
<tr>
<td>LCX</td>
<td>Negative</td>
<td>1/126</td>
<td></td>
<td></td>
<td></td>
<td>0.333</td>
</tr>
<tr>
<td>RCA and LCX</td>
<td>Positive</td>
<td>2/2</td>
<td>50%</td>
<td>98.5%</td>
<td>40%</td>
<td>99%</td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td>3/203</td>
<td></td>
<td></td>
<td></td>
<td>0.643</td>
</tr>
</tbody>
</table>

**DISCUSSION**

Although CAG is the gold standard for the evaluation of CAD, noninvasive modalities have been used first for the selection of proper patients who need to undergo such an invasive procedure. The use of MPI has been dramatically increased in European countries. Based on a meta-analysis, MPI has been associated with an average sensitivity of 87% and a specificity of 73% for the detection of CAD diagnosed by angiography; however, there has been a post-test referral bias leading to a decrease in the specificity of MPI. On the other hand, a previous study showed that without post-test referral bias, MPI had less sensitivity and slightly higher specificity. Due to study designs and population sizes, the amounts of sensitivity and specificity have been varied among studies. The main factors influencing the different diagnostic values include referral bias, the intensity of the exercise test, the use of anti-anginal medications before the test, the absence of clinical information upon interpreting scan, tracer activity below the diaphragm, some technical issues related to MPI, image quantification, and concomitant electrocardiogram-gating. The retrospective nature of our study precluded a distinction between low- and high-risk probabilities of CAD among patients referred for MPI; we, therefore, used only positive MPI reports to detect the anatomical significance of MPI compared with that of invasive CAG.

The diagnosis of CAD by noninvasive imaging such as MPI and stress echocardiography is based on the assessment of myocardial territories perfused by distinct coronary arteries and the physiological significance of CAD, not the anatomical extent of CAD. However, multi-slice computed tomography angiography (CTA) is another noninvasive imaging method which has been used for the evaluation of atherosclerosis and subsequent CAD similar to invasive CAG. Stein et al. found a strong NPV for CTA capable of excluding significant CAD and, thus, concluded that CTA findings should...
be also strengthened by concomitant use of pretest clinical probability assessments. In a large study comparing CTA and SPECT MPI, with the increasing severity of stenosis detected by CTA, there was an increase in abnormal MPI tests, suggesting that normal coronary arteries on CTA had a high PPV for a normal MPI.\(^\text{15}\)

Schwartz et al\(^\text{16}\) matched anatomically invasive CAG to SPECT MPI in order to evaluate the diagnostic value of SPECT MPI for the detection of CAD in the distribution of first-order branches. They demonstrated that SPECT MPI had intermediated sensitivity, specificity, and accuracy to detect CAD in the distribution of first-order coronary arteries (all values=67%). In addition, this sensitivity of MPI was higher in patients without a prior history of coronary artery bypass surgery. In our study, an abnormal MPI at the anterior and anteroseptal territories had a PPV of 68.1% to detect CAD in the LAD and it was higher than that value for the RCA; nonetheless, the RCA had more sensitivity and both LAD and RCA together had the least accuracy. An abnormal MPI in the inferior segment had a PPV of 65.1% to detect a diseased LAD and it was found to have a sensitivity of 83.9% to detect the involved RCA. For the abnormal SPECT MPI at the posterior wall, the RCA and LCX had similar PPVs (66.7%), but it had the highest sensitivity for diseased RCA and LCX together (50%). In summary, all MPI segments as defined in our study had the highest PPV for the detection of single-vessel CAD. In addition, the NPV was highest for double-vessel CAD at each segment for the anterior and inferior segments. However, in the patients with posterior wall abnormalities in MPI, the NPV was similar for single and double-vessel CAD.

**Study Limitations**

This study has some limitations that need to be taken into account in the interpretation of the results. Firstly, our sample size is relatively small and our test accuracies may not be generalizable to other populations. Secondly, if only patients with abnormal MPS undergo angiography, then the observed sensitivity and specificity will be 100% and 0%, respectively. Accordingly, we have not been able to use the findings of the current study for the overall diagnostic accuracy of MPI compared with invasive CAG, as the old standard method. Thirdly, due to the small sample size and the nature of MPI reports in our department, we categorized our population into the anatomical territories mentioned in the methods. All MPI segments and matched coronary arteries can be presented in another way for more precision; however, this classification was based on our saved MPI reports and cannot be changed in another categorization. Further studies are required to find the precise diagnostic performance of SPECT MPI in the detection of matched anatomical CAD diagnosed by invasive CAG.

**CONCLUSIONS**

SPECT MPI provides relatively good diagnostic accuracy to detect abnormal segments matched to the significant involvement of coronary arteries in CAG. The diagnostic values were more pronounced in matching single-vessel CAD compared with double-vessel CAD.

**Conflict of Interest:** The authors have no conflict of interest.

**REFERENCES**

1. Dehghani MR, Rezaei Y, Taghipour-Sani L. Superiority of total white blood cell count over other leukocyte differentials for predicting long-term outcomes in patients with non-st elevation
Diagnostic MPI to Detect Anatomical Location of CAD Compared With Invasive Coronary Angiography

Eskandari et al


Original Article

Comparison of the Results of Left Ventricular Epicardial and Endocardial Pacing Through the Coronary Sinus in Patients With Triple-Chamber Pacing

Aboalfath Alizadeh¹, MD; Ehsan Ghourchian *², MD; Sajad Naderi², MD; Mohammadesmaeil Zanganehfar², MD; Ali Ghasemi², MD; Najand Salek², MD; Sara Baramaki², MD

ABSTRACT

Background: Considering the many reports of elevated threshold levels and left ventricular dysfunction in epicardial leads, the evaluation of the short- and long-term efficacy of this type of leads is necessary in comparison with the coronary sinus (CS) leads. The present study compared left ventricular epicardial pacing via surgery and CS pacing in patients with triple-chamber pacemakers.

Methods: This retrospective cohort study was performed on patients referred for cardiac resynchronization therapy. The patients were re-evaluated with ECG after pacemaker implantation and before discharge. The evaluations were performed in 2 patient groups under left ventricular epicardial pacing and CS pacing.

