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The Independent Association of Renal Dysfunction and Arrhythmias in Critically Ill Patients*

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Study objectives: **The purpose of this study was to quantify the impact of baseline renal dysfunction on incidence and occurrence of cardiac arrhythmias in the coronary ICU.**
Background: **Renal dysfunction is an established predictor of all-cause mortality in the ICU setting. We set out to evaluate the independent contributory effect of renal dysfunction to arrhythmias and mortality in this population.**
Design and setting: **We analyzed a prospective coronary care unit registry of 12,648 admissions by 9,557 patients over 8 years at a single, tertiary center. An admission serum creatinine level was available for 9,544 patients. Those patients not receiving long-term dialysis were classified into quartiles of corrected creatinine clearance with cutpoints of 46.2 mL/min/72 kg (group 1), 63.1 mL/min/72 kg, and 81.5 mL/min/72 kg. Dialysis patients (n = 527) were considered as a fifth comparison group (group 5).**
Measurements and results: **Baseline characteristics including older age, African-American race, diabetes, hypertension, history of previous coronary disease, and heart failure were incrementally more common with increasing renal dysfunction strata. There were graded, independent increased risks for accelerated idioventricular rhythm (relative risk [RR], 2.43; 95% confidence interval [CI], 1.40 to 4.20; p = 0.002), sustained ventricular tachycardia (RR, 2.07; 95% CI, 1.02 to 4.22; p = 0.04), ventricular fibrillation (RR, 2.42; 95% CI, 1.13 to 5.15; p = 0.02), and complete heart block (RR, 3.64; 95% CI, 1.77 to 7.48; p = 0.0004, group 5 vs group 1).**
Conclusions: **We conclude that baseline renal function is a powerful, independent predictor of cardiac arrhythmias in the coronary ICU population.** ***(CHEST 2002; 122:669–677)***

Key words: arrhythmias; complications; coronary care unit; renal failure; survival

Abbreviations: AMI = acute myocardial infarction; CHF = congestive heart failure; CI = confidence interval; CICU = cardiac ICU; CorrCrCl = corrected creatinine clearance; ESRD = end-stage renal disease; LV = left ventricular; LVH = left ventricular hypertrophy; RR = relative risk

We and others[1–4] have shown a graded, independent risk of acute renal failure after percutaneous coronary intervention, coronary artery bypass surgery, and other cardiac events driven in part by baseline renal function. The consequences of acute renal failure developing *de novo* after hospital admission requiring dialysis include high rates of in-hospital mortality and shortened long-term survival, whether or not dialysis becomes permanent.[1,5] In addition, increased arrythmogenicity documented by ECG has been described in patients during hemodialysis, as well as in patients with left ventricular hypertrophy (LVH) and hypertension in the setting of renal dysfunction.[6–8] Increased risk for arrhythmias was reported with mildly impaired renal function in patients undergoing cardiac valve replacement surgery.[9]

These investigations have been limited by the various definitions used to categorize and describe the degrees of renal dysfunction, and by the exclusion of patients with more advanced renal insuffi-

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ciency, including those receiving dialysis treatment. We sought to evaluate the independent risk of baseline renal dysfunction on cardiac arrhythmia events in the cardiac ICU (CICU).

Materials and Methods

Setting, Data Collection, Follow-up

Henry Ford Hospital is a 903-bed tertiary-care center located in the urban core of the Detroit metropolitan area, and receives patients whose care is provided primarily within Henry Ford Health System, a vertically integrated, mixed-model managed care organization with an advanced information technology infrastructure.[10–12] The Henry Ford CICU database has been previously described.[2] In brief, this was a registry in which every admission to this 16-bed unit had clinical data (approximately 250 discrete elements) prospectively recorded on case report forms by trained research assistants. Data collected from May 1, 1990, to August 22, 1998, included baseline demographics, laboratory values, and events occurring during the unit stay, including arrhythmias. Trained research nurses prospectively assessed arrhythmias with daily checks of telemetry, 12-lead ECGs, and hospital charts. Once an arrhythmia occurred, it was recorded. Multiple occurrences of the same arrhythmia were only counted once. The data collection period was stopped after discharge from the unit, either to another floor or to home. In-hospital events were also recorded and detailed, and only the first CICU admission was used in the analysis. Subsequent CICU admissions by the same patients were excluded to avoid double counting.

Assessment of Baseline Renal Function

The database was augmented with merged data from laboratory tables in order to obtain complete renal function data in 9,544 patients (99.9%). Because weight was not available in the database, the corrected creatinine clearance (CorrCrCl) [per 72 kg of body weight] was used as the best measure of baseline renal function as follows[13,14]:

$$\text{CorrCrCl male} = (140 - \text{age in years})/\text{SCr}$$

$$\text{CorrCrCl female} = 0.85[(140 - \text{age in years})/\text{SCr}],$$

where SCr = serum creatinine.

