ORIGINAL ARTICLE

UDC: 616.12-009.17:616.61
https://doi.org/10.2298/VSP170226038L

Worsening renal function in patients hospitalized with acutely decompensated heart failure

Bubrežna disfunkcija kod bolesnika sa akutnom dekompenzacijom srčane slabosti

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Abstract

Background/Aim. A predictor of a poor prognosis, renal dysfunction often manifests in patients with heart failure, and is associated with an increased mortality in these patients. The aim of the parent study was to determine risk factors associated with worsening renal function (WRF) in patients hospitalized for acutely decompensated heart failure. **Methods.** The study included 330 patients with acutely decompensated heart failure. Patients who developed WRF (n = 215, mean age 72.4 ± 9.8 years) were in the clinical group, and patients without WRF (n = 115, mean age 59.8 ± 11.7 years) were in the control group. Patients in the clinical group were observed according to: the age, gender, lipids, electrolytes, smoking, hypertension, and type of heart failure, with reduced or preserved left ventricle ejection fraction (HFrEF or HFpEF). We used logistic regression to calculate non-adjusted odds ratio (OR) and 95% confidence intervals for occurrence of WRF. **Results.** WRF was determined in 65.2% of patients with heart failure. Non-adjusted OR showed that there was a significant risk for development of WRF with age (OR = 4.3; $p < 0.01$), total cholesterol > 5.2 mmol/L (OR = 1.6; $p < 0.05$), hyponatremia < 135 mmol/L, (OR = 2.8; $p < 0.01$), smoking (OR = 3.9; $p < 0.01$), hypertension (OR = 2.0; $p < 0.05$), and with the presence of HFrEF (OR = 1.3; $p < 0.01$). Presence of HFpEF, hypokalemia, < 3.5 mmol/L, plasma triglycerides, > 1.7 mmol/L, and gender, did not have any significance for the development of renal damage. **Conclusion.** Patients' age, total cholesterol, hyponatremia, smoking, hypertension, and HFrEF were significant risk factors for worsening renal function in heart failure patients. Comparing predictive values, age could be the best prognostic tool for early identification of patients at risk for WRF.

Key words:
heart failure; cardio-renal syndrome; risk factors.

Apstrakt

Uvod/Cilj. Bubrežna disfunkcija se često javlja kod bolesnika sa srčanom slabošću, predstavlja loš prognostički faktor i povezana je sa porastom mortaliteta kod ovih bolesnika. Cilj istraživanja je bio da se utvrde faktori rizika povezani sa razvojem bubrežne disfunkcije kod bolesnika sa akutnom dekompenzacijom srčane slabosti. **Metode.** Istraživanjem je obuhvaćeno 330 bolesnika sa akutnom dekompenzacijom srčane slabosti. Bolesnici koji su razvili bubrežnu disfunkciju (n = 215 ispitanika, starosti 72,4 ± 9,8 godina) činili su kliničku grupu, a bolesnici bez bubrežne disfunkcije (n = 115 ispitanika, starosti 59,8 ±11,7 godina) bili su kontrolna grupa. Kod ispitanika kliničke grupe analizirani su sledeći parametri: godine starosti, pol, lipidni status, koncentracija elektrolita u plazmi, prisustvo pušenja i hipertenzije i tip srčane slabosti. Korišćena je logistička regresija za izračunavanje *odds ratio* (OR) i 95% intervala poverenja za razvoj bubrežne disfunkcije kod ovih bolesnika. **Rezultati.** Bubrežna disfunkcija je ustanovljena kod 65,2% bolesnika sa srčanom slabošću. Pokazano je da su se kao značajni faktori rizika od razvoja bubrežne disfunkcije izdvojili starost ispitanika (OR = 1,6; $p < 0,05$), porast koncentracije ukupnog holesterola, > 5,2 mmol/L (OR = 1,6; $p < 0,05$), hiponatrijemija, < 135 mmol/L, (OR = 2,8; $p < 0,01$), pušenje (OR = 3,9; $p < 0,01$), hipertenzija (OR = 2,0; $p < 0,05$) i postojanje srčane slabosti sa smanjenom ejekcionom frakcijom (OR = 1,3; $p < 0,01$). Srčana slabost sa očuvanom ejekcionom frakcijom, hipokalijemija, < 3,5 mmol/L, visoka koncentracija triglicerida u plazmi, > 1,7 mmol/L i pol ispitanika nisu pokazali statistički značaj za razvoj bubrežne disfunkcije. **Zaključak.** Godine starosti, povišene vrednosti totalnog holesterola, hiponatrijemija, pušenje, hipertenzija i smanjenje ejekcione frakcije značajni su i nezavisni faktori rizika od razvoja bubrežne disfunkcije kod bolesnika sa srčanom slabošću. Poređenjem prediktivnih vrednosti, godine starosti bi mogle da budu najznačajniji faktor rizika za ranu identifikaciju bolesnika koji su pod povećanim rizikom od razvoja bubrežnog oštećenja.