Results: At 12 months’ follow-up, the mean left ventricular pacing lead threshold was significantly higher in the patients with epicardial lead pacing than in those with endocardial lead pacing. Additionally, regarding the ECG pattern after lead pacing, the morphology of QRS at V₁ lead and also the type of the QRS axis significantly differed between epicardial pacing and CS pacing 6–12 months after pacemaker implantation. The mean left ventricular pacing lead threshold was at its highest in the posterolateral area and at its lowest in the anterolateral area, but without any significant difference.

Conclusions: Comparisons between the results and the long-term effects of CS pacing and surgical epicardial lead pacing in the present study indicated that the increase and changes in the left ventricular leading threshold in the epicardial pacing lead were much more pronounced than those in CS pacing through the CS. Therefore, the use of CS leads might be preferred to pericardial leads due to the stability of left ventricular leads. (Iranian Heart Journal 2019; 20(2): 69-74)

KEYWORDS: Epicardial LV lead, Endocardial LV lead, Coronary sinus

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Treatment by cardiac resynchronization therapy (CRT) synchronicity preserves and stores ventricular, interventricular, and intraventricular contractility and results in improved clinical outcomes and cardiac function in patients with congestive heart failure along with a broad QRS complex.\(^1\) However, a significant percentage of patients with CRT (about 40%) do not show improvement in clinical manifestations or cardiac function.\(^2\) A lack of left ventricular dyssynchrony, the inappropriate placement of the left ventricle lead, a high myocardial pulsation rate, and undesirable programming of CRT devices all contribute to the absence of a proper response to CRT.\(^3\) In particular, the proper positioning of the left ventricular lead in a branch of the coronary sinus (CS) is one of the technical challenges in implanting the CRT device. A comprehensive evaluation of CRT candidates should include an evaluation of all these CRT responses (the last level of the activation of the left ventricle, the presence of various branches of the CS, and the assessment of the location of myocardial scar). In addition, recent experience has shown that the placing of leads in multiple zones has far more benefits than implanting leads in a single region.\(^4,5\) Therefore, in order to achieve a successful placing of biventricular pacing, the operator should perform lead placing by considering 3 characteristics of determining the last region activated in the left ventricle, the lack of implantation in the area without myocardial scar, and the determination of the exact anatomy of the CS. However, between 8% and 10% of patients under CRT experience unsuccessful CS cannulation.\(^6,7\) The surgical procedure for the insertion of epicardial pacing may be prioritized. In addition to the pacing of the left ventricular epicardial area using the transvenous method or the surgical technique, alternate sites for pacemakers are also considered.\(^8,9\) In particular, endocardial pacing has yielded favorable results for the clinical and hemodynamic improvement of patients compared with epicardial pacing. Instead, the endocardial pace may be more activated by physiological electrical activation.\(^10\) Improving the quality of life and the survival of patients with left ventricular dysfunction has been successful with CRT implantation. This is achieved by 2 methods of the insertion of the leads through the CS and the other through an open epicardial surgery in the left ventricle. However, what has not been thus far evaluated is the impact of some other factors such as gender and age of the patients, ischemic patterns, ECG parameters, types of pacemakers, left ventricular ejection fraction, mortality and threshold, and features of the pace device. Furthermore, in many cases, due to the lack of an appropriate branch of the CS, the implantation of the epicardial lead in the left ventricle is necessary. Considering the many reports of elevated threshold levels and left ventricular dysfunction in epicardial leads, the evaluation of the short- and long-term efficacy of this type of leads is necessary in comparison with CS leads. The present study aimed to compare left ventricular epicardial pacing and CS pacing in patients with triple-chamber pacemakers.

**METHODS**

This retrospective cohort study was performed on patients referred to Rajaie Cardiovascular, Medical, and Research Center between 2011 and 2016 for CRT implantation. At the time of referral, baseline 12-lead ECG at rest was considered for all the patients. The patients’ baseline characteristics, as well as their ECGs, were all collected from the records in the hospital. The patients were re-evaluated with ECG after device implantation and before discharge. The evaluations were performed in 2 groups of patients under left ventricular epicardial pacing and CS pacing. In addition, the characteristics of pacing, the type of lead, the time course, the increase in threshold, and the risk of lead dysfunction were evaluated within 1 year after lead implantation. Finally,
the characteristics of repolarization were evaluated before and after implantation. ECG parameters such as baseline QRS and post-CRT QRS were assessed. Additionally, pacing parameters and probable mortality events were assessed during the 1-year period after pace implantation and compared between the 2 groups.

Statistical Analysis
For the statistical analysis, the results were presented as mean ± standard deviation (SD) for the quantitative variables and were summarized by absolute frequencies and percentages for the categorical variables. The normality of the data was analyzed using the Kolmogorov–Smirnov test. The categorical variables were compared using the χ² test or the Fisher exact test when more than 20% of the cells with expected counts <5 were observed. The quantitative variables were also compared using the t-test or Mann–Whitney U-test. For the statistical analyses, the SPSS software, version 16.0, for Windows (SPSS Inc, Chicago, IL) was used. A P value ≤0.05 was considered statistically significant.

RESULTS
The study population was divided into 2 groups: the group with left ventricular epicardial pacing (n=25) and the group with CS pacing (n=25). As is shown in Table 1, comparisons of the baseline characteristics showed a significantly higher mean age in those with endocardial lead pacing than in those with epicardial pacing, but there were no differences in terms of gender distribution, baseline diagnosis (ie, dilated cardiomyopathy or inflammatory cardiomyopathy), and traditional cardiovascular risk factors including hypertension and diabetes mellitus. In 12-lead ECG and echocardiography assessments (Table 2), the mean left ventricular ejection fraction was significantly higher in the patients with epicardial lead pacing. The mean PR segment was significantly more prolonged in the patients with endocardial lead pacing. There was no difference in the QRS pattern between the 2 groups. Within the follow-up period (2 months after lead pacing), no difference was revealed between the 2 groups with epicardial and CS pacing with respect to the average left ventricular pacing lead threshold, right ventricular pacing lead threshold, and right ventricular lead sensing. A 6 and 12 months’ follow-up, the mean left ventricular pacing lead threshold was significantly higher in the patients with epicardial lead pacing than in those with endocardial lead pacing (Table 3). Further, regarding the ECG pattern after lead pacing (Table 4), the morphology of QRS at V₁ lead and also the type of the QRS axis significantly differed between the 2 groups of epicardial and endocardial lead pacing. In total, as is shown in Table 5, at 6 and 12 months after pacemaker implantation, the mean left ventricular pacing lead threshold was at its highest in the posterolateral area and at its lowest in the anterolateral area, but without any significant difference.