We have previously validated the predictive capabilities of CorrCrCl on all-cause mortality in the parent population.[2] The CorrCrCl was found to be unimodal and normally distributed. Therefore, patients were classified into quartiles at the cutpoints of 46.2, 63.1, and 81.5 mL/min/72 kg. Patients receiving long-term dialysis (n = 527) were considered again as a fifth comparison group. Tables were created with these groups as the column headings. There were no directional changes in the final calculated univariate and multivariate relative risks (RRs). Based on the established validity of estimated creatinine clearance as a surrogate for glomerular filtration rate and its frequency distribution in this data set, the investigators decided to retain the CorrCrCl as the measure of baseline renal function throughout the analysis.[15–16]

Admitting Diagnoses

The admitting diagnosis categories ranked according to their increasing in-hospital mortality were as follows: coma, shock, noncardiac diagnoses, other cardiac diagnoses, congestive heart failure (CHF), acute myocardial infarction (AMI), arrhythmias, and unstable angina pectoris. This diagnosis rank code was used in multivariate modeling to account for the severity of illness on admission. Intubation and mechanical ventilation was performed in 1,355 patients (14.2%). In addition, sepsis was listed as a complicating factor in 1,504 patients (15.7%).

Outcome Validation

Eleven arrhythmic outcomes, including atrial flutter, atrial fibrillation, ventricular tachycardia, ventricular fibrillation, asystole, junctional rhythm, and accelerated idioventricular rhythm, were selected for validation with blinded chart abstraction. A random sample (n = 20) from each outcome category was chosen, and each record was compared against chart abstraction by an independent team comprising an internist and a cardiologist for the development of the outcome during the ICU stay. Agreement statistics were computed for each outcome and then averaged over the seven categories. The mean percent agreement was 92.7% across the 11 outcomes.

Statistical Analysis

Baseline characteristics are reported with means ± SD or proportions with 95% confidence intervals (CIs), as appropriate, with exclusion of missing data points. Univariate comparisons were carried out using analysis of variance, or χ^2 as appropriate. The χ^2 test for linear trend was used for comparisons of baseline characteristics across ascending levels of renal dysfunction. Multiple logistic regression was performed for the outcomes of arrhythmias and in-hospital death, with independent RRs reported with 95% CIs. Multivariate risks were adjusted for age, gender, race, admission diagnosis, history of heart failure, previous aspirin, β-blocker, and angiotensin-converting enzyme inhibitor use, diabetes, and baseline hemoglobin. All univariate significant predictors were entered in the model manually and removed at $p > 0.10$. All models were tested for interactions. Variables in the causal pathway, including the developing admission diagnosis (such as shock), were included in the final models. Cox proportional hazards model was used to derive the independent hazard of estimated renal function with cumulative, long-term survival. The log-rank test was used to evaluate the independent differences in survival across the strata. All p values are two tailed and considered significant at < 0.05.

Results

Baseline Characteristics

Table 1 shows baseline characteristics of the patient groups stratified by renal risk. The overall mean age was 63.4 ± 13.8 years (range, 15 to 98 years). The mean age for women and men was similar (63.6 ± 13.8 years and 63.3 ± 13.7 years, respectively; $p = 0.22$). The overall female-to-male ratio was 0.73, with male gender predominant in all groups. For the study group as a whole, 5,080 patients (53.2%) were white, 4,189 patients (43.9%) were African American, and 275 patients (2.9%) were categorized as "other" race. African-American race increased in proportion from group 1 to group 5, including 60% of those receiving long-term dialysis. Diabetes and hypertension were more common

Table 1—*Baseline Clinical Characteristics of 9,544 Patients Admitted to a CICU Stratified by Renal Risk Group