Ključne reči:
srce, insuficijencija; sindrom, kardio-renalni; faktori rizika.

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Introduction

Worsening renal function (WRF) as a predictor of a poor prognosis often manifests in patients with heart failure (HF). WRF is associated with an increased mortality in these patients [1] as well as increased in-hospital costs, in-hospital mortality, length of stay and likelihood of readmission [2]. According to data from large registries, 30% of patients hospitalized for acutely decompensated heart failure (ADHF) exhibit moderate to severe WRF. If patients with mild WRF are included, there is more than 50% of them [3]. WRF is also closely linked with deterioration of renal function over time, after an initial hospitalization, which leads to the development of renal failure, respectively.

In patients with acute HF, hemodynamic balance maintained by kidneys is often disrupted, resulting in decreased organ perfusion and ultimately organ failure and possibly death. Heart failure with reduced left ventricle ejection fraction (HFrEF) is characterized by impaired left ventricular systolic function and poor cardiac output with activation of compensatory mechanisms such as the renin-angiotensin-aldosterone system, the sympathetic nervous system, and other mediators, which interact to maintain the fluid volume [4]. Furthermore, decreased renal perfusion, in addition to nephrotoxic agents, eventually leads to kidney injury in those patients [5]. Heart failure with preserved left ventricle ejection fraction (HFpEF), mostly in patients with thick ventricular walls and a small ventricular cavity, is also characterized by a low cardiac output in acute deterioration of HF. The high end-diastolic pressure is transferred back to the pulmonary capillaries which results in dyspnoea upon exertion, and these pathophysiological abnormalities trigger neurohormonal activation, as happens in HFrEF [6]. The identification of risk factors associated with WRF in patients with HD may provide an opportunity to reduce the risk of complications and improve the outcome in this setting.

Therefore the aim of the parent study was to determine risk factors associated with WRF in patients hospitalized for acutely decompensated heart failure.

Methods

We observed 330 patients with ADHF, of both sexes, hospitalized at the Clinic for Cardiovascular Diseases, Clinical Center Niš, Serbia, between March and November 2014. The study was designed as a cross-sectional, retrospective study, approved by the Ethic Committee of Clinical Center Niš, and conducted in compliance with the Declaration of Helsinki and Good Clinical Practice Guidelines.

The diagnosis of HF was established according to the guidelines of the European Society of Cardiology (ESC) [7]. All patients with left ventricular ejection fraction (LVEF) $\leq$ 45% –HFrEF, or with heart failure with preserved left ventricle ejection fraction (HFpEF), having the New York Heart Association (NYHA) function class II to IV [8], were enrolled in the study. Echocardiography was performed on VIVID 4GE ultrasound system and LVEF was measured according to Simpson biplane method. These measurements were performed as soon as the patients were able to have compliance during the examination.

The reasons for hospitalization were hypertensive crisis, n = 25 (7.5%), chronic ischemic cardiomyopathy, without increased specific markers of myocardial necrosis, n = 58 (17.5%), valvular heart disease, n = 69 (21%), and dilated cardiomyopathy, n = 178 (53.9%), as underlying conditions for the development of ADHF (Table 1). There suffered 95 (28.7%) of patients from acute heart failure and 235 (71.3%) patients from acute decompensation of a preexisting heart disease. Patients who had previous diagnosis of diabetes mellitus (type 1 and 2), chronic renal failure grade 4 and 5, malignant diseases, and chronic inflammatory diseases were not included in the study. The patients with acute coronary syndrome, coronarography or percutaneous coronary intervention during hospitalization and 30 days before were also excluded.

