A QUANTITATIVE ANALYSIS OF PATIENTS WITH POSSIBLE AUGMENTED RENAL CLEARANCE AND ITS RELEVANCE TO PREDOMINANTLY RENALLY EXCRETED DRUGS

Master’s Thesis

Thesis supervisor
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A QUANTITATIVE ANALYSIS OF PATIENTS WITH POSSIBLE AUGMENTED RENAL CLEARANCE AND ITS RELEVANCE TO PREDOMINANTLY RENALLY EXCRETED DRUGS

Master’s Thesis

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The thesis performed by undergraduate Ran Eivensitz

KAUNAS 2014
# Table of contents

<table>
<thead>
<tr>
<th>Section</th>
<th>Pages</th>
</tr>
</thead>
<tbody>
<tr>
<td>SUMMARY</td>
<td>4-6</td>
</tr>
<tr>
<td>ABBREVIATIONS</td>
<td>7</td>
</tr>
<tr>
<td>CONCEPTS</td>
<td>8</td>
</tr>
<tr>
<td>INTRODUCTION</td>
<td>9-10</td>
</tr>
<tr>
<td>THESIS AIM AND TASKS</td>
<td>11</td>
</tr>
<tr>
<td>1. LITERATURE REVIEW</td>
<td>12-20</td>
</tr>
<tr>
<td>1.1 Augmented renal clearance</td>
<td>12</td>
</tr>
<tr>
<td>1.2 Creatinine</td>
<td>12</td>
</tr>
<tr>
<td>1.3 Glomerular filtration rate</td>
<td>13-14</td>
</tr>
<tr>
<td>1.4 Creatinine clearance</td>
<td>14</td>
</tr>
<tr>
<td>1.5 Kidney function</td>
<td>14</td>
</tr>
<tr>
<td>1.6 Cockcroft-Gault</td>
<td>15</td>
</tr>
<tr>
<td>1.7 MDRD</td>
<td>15</td>
</tr>
<tr>
<td>1.8 CKD-EPI</td>
<td>16</td>
</tr>
<tr>
<td>1.9 Possible causes of ARC</td>
<td>17-19</td>
</tr>
<tr>
<td>2 Therapeutic Drugs and ARC</td>
<td>20</td>
</tr>
<tr>
<td>METHODOLOGY</td>
<td>21</td>
</tr>
<tr>
<td>RESULTS</td>
<td>22-34</td>
</tr>
<tr>
<td>CONCLUSIONS</td>
<td>35</td>
</tr>
<tr>
<td>DISCUSSIONS</td>
<td>36</td>
</tr>
<tr>
<td>RECOMMENDATIONS</td>
<td>37</td>
</tr>
<tr>
<td>REFERENCES</td>
<td>38-43</td>
</tr>
<tr>
<td>APPENDIXES</td>
<td>42-46</td>
</tr>
</tbody>
</table>
SUMMARY

Master Thesis of R. Eivensitz “a quantitative analysis of patients with possible augmented renal clearance and its relevance to predominantly renally excreted drugs”, supervisor Prof. R. Mačuilaitis; Lithuanian University of Health Sciences, Academy of Medicine, Faculty of Pharmacy, Institute of Physiology and Pharmacology – Kaunas.

Objective of work: the aim of this study was to conduct a retrospective, quantitative, descriptive survey accompanied with a comparative statistical research, in which cases of patients with augmented renal clearance were examined and analyzed regarding the similarities and differences between them and their relevance for possible under-dosage of predominantly renally excreted drugs.

Tasks: 1. to detect all cases of lower than 50 µmol/L Scr measurements and calculate possible ARC using Cockcroft-Gault equation in a defined period of time in a Lithuanian hospital in Kaunas. 2. To compare the performance of 3 different equations to distinguish the ARC as assessed by Cockcroft-Gault equation from non-ARC cases. 3. To analyze possible reasons associated with these ARC cases. 4. To search for the cases when predominantly renally excreted drugs were prescribed to these patients.

Methodology: All consecutive laboratory tests were assessed during the period of 2013/10/01 --- 2014/01/19 and the serum creatinine values of 50µmol/L were used for ARC estimation using Cockcroft-Gault estimation and CrCl >130 mL/min. That was the research group (ARC group) that consisted of 31 patients. Two comparative groups were formed as well. The 5 patients were chosen for the “normal GFR” (serum creatinine values had to be above 50µmol/L and by calculating CrCl according to Cockcroft-Gault (mL/min) - creatinine clearance had to be below 130 mL/min 1.73 m²). This was the comparative group no1 (Non-ARC). Another 15 patients were chosen for the normal GFR but with the low serum creatinine as for the research group (serum creatinine values had to be below 50µmol/L and by calculating CrCl according to Cockcroft-Gault (mL/min) - creatinine clearance had to be below 130 mL/min 1.73 m²). This was the comparative group no2 (Non-ARC, Low-Scr).

The performance of Cockcroft-Gault estimation to detect ARC was compared to the MDRD and CKD-EPI equation. Patient demographics, conditions and drugs received were assessed. Data were analyzed by using descriptive and comparative statistical analysis, considering statistically significant difference between the groups if p value was <0.05.
Results

(1) Out of 60 patients with serum creatinine (Scr) less than 50 µmol/L, based on estimated GRF calculations - ARC was detected in 45 cases (71.43%).

