Risk factors of kidney injury after heart transplantation; a single center study

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ABSTRACT

Background: Chronic kidney disease (CKD) is a common complication after heart transplantation, and end stage renal disease (ESRD) has been reported to be as high as 8% after heart transplantation.

Objectives: We aimed to determine the risk factors associated with CKD after heart transplantation.

Patients and Methods: The present study retrospectively assessed patients undergoing heart transplantation at Shariati hospital during 1998-2011. All the patients who had undergone heart transplantation and referred to the heart clinic of the hospital or were admitted in the cardiac ward were included in the study and patients who passed away during the study period or had incomplete records were excluded from the study. Data extracted from the medical records of patients.

Results: Of 43 patients, 76.7% were men and the mean ± standard deviation (SD) age of the patients was 40 ± 8.4 years. There was no significant difference in estimated glomerular filtration rate (eGFR) between the men and women (79.86 vs. 87.34, \(P = 0.33\)). Additionally, eGFR was negatively associated with age (\(r = -0.344, P = 0.048\)). Mean ± SD dose of cyclosporine was 3.3 ± 0.7 mg/kg. Dose and trough level of cyclosporine were negatively associated with eGFR (\(r = -0.667, P = 0.012\) and \(r = -0.5443, P = 0.014\), respectively). Furthermore, eGFR was not different among patients using and patients not using hemofilter (\(P = 0.19\)), cellcept (\(P = 0.205\)), losartan (\(P = 0.207\)), aspirin (\(P = 0.87\)), but was significantly different between those using and not using prednisolone (\(P = 0.03\)).

Conclusions: Adjustment of dose of cyclosporine or replacing it with other drugs is strongly suggested for reducing the risk of CKD after heart transplantation. It is suggested the protocol of the drugs’ adjustment be advised or supervised by nephrologists after heart transplantation.

1. Background

Heart transplantation is the final treatment for various heart diseases, including cardiomyopathy and congenital and valvular heart diseases (1). According to the International Society for Heart and Lung Transplantation (ISHLT) registry, about 4000 heart transplantations have been reported in 2010 at a mean age of 42 years (1). The trend of heart transplantation has also changed in recent years. Patients undergoing heart transplantation are older and have higher rates of comorbidities (2). Beside the risk of early and late complications after heart transplantation leading to morbidity and mortality for the affected patients (3), chronic kidney disease (CKD) is a common complication after heart transplantation (4)
and end-stage renal disease (ESRD) has been reported to be as high as 8% after heart transplantation (5). In addition to the increased incidence of CKD in patients with heart failure (6), studies have reported decrease in estimated glomerular filtration rate (eGFR) and renal blood flow after heart transplantation (7). Therefore, patients undergoing heart transplantation are considered vulnerable to renal failure, which is maximum in the first post operational year, known as cardiorenal syndrome (8,9). It has been hypothesized that ischemia/reperfusion injury that occurs during cardiac surgery, deprives the heart tissue of blood and oxygen and the abrupt re-oxygenation causes additional damage (10), which causes an inflammatory response and oxidant production, resulting in microvascular and endothelial dysfunction, associated with increased risk of vasospasm, thrombosis and accelerated atherosclerosis (11,12). Ischemia/reperfusion injury causes complications after cardiac procedures (cardiorenal syndrome), especially after heart transplantation. Additionally, the close relationship of cardiac and renal system is a well-known entity, called the cardiorenal system (8). Therefore, heart transplantation needs to be performed with close observation of the kidney system. Some studies have also suggested simultaneous transplantation of the kidney and heart, due to the significance of this issue (13). As renal impairment increases the mortality rate of patients undergoing heart transplantation (4,5) studies have investigated the possible risk factors that might be associated with CKD after heart transplantation. These studies have shown that age, female gender, renal status before surgery, and underlying diseases such as hepatitis C, diabetes mellitus, and hypertension as possible risk factors (14-16). Asian race could also be a predictive risk factor (4).

2. Objectives
We aimed to evaluate all possible factors that could have an impact on the incidence of renal failure up to 12 years after heart transplantation in an Iranian population, to take farther steps towards reducing this serious complication.

3. Patients and Methods
3.1. Study design
The present cohort study retrospectively assessed the patients undergoing heart transplantation at Shariati hospital during 1998-2011. All patients who referred to the heart clinic of the hospital or were admitted to the cardiac ward during the study period were included in the study and patients who passed away during the study period or had incomplete records were excluded from the study.

The biatrial bicaval heart transplantation surgery performed for all patients. According to the protocol of the center, patients receive prednisolone, cyclosporine, and azathioprine, which then the latter changed to mycophenolate mofetil and were visited every two months.