<table>
<thead>
<tr>
<th>Item</th>
<th>Epicardial Lead</th>
<th>Endocardial Lead</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>14 (56)</td>
<td>29 (56.9)</td>
<td>0.943</td>
</tr>
<tr>
<td>Women</td>
<td>11 (44)</td>
<td>22 (43.1)</td>
<td></td>
</tr>
<tr>
<td>Mean age, (y)</td>
<td>55.40 ±13.43</td>
<td>63.08 ± 10.75</td>
<td>0.009</td>
</tr>
<tr>
<td>Basic Diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dilated cardiomyopathy</td>
<td>12 (48)</td>
<td>21 (41.2)</td>
<td>0.573</td>
</tr>
<tr>
<td>Ischemic cardiomyopathy</td>
<td>13 (52)</td>
<td>30 (58.8)</td>
<td></td>
</tr>
<tr>
<td>Risk Factor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>2 (8)</td>
<td>4 (7.8)</td>
<td>0.939</td>
</tr>
<tr>
<td>Diabetes</td>
<td>5 (20)</td>
<td>9 (17.6)</td>
<td></td>
</tr>
<tr>
<td>Hypertension and diabetes</td>
<td>4 (16)</td>
<td>6 (11.8)</td>
<td></td>
</tr>
</tbody>
</table>
Table 2. ECG and echocardiography findings in epicardial and endocardial leading pace

<table>
<thead>
<tr>
<th>Item</th>
<th>Epicardial Lead</th>
<th>Endocardial Lead</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Echocardiography</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean LVEF</td>
<td>20.40 ± 6.11</td>
<td>19.96 ± 5.75</td>
<td>0.019</td>
</tr>
<tr>
<td>Mean pacing threshold</td>
<td>0.59 ± 0.35</td>
<td>0.72 ± 0.86</td>
<td>0.479</td>
</tr>
<tr>
<td><strong>ECG</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean PR segment</td>
<td>15.00 ± 2.74</td>
<td>17.10 ± 2.34</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>QRS pattern</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IVCD</td>
<td>3 (12)</td>
<td>5 (9.8)</td>
<td>0.532</td>
</tr>
<tr>
<td>LBBB</td>
<td>19 (76)</td>
<td>42 (82.4)</td>
<td></td>
</tr>
<tr>
<td>RBBB</td>
<td>2 (8)</td>
<td>4 (7.8)</td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>1 (4)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Mean QRS interval, ms</td>
<td>15.58 ± 16.8</td>
<td>16.13 ± 13.56</td>
<td>0.995</td>
</tr>
<tr>
<td><strong>QRS Axis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAD</td>
<td>10 (40)</td>
<td>18 (35.3)</td>
<td>0.911</td>
</tr>
<tr>
<td>Extreme</td>
<td>2 (8)</td>
<td>5 (9.8)</td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>13 (52)</td>
<td>28 (54.9)</td>
<td></td>
</tr>
</tbody>
</table>

LVEF, Left ventricular ejection fraction; IVCD, Intraventricular conduction delay; LBBB, Left bundle branch block; RBBB, Right bundle branch block; LAD, Left axis deviation

Table 3. Pacing characteristics within the follow-up period

<table>
<thead>
<tr>
<th>Item</th>
<th>Epicardial Lead</th>
<th>Endocardial Lead</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>2 months</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean left ventricular pacing lead threshold</td>
<td>0.76 ± 0.88</td>
<td>0.76 ± 0.98</td>
<td>0.997</td>
</tr>
<tr>
<td>Mean right ventricular pacing lead threshold</td>
<td>0.50 ± 0.56</td>
<td>0.42 ± 0.40</td>
<td>0.456</td>
</tr>
<tr>
<td>Right ventricular lead sensing</td>
<td>14.02 ± 5.04</td>
<td>13.48 ± 3.25</td>
<td>0.584</td>
</tr>
<tr>
<td><strong>6 months</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean left ventricular pacing lead threshold</td>
<td>1.30 ± 1.37</td>
<td>0.77 ± 1.09</td>
<td>0.046</td>
</tr>
<tr>
<td>Mean right ventricular pacing lead threshold</td>
<td>0.91 ± 1.75</td>
<td>0.65 ± 0.40</td>
<td>0.091</td>
</tr>
<tr>
<td>Right ventricular lead sensing</td>
<td>13.21 ± 6.68</td>
<td>3.94 ± 3.57</td>
<td>0.548</td>
</tr>
<tr>
<td><strong>12 months</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean left ventricular pacing lead threshold</td>
<td>1.66 ± 1.48</td>
<td>0.88 ± 1.23</td>
<td>0.027</td>
</tr>
<tr>
<td>Mean right ventricular pacing lead threshold</td>
<td>0.88 ± 1.63</td>
<td>0.63 ± 0.44</td>
<td>0.456</td>
</tr>
<tr>
<td>Right ventricular lead sensing</td>
<td>14.47 ± 6.07</td>
<td>14.06 ± 4.00</td>
<td>0.758</td>
</tr>
</tbody>
</table>