(2) The mean ARC values of the research group were: 159.87± 26.43 mL/min as calculated by Cockcroft-Gault equation, 159.87± 25.4 mL/min/1.73m² by MDRD equation and 119.16±11.97 mL/min/1.73m² by CKD-EPI equation. The percentage of patients identified to have ARC by MDRD was 87.1% and 25.8% by CKD-EPI.

(3) The mean estimated creatinine clearance (CrCl) of the comparative group no1 (Non-ARC) were: 102± 13.93 mL/min as calculated by Cockcroft-Gault equation, 88.8±13.44 mL/min/1.73m² by MDRD equation and 91.4±15.95 mL/min/1.73m² by CKD-EPI equation. (Not a single patient was found to have ARC by any equation.

(4) The mean ARC values of the comparative group no2 (Non-ARC, low Scr) were: 98.93± 16.29 mL/min as calculated by Cockcroft-Gault equation, 144.93±22.97mL/min/1.73m² by MDRD equation and 103.8±11.52 mL/min/1.73m² by CKD-EPI equation. The percentage of patients identified to have ARC by MDRD was 73.33% and 0% by CKD-EPI.

(5) ARC was detected not only in the ICU department (29.03% of cases, including central ICU, neurosurgery and cardiology units) as it was expected but also in non-ICU department, most frequently in “endocrinology” (25.81% of cases), “surgery” (22.58%, including chest surgery), followed by “obstetric” (6.45%) and “pulmonology and allergy” (6.45%) departments and less frequently in psychiatry, neurology, hematology departments.

(6) The most frequent diseases and conditions associated with ARC were “diabetes” (22.58%), “traumatic brain injury” (22.58%), “empyema with pneumonia” (9.67%), “pregnancy” (6.45%) and “hyperthyroidism” (6.45%). The ARC experienced patients had several possible causes associated with ARC, most frequently – young age (below 60 years, in 70.96%). Other possible causes know to be associated with ARC we found were “surgery or neurosurgery” (32.25%), “diabetes“(32.25%), and “trauma” (12.9%).

(7) The most frequently renally only excreted drugs that are at risk of under dosage if dosed at minimal dosage levels for the patients in the arc group were: fraxiparine (9 patients, 29.03%), cefuroxime (8 patients, 25.8%), potassium chloride (6 patients 19.35%), metoprolol (4 patients, 12.9%) and ranitidine (4 patients, 12.9%).
Conclusions

(1) The augmented Renal clearance (ARC) as Glomerular Filtration rate (GFR) more than 130 mL/min (assessing by standard Cockcroft-Gault equation) was found in majority of patients when serum creatinine (Scr) was less that 50 µmol/L.

(2) The ARC assessed by Cockcroft-Gault was also detected by MDRD equation but not with CKD-EPI equation; all three estimations were distinguishing non-ARC patients with Scr higher that 50 µmol/L while MDRD equation did not distinguish non-ARC population if Scr was less that 50 µmol/L.

(3) ARC was detected not only in the ICU department as it was expected but also in non-ICU department, most frequently in “endocrinology”, “surgery”, “obstetric” and “pulmonology and allergy” departments and less frequently in psychiatry, neurology, hematology departments. The most frequent diseases and conditions associated with ARC were “diabetes”, “traumatic brain injury”, “empyema with pneumonia”, “pregnancy” and “hyperthyroidism”.

(4) The ARC experienced patients had several possible causes associated with ARC, most frequently – young age (below 60 years.). Other possible causes known to be associated with ARC we found were “surgery or neurosurgery”, “diabetes” and “trauma”.

(5) The most frequently renally only excreted drugs that are at risk of under dosage if dosed at minimal dosage levels for the patient in an ARC group were: fraxiparine, cefuroxime, potassium chloride, metoprolol and ranitidine.

Acknowledgment: I would like to thank my supervisor, Prof. Romas Mačiulaitis for guiding and assisting in writing this paper.
ABBREVIATIONS

ARC       Augmented Renal Clearance
CKD       Chronic Kidney Disease
CrCl      Creatinine Clearance
EPI       Epidemiology collaboration
GFR       Glomerular Filtration Rate
ICU       Intensive Care Unit
MDRD      Modification Diet in Renal Disease
PK        Pharmacokinetics
SD        Standard Deviation
Scr       Serum Creatinine
TBI       Traumatic Brain Injury
TDM       Therapeutic Drug Monitoring
CONCEPTS

Intensive Care unit – a special department in the hospital where patients with severe and life-threatening illnesses and injuries are admitted. They are staffed by a highly trained staff of doctors and nurses. It has special machinery to keep a constant care and monitor the patients.