Tabele 1

Reasons for hospitalization

Reasons	Number (%) of patients
Hypertensive crisis	25 (7.51)
Chronic ischemic cardiomyopathy*	58 (17.5)
Valvular heart disease	69 (21)
Dilated cardiomyopathy	178 (53.9)

***Without increased specific markers of myocardial necrosis.**

All patients hospitalized with the HF were divided into two groups, according to the presence of WRF, 7 days after admission. The first subgroup consisted of 215 (65.2%) patients, who developed WRF during hospitalization and they were observed as the clinical group. The second subgroup consisted of 115 (34.8%) patients, without WRF during the hospitalization, and they represented the control group. In the group of patients with WRF, 163 (75.8%) patients were older than 65 years of age and 121 (56.28%) were males. HF with reduced left ventricle ejection fraction was observed in 134 (62.3%) patients while 185 (86.0%) patients had arterial hypertension, or received antihypertensive therapy. Regarding the smoking habits, 112 (52.0%) patients were smokers. In the control group, without WRF, 85 (73.9%) were older than 65 years of age and 72 (62.6%) were males. HFrEF was observed in 38 (33.0%) patients and 89 (77.3%) patients had arterial hypertension, or received antihypertensive therapy.

We assessed kidney function by measuring serum creatinine concentration. An increase in serum creatinine by at least 25%, or more, compared to the baseline values, was defined as worsening renal function [9]. Using the simplified Modification of Diet in Renal Disease (MDRD) formula, a suggested method for assessment in patients with HF, we also estimated glomerular filtration rate (eGFR) [10]. According to this method, we determined stages of chronic kidney disease at admission and after 7 days of hospitalization.

Previous medication included angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers (75.3%), aldosterone antagonists (62.5%), digoxine (69.8%), oral anticoagulants (49%), beta blockers (72.4%) and oral furosemide (87.1%). However, during hospitalization, all pa-

tients with ADHF received furosemide intravenously and vasodilators.

Laboratory measurements

Using standard clinical laboratory methods, biochemical measurements: urea, creatinine, glycemia, total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglycerides and electrolytes were obtained from fasting blood samples (5 mL) from each participant at admission, and all analysis were performed by using Erba Mannheim XL600 analyzer (ERBA Diagnostics Mannheim Gmbh, Baden-Wurttemberg, Germany). Impaired lipid level (total cholesterol, LDL, HDL, and triglycerides) were defined according to the National Guidelines for Good Clinical Practice for Diagnostics and Treatment of Dyslipidemia (2012) [11].

Statistical analyses

Characteristics of the study group were expressed as mean ± standard deviation (SD) (continuous variables) with number and % in brackets (categorical variables). We compared data of patients using Student *t*-test for normally distributed data (expressed as mean ± SD) and Mann–Whitney U test for non-parametric variables. Univariate logistic regression was used to calculate odds ratio (OR) and 95% confidence intervals (CI) for occurrence of WRF. The relationship between selected variables was determined by Pearson's correlation coefficient I. All analyses were performed with SPSS version 16.0 (SPSS, Chicago, IL, United States). The significance level was set at $p < 0.05$.

Results

Worsening renal function was determined in 215 (65.2%) patients hospitalized with heart failure after 7 days of hospitalization. Significant differences were found between patients who developed WRF and the control group. The patients with heart failure who developed WRF were older, more hypertensive and less likely to be with the first episodes of acute heart failure and preserved ejection fraction. They had similar lipid profile except higher triglycerides ($p < 0.01$), higher fasting glycemia ($p < 0.05$), serum urea and creatinine concentration ($p < 0.01$). The patients in the clinical group had lower serum potassium ($p < 0.01$), sodium concentration ($p < 0.01$), lower values of systolic ($p < 0.01$), and diastolic blood pressure ($p < 0.01$) and eGFR ($p < 0.01$) at admission, compared to the control group. There were no significant differences according to the patients' gender, LDL and HDL cholesterol concentrations. All data are presented in Table 2.

The analysis of the stages of chronic kidney disease showed significant differences in distribution among subgroups of the HF patients. The patients in the clinical group had severely impaired kidney function compared to the control group at admission ($p < 0.01$). This is presented in Table 2. Moreover, the development of chronic kidney disease grade 3 was registered in 102 (47.4%) of the WRF patients after 7 days of hospitalization (data not shown).