Table 4. ECG characteristics after lead pacing

<table>
<thead>
<tr>
<th>Item</th>
<th>Epicardial Lead</th>
<th>Endocardial Lead</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean QRS duration</strong></td>
<td>146.25±17.15</td>
<td>140.39±15.23</td>
<td>0.140</td>
</tr>
<tr>
<td><strong>QRS Axis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal axis</td>
<td>2 (8)</td>
<td>11 (21.6)</td>
<td>0.021</td>
</tr>
<tr>
<td>Axis extreme</td>
<td>12 (48)</td>
<td>17 (33.3)</td>
<td></td>
</tr>
<tr>
<td>Axis LAD</td>
<td>5 (20)</td>
<td>20 (39.2)</td>
<td></td>
</tr>
<tr>
<td>Axis RAD</td>
<td>3 (12)</td>
<td>3 (5.9)</td>
<td></td>
</tr>
<tr>
<td><strong>QRS Morphology at V1</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>QS pattern</td>
<td>7 (28)</td>
<td>3 (5.9)</td>
<td>0.019</td>
</tr>
<tr>
<td>RS pattern</td>
<td>3 (12)</td>
<td>2 (3.9)</td>
<td></td>
</tr>
<tr>
<td>qR pattern</td>
<td>3 (12)</td>
<td>12 (23.5)</td>
<td></td>
</tr>
<tr>
<td>rS pattern</td>
<td>12 (48)</td>
<td>34 (66.7)</td>
<td></td>
</tr>
</tbody>
</table>

LAD, Left axis deviation; RAD, Right axis deviation
DISCUSSION

In the present study and in line with previous studies, we sought to evaluate the implications of implanting 2 types of pacemakers: surgical epicardial lead pacing and endocardial lead pacing through the CS. The most notable finding in the current study was that the mean left and right ventricular lead thresholds were not significantly different between the 2 types of epithelial and endocardial lead pacing at baseline and 2 months later; nonetheless, at 6 and 12 months’ follow-up, the mean left ventricular lead threshold was higher in epicardial pacing than in CS lead pacing. Moreover, there was no difference in sensing the right ventricle at different times after the pacemaker implantation. Also of note was that the increase in the threshold of left ventricular leading was observed within 1 year after the implantation of the lead only in the epicardial lead pacing group, while it was not visible in the endocardial lead pacing group. What is considered to be optimal by experts is that the stability of the threshold of the lead in patients with chronic and advanced heart failure is particularly high. In other words, the occurrence of changes in the pacing threshold is always associated with the cause of the pathological background such as the failure of the implant and the displacement of the lead.

The results of various studies on the threshold values for pacing leads are completely different in each lead type. In a study by Mair et al., the pacing threshold of the CS leads increased more than that of the epicardial leads, which is in complete contradiction with our study. In a study by Izutani et al., there was no difference between the 2 groups in terms of thresholds; their finding is not consistent with our study. In an investigation by van Gelder et al., at 2 months’ follow-up of endocardial lead implantation, the threshold of stimulation showed a significant increase. In our study, this increase was significantly higher in epicardial lead pacing. Nega et al. reported that the pacing threshold in the epicardial lead significantly increased, which is consistent with our study. In point of fact, what we see as the final product in our study is that, firstly, the increase in the threshold of epicardial pacing leads is far more than that of endocardial pacing leads through the venous sinus and secondly, changes to the threshold of pacing are not affected by sensing. In comparison with CS pacing, epicardial pacing offered a more invasive approach and lead to the following changes:

1) more injury and bleeding in the epicardial area,
2) more inflammatory response, and
3) more fibrosis after repair.

For these reasons, the pacing threshold in the epicardial approach will increase over time.

CONCLUSIONS

Comparisons of the results and the long-term effects between endocardial and epicardial lead pacing in the present study indicate that the increase and changes in the left ventricular leading threshold in the epicardial pacing lead are much more pronounced than those in the endocardial pacing lead through the venous sinus. Therefore, the use of CS leads will be
preferred to pericardial leads due to the stability of the pacing threshold over time.

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Impact of Obstructive Sleep Apnea on Cardiac Troponin I: Comparisons of the Effects of Nasal O\textsubscript{2} and Positive Airway Pressure on this Biomarker

Atoosa Mostafavi\textsuperscript{1}, MD; Khosro Sadeghniiat-Haghghi\textsuperscript{2}, MD; Seyed Abdol Hussein Tabatabaei\textsuperscript{1\textasteriskcentered}, MD

ABSTRACT

Background: Sleep apnea is a common disorder and is known to impact myocardial stress and increase morbidity and mortality. The concentrations of cardiac highly sensitive troponin I (hs-TnI) are currently in clinical use as markers of myocardial injury. That obstructive sleep apnea (OSA) may lead to myocardial injury and elevated cardiac troponin levels suggests that the treatment of sleep apnea with positive airway pressure (PAP) should decrease myocardial injury.

Methods: We studied 114 patients with a diagnosis of moderate-to-severe OSA who were referred to our cardiovascular department. None of the patients had a history of cardiovascular problems and diabetes. The mean age was 30.65±3.96 years. The patients were divided into 2 groups: the first group (the O\textsubscript{2} group) received nasal O\textsubscript{2} for 2 weeks, and the second group (the PAP group) received PAP for about 2 weeks. The concentrations of hs-TnI were measured in evening blood samples in selected patients. After 2 weeks of treatment with O\textsubscript{2} or PAP, the serum hs-TnI level was rechecked and compared with the baseline and between the 2 groups.

Results: The level of hs-TnI did not differ significantly between the 2 groups. No patients in either O\textsubscript{2} or PAP group showed elevated troponin levels before the treatment. The cardiac biomarker, hs-TnI, was detectable (≥1 ng/L) in none of the patients in the O\textsubscript{2} group before and after the treatment and only in 2 (3%) patients in the PAP group after treatment. There was no significant difference in the hs-TnI level before and after the treatment with nasal O\textsubscript{2} (P=0.4).

Conclusions: Although OSA is well known to impact myocardial stress, we did not find increased amounts of cardiac hs-TnI as a biomarker of myocardial damage even in the severe form of OSA. PAP did not cause any myocardial damage detectable with the hs-TnI level and it was somewhat more effective than was O\textsubscript{2} in decreasing the baseline level of troponin. (Iranian Heart Journal 2019; 20(2): 75-80)

KEYWORDS: Obstructive sleep apnea, Positive airway pressure, Troponin I

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Sleep apnea is a disorder characterized by a reduction or a pause in breathing during sleep. It is a relatively common sleep disorder and leads to increased morbidity and mortality.