Retrospective research – a research in which the factors related to the development of a particular outcome (in this case - the condition of ARC) are studied after the outcome has already occurred.
INTRODUCTION

Renal deficiency and its consequences are well known. When it comes to renal impairment, most clinicians are well aware of the need to regulate a different drug regimen by lowering the dosage in order to avoid toxicity. Augmented renal clearance (ARC), however, is considered to be quite a new phenomenon, with only recently a growing number of literatures have begun to identify this phenomenon and consider it during treatment. Because ARC is characterized by increased renal clearance, it is important for clinicians to adapt their drug therapy and to even build strategies as to how to handle these cases when ARC is observed or even hinted at.

There are certain patient’s conditions and departments where ARC is quite common, and clinicians should suspect enhanced renal filtration before prescribing and administrating the drug’s dosage in these departments as it is quite difficult to find an accurate pharmaceutical prescription for such patients particularly in the ICU.

The survey was conducted in order to find the relevance of ARC in patients admitted to a hospital located in Kaunas, Lithuania in different departments. Patients identified as having ARC were examined regarding their similarities and differences.

By using their collected date regarding their measures (gender, age, weight and Scr levels), different standard equations were filled and compared.

The recurrence of therapeutic drugs prescribed to these patients was documented to include several relevant criteria such as renally excreted ones.

Detection of number of renally excreted drugs and percentage out of total amount of drugs gives emphasis on the risk of under-dosage if these patients are dosed at minimal dosage levels.

Each group (research and two comparative) was examined numerically and statistically and comparisons of relevant differences were made.

The research acknowledges the fact those certain patients’ characteristics make him/her more ‘prone’ to have ARC such as age, condition, illness etc.

The Theoretical part includes a number of studies and research relating to the subject that supports the finding.
The results section includes an elaborated quantitative, statistical and descriptive date about each group with focus on the research group.

This research gives emphasis that by not accurately assessing renal function and clearance; it is less likely to achieve an optimal pharmaceutical dosage treatment and by so can lead to worse patient outcomes.
THE THESIS AIM AND TASKS

Thesis aim

Conducting a retrospective, quantitative, descriptive survey accompanied with a comparative statistical research, in which cases of patients with augmented renal clearance were examined and analyze regarding the similarities and differences between them and their relevance for possible under-dosage of predominantly renally excreted drugs.

Thesis tasks

1. To detect all cases of lower that 50 µmol/L Scr measurements and calculate the possible ARC using Cockcroft-Gault equation in a defined period of time in a Lithuanian hospital in Kaunas.
2. To compare the performance of 3 different equations to distinguish the ARC as assessed by Cockcroft-Gault equation from non-ARC cases.
3. To analyze possible reasons associated with these ARC cases.
4. To search for the cases when predominantly renally excreted drugs were prescribed to these patients.
LITERATURE REVIEW

1.1 Augmented renal clearance

Augmented renal clearance (ARC) is considered to be a quite new phenomenon in patient’s pathophysiology without well-known and accepted causes of it. [1]

However, there have been a growing number of literatures regarding ARC.

ARC is defined as the enhanced renal elimination of circulating solutes in the bloodstream (such as waste products or pharmaceuticals). It is quantified by the volume of plasma cleared (ml) of a given substance by the kidneys per unit time (min). [2]

A recent definition suggests ARC when CrCl exceeds 130 mL/min per 1.73 m². [3]

1.2 Creatinine

Creatinine is a metabolic breakdown product of creatinine phosphate in the muscles – reflecting muscle mass. [4]

Creatinine is produced at a constant rate by the body, known worldwide as a biochemical marker for measurement of kidney function. Normal creatinine values are approximately 110-150 mL/min in males and 100-130 mL/min in females. [5]

It is an amino acid derivative, an endogenous filtration marker for estimation of GFR that is secreted by proximal tubular cells that is also affected by dietary intake. [6]

Based on creatinine clearance, a substance that is not bound to proteins, freely filtered by the glomerulus, not synthesized, transported or metabolized by the kidney – a measurement of GFR is done.

Men tend to have higher levels of creatinine because they generally have more skeletal muscle mass than women. Vegetarians have been shown to have lower creatinine levels. [7]
1.3 Glomerular filtration rate

Although the kidneys have a wide range of functions in normal homeostasis, the GRF remains the most widely accepted index of renal function in both health and disease. GFR is measured as the urinary or plasma clearance of an ideal filtration.

Usually, any assessment of GFR in clinical practice focuses on identifying renal impairment, where serum creatinine concentrations are typically employed as a key biomarker for this purpose.

Exact estimation of GFR to assess kidney function is important for several reasons:

1. Early possible detection of renal failure.
2. Correct adjustment of administered drugs that are affected by impaired kidney function leading to decreased GFR or in case of ARC – increased GFR.
3. In cases of CKD (chronic kidney dysfunction), the kidney dysfunction can be monitored.