Table 2

Clinical data of 330 heart failure (HF) patients in the control and clinical group at admission

Parameter	Control group (n = 115)	Patients with WRF (n = 215)	*p*
Age (years), mean ± SD	59.8 ± 11.7	72.4 ± 9.8	0.05
Acute heart failure, n (%)	52 (45.2)	43 (20.0)	0.05
Acute decompensation, n (%)	63 (54.8)	172 (80.0)	0.05
Chronic kidney disease, n (%)			
stage 1 (eGFR > 90 mL/min/1.73m^2)	67 (58.2)	48 (22.3)	0.01
stage 2 (eGFR 60–89 mL/min/1.73m^2)	39 (34.0)	85 (39.5)	
stage 3 (eGFR 30–59 mL/min/1.73m^2)	9 (7.8)	92 (42.7)	
Males, n (%)	72 (62.6)	121 (56.2)	NS
Smokers, n (%)	46 (40.0)	112 (52.0)	0.01
Glycemia, (mmol/L), mean ± SD	5.2 ± 0.9	5.9 ± 0.4	0.05
Cholesterol, (mmol/L), mean ± SD	5.5 ± 1.5	5.9 ± 1.5	NS
LDL, (mmol/L), mean ± SD	3.5 ± 1.2	4.0 ± 1.3	NS
HDL, (mmol/L), mean ± SD	1.1 ± 0.3	1.2 ± 0.3	NS
Triglycerides, (mmol/L), mean ± SD	1.2 ± 0.5	2.1 ± 0.6	0.01
Urea, (mmol/L), mean ± SD	6.2 ± 2.4	10.3 ± 6.1	0.01
Serum creatinine (μmol/L), mean ± SD	84.5 ± 12.6	139.4 ± 21.8	0.01
eGFR (mL/min/1.73 m^2), mean ± SD	79.5 ± 11.7	59.5 ± 22.4	0.01
Na, (mmol/L), mean ± SD	136.5 ± 4.9	132.7 ± 2.2	0.01
K, (mmol/L), mean ± SD	4.4 ± 0.7	3.3 ± 0.5	0.01
Hypertension, n (%)	89 (77.3)	185 (86.0)	0.01
SBP, (mmol/L), mean ± SD	138 ± 15	107 ± 10	0.01
DBP, (mmol/L), mean ± SD	80 ± 10	68 ± 8	0.01
HFrEF, n (%)	38 (33.0)	134 (62.3)	0.05
LVEF (%), mean ± SD	50.2 ± 12.3	39.7 ± 12.1	0.01

Data are expressed as mean ± standard deviation (SD) – compared with Student-*t* test or expressed as n (%) compared with *U* test.

WRF – worsening renal function; SBP – systolic blood pressure; DBP – diastolic blood pressure; LVEF– left ventricular ejection fraction; eGFR – estimated glomerular filtration rate; HFrEF – heart failure reduced left ventricle ejection fraction.

Table 3

Analysis of risk factors according to age, gender and left ventricle ejection fractions (LVEF) in 215 patients with worsening renal function

Parameters	n	Urea (mmol/L) mean ± SD	Creatinine (μmol/L) mean ± SD	eGFR (ml/min/1,73m^2) mean ± SD	LVEF (%) mean ± SD
Age (years)	52	7.23 ± 3.8	121.7 ± 38.3	61.9 ± 15.4	47.8 ± 14.2
< 65					
> 65	163	12.1 ± 7.2**	129.9 ± 39.2*	52.8 ± 17.1**	42.9 ± 11.7*
Sex	121	8.4 ± 4.2	117.3 ± 49.7	66.7 ± 18.8	43.1 ± 13.2
male					
female	94	9.9 ± 8.1*	115.8 ± 60.8	55.5 ± 17.9**	48.0 ± 14.4**
HFrEF	134	10.2 ± 4.8	124.6 ± 19.9	57.1 ± 9.3	40.4 ± 12.3
HFpEF	81	8.9 ± 3.2	116.8 ± 19.1*	63.5 ± 18.4**	49.8 ± 11.4**

***p* < 0.05, ****p* < 0.01.**

n – number of patients; SD – standard deviation.

eGFR – estimated glomerular filtration rate; LVEF – left ventricular ejection fraction; HFrEF – heart failure with reduced left ventricle ejection fraction; HFpEF – heart failure with preserved left ventricle ejection fraction.