Characteristics	Group 1, CorrCrCl > 81.5	Group 2, 63.1 < Corr-CrCl≤ 81.5	Group 3, 46.2 < Corr-CrCl≤ 63.1	Group 4, CorrCrCl < 46.2 Not Receiving Dialysis	Group 5, Long-term Dialysis	p Value Group 1 vs Group 5	p Value for Trend
Patients, No.	2,254	2,255	2,254	2,254	527		
Demographics							
Age, yr	54.3 ± 13.0	62.1 ± 12.2	67.9 ± 11.8	70.0 ± 12.9	64.4 ± 13.8	< 0.0001	< 0.0001
Female/male ratio	0.79	0.61	0.69	0.86	0.74		
African American	782 (34.7)	888 (39.4)	952 (42.2)	1,251 (56.5)	316 (60.0)	< 0.0001	< 0.0001
White	1,384 (61.4)	1,287 (57.1)	1,244 (55.2)	968 (42.9)	197 (37.4)	0.0001	< 0.0001
Other race	88 (3.9)	80 (3.5)	58 (2.6)	35 (1.6)	14 (2.7)	0.17	
Medical history							
Diabetes	534 (23.7)	544 (24.1)	613 (27.2)	811 (36.0)	257 (48.8)	< 0.0001	< 0.0001
Hypertension	1,211 (53.7)	1,307 (58.0)	1,408 (62.5)	1,669 (74.0)	406 (77.0)	< 0.0001	< 0.0001
Dyslipidemia	756 (33.5)	761 (33.7)	731 (32.4)	595 (26.4)	132 (25.0)	< 0.0001	< 0.0001
Tobacco use	1,226 (54.4)	1,174 (52.1)	1,078 (47.8)	944 (41.9)	226 (42.9)	< 0.0001	< 0.0001
Prior angina	609 (27)	738 (32.7)	813 (36.06)	753 (33.4)	195 (37.0)	< 0.0001	< 0.0001
Prior AMI	466 (20.6)	527 (23.4)	621 (27.6)	667 (29.6)	167 (31.7)	< 0.0001	< 0.0001
Prior PTCA	214 (9.5)	215 (9.53)	184 (8.16)	125 (5.55)	25 (4.7)	0.002	< 0.0001
Prior CABG	155 (6.9)	201 (8.9)	248 (11.0)	229 (10.2)	80 (15.2)	< 0.0001	< 0.0001
Any prior revascularization	332 (14.7)	378 (16.8)	388 (17.2)	319 (14.2)	89 (16.9)	0.21	0.008
Prior CHF	312 (13.8)	343 (15.2)	485 (21.5)	850 (37.7)	237 (45.0)	< 0.0001	< 0.0001
Prosthetic valve	24 (1.1)	33 (1.46)	46 (2.04)	55 (2.4)	13 (2.5)	0.007	0.06
Prior medications							
Aspirin	706 (31.3)	766 (34.0)	723 (32.1)	659 (29.2)	143 (27.1)	0.326	0.03
Warfarin	106 (4.7)	126 (5.6)	132 (5.9)	158 (7.0)	45 (8.5)	0.0006	< 0.0001
β-blockers	463 (20.5)	466 (20.7)	456 (20.2)	391 (17.4)	78 (14.8)	0.002	0.0009
ACEI	373 (16.6)	411 (18.2)	493 (21.9)	623 (27.6)	151 (28.7)	< 0.0001	< 0.0001
Calcium-channel blockers	416 (18.5)	500 (22.2)	471 (20.9)	655 (29.1)	169 (32.1)	< 0.0001	< 0.0001
Nitrates	752 (33.4)	868 (38.5)	922 (40.1)	917 (40.7)	234 (44.4)	< 0.0001	< 0.0001
Diuretics	429 (19.0)	504 (22.4)	662 (29.4)	979 (42.4)	261 (49.5)	< 0.0001	0.02
Digitalis	212 (9.4)	250 (11.1)	359 (15.9)	504 (22.4)	144 (27.3)	< 0.0001	0.001

*Data are presented as No. (%) or mean ± SD unless otherwise indicated. Only the first admission is counted in these comparisons. PTCA = percutaneous transluminal coronary angioplasty; ACEI = angiotensin-converting enzyme inhibitor; CABG = coronary artery bypass graft surgery.

across the ascending risk groups 1 to 5 ($p < 0.0001$ for both trends). Conversely, smoking and hyperlipidemia were more common in the lower risk groups ($p < 0.0001$ for both trends). Previous coronary artery disease increased only slightly over the renal strata from 27 to 37% for a prior history of angina, and 20.6 to 31.7% for a previous AMI ($p < 0.0001$ for both). Rates of prior coronary revascularization were similar among the groups. There was, however, a graded increase from 13.8 to 45.0% in the frequency of prior CHF from group 1 to 5 ($p < 0.0001$). Rates of CHF medications including angiotensin-converting enzyme inhibitors, diuretics, and digoxin also increased over the strata, consistent with the CHF and hypertension frequencies observed. A history of prior atrial fibrillation (either chronic or paroxysmal) was collected only in a later group of cases (n = 373) from March 1, 1997, to August 22, 1998, and the frequencies for renal risk groups 1 to 5 were 4 of 130 cases (3.0%), 6 of 75 cases (8.0%), 7 of 76 cases (9.2%), 9 of 80 cases (11.3%), and 1 of 8 cases (12.5%), respectively ($p = 0.26$ for group 1 vs 5; $p = 0.05$ for trend).