Table 1. Chronic kidney disease stages [10]

<table>
<thead>
<tr>
<th>GRF (mL/min/1.73²)</th>
<th>description</th>
</tr>
</thead>
<tbody>
<tr>
<td>90-120</td>
<td>At risk</td>
</tr>
<tr>
<td>≤90</td>
<td>Kidney damage with normal or elevated GFR</td>
</tr>
<tr>
<td>60-89</td>
<td>Kidney damage with mildly reduced GFR</td>
</tr>
<tr>
<td>30-59</td>
<td>Moderately reduced GFR</td>
</tr>
<tr>
<td>15-29</td>
<td>Severely reduced GFR</td>
</tr>
<tr>
<td>&lt;15 (or dialysis)</td>
<td>Kidney Failure</td>
</tr>
</tbody>
</table>
**Table 2.** Reference values for GFR [11]

<table>
<thead>
<tr>
<th>Adults (age group, years)</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-29</td>
<td>77–179</td>
<td>71–165</td>
</tr>
<tr>
<td>30-39</td>
<td>70–162</td>
<td>64–149</td>
</tr>
<tr>
<td>40-49</td>
<td>63–147</td>
<td>58–135</td>
</tr>
<tr>
<td>50-59</td>
<td>56–130</td>
<td>51–120</td>
</tr>
<tr>
<td>60-69</td>
<td>49–113</td>
<td>45–104</td>
</tr>
<tr>
<td>70-79</td>
<td>42–98</td>
<td>39–90</td>
</tr>
<tr>
<td>80-89</td>
<td>35–81</td>
<td>32–75</td>
</tr>
</tbody>
</table>

**1.4 Creatinine clearance**

Creatinine clearance can be estimated by a 24-hour urine collection and blood sampling during the collection time.

Creatinine is cleared by the kidneys not only by filtration but also by tubular secretion. [12]

**1.5 kidney function**

The kidneys perform the essential function of removing waste products from the blood and regulating the water fluid levels. The kidneys receive blood through the renal artery. The blood is passed through the structure of the kidneys called nephrons, where waste products and excess water pass out of the blood stream. [13]

The filtration of plasma in the kidney occurs through the capillary wall of the glomerulus. The filtration barrier is composed of glomerular endothelial cells (GECs), the glomerular basement membrane (GBM) and podocyte cells. [14]
1.6 Cockcroft-Gault

(1) A well-known and widely used equation. First described in 1976 on 249 people (approximately 96% male) with CrCl from 30 to 130 mL/min.

(2) Used as a surrogate of GFR in both clinical and research practice.

(3) Calculated by using the patient’s gender, age, weight and a 24-hour Scr output.

(4) The values are not adjusted for body-surface area.

(5) Overestimates the ClCr in the case of low Scr concentrations.

\[
GRF \ (mL/min) = \frac{(140-\text{age (years)}) \times \text{weight (kg)}}{72 \times \text{creatinine (mg/dL)}}
\]

[15][16]

1.7 MDRD

(1) First developed in 1999 with the use of data from 1628 patients and Re-expressed in 2005 with serum creatinine values lower by 5%.

(2) Estimates GFR adjusted with body surface area – so it is more accurate than Cockcroft-Gault in older and obese patients.

(3) The most pronounced limitation of the MDRD equation is a systematic underestimation of eGFR at higher levels (>60 mL/min/1.73 m2).

(4) Uses race as a factor but not weight.

\[
GFR \ (mL/min/1.73m^2) = 186 \times (SCr)^{1.154} \times [Age]^{-0.203} \times 0.742 \ (if \ female) \times 1.212 \ (if \ black)
\]

[17][18]
1.8 CKD-EPI

\[
GFR \text{ (mL/min/1.73m}^2\text{)} = 141 \times \min(\text{Scr/k,1})^a \times \max(\text{Scr/k,1})^{-1.209} \times 0.993^{\text{age}} \times 1.018(\text{if female}) \times 1.159(\text{if black})
\]

\[k=0.7 \text{ if female, 0.9 if male, } a= -0.329 \text{ if female, -0.411 if male}\]

\[\text{Min= the minimum of Scr/k or 1, max= the maximum of Scr/k or 1}\]

1. Published in 2009 and intended to be more generalizable across various clinical settings than the MDRD equation.

2. Developed using a sample size of 8254, 71% (\(n=5858\)) of whom came from high-risk populations.

3. Overestimates GFR in individuals with low BMI (<20 kg/m2).


5. Uses four basic predictor variables: creatinine, age, sex and race.

6. More suitable to patients with CKD.

[19] [20]

An example of comparison between the three equations

Comparison of (A) MDRD values for eGFR (B), Cockcroft-Gault eGFR calculated using patient ideal body weight and (C) CKD-EPI with body surface area normalization removed with Cockcroft-Gault eCrCl using actual body weight. Data is from 32,000 Australians presenting for routine measurement of serum creatinine. The solid line is the line of identity and the dashed lines indicate differences of +/- 30%

[21]
1.9 Possible causes of ARC

There have been a handful of studies regarding the possible causes of ARC.

Patient-related factors

Younger age (<60 years)

Pregnancy

Disease-related factors

Sepsis

Trauma

Surgery or Neurosurgery

Neutropenia

Burns injury

Cystic Fibrosis

Diabetes

Sepsis

Sepsis is considered to be a major recurring possible cause for ARC. [22]

The body’s response to the systemic inflammation is featured by vasodilated, hyper-metabolic cardiovascular state that is characterized by high cardiac output and increased blood flow to the major organs. Coupled with aggressive intravascular crystalloid fluid loading resuscitation and vasopressor support is most likely to augment both drug delivery to the kidneys and renal elimination.