Table 4

Non-adjusted odds ratio (OR) and 95% confidence intervals (CI) for worsening renal function in the study patients

	Control group	Clinical group	OR	95%CI	*p*
Age (years)					
< 65	30 (26.1)	52 (24.1)			
65+	85 (73.9)	163 (75.8)	4.31	3.80–6.00	< 0.01
Sex					
male	72 (62.6)	121 (56.2)	1.09	0.99–1.12	0.11
female	43 (37.4)	94 (43.8)			
Smoking	46 (40.0)	112 (52.0)	3.98	2.55–5.79	< 0.01
TC > 5.2 mmol/L	101 (88.3)	195 (90.6)	1.66	1.46–3.23	< 0.05
TG > 1.7 mmol/L	93 (81.1)	201 (93.5)	0.96	0.33–3.90	0.56
Na < 135 mmol/L	70 (60.9)	177 (82.5)	2.82	2.68–3.22	< 0.01
K < 3.5 mmol/L	54 (47.5)	116 (54.0)	1.27	0.92–1.44	0.886
Hypertension	89 (77.3)	185 (86.0)	2.06	1.15–8.53	0.045
HFrEF	38 (33.0)	134 (62.3)	1.29	1.12–2.81	< 0.01
HFpEF	77 (67.0)	81 (37.6)	1.16	0.68–1.62	0.32

Data are expressed as n (%).

TC – total cholesterol, TG – triglycerides; HFrEF – heart failure with reduced left ventricle ejection fraction; HFpEF – heart failure with preserved left ventricle ejection fraction.

The parameters of global renal function (plasma concentration of urea, creatinine and eGFR) and LVEF according to the age, gender and type of HF (HFrEF or HFpEF) in the subgroup of patients with WRF are shown in Table 3. We found that urea and creatinine concentration were significantly higher and eGFR and LVEF lower in the patients older than 65 years of age. The female patients also had significantly higher urea and lower eGFR compared to the males. The patients with HFrEF had significantly higher creatinine concentration and lower eGFR, thus presenting the older female patients with reduced EF as particularly predisposed to WRF.

Non-adjusted OR for renal dysfunction were presented in Table 4. Non-adjusted ORs showed that there was a significant risk for development of WRF during hospitalization in the patients older than 65 years (OR = 4.3; 95% CI 3.8–6.0), history of smoking (OR = 3.9; 95% CI 2.5–5.7), total plasma cholesterol > 5.2 mmol/L (OR = 1.6; 95% CI 1.4–3.2), hyponatremia < 135 mmol/L, (OR = 2.8; 95% CI 2.6–3.2), hypertension (OR = 2.0; 95%CI 1.1–8.5), and in patients with reduced left ventricle ejection fraction compared to those with preserved LVEF (OR = 1.3; 95% CI 1.1–2.8). Heart failure with preserved left ventricle ejection fraction, elevated plasma triglycerides, > 1.7 mmol/L, hypokalemia, < 3.5 mmol/L, and sex did not prove significant for worsening renal function in the patients with heart failure. Thus, the presence of any of the evaluated risk factors (age over 65 years, smoking, hypertension and hyponatriemia) increased the probability for WRF more than two times.

Discussion

Heart failure is a leading cause of hospitalization in the age group of 65 years and older, represents a significant economic burden [5], and eventually leads to kidney injury. The present study adds to the current data that WRF is an expecting finding among older patients hospitalized for HF. WRF frequency ranges from 35% to 70% in various studies [12], and have a high in-hospital mortality [13]. In a meta-analysis unadjusted mortality rate at one year, follow-up was 51% in the patients with moderate to severe renal impairment, compared to 26% in those without any renal impair-

ment [14]. The prevalence of WRF, as well as the development of kidney failure stages III, (determined as eGFR < 60/mL/min/m^2), in our patients hospitalized with ADHF was 65.2%, and 47.4% prospectively, which is in accordance with current data. Some researchers found "moderate" renal failure (creatinine clearance < 60/mL/min/m^2) in 22.5% of their heart failure patients [15], while in the Valsartan in Heart Failure (Val-HeFT) trial [16] (n = 5010), eGFR was found to be below 60 mL/min/m^2 in 58% of patients. In both studies, however, decreased eGFR was a predictor of a poor prognosis.