The risk factors for sleep apnea in the adult population are the male gender, obesity, increased neck circumference, diabetes, and the anomaly of the upper respiratory tract. The symptoms are insidious and are present from a few years before the diagnosis.

Some surveys have assessed peri-apneic hemodynamic alterations, the heart rate, blood pressure, the cardiac output, and peripheral resistance and shown that the heart rate is elevated significantly 10 beats immediately after apnea. Both hypoxemia and sympathetic arousals cause rapid hemodynamic changes that may escape autoregulatory mechanisms and make patients suffering from OSA vulnerable to acute cardiovascular events.

Previous investigations have demonstrated that obstructive sleep apnea (OSA) is associated with a rise in the incidence of coronary heart disease, heart failure, stroke, and atrial fibrillation. Additionally, treatment with continuous positive airway pressure (PAP) improves not only daytime sleepiness, the quality of life, and mood but also intermediate cardiovascular end points such as high blood pressure, the cardiac ejection fraction, vascular parameters, and arrhythmias. However, data from a large-scale randomized trial did not support a role for PAP therapies to reduce cardiovascular mortality.

Using a highly sensitive troponin I (hs-TnI) assay, some researchers have shown that the severity of OSA is associated with myocardial injury, independent of comorbidities, and have suggested that frequent apneas or hypoxemia in OSA may cause low-grade myocardial injury. Nonetheless, some other researchers have not observed such higher proportions of detectable hs-TNT in this group of patients and concluded that this association is caused by a larger amount of cardiovascular risk factors among this population.

It is known that hs-TnI has superior low-range sensitivity in comparison with the hs-TnT assay and assays. In addition, the quantification of the concentrations of cardiac troponin hs-TnI—as markers of myocardial injury—is currently in clinical use.

The fact that obstructive sleep apnea may lead to myocardial injury and elevated cardiac troponin levels leads to the thought that the treatment of OSA with PAP should decrease myocardial injury; the current evidence, however, fails to confirm this notion.

In this study, we sought to determine whether OSA can cause elevated troponin levels and whether hypoxemia by itself can be the cause of such a rise in the level of cardiac troponin. We also compared the troponin level after treatment with supplement nasal oxygen alone or with PAP in 2 different groups of nasal O2 and PAP and then compared the level of CTn-I between the 2 groups.

**METHODS**

The present study was approved by the Ethics Committee of Tehran University of Medical Sciences, Iran. Informed consent was obtained from all the patients.

**Study Population**

We studied 200 patients with a diagnosis of moderate-to-severe OSA who were referred to our cardiovascular department. None of the patients had a history of cardiovascular problems and diabetes.

After adjustments were made for age and gender, the patients with high levels of estimated creatinine clearance, a history of known coronary artery disease and diabetes mellitus, a history of anginal chest pain, a history of other cardiac diseases, and mild sleep apnea were excluded. Ultimately, 114 Patients with a moderate and high apnea-hypopnea index (AHI) were enrolled. Electrocardiography
polysomnography were done for all the patients, and those with abnormal echocardiography and ECG were excluded.

Polysomnography
The severity of OSA, expressed as the AHI, was assessed with in-hospital polysomnography. All the participants underwent in-hospital polysomnography (sleep length=6.2±1.2 h [mean ± SD]). The registrations were thereafter analyzed by trained sleep technologists manually, revised by a sleep medicine specialist (RPSGT), and scored according to the 2017 manual of the American Academy of Sleep Medicine (AASM). The severity of OSA was expressed as the AHI. Apnea was defined as the absence of the airflow for more than 10 seconds. Hypopnea was defined as >30% reduction in the airflow followed by a decrease in SPO2 of >3%. The AHI was calculated as the mean number of apneas and hypopneas as per hour of sleep according to the recommendations of the AASM.9

Ultimately, 114 patients with an AHI ≥15 were defined as having moderate-to-severe OSA and were enrolled in this study.

Measurement of Cardiac Troponin I
The concentrations of hs-TnI were measured in evening blood samples in selected patients. The quantitative measurement of hs-TnI was achieved via an immunoassay for the quantitative determination of cardiac hs-TnI in plasma, with the upper limit of normal of 1 ng/mL representing the 99th percentile in a normal reference population and a coefficient of variation of <10%. The values of hs-TnI below the limit of blank are reported as 0.005 ng/L. After 2 weeks of treatment with O2 or PAP, the serum troponin level was rechecked and compared with the baseline and between the 2 groups.

Statistical Analysis
The statistical analyses were conducted using the SPSS, version 16. The continuous variables are presented as the mean (SD) or the median (interquartile range for data with skewed distributions). The patients’ characteristics were compared using the Student t-test and the analysis of variance. A P value<0.05 was considered statistically significant.

RESULTS
Totally, 114 patients with a diagnosis of moderate-to-severe OSA were enrolled in this study.

The mean age was 30.65±3.96 years. The patients were divided into 2 groups: the O2 group received nasal O2 for 2 weeks and the PAP group received PAP for about 2 weeks.

The demographic characteristics of the 2 groups are summarized in Table 1. No significant differences were observed between the PAP and O2 groups regarding age, sex, a history of smoking, and hypertension.

<table>
<thead>
<tr>
<th>Table 1. Patient characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variable</td>
</tr>
<tr>
<td>Number</td>
</tr>
<tr>
<td>Age (y)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
</tr>
<tr>
<td>Gender (number of men)</td>
</tr>
<tr>
<td>Smoker (number, percent)</td>
</tr>
<tr>
<td>History of hypertension (number)</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg (range, median)</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg (range, median)</td>
</tr>
</tbody>
</table>

The levels of the cardiac marker, hs-TnI, did not differ significantly between the 2 groups. None of the patients in either O2 or PAP group showed elevated troponin levels before the treatment. The level of hs-TnI was detectable (≥1 ng/L) in none of the patients in the O2
group before and after the treatment and only in 2 (3%) patients in the PAP group after the treatment (Table 2). The hs-TnI level before and after the treatment was compared using the Wilcoxon signed-rank test. The median of the hs-TnI level before the treatment with O2 at the range of 0.005–0.08 was 0.02 and after 2 weeks of treatment at the range of 0.005–0.09 was 0.007. There was no significant difference in the troponin level before and after the treatment with nasal O2 (P=0.4). Figures 1 and 2 show the box plot diagram of the hs-TnI level before and after the treatment in both groups. The changes in the troponin level are depicted in Table 2.