CICU Admission Clinical Findings and Diagnoses

The admitting diagnoses, physical examination findings, and baseline laboratory values are given in Table 2. The overall mean CICU length of stay was 2.6 ± 3.7 days. Patients in group 5 were more likely to be admitted with CHF with the expected physical examination findings of an S_3, rales, and peripheral edema. There were increasing levels of BP and heart rate across the renal risk strata. In addition, there were higher rates of atrial fibrillation, complete heart block, and bundle-branch blocks on the admission

Table 2—*Admission Diagnoses, Physical Examination Findings, ECG Findings, and Laboratory Values of 9,544 Patients Admitted to a CICU Stratified by Renal Risk Group

Variables	Group 1, CorrCrCl > 81.5	Group 2, 63.1 < Corr-CrCl ≤ 81.5	Group 3, 46.2 < Corr-CrCl ≤ 63.1	Group 4, CorrCrCl ≤ 46.2 Not Receiving Dialysis	Group 5, Long-term Dialysis	p Value Group 1 vs Group 5	p Value for Trend
Patients, No.	2,254	2,255	2,254	2,254	527		
Admitting diagnosis							
UAP	858 (38.1)	900 (39.9)	845 (37.5)	645 (28.6)	175 (33.2)	0.01	< 0.0001
AMI	686 (30.4)	554 (24.6)	510 (22.6)	350 (15.5)	57 (10.8)	< 0.0001	< 0.0001
CHF	165 (7.3)	203 (9.0)	294 (13.0)	496 (22.0)	121 (23.0)	< 0.0001	< 0.0001
Arrhythmias	142 (6.3)	207 (9.2)	186 (8.3)	257 (11.4)	75 (14.2)	< 0.0001	< 0.0001
Other cardiac diagnoses	177 (7.9)	178 (7.9)	175 (7.8)	169 (7.5)	48 (9.1)	0.32	0.17
Shock	20 (0.9)	19 (0.8)	27 (1.2)	58 (2.6)	8 (1.5)	0.13	< 0.0001
Coma	6 (0.3)	11 (0.5)	12 (0.5)	24 (1.1)	3 (0.6)	0.42	0.01
Noncardiac diagnoses	137 (6.1)	113 (5.0)	123 (5.5)	197 (8.7)	34 (6.5)	0.76	< 0.0001
Physical examination findings							
Heart rate, beats/min	81.8 ± 22.4	81.8 ± 21.7	82.6 ± 22.9	86.0 ± 23.5	85.8 ± 24.5	< 0.0001	< 0.0001
Systolic BP, mm Hg	131.7 ± 25.2	134.1 ± 25.7	135.6 ± 28.6	138.8 ± 34.4	142.3 ± 37.2	< 0.0001	< 0.0001
Diastolic BP, mm Hg	75.3 ± 15.5	77.1 ± 16.0	76.3 ± 16.2	76.4 ± 19.6	77.4 ± 20.2	0.02	0.06
Jugular venous distension, %	173 (7.7)	199 (8.8)	257 (11.4)	452 (20.05)	127 (24.1)	< 0.0001	< 0.0001
Pulmonary rales, %	295 (13.08)	358 (15.9)	499 (22.1)	737 (32.7)	205 (38.9)	< 0.0001	< 0.0001
S_3, %	161 (7.1)	217 (9.6)	279 (12.4)	425 (18.9)	116 (22.0)	< 0.0001	< 0.0001
S_4, %	266 (11.8)	313 (13.9)	376 (16.7)	344 (15.3)	91 (17.3)	< 0.0001	< 0.0001
Hepatomegaly, %	65 (2.9)	56 (2.5)	109 (4.8)	158 (7.01)	49 (9.3)	< 0.0001	< 0.0001
Peripheral edema, %	169 (7.5)	225 (10)	263 (11.7)	481 (21.3)	115 (21.8)	< 0.0001	< 0.0001
ECG findings in subset (n = 9,171)	n = 2,120	n = 2,180	n = 2,178	n = 2,174	n = 519		
Atrial fibrillation/flutter, %	87 (4.1)	109 (9.32)	145 (6.7)	188 (8.6)	49 (9.4)	< 0.0001	< 0.0001
Complete heart block, %	19 (0.7)	27 (2.3)	43 (2.0)	62 (3.3)	18 (3.5)	< 0.0001	< 0.0001
RBBB, %	74 (3.5)	95 (4.4)	114 (5.23)	131 (6.03)	37 (7.1)	0.0001	< 0.0001
LBBB, %	76 (3.6)	91 (4.2)	110 (5.1)	171 (7.9)	43 (8.3)	< 0.0001	< 0.0001
LVH, %	142 (7.1)	200 (9.2)	234 (10.7)	333 (15.3)	96 (18.5)	< 0.0001	< 0.0001
Laboratory findings							
Sodium, mEq/L	137.8 ± 6.9	138.0 ± 6.1	138.1 ± 6.9	137.2 ± 6.5	136.4 ± 6.5	< 0.0001	< 0.0001
Potassium, mEq/L	4.1 ± 0.8	4.2 ± 0.8	4.2 ± 0.8	4.5 ± 1.0	4.6 ± 1.0	< 0.0001	< 0.0001
Hemoglobin, g/dL	13.1 ± 2.0	13.3 ± 2.0	13.0 ± 2.1	11.8 ± 2.4	10.6 ± 2.3	< 0.0001	< 0.0001
Hematocrit, %	38.7 ± 6.0	39.3 ± 6.0	38.6 ± 6.2	35.2 ± 7.3	32.0 ± 6.9	< 0.0001	< 0.0001
Creatinine, mg/dL	0.8 ± 0.2	1.0 ± 0.2	1.2 ± 0.2	3.0 ± 2.8	4.9 ± 3.7	< 0.0001	< 0.0001
BUN, mg/dL	16.8 ± 22.1	18.0 ± 19.3	21.7 ± 33.9	38.9 ± 44.5	55.1 ± 64.9	< 0.0001	< 0.0001