Baseline renal insufficiency was reported to increase the number of hospitalizations due to worsening of HF, and these individuals had high likelihood of cardiovascular death [12]. Possible mechanism for development of renal dysfunction is arterial hypotension followed by severe and prolonged kidney hypoperfusion. In 10.2% of our patients with HF, prompt decrease in kidney function at hospital admission was noticed. Age and baseline renal function were determined as risk factors for WRF and exacerbation in chronic HF patients [17].

Several studies showed that the prevalence of kidney failure rises with age [15–18]. Accordingly, in our study significantly more patients older than 65 years experienced WRF, and this was an independent risk factor for its occurrence, (OR 4.3). Traditional risk factors for heart disease, such as hypertension, smoking and total cholesterol, > 5.20 mmol/L, also showed significance for WRF, although with a slightly smaller predictive values.

WRF in our study was equally distributed between gender, despite the fact that cardiovascular diseases are more frequent in males compared to females. This could be explained by physiological changes after menopause, most probably due to the loss of protective estrogen effect on vasculature and great proportion of patients aged over 65 years. Estrogen decreases expression of angiotensin type 1 receptor and angiotensin-converting enzyme and causes the release of angiotensinogen substrate [19].

In our study, HFrEF (≤ 45% LVEF) was found to be a significant risk factor for WRF with moderately higher risk (OR 1.3), unlike HFpEF. However, in other studies various relations between heart and kidney function parameters were determined. Apparently, elevation in both ventricles end-diastolic pressures and venous pressure contribute to renal dysfunction by impairing forward blood flow and by increasing renal venous pressure [20]. Predomination of a single process is probably influenced by a stage of heart disease and neurohormonal status of a patient. Acute renal injury, as a complication in congestive HF patients treated with diuretics, was observed more often in those with HFrEF (40%) than with HFpEF (28%) [17]. Additionally, WRF is certainly favored by pronounced vasoconstriction and sodium retention in acutely decompensated HF patients [21]. Worsening renal function during the first 3 days of hospitalization was also reported in 47% of patients with acutely decompensated HF [22]. Heart failure with reduced left ventricle ejection fraction as the significant risk factor for kidney injury in our HF patients was likely due to its prolonged hypoperfusion effect on kidneys.

Urea, creatinine and eGFR were higher in our patients with WRF that were older than 65 years compared to the younger ones. As a consequence of HF related increase in venous pressure in kidneys, pressures in interstitial space and Bowman's capsule also increase and lead to greater urea reabsorption. Besides, in low-output HF, arterial perfusion is maintained by releasing neurohumoral mediators, among which is arginine vasopressin that mediates urea reabsorption [12, 20]. However, urea may not be reliable index of WRF, mostly compared to eGFR, because its serum concentrations are affected by different elements of metabolism [12]. This is perhaps the reason of insignificant correlation between LVEF and urea, and creatinine values in our study. Prolonged hyponatremia was proven to be an independent cardiovascular risk factor, and also an independent factor of mortality in this group of patients, mostly due to the long-term diuretic therapy.

We suppose that higher urea concentrations in our female patients are due to lower percent of total body water and significantly faster decline of eGFR with age, compared to the males [23].

Conclusion

Worsening renal function is common in patients hospitalized with ADHF. We have demonstrated that age over 65 years, heart failure with reduced left ventricle ejection fraction, smoking, hyponatremia, elevated total cholesterol and hypertension, were significant risk factors for worsening renal function. Our results indicate that age over 65 years could be the best prognostic tool, among evaluated, for identification of worsening renal function in patients with heart damage. The other assessed parameters, heart failure with preserved left ventricle ejection fraction, elevated triglycerides level, hypokalemia, and gender did not have any significance for worsening renal function in patients hospitalized with heart failure.

The results of our study may provide clinicians with very important knowledge about the elderly patients, who are under a greater risk for renal damage and therefore possible prevention of irreversible changes.

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Received on December 15, 2016.
Revised on March 02, 2017.
Accepted on March 03, 2017.
Online First March, 2017.