**Table 2.** Changes in the troponin level before and after the treatment

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline hs-TnI</th>
<th>hs-TnI After Treatment</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>O2 group</td>
<td>0.005-0.08 (median=0.02)</td>
<td>0.005-0.09 (median=0.007)</td>
<td>0.4</td>
</tr>
<tr>
<td>PAP group</td>
<td>0.05-0.08 (median=0.06)</td>
<td>0.05-0.00 (median=0.06)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

hs-TnI, Highly sensitive troponin I; PAP, Positive air pressure

Although there was a significant rise in the cardiac troponin after the treatment with PAP, the amount of the increase in only 2 patients was above the cutoff point of 1 ng/L and showed myocardial injury. The level of changes in cardiac troponin was compared between the O2 and PAP groups, and the results are summarized in Table 3.

**Table 3.** Comparison of the troponin level between the 2 groups

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mean ±SD</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAP</td>
<td>0.036±0.032</td>
<td>0.03</td>
</tr>
<tr>
<td>O2</td>
<td>0.78±0.81</td>
<td></td>
</tr>
</tbody>
</table>

PAP, Positive air pressure

None of the participants (100%) had hs-TnI concentrations above the limit of detection (1 ng/L). Furthermore, the concentration of cardiac troponin was even lower in the PAP group than in the O2 group.

**DISCUSSION**

Sleep apnea is a reduction or pause in breathing during sleep. This disorder not only leads to daytime sleepiness and reduces the quality of life but also causes several other significant problems such as myocardial injury and cerebrovascular accident. Researchers have shown that treatment with PAP can reduce the incidence of these problems and promote the quality of life. Sleep apnea can lead to myocardial injury by several mechanisms. Intermittent apneas lead to nocturnal hypoxemia and sympathetic arousal, which results in pulmonary and systemic hypertension, increased myocardial load, wall stress, and ultimately myocardial injury.10,11,12 Troponin I is a highly sensitive and specific marker of myocardial injury. Troponin T is another marker for myocardial injury but is not as specific as troponin I. The specificity and correlation with angiographic findings are higher in hs-TnI than in hs-TnT.13 Accordingly, we used hs-TnI as a marker of myocardial injury.

Our main objective was to determine whether hypoxemia alone can lead to myocardial injury and whether the amount of the increase in cardiac troponin I can be reversed by the use of nasal O2 without PAP. The existing literature abounds with discrepancies in the results of previous studies on the effects of OSA on cardiac troponin. Some researchers have reported high hs-TnT levels in patients with OSA,4,14,15 whereas others have demonstrated that even patients suffering from OSA with coexisting coronary artery disease have no episodes of myocardial injury detectable by cardiac TnT assays.6-16 In the current study, we did not find high troponin I levels in our patients with OSA, all of whom had normal baseline troponin levels, which was increased by the use of neither O2 nor PAP.

Although the baseline troponin level was not high in both groups, after the treatment, the
total average of this level was lower in the patients who received PAP than in those who received O2. Some previous investigations have compared treatment with PAP and O2 from different aspects. Phillips et al. showed that PAP was more effective than O2 in reducing apnea, whereas nasal O2 improved oxygenation more optimally. Some other researchers have concluded that PAP is more effective than is supplemental nocturnal O2 in controlling daytime and nighttime blood pressure and on heart rate variability, which is a predictor of cardiovascular mortality.

Our finding is in stark contrast to some previous studies that have demonstrated increased troponin levels after treatment with PAP. Nonetheless, some other investigations have shown that PAP has no effect on troponin and cardiac remodeling. This discrepancy between the results may be due to the assessment of parameters such as the AHI, as a marker of OSA. A previous study reported that the effects of PAP on cardiac troponin had no association with the AHI but were mostly dependent on the severity of hypoxia.

In summary, although OSA is well known to impact myocardial stress, we did not find increased amounts of cardiac troponin as a biomarker of myocardial damage even in the severe form of OSA. PAP did not cause any myocardial damage detectable by high troponin levels and it was somewhat more effective than was O2 in decreasing the baseline level of troponin.

The major limitation of our study is its small sample size; our results should, therefore, be viewed with caution. Further studies with large samples are needed.

**Conflict of Interest** None declared.

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Case Report

Multiple Ruptured Chordae in an Amphetamine-Addicted Woman: A Rare Manifestation of Illicit Drugs

Azin Alizadehasl¹, MD; Behshid Ghardroost¹, MD; Ahmad Amin¹, MD; Mohaddeseh Behjati¹*, MD

ABSTRACT

A 48-year-old woman presented to our hospital with exacerbating cyanosis, edema, lethargy, and dyspnea. The patient declared amphetamine usage until 3 days earlier. Her respiratory function deteriorated gradually, resulting in intubation. During the hospitalization course, she became febrile with a positive blood culture due to an infected central venous catheter. Transeophageal echocardiography revealed a normal left ventricular systolic function, severe left ventricular hypertrophy, and a severe pulmonary arterial hypertension. We found multiple ruptured chordae, resulting in a flail mitral valve and severe mitral regurgitation. To the best of our knowledge, this is the first report of multiple ruptured chordae in the setting of amphetamine intoxication. (Iranian Heart Journal 2019; 20(2): 81-84)

KEYWORDS: Amphetamine, Flail mitral valve, Ruptured chordae

Amphetamine is a synthetic stimulant with a strong impact on the cardiovascular system.¹ A spectrum of the cardiovascular manifestations of amphetamine intoxication such as palpitation, hypertension, arrhythmias, acute coronary syndrome, aortic dissection, sudden cardiac death, and methamphetamine-associated cardiomyopathy has been previously reported.² Hereby, we report multiple ruptured chordae in a case with a long-term amphetamine addiction.