Trauma

Trauma patients are at high risk of having ARC for several reasons: 1. the inflammatory state as a result of the multiple trauma of emergency surgery. 2. The vasoactive drugs coupled with large quantities of fluids that are given to them. 3. They usually have to go through surgical intervention.
**Neurosurgery**

A subgroup of critically-ill patients. As a result of traumatic brain injury that is usually coupled with subarachnoid hemorrhage, the clinicians have to give large amounts of anti-hypotensive drugs with hypertonic saline solutions, to keep a reasonable cerebral perfusion pressure.

**Burns**

Burn injury patients are also at high risk of having ARC for several reasons: 1. First treatment is giving large quantities of crystalloid fluid. 2. Inflammation as a result as a result of the injury. 3. Going through surgical intervention.

**Cystic fibrosis**

Data have not been readily researched yet. Elevated inulin clearance (an exogenous marker to measure GFR) and creatinine (an endogenous marker to measure GRF) have shown dependence to increased drug elimination in cystic fibrosis patients.

**Neutropenia**

The systemic inflammation coupled with the renal reserve caused increased drug elimination when patients were subjected to empirical broad-spectrum antimicrobials to treat the febrile neutropenia caused by hematological malignancy.

**Younger age**

Several studies have found younger age to be recurring a characteristic found in patients identified with ARC:

1. "Available data suggest that the patient groups most likely to develop ARC are young patients, without pre-existing co-morbidity or organ dysfunction, presenting with trauma". [24]
2. “Using linear regression analysis and controlling for gender and start of treatment, GFR values were significantly higher in younger children in both group A and group B (P < 0.027 and 0.001, respectively) compared to older children in each group”. [25]

**Pregnancy**

Characterized by primary systemic arterial vasodilation. Relaxin, a major pregnancy hormone and a member of insulin family, increases endothelin and nitric oxide production in the renal circulation, which leads to generalized renal vasodilation, including decreased renal afferent and efferent arteriolar resistance – results in increase in renal blood flow and GFR.

**Diabetes**

Primary abnormalities in vascular control leading to renal vasodilation and increased renal flow have been observed in several human studies. GFR seems to be correlated with poor diabetes control.

[26]
2. Therapeutic Drugs and ARC

The purposes of acknowledging ARC and by that adapting a different strategy of drug dosage regimen in certain patients are several:

1. To find the correct drugs dosage in order to optimize exposure.
2. To avoid sub-therapeutic drug dosing concentrations.
3. To achieve improved clinical outcomes.
4. Minimize possible side effects.

ARC may lead to lower blood concentrations of drugs that are cleared by the kidney. [27]

In recent years, there have been a growing retrospective studies to examine ARC implication on hospitalized patients, specifically in the ICU which include critically-ill patients, patients with TBI (traumatic brain injury), septic patients etc. these studies have proved that there is hard evidence regarding the clinical impact of ARC and the potential need for increased doses in critically ill patients. [28]

Some studies focused on specific therapeutic drugs families (antimicrobials, aminoglycoside, Beta-lactams and glycopeptides). [29]

And some studies went to check specific drugs such as Meropenem [30] and Vancomycin. [31]
Research methodology

Study was performed retrieving all Scr results from the laboratory of tertiary clinic during the period between 2013/10/01 - 2014/01/19 - we retrieved 63 events.

The data analysis was done by using the “EXCEL” program with entering the information from the surveys. The calculations were done using “EXCEL” descriptive and comparative formulations, using t-test for group comparisons. P value less that 0.05 was considered as statistically significant. The descriptive statistics were written in numbers and percentage.

We split our groups into (1) research group (ARC(+)) consists of 31, the comparative group no1 (Non-ARC) consists of 5 and the comparative group no2 (Non-ARC, Low Scr) consists of 15.
Results
During our study period we retrieved 46 patients that had Scr less than 50 µmol/l. For the comparative group we selected first consequential 5 subjects with normal Scr values that were more than 50 µmol/l. Thus, the total number of subjects is 51 people.

After calculations of ARC using Cockcroft-Gault estimation, we split our groups into (1) research group (ARC(+)) that consists of 31 patient, (2) the comparative group no1 (Non-ARC, normal Scr) that consists of 5 patients and (3) the comparative no 2 (Non-ARC, Low Scr) that consists of 15 patients.

Demographic Data

Gender

In the research group:
15 males (48.39%)
16 females (51.61%)

In the comparative group no1 (Non-ARC)
3 males (60%)
2 females (40%)

In comparative group no2 (Non-ARC, Low Scr)
12 females (80%)
3 males (20%)
AGE - young age is a possible cause for ARC (<60 years)

**Research group**
22 patients below the age of 60 (70.96%)
9 patients 60 and above (29.04%)
Average age 48.6

**Comparative group no1 (Non-ARC)**
3 patients below age of 60 (60%)
2 patients 60 and above (40%)
Average age 47.6

**Comparative group no2 (Non-ARC, Low Scr)**
10 patients 60 and above (66.67%)
5 patients below age 60 (33.33%)
Average age 66.3