Data were extracted from the medical records of the patients, which included demographic characteristics, drug history, the surgical details, ejection fraction (EF), and serum levels of BUN, creatinine, and calculation of eGFR (creatinine clearance).

CKD was defined as eGFR less than 90 (mL/min/1.73 m²) and based on revised CKD classification the glomerular filtration rate 60–89 (mL/min/1.73 m²) is defined as mildly decreased (17).

3.2. Ethical issues
The research followed the tenets of the Declaration of Helsinki. The protocol of the study was approved by heart transplantation research center and research deputy of Tehran University of Medical Sciences. All information about individuals was coded and kept confidential.

3.3. Statistical analysis
Quantitative variables were presented as mean ± standard deviation (SD) and categorical variables by frequency (percentage). Kolmogorov-Smirnov test was used to test the normality of distribution of the eGFR variable, which showed normal distribution; thus, variables were compared using t test and analysis of variance (ANOVA) and association of variables were measured by Pearson's coefficient correlation. For the statistical analysis, SPSS software, version 18.0 (SPSS Inc., Chicago, IL) was used. P values less than 0.05 were considered statistically significant.

4. Results
Of 74 patients, 43 were analyzed and enrolled to the study. Remaining patients were excluded due to death or incomplete medical records. Mean ± SD age of the patients was 40 ± 8.4 (range: 24-59) years. Around 76.7% of patients were men; 53.5% were >40 years, 32.6% were 30-40 years, and 14% were <30 years. With respect to surgical details, 79.1% used hemofilter and none-used balloon pump. Arrhythmia after surgery occurred in 7% of the patients and none required DC shock. Around 92% of the patients had an EF>50%.

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We found, 62.8% of patients received mycophenolate mofetil, 44.2% losartan, 60.5% prednisolone, and 55.8% used aspirin.

Regarding the renal tests, mean ± SD of blood urea nitrogen was 18.55 ± 4.17, while 67.4% had a BUN...
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Table 1. Serum levels of BUN and creatinine in the study population (mg/dL)

<table>
<thead>
<tr>
<th></th>
<th>Number</th>
<th>%</th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>BUN</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10-20</td>
<td>10</td>
<td>29</td>
<td>67.4</td>
</tr>
<tr>
<td>20-30</td>
<td>20</td>
<td>14</td>
<td>32.6</td>
</tr>
<tr>
<td>Total</td>
<td>30</td>
<td>43</td>
<td>100</td>
</tr>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>creatinine &lt;1</td>
<td>1</td>
<td>29</td>
<td>67.4</td>
</tr>
<tr>
<td>creatinine &gt;1</td>
<td>1</td>
<td>14</td>
<td>32.6</td>
</tr>
<tr>
<td>Total</td>
<td>2</td>
<td>43</td>
<td>100</td>
</tr>
<tr>
<td>Creatinine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>after 1 week</td>
<td>&lt;1</td>
<td>30</td>
<td>69.8</td>
</tr>
<tr>
<td></td>
<td>&gt;1</td>
<td>13</td>
<td>30.2</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>43</td>
<td>100</td>
</tr>
</tbody>
</table>

Abbreviations: BUN, blood urea nitrogen.

Table 2. Distribution of the study population based on mean dose and trough level of cyclosporine and its association with eGFR

<table>
<thead>
<tr>
<th></th>
<th>%</th>
<th>Mean ± SD</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose of cyclosporine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.3 mg/kg</td>
<td>14</td>
<td>85.50</td>
<td></td>
</tr>
<tr>
<td>3.4 mg/kg</td>
<td>69.8</td>
<td>79.50</td>
<td>0.012*</td>
</tr>
<tr>
<td>4.5 mg/kg</td>
<td>16.3</td>
<td>75.34</td>
<td></td>
</tr>
<tr>
<td>Trough level of</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>cyclosporine &lt;120</td>
<td>20.9</td>
<td>84.12</td>
<td></td>
</tr>
<tr>
<td>120-200</td>
<td>72.1</td>
<td>79.92</td>
<td>0.014*</td>
</tr>
<tr>
<td>&gt;200</td>
<td>7.0</td>
<td>73.76</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: eGFR, estimated glomerular filtration rate.

* P < 0.05 was considered statistically significant.