CASE PRESENTATION

A 48-year-old woman referred to us with exacerbating cyanosis, extremity edema, lethargy, and dyspnea both on exertion and at rest. The patient was under treatment with furosemide, metoprolol, lisinopril, and hydralazine for systemic and severe pulmonary arterial hypertension. She declared amphetamine usage until 3 days prior to the admission. On admission, she was confused with skin erythema, pallor of the sclera, remarkable cyanosis, and edema of the face and
the extremities. On physical examination, muffled heart sounds, coarse crackles of the lungs, and extremity edema were noticeable. Electrocardiography demonstrated a poor R progression and evidence of elevated pulmonary artery pressure (Fig. 1). Ultrasonography demonstrated enlarged mediastinum, bilateral pleural effusion with collapsed underlying lung, and infiltration. The oxygen saturation at rest was 72%, and the respiratory function deteriorated gradually and ultimately necessitated intubation. During her hospitalization course, the patient had prolonged hyponatremia, leukopenia, neutrophilia, an elevated erythrocyte sedimentation rate (90 mg/dL), positive highly sensitive C-reactive protein (58 mg/dL), a negative urine culture, and a positive blood culture for coagulase-negative *Staphylococcus*; the source of infection was the central venous catheter. She became febrile, which was subsequently subsided by antibiotic treatment. The treating physician requested echocardiography to rule out infectious endocarditis. Transesophageal echocardiography revealed the following data: a normal left ventricular size and systolic function, severe concentric left ventricular hypertrophy, moderate diastolic dysfunction, moderate right ventricular enlargement and systolic dysfunction, a malapposed tricuspid valve, severe pulmonary arterial hypertension, moderate circumferential pericardial effusion without compressive effects, and a plethoric inferior vena cava. Interestingly, there were multiple ruptured chordae, resulting in a flail mitral valve and severe mitral regurgitation without any evidence of endocarditis. Diffuse atherosclerotic plaques were also noticeable in the descending aorta (Fig. 2). Unfortunately, the patient expired a week later.

**Figure 1.** Electrocardiogram, demonstrating poor R progression and evidence of elevated pulmonary artery pressure
DISCUSSION

The most common cardiotoxic complications of amphetamine abuse are associated with excess peripheral catecholamine levels and coronary vasoconstriction. Amphetamine abuse could lead to the development of various valvular heart diseases, including mitral regurgitation. The most common reported mechanism for mitral regurgitation is annular dilatation due to a dilated left ventricle with the consequent tethering of the posterior mitral leaflet and the mitral leaflet thickening. Nonetheless, multiple ruptured chordae as the pathologic mechanism for mitral regurgitation have not been reported in the setting of amphetamine abuse.

CONCLUSIONS

The mechanism of mitral regurgitation in the setting of amphetamine intoxication could be a flail mitral valve. To the best of our knowledge, our report is the first of its kind to report multiple ruptured chordae in the setting of amphetamine intoxication.

REFERENCES


Instructions to Authors

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**Extracorporeal Life Support Training Course**
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**Forthcoming Meetings**

**Chest Wall Injury Summit**
Thursday, March 28, 2019 to Saturday, March 30, 2019
Eldorado Hotel & Spa
Santa Fe, NM
United States
See map: [Google Maps](#)

**AATS Post Graduate Course on Heart Valve Disease**
Friday, March 29, 2019
Royal Seginus Convention Center
Antalya
Turkey
See map: [Google Maps](#)

**Mayo Clinic Advanced Extracorporeal Membrane Oxygenation Symposium**
Friday, March 29, 2019 to Saturday, March 30, 2019
Mayo Clinic – Center for Procedural Innovation
13400 East Shea Blvd
Scottsdale, AZ  85259
United States
See map: [Google Maps](#)

**2019 Workshop on Robotic Cardiac Surgery**
Friday, March 29, 2019 to Saturday, March 30, 2019
Intuitive Surgical
Atlanta, GA
United States
See map: [Google Maps](#)

**Thoracic Surgery: Part I**
Thursday, April 4, 2019 to Saturday, April 6, 2019
EACTS House
Windsor
United Kingdom
See map: [Google Maps](#)

**AATS Cardiovascular Valve Symposium**
Thursday, April 4, 2019
Fundação Dom Cabral – Campus Aloysio Faria
Belo Horizonte
Brazil
See map: Google Maps

**STS TEVAR Symposium**
Thursday, April 4, 2019 to Friday, April 5, 2019
JW Marriott Chicago
Chicago, IL
United States
See map: Google Maps

**Structural Heart Disease Asia Pacific Symposium**
Thursday, April 4, 2019 to Saturday, April 6, 2019
Grand Millennium Hotel
Auckland
New Zealand
See map: Google Maps

**Re-Evolution Summit - Minimally Invasive Cardiac Surgery (MICS): The Ultimate Hands-On Summit - 10th Annual**
Thursday, April 4, 2019 to Friday, April 5, 2019
Houston Methodist Research Institute
6670 Bertner Avenue The John F. Bookout Auditorium is located on the 2nd floor
Houston 77030
United States
See map: Google Maps

**Hands-on Cardiac Morphology**
Wednesday, April 10, 2019 to Friday, April 12, 2019
Royal Brompton Hospital
London
United Kingdom
See map: Google Maps

**5th World Heart Congress 2019**
Monday, April 15, 2019 to Tuesday, April 16, 2019
Amsterdam, Netherlands
Amsterdam
Netherlands
See map: Google Maps

**AATS Mitral Conclave**
Thursday, May 2, 2019 to Friday, May 3, 2019
New York Hilton Midtown
New York City, NY
United States
See map: Google Maps

**9th Annual London Core Review Cardiothoracic Surgery Course**
Thursday, May 9, 2019 to Sunday, May 12, 2019
Royal College Of Physicians
London
United States
See map: Google Maps