*Data are presented as No. (%) or mean ± SD unless otherwise indicated. Only the first admission is counted in these comparisons. UAP = unstable angina pectoris; RBBB = right bundle-branch block; LBBB = left bundle-branch block.

ECG across the renal risk strata. LVH by ECG criteria was present in 18.5% of group 5 compared to 7.1% of group 1 ($p < 0.0001$), consistent with the prevalence of hypertension across these groups. These rates of LVH determined by ECG are, as expected, far below those ascertained in prior studies where echocardiography was used. Finally, as expected, there were higher levels of baseline potassium, creatinine, and BUN on CICU admission across the groups. Hemoglobin was found to be significantly lower across the groups, with mean hemoglobin of 10.6 ± 2.3 g/dL in the group receiving long-term dialysis.

Tachyarrhythmias

Table 3 displays the univariate and multivariate RRs of developing atrial fibrillation, with the highest adjusted risk for group 4 (CorrCrCl ≤ 46.2) of 1.55 (95% CI, 1.19 to 2.03; $p = 0.001$). The adjusted risk for group 5, patients with end-stage renal disease (ESRD) receiving dialysis, however, was not statistically significant. The adjusted risks for ventricular tachyarrhythmias including accelerated idioventricular rhythm, ventricular tachycardia, and ventricular fibrillation were all increased in a graded fashion across the renal risk strata. However, there was no was no clear risk pattern seen for levels of renal dysfunction and nonsustained ventricular tachycardia.

Bradyarrhythmias

There was a clear dose-response relation seen between level of renal dysfunction and the development of complete heart block (Table 4). The highest adjusted risk of complete heart block was in group 5 (ESRD patients receiving dialysis) of 3.64 (95% CI, 1.77 to 7.48; $p = 0.0004$). However, the adjusted risk pattern for asystole was inconsistent, likely related to the small number of events, which was on average was 2.7%. Figure 1 summarizes the adjusted RRs for the devel-