**Departments**

**The research group:**
9 patients in “ICU departments including central ICU, neurosurgery and cardiology units” (29.03%).
8 patients in “Endocrinology” (25.81%)
7 patients in “surgery including Chest surgery” (22.58%)
2 patients in “obstetric” (6.45%)
2 patients in “pulmonology and allergy” (6.45%)
1 patient in “psychiatry” (3.22%)
1 patient in “spinal-cord and peripheral nerve surgery (Neurology)” (3.22%)
1 patient in “hematology” (3.22%)

**The comparative group no1 (Non-ARC):**
3 patients in “Nephrology” (60%)
2 patients in “Gastroenterology” (40%)
**Diagnosis**

**The research group:**
- 7 patients have diagnosis related to “diabetes” (22.58%)
- 7 patients have diagnosis related to “traumatic brain injury” (22.58%)
- 3 patients have diagnosis related to “empyema with pneumonia” (9.67%)
- 2 patients have diagnosis related to “pregnancy” (6.45%)
- 2 patients have diagnosis related to “hyperthyroidism” (6.45%)
- 1 patient has diagnosis related to “vertebral osteomyelitis” (3.22%)
- 1 patient has diagnosis related to “pancreatitis” (3.22%)
- 1 patient has diagnosis related to “Large malignant lymphoma” (3.22%)
- 1 patient has diagnosis related to “Diaphragmatic hernia” (3.22%)
- 1 patient has diagnosis related to “depression” (3.22%)
- 1 patient has diagnosis related to “cholangitis” (3.22%)
- 1 patient has diagnosis related to “Ileostomy” (3.22%)
- 1 patient has diagnosis related to “carcinoma in colon” (3.22%)
- 1 patient has diagnosis related to “cystic fibrosis” (3.22%)
- 1 patient had diagnosis related to “colon obstruction” (3.22%)

**The comparative group no1 (Non-ARC):**
- 2 patients have diagnosis related to “acute tubular and interstitial nephritis tissue” (40%)
- 1 patient has diagnosis related to “Hematuria” (20%)
- 1 patient has diagnosis related to “ulcerative colitis” (20%)
- 1 patient has diagnosis related to “ulcerative rectosigmoiditis” (20%)
Possible Causes of ARC

16 patients had “young age” as a cause for ARC (51.61%)
10 patients had “diabetes” as cause for ARC (32.25%)
10 patients had “surgery or neurosurgery” as cause for ARC (32.25%)
4 patients had “trauma” as a cause for ARC (12.9%)
3 patients had “sepsis” as a cause for ARC (9.67%)
2 patients had “pregnancy” as a cause for ARC (6.45%)
2 patients had “other - unknown reason” cause for ARC (6.45%)
1 patient had “cystic fibrosis” as cause for ARC
Creatinine clearance

The research group

According to Cockcroft-Gault (mL/min.)
Max CrCl was 236 – a 49 y/o Female with “diabetes mellitus type 2” from “endocrinology”
Min CrCl was 131 – a 38 y/o Female with “large malignant lymphoma” from “hematology”
Average CrCl was 159.87± 26.43

According to MDRD simplified (mL/min)
Max CrCl was 225 – a 65 y/o male with “traumatic brain injury” from “intensive-care
Min CrCl was 118 – a 61 y/o female with “carcinoma in colon” from “surgery”
Average CrCl was 159.87± 25.4

According to CKD-EPI (mL/min.)
Max CrCl was 150 – a 19 y/o male with “cystic fibrosis” from “pulmonology and allergy”
Min CrCl was 101 – a 61 y/o female with “carcinoma in colon” from “surgery”
Average CrCl was 119.16±11.97

The average CrCl according to Cockcroft-Gault is the same as the average CrCl according to MDRD.
Both are bigger than the average CrCl according to CKD-EPI.

Comparison

Between Cockcroft-Gault and MDRD - > 0.05 not statistically significant
Between Cockcroft-Gault and CKD-EPI - <0.05 statistically significant
Between MDRD and CKD-EPI - <0.05 statistically significant
The comparative group no1 (Non-ARC)

**According to Cockcroft-Gault (mL/min.)**
Max CrCl was 125 – a 34 y/o male with “acute tubular and interstitial nephritis tissue” from “Nephrology”.
Min CrCl was 91 – a 72 y/o male with “acute tubular and interstitial nephritis tissue” from “Nephrology”.
Average CrCl was 102± 13.93

**According to MDRD simplified (mL/min)**
Max CrCl was 106 – a 34 y/o male with “acute tubular and interstitial nephritis tissue” from “Nephrology”.
Min CrCl was 70 – a 47 y/o male with “ulcerative colitis” from “gastroenterology”
Average CrCl was 88.8±13.44

**According to CKD-EPI (mL/min.)**
Max CrCl was 112 - a 34 y/o male with “acute tubular and interstitial nephritis tissue” from “Nephrology”.
Min CrCl was 72 - a 47 y/o male with “ulcerative colitis” from “gastroenterology”.
Average is 91.4±15.95

The average CrCl according to Cockcroft-Gault is bigger than the average CrCl according to MDRD.
Both are bigger than the average CrCl according to CKD-EPI.