5. Discussion

According to the results of the current study, age, using prednisolone and, dose and trough level of cyclosporine were significantly and negatively associated with eGFR. Other studies have also investigated the risk factors that might be associated with renal failure after heart transplantation. A large cohort study that considered CKD after organ transplants has evaluated 24 024 patients undergoing heart transplantation with mean age of 47 ± 18 years with 76.1% male patients and have reported age, pre-transplantation eGFR, postoperative acute kidney injury (AKI), Asian race, cyclosporine, and underlying diseases (such as hypertension and diabetes mellitus) (4), which is consistent with the results of the present study. A recent review article showed that increasing age, female sex, and renal function before and early after surgery as significant risk factors, and underlying diseases, such as diabetes, hypertension, and hepatitis C as possible risk factors, and have declared that ethnicity and cardiac function have no effect (16). Cyclosporine is postulated to induce irreversible renal impairment and higher dose of cyclosporine was found to have a significant impact on renal failure after heart transplantation (7). Zietse and colleagues have retrospectively investigated 200 patients undergoing heart transplantation and administered 8 mg/kg cyclosporine and prednisolone to patients, reporting impaired renal function in 52% of the patients, although they were unable to find any significant association between the studied factors and levels of serum creatinine in their study (9). Van Gelder et al suggested, higher dose of cyclosporine and prednisolone used in their study as the reason for the higher rate of ESRD in their study, compared to similar studies (5), which were similarly associated with lower eGFR in the present study. However, they suggested the individual susceptibility to cyclosporine as the reason of cyclosporine nephrotoxicity (5). Although cyclosporine has decreased the rate of
rejection rate in heart transplantation as an effective immunosuppressant, but its various complications and variant pharmacokinetics limits its wide administration. Therefore, some studies have suggested that decreasing the dose of cyclosporine (by addition of other drugs) could reduce the nephrotoxicity of cyclosporine after heart transplantation (5). Some other studies have suggested the use of complementary medications such as calcium channel blockers to alleviate its renal complication (18), while others have disapproved its efficacy (9). The efficacy of addition of other drugs to treatment, such as sirolimus and everolimus to reduce the dose of cyclosporine is also controversial (2), but recent studies have reported that they might improve the outcomes in patients with renal dysfunction (19). Yet, more research is required to confirm their efficacy to replace cyclosporine. Zietse et al have suggested that decreasing the dosage would not be effective and its administration should be discontinued in patients who are prone to renal impairment (9). Some studies have shown that metabolism of cyclosporine may be different based on the genetic polymorphisms, which significantly varies according to race and ethnicity (20,21). In the present study, in the third year after transplantation, the mean levels of cyclosporine was more than 150 ng/mL that was higher than the expected level at this point of time. Thus, we suggest, cyclosporine should be administered with caution and continuous renal monitoring. In addition, due to the nephrotoxicity of cyclosporine, recent studies have evaluated the efficacy of other immunosuppressant drugs in heart transplantation. These studies suggested maintenance of tacrolimus instead of cyclosporine as immunosuppressor, due to the lower rate of renal adverse effects for tacrolimus versus cyclosporine, which might be due to higher immunosuppressive potency (22,23). The new generation of immunosuppressors, including drugs acting through T-cell regulation (24,25), or belatacept (26) may have less complications than the standard treatment protocol and may be able to open a new window towards immunosuppressors used for transplantation. However, future studies should compare the efficacy and complications of them, in order to obtain decisive results.

Although the administration of prednisolone have been statistically associated with the risk of CKD after heart transplantation in this study, we hypothesize that this association might be due to the higher dose of cyclosporine, prescribed in addition to prednisolone, in cases with suspected graft rejection. Moreover, the administration of corticosteroids is gradually tapered in one year in patients, and as reported by other studies, as well, more than half of patients become steroid-free after 5 years (1). Although prednisolone is the standard treatment protocol, its association with renal failure is not well established by studies focusing on heart transplantation. The protocol of the drugs adjustment should thus be advised or supervised by a nephrologist after heart transplantation.

The strengths of the present study included evaluation of a fair number of patients followed for more than 12 years, which enabled us to evaluate the risk factors precisely.

6. Conclusion
In conclusion, adjustment of dose of cyclosporine or replacing it with other drugs is strongly suggested for reducing the risk of CKD after heart transplantation. Future prospective studies considering other risk factors, including underlying disease and smoking can better illustrate the probable risk factors associated with the risk of renal failure after heart transplantation. It is suggested the protocol of the drugs’ adjustment be advised or supervised by nephrologists after heart transplantation.

Limitations
Our study had some limitations, including lack of a matched control group and the retrospective nature of the study. Hence, there could be some missing data and increased the effect of possible confounding factors in the analysis.

Authors’ contribution
In this study, MA as corresponding author and supervisor conducted the study. MA, JB and FS contributed to the design. MAK analyzed the results and interpreted data. MA wrote the manuscript and with collaboration of JB, MAK, MJ, MHM, MRS collected the data.

Conflicts of interest
The authors declare that they have no conflict of interest.

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