**2019 Workshop on Robotic Thoracic Surgery**
Thursday, May 16, 2019 to Saturday, May 18, 2019
Intuitive Surgical
Atlanta, GA
United States
See map: Google Maps

**68th International Congress of the European Society of Cardiovascular and Endovascular Surgery (ESCVS)**
Wednesday, May 22, 2019 to Saturday, May 25, 2019
Martiniplaza
Groningen
Netherlands
See map: Google Maps

**MGH General Thoracic Surgery Post Graduate Course**
Thursday, May 23, 2019 to Friday, May 24, 2019
Royal Sonesta Hotel
Cambridge, MA
United States
See map: Google Maps

**Congenital Heart Campus 2019**
Thursday, May 23, 2019 to Sunday, May 26, 2019
San Zosimo Palace - Ortigia
Siracusa
Italy
See map: Google Maps

**Toronto Thoracic Refresher Conference**
Friday, June 7, 2019 to Saturday, June 8, 2019
MaRS Discovery District
Toronto
Canada
See map: Google Maps

**27th European Conference on General Thoracic Surgery**
Sunday, June 9, 2019 to Wednesday, June 12, 2019
The Convention Centre Dublin
Dublin
Ireland
See map: Google Maps
29th International Conference on Cardiology and Healthcare
Monday, June 10, 2019 to Tuesday, June 11, 2019
Helsinki, Finland
See map: Google Maps

7th International Conference on Hypertension & Healthcare
Monday, June 10, 2019 to Tuesday, June 11, 2019
Helsinki, Finland
See map: Google Maps

31st Annual Cardiologists Conference
Monday, June 17, 2019 to Wednesday, June 19, 2019
Rome, Italy
See map: Google Maps

6th MAORI Symposium: Complex Diseases of Thoracic and Thoraco-Abdominal Aorta
Tuesday, June 18, 2019 to Wednesday, June 19, 2019
Catanzaro, Italy
See map: Google Maps

EACTS Aortic Valve Repair Summit
Thursday, June 20, 2019 to Friday, June 21, 2019
Brussels, Belgium
See map: Google Maps

Liverpool Aortic Symposium VIII
Friday, June 28, 2019 to Saturday, June 29, 2019
Liverpool, United Kingdom
See map: Google Maps

4th International Conference on Cardiovascular Medicine and Cardiac Surgery
Monday, July 22, 2019 to Tuesday, July 23, 2019
London, UK
See map: Google Maps

20th Chest Wall International Group Meeting
Thursday, July 25, 2019 to Sunday, July 28, 2019
Pretoria, South Africa
See map: Google Maps

World Congress on Cardiology and Critical Care
Thursday, July 25, 2019 to Friday, July 26, 2019
Singapore, Singapore
See map: Google Maps

27th International Conference & Exhibition on Cardiology and Cardiovascular Medicine
Friday, July 26, 2019 to Saturday, July 27, 2019
Kyoto, Japan
See map: Google Maps

AATS Cardiovascular Valve Symposium
Argentina
Wednesday, September 4, 2019 to Friday, September 6, 2019
Buenos Aires, Argentina
See map: Google Maps

29th Congress of the World Society of Cardiovascular and Thoracic Surgeons (WSCTS 2019)
Friday, September 6, 2019 to Sunday, September 8, 2019
Sofia, Bulgaria
See map: Google Maps

2019 Cardiac Surgery and Cardiology Conference
Tuesday, September 10, 2019 to Wednesday, September 11, 2019
2019 World Heart and Cardiothoracic Surgery Conference (2019 WHCS)
Tuesday, September 10, 2019 to Wednesday, September 11, 2019
Singapore
See map: Google Maps

3rd International Congress and Expo on Heart & Cardiology
Thursday, September 19, 2019 to Friday, September 20, 2019
Miami, Florida, USA
Miami, FL
United States
See map: Google Maps

AATS Mechanical Support for the Heart and Lung Symposium
Friday, September 20, 2019 to Saturday, September 21, 2019
Marriott Marquis Houston
Houston, TX
United States
See map: Google Maps

World Congress on Cardiology and Cardiovascular diseases
Monday, September 23, 2019 to Tuesday, September 24, 2019
Barcelona, Spain
Barcelona
Spain
See map: Google Maps

AATS International Thoracic Surgical Oncology Summit
Friday, September 27, 2019 to Saturday, September 28, 2019
Sheraton New York Times Square Hotel
New York City, NY
United States
See map: Google Maps

39th Annual Cardiothoracic Surgery Symposium
(CREF 2019)
Wednesday, October 9, 2019 to Sunday, October 13, 2019
Marriott Marquis San Diego Marina
San Diego, CA
United States
See map: Google Maps

CSS Cardiovascular Surgical Symposium Riegersburg
Friday, October 11, 2019 to Sunday, October 13, 2019
Riegersburg Austria/Genusshotel Riegersburg
Riegersburg
Austria
See map: Google Maps

30th Annual Cardiovascular Interventions
Tuesday, October 29, 2019 to Friday, November 1, 2019
Hilton La Jolla Torrey Pines
La Jolla, CA
United States
See map: Google Maps

Controversies and Advances in the Treatment of Cardiovascular Disease, the Nineteenth in the Series
Thursday, November 14, 2019 to Friday, November 15, 2019
Montage Beverly Hills
Beverly Hills, CA
United States
See map: Google Maps

Latin America Cardiovascular Surgery Conference
Friday, November 22, 2019 to Sunday, November 24, 2019
Cancun International Convention Center
Cancun
Mexico
See map: Google Maps

28th Congress of the Asian Society for Cardiovascular & Thoracic Surgeon
Friday, February 7, 2020 to Monday, February 10, 2020
Shangri La Hotel, Chiang Mai
Chiang Mai
Thailand
See map: [Google Maps](https://www.google.com/maps)

**ATCSA 2020 - Annual Congress of the Association of Thoracic and Cardiovascular Surgeons of Asia**

Thursday, November 5, 2020 to Sunday, November 8, 2020
Hilton Arcadia
Phuket
Thailand
See map: [Google Maps](https://www.google.com/maps)
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