**Comparisons**
Between Cockcroft-Gault and MDRD - > 0.05 not statistically significant
Between Cockcroft-Gault and CKD-EPI - > 0.05 not statistically significant
Between MDRD and CKD-EPI - > 0.05 not statistically significant
Comparative group no.2 (Non-ARC, Low Scr)

According to Cockcroft-Gault (mL/min.)
Max CrCl was 123
Min CrCl was 65
Average CrCl was 98.93±16.29

According to MDRD simplified (mL/min)
Max CrCl was 182
Min CrCl was 112
Average CrCl was 144.93±22.97

According to CKD-EPI (mL/min.)
Max CrCl was 123
Min CrCl was 87
Average is 103.8±11.52

The average CrCl according to CKD-EPI is smaller than the average CrCl according to MDRD. Both are bigger than the average CrCl according to Cockcroft-Gault.

Comparisons
Between Cockcroft-Gault and MDRD - <0.05 statistically significant
Between Cockcroft-Gault and CKD-EPI - > 0.05 not statistically significant
Between MDRD and CKD-EPI - <0.05 statistically significant
Comparisons between all the groups

Research group and comparative group 1 (Non-ARC)

Between the research group and the comparative group no1 (Non-ARC) in relation to CrCl according to Cockcroft-Gault – <0.05 statistically significant
Between the research group and the comparative group no1 (Non-ARC) in relation to CrCl according to MDRD – <0.05 statistically significant
Between the research group and the comparative group no1 (Non-ARC) in relation to CrCl according to CKD-EPI – <0.05 statistically significant

Research group and comparative group 2 (Non-ARC, low Scr)

Between the research group and the comparative group no2 (Non-ARC, Low Scr) in relation to CrCl according to Cockcroft-Gault < 0.05 statistically significant
Between the research group and the comparative group no2 (Non-ARC, Low Scr) in relation to CrCl according to MDRD – > 0.05 not statistically significant
Between the research group and the comparative group no2 (Non-ARC, Low Scr) in relation to CrCl according to CKD-EPI – < 0.05 statistically significant

Comparative group 1 (Non-ARC) and Comparative group 2 (Non-ARC, low Scr)

Between the comparative group no1 (Non-ARC) and the comparative group no2 (Non-ARC, Low Scr) in relation to CrCl according to Cockcroft-Gault - > 0.05 not statistically significant
Between the comparative group no1 (Non-ARC) and the comparative group no2 (Non-ARC, Low Scr) in relation to CrCl according to MDRD – < 0.05 statistically significant
Between the comparative group no1 (Non-ARC) and the comparative group no2 (Non-ARC, Low Scr) in relation to CrCl according to CKD-EPI - > 0.05 not statistically significant
Pharmaceutical drugs

Research group
Out of the drugs that were given to the patients:
  o 44.28% ± 29.08% were only renally excreted:

Amantidine (1 patient, 3.22%), Ceftazidime (3 patients, 9.67%), Cefuroxime (8 patients, 25.8%),
Clemastine (1 patient, 3.22%) Diazepam (2 patients, 6.45%), Fraxiparine (9 patients, 29.03%),
Furosemide (2 patients, 6.45%), Gabapentin (1 patient, 3.22%), Gentamicin (1 patient, 3.22%),
Ketoprofen (1 patient, 3.22%), Meropenem (2 patients, 6.45%), Metformin (3 patients, 9.67%),
Metoclopramide (1 patient, 3.22%), Metoprolol (4 patients, 12.9%), Nadroparin (2 patients, 6.45%),
Omeprazole (2 patients, 6.45%), Perindopril (1 patient, 3.22%), Pethidine (1 patient, 3.22%),
Potassium Chloride (6 patients, 19.35%) and Vancomycin (3 patients, 9.67%).

27.48% ± 32.72% were only biliary excreted
28.24%± 22.22% were both renally and biliary excreted

Comparative group1 (Non-ARC)
Out of the drugs that were given to the patients:
53.33%± 39.79% were only renally excreted
21.67%± 21.73% were only biliary excreted
25%± 18.63% were both renally and biliary excreted

The comparative group no1 (Non-ARC) has a larger percentage of drugs that were renally excreted out of the total drugs given than the research group.
The comparative group no1 (Non-ARC) has a smaller percentage of drugs that were biliary excreted out of the total drugs given than the research group.
Both groups have almost equally percentage of drugs that were both renally and biliary excreted out of total drugs given, with the comparative group no1 (Non-ARC) a little bigger.
Fig. 2 Comparison of GFR results calculated according three different equations (Cockcroft-Gault, MDRD, CKD-EPI) in comparative group 1 (NON-ARC)

Fig. 3 Comparison of GFR results calculated according three different equations (Cockcroft-Gault, MDRD, CKD-EPI) in comparative group 2 (NON-ARC, low-Scr)
Fig. 4 *Renally only excreted drugs administered to research group*

Fig. 5 *ways of excretion of Drugs administered to research group (%)*
Fig. 6 Possible causes for ARC in research group

Fig 7. Departments in research group
Conclusions

(1) The augmented Renal clearance (ARC) as Glomerular Filtration rate (GFR) - more than 130 mL/min (assessing by standard Cockcroft-Gault equation), was found in majority of patients when serum creatinine (Scr) was less than 50 µmol/L.