Table 3—*Risks of Tachyarrhythmias Stratified by Renal Risk Group**

Variables	Group 1, CorrCrCl > 81.5	Group 2, 63.1 < Corr-CrCl ≤ 81.5	Group 3, 46.2 < Corr-CrCl ≤ 63.1	Group 4, CorrCrCl ≤ 46.2 Not Receiving Dialysis	Group 5, Long-term Dialysis
Patients, No.	2,254	2,255	2,254	2,254	527
Atrial fibrillation/flutter					
RR (95% CI)	1.00	1.14 (0.93–1.40)	1.40 (1.15–1.71)	1.81 (1.49–2.19)	2.00 (1.52–2.66)
p value		0.21	0.001	< 0.0001	< 0.0001
Adjusted RR (95% CI)		1.31 (1.03–1.67)	1.42 (1.10–1.83)	1.55 (1.19–2.03)	1.29 (0.87–1.94)
p value		0.03	0.007	0.001	0.21
Patients, No. (%)	187 (8.3)	211 (9.4)	254 (11.3)	317 (14.1)	81 (15.4)
Accelerated idioventricular rhythm					
RR (95% CI)	1.00	1.28 (0.97–1.70)	1.53 (1.17–2.00)	1.39 (1.06–1.83)	1.91 (1.30–2.80)
p value		0.08	0.002	0.02	0.001
Adjusted RR (95% CI)		1.31 (0.96–1.80)	1.55 (1.10–2.17)	1.56 (1.07–2.28)	2.43 (1.40–4.20)
p value		0.09	0.01	0.02	0.002
Patients, No. (%)	93 (4.1)	118 (5.2)	139 (6.2)	127 (5.6)	40 (7.6)
Nonsustained ventricular tachycardia					
RR (95% CI)	1.00	1.30 (0.93–1.82)	1.75 (1.27–2.40)	1.45 (1.05–2.02)	1.04 (0.59–1.84)
p value		0.13	0.001	0.03	0.90
Adjusted RR (95% CI)		1.41 (1.00–1.20)	1.70 (1.14–2.53)	1.39 (0.89–2.18)	1.24 (0.60–2.60)
p value		0.08	0.009	0.15	0.56
Patients, No. (%)	62 (2.8)	80 (3.5)	106 (4.7)	89 (3.9)	15 (2.8)
Sustained ventricular tachycardia					
RR (95% CI)	1.00	1.43 (0.99–2.05)	1.69 (1.19–2.41)	1.82 (1.28–2.57)	1.70 (1.01–2.88)
p value		0.06	0.003	0.001	0.05
Adjusted RR (95% CI)		1.66 (1.10–2.50)	2.00 (1.29–3.13)	2.19 (1.36–3.50)	2.07 (1.02–4.22)
p value		0.02	0.002	0.001	0.04
Patients, No. (%)	51 (2.3)	72 (3.2)	85 (3.8)	91 (4.0)	20 (3.8)
Ventricular fibrillation					
RR (95% CI)	1.00	1.55 (1.09–2.20)	1.59 (1.12–2.25)	1.99 (1.42–2.78)	1.47 (0.85–2.52)
p value		0.01	0.009	< 0.0001	0.16
Adjusted RR (95% CI)		1.63 (1.08–2.47)	1.91 (1.22–2.98)	2.05 (1.29–3.26)	2.42 (1.13–5.15)
p value		0.02	0.005	0.002	0.02
Patients, No. (%)	53 (2.4)	81 (3.6)	83 (3.7)	103 (4.6)	18 (3.4)

*Unadjusted and adjusted RRs with 95% CIs are presented with group 1 as the referent. Multivariate risks are adjusted for the following: age; gender; race; admission diagnosis; history of heart failure; previous aspirin, β-blocker, and angiotensin-converting enzyme inhibitor use; diabetes; and baseline hemoglobin. The final model included 3,607 cases with complete data on all covariates.

Table 4—*Risks of Bradyarrhythmias Stratified by Renal Risk Group

Variables	Group 1, CorrCrCl > 81.5	Group 2, 63.1 < CorrCrCl ≤ 81.5	Group 3, 46.2 < CorrCrCl ≤ 63.1	Group 4, CorrCrCl ≤ 46.2 Not Receiving Dialysis	Group 5, Long-term Dialysis
Patients, No.	2,254	2,255	2,254	2,254	527
Complete heart block					
RR (95% CI)	1.00	1.79 (1.18–2.72)	2.27 (1.52–3.40)	2.94 (1.99–4.35)	3.56 (2.14–5.90)
p value		0.006	< 0.0001	< 0.0001	< 0.0001
Adjusted RR (95% CI)		1.73 (1.08–2.77)	2.73 (1.68–4.43)	2.82 (1.71–4.65)	3.64 (1.77–7.48)
p value		0.02	< 0.0001	< 0.0001	0.0004
Patients, No. (%)	35 (1.6)	62 (2.7)	78 (3.5)	100 (4.4)	28 (5.3)
Asystole					
RR (95% CI)	1.00	1.65 (1.07–2.56)	1.65 (1.07–2.56)	3.13 (2.10–4.65)	1.84 (0.98–3.46)
p value		0.02	0.02	< 0.0001	0.06
Adjusted RR (95% CI)		1.75 (1.08–2.83)	1.57 (0.92–2.66)	2.80 (1.69–4.63)	2.36 (1.00–5.57)
p value		0.02	0.10	0.0001	0.05
Patients, No. (%)	33 (1.5)	54 (2.4)	54 (2.4)	100 (4.4)	14 (2.7)

*Data are presented as in Table 3.

opment of bradyarrhythmias and tachyarrhythmias and in-hospital death across the renal dysfunction strata.

Discussion

Renal Dysfunction as a Risk for Cardiac Arrhythmias

As reported before, our study has shown that a surrogate for baseline renal function, the CorrCrCl in mL/min/72 kg stratified patients entering the CICU with a variety of diagnoses, with respect to in-hospital complications and death.[2] Through a range of "normal" serum creatinine levels, 0.8 ± 0.2 mg/dL (70.7 ± 17.7 mol/L) to 1.2 ± 0.2 mg/dL (106.1 ± 17.7 mol/L) in groups 1 through 3, there are measurable, graded increases in risk of arrhythmias. At the highest level of renal dysfunction not yet requiring dialysis, the risk appears to be the greatest for several arrhythmias including atrial fibrillation, nonsustained ventricular tachycardia, sustained ventricular tachycardia, and asystole. Patients with ESRD receiving dialysis appeared to have the greatest adjusted risk of accelerated idioventricular rhythm, ventricular fibrillation, and complete heart block. Overall, as the renal function worsened, the risks for arrhythmias increased across the groups.

There were significant ethnic differences across the renal risk groups with higher proportions of African Americans in the higher risk groups, including 60.0% of those receiving long-term dialysis compared to 37.6% of those in the lowest risk group. The impact of baseline comorbidities across the renal strata was evident. Those patients receiving long-term dialysis therapy had, as expected, significantly higher rates of diabetes, hypertension, and CHF. Patients with renal dysfunction were more likely to be admitted to the hospital with CHF than acute ischemic syndromes. Although measurement of left ventricular (LV) function was not done routinely on patients, when it was evaluable by indexes such as cardiothoracic ratio, echocardiography, and radionucleotide ventriculography, it was lower in the higher risk strata consistent with higher rates of history and hospital admission diagnoses of CHF. The multivariate analysis, however, indicates that not all the risk observed in the upper strata can be explained by decreased LV function alone and confirmed, in a consistent manner, the independent relation between renal function and the development of arrhythmias. Another confounder, baseline hemoglobin, was found to be lower as renal failure advanced across the groups. This finding is consistent with the anemia associated with renal dysfunction and was appropriately accounted for in all the multivariate analyses of this population.

Potential Mediators of Cardiac Arrhythmias in Renal Dysfunction

This study suggests that there are other unmeasured intermediate factors present that mediate risk for arrhythmias and death. We describe a wide range of arrhythmias to highlight potentially different relative associations, or different mechanisms for various arrhythmias. For instance, changes in the intracellular matrix and fibrous replacement of the cardiac tissue over time are thought to be related to the development of heart block. Conversely, electrolyte disturbances and LVH are thought to trigger and facilitate, respectively, re-entrant ventricular arrhythmias such as ventricular tachycardia. In addition, the likely structural and physiologic substrates for arrhythmias in renal dysfunction include diastolic

dysfunction, volume overload, electrolyte abnormalities, and adverse pharmacologic interactions.[17–19] Ample evidence from the literature exists to expect a high rate of LVH in the predialysis and dialysis populations by echocardiography.[20] In these groups, LVH has been related to higher rates of asymptomatic ventricular arrhythmias, and cardiac events including AMI, revascularization, CHF, and cardiac death.[21–23] Volume overload is anticipated in groups 4 and 5, with the distinct possibility that the volume excess is better handled by dialysis than by high-dose diuretics in those with significant impairment in renal function. This may explain, in part, the plateau in risk seen in group 4 for many of the adverse arrhythmias.

In addition to the structural and physiologic substrates, there are likely to be components of autonomic dysfunction, myocyte dysfunction, and altered electrolyte metabolism that impact on the cellular electrophysiology. There are several lines of evidence that suggest a role for the autonomic nervous system in the pathogenesis of arrhythmias in renal failure.[24] Cardiac β-adrenergic responses are blunted in uremia due to reduced isoprenaline-dependent activation of adenylate cyclase. This is thought to be due to an uncoupling of the receptor or by an inhibition of the receptor by the uremic toxins.[25] In chronic uremic rats, the density of α_1 and α_2 receptors in the cerebral cortex was found to be significantly increased, while the β-adrenergic and muscarinergic receptors in the heart as well as cardiac α_1 adrenoceptors were unchanged.[26–28] The reduced chronotropic responsiveness in the uremic heart may be partly related to the reduced activity of adenylate cyclase.[29] Studies in uremic rats have shown a significant decrease in contraction of isolated myocytes along with a decrease in the velocity of shortening and relaxation.[30] However, this was not reproduced in an experimental model involving foxhounds, wherein there was no anemia, hypertension, or heart failure.[31,32] It has been postulated that altered calcium metabolism may result in the decreased contractility in rat myocytes perfused with uremic serum. There is also activation of cellular metabolism and of both energy production and consumption.[33,34] Increased regional and transmyocardial dispersion of ventricular depolarization in ESRD patients may be a contributory factor in the pathogenesis of increased cardiac arrhythmias and mortality.[35] Renal failure is associated with rapid inactivation of cardiac ventricular myocyte L-type Ca2+ currents, which may reduce Ca2+ influx and contribute to shortening of the action potential duration.[36] There is also a decrease in the sodium pump number in cardiac myocytes in chronic uremia, though the functional significance of this is unclear as intracellular sodium is unchanged and active cation flux rates are maintained.[37] Lastly, parathyroid hormone-mediated intermyocardiocytic

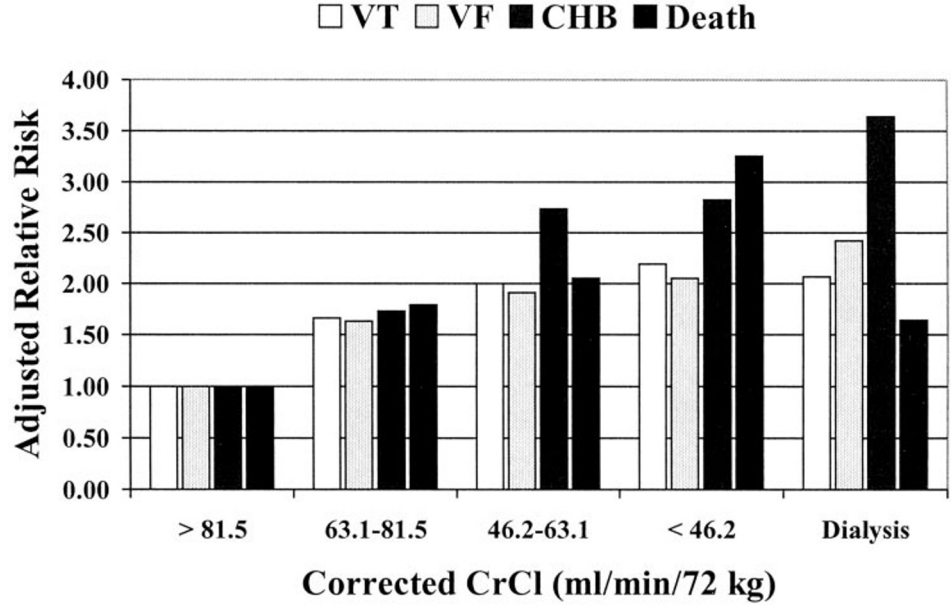

FIGURE 1. Adjusted RR for life-threatening arrhythmias and death in critically ill patients with renal dysfunction. Multivariate risks are adjusted for age, gender, race, admission diagnosis, history of heart failure, previous aspirin, β-blocker, and angiotensin-converting enzyme inhibitor use, diabetes, and baseline hemoglobin. VT = sustained ventricular tachycardia; VF = ventricular fibrillation; CHB = complete heart block; corrected creatinine clearance (CrCl) is presented in mL/min/72 kg ($p < 0.0001$ for all trends except death).

fibrosis has been demonstrated in patients with ESRD.[38–40] This potentially unique form of fibrosis may lead to differential rates of conduction, and hence be a setup for re-entrant rhythms.[41,42]

Another very important superimposed factor may be clinically overt or silent ischemia in patients with renal dysfunction leading to arrhythmias. Autopsy studies of ESRD patients who received dialysis have shown lower length density of myocardial capillaries, and increased myocyte diameter and volume density of myocardial interstitial tissue. Diminished LV capillary supply in renal failure increases critical oxygen diffusion distance in the myocardium, thus exposing cardiomyocytes to the risk of hypoxia.[42,43] In addition, because of LVH, as well as an inflammatory state that may exist with uremia, the oxygen supply becomes diminished, while the demand generally stays high, creating an imbalance to the heart.[41]

Impact of Dialysis

We found an increased hazard with respect to some arrhythmias for those with reduced CorrCrCl < 46.2 mL/min/72 kg, but not yet receiving dialysis. This suggests that dialysis therapy, whether by selection or biological action, has at least a stabilizing effect on arrhythmias. This is at variance from other studies done in the outpatient setting, which describe a higher incidence of arrhythmias in ESRD especially during dialysis related to potassium flux and changes in repolarization.[44–47] Our study did record