(2) The ARC assessed by Cockcroft-Gault was also detected by MDRD equation but not with CKD-EPI equation; all three estimations were distinguishing non-ARC patients with Scr higher that 50 µmol/L while MDRD equation did not distinguish non-ARC population if Scr was less that 50 µmol/L.

(3) ARC was detected not only in the ICU department as it was expected but also in non-ICU department, most frequently in “endocrinology”, “surgery”, “obstetric” and “pulmonology and allergy” departments and less frequently in psychiatry, neurology, hematology departments. The most frequent diseases and conditions associated with ARC were “Diabetes”, “traumatic brain injury”, “empyema with pneumonia”, “pregnancy” and “hyperthyroidism”.

(4) The ARC experienced patients had several possible causes associated with ARC, most frequently – young age (below 60 years.). Other possible causes known to be associated with ARC we found were “surgery or neurosurgery”, “diabetes” and “trauma”.

(5) The most frequently renally only excreted drugs that are at risk of under dosage if dosed at minimal dosage levels for the patient in an ARC group were: fraxiparine, cefuroxime, potassium chloride, metoprolol and ranitidine.
DISCUSSIONS

In a study done In a Lithuanian hospital, came a conclusion that ARC can be an expected event in almost half of the patients admitted to the hospital (ICU and Non-ICU) that had standard levels of CrCl (>90 mL/min).

The results in my study confirm the notion that although ARC is likely to be established in patients in the ICU – it may also be detected in other Non-ARC departments.

In my study approximately half of the patients fit into that speculation. (51.62%, 16 patients were in the ICU, 48.38% 15 patients were in Non-ICU).

(R.Minkutė, 2013)
RECOMMENDATIONS

1. The 3 known equations for measuring GFR (Cockcroft-Gault, MDRD and CKD-EPI) should each be used appropriately according the patient’s circumstances such as using the CKD-EPI equation if the patient has only CKD.

2. Hospital staff should pay attention to patients that seem to fit to the pattern of more likely to have ARC such as age, diabetes, critically-ill by understanding that a standard drug regimen is more likely to be not therapeutic and might cause harm.

3. TDM (therapeutic drug monitoring) is an approach that most clinician should adopt in order to bypass the fact of the changed PK of the drug as a result of ARC.

4. Further study and research is needed in order to better asses and understand this phenomenon.
References


http://ccforum.com/content/15/3/R139


## Appendixes

1 Appendix. ARC patient survey

### Augmented renal clearance (ARC) survey No. _____

___________

Date of the first observation

### I. General information

<table>
<thead>
<tr>
<th>Clinic, department</th>
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<tbody>
<tr>
<td>Doctor’s name</td>
<td>Patient’s case history No.</td>
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<td>Patient’s code</td>
<td>Date of hospitalization</td>
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<td>Disease code</td>
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<thead>
<tr>
<th>Gender (M/F)</th>
<th>Height</th>
<th>General health status</th>
<th>Pulse rate</th>
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</thead>
<tbody>
<tr>
<td>Age</td>
<td>Weight</td>
<td>Blood pressure</td>
<td>Breathing rate</td>
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### 2. Diagnosis (main condition, complications)

|  |  |  |  |  |
### 3. Patient’s condition at this moment

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### II. Data about kidney damage

| Initial creatinine conc. (Cre) | Creatinine clearance was calculated: (Cockcroft Gault: CrCl=(A × (140-age) × weight)/Cre A: **1.23** - male, **1.04** - female) |
| Date |  |
| MDRD |  |
| CKD-EPI |  |

1. Currently used medication (data is written during the first day of investigation, changes made– in case dosing changed, since when and how long)

<table>
<thead>
<tr>
<th>Name, dosing, changes made and date</th>
<th>Name, dosing, changes made and date</th>
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<td>13.</td>
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<td>3.</td>
<td>15.</td>
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<td>Date</td>
<td>Result and comment</td>
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2. Laboratory test results (*In case of ARC data is registered starting from the beginning of ARC!*)

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<th>Date</th>
<th>Result and comment</th>
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3. ARC influence on the treatment

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<th>Date</th>
<th>Influence on the treatment</th>
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4. Laboratory data to evaluate the impact of ARC

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<tr>
<th>Laboratory tests/data, efficiency</th>
<th>Laboratory tests/data, safety</th>
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<tbody>
<tr>
<td>Date</td>
<td>Result and comment</td>
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5. Possible reasons for ARC

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<tr>
<td>Younger age (&lt;60 years)</td>
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<tr>
<td>Pregnancy</td>
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<td>Sepsis</td>
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<td>Trauma</td>
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<td>Surgery or neurosurgery</td>
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<tr>
<td>Neutropenia</td>
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<td>Burns injury</td>
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6. Patient belongs to group:

| ARC (CrCl >130 mL/min.) | Control group (CrCl 90-130 mL/min.) | Not included to investigation (CrCl < 90 mL/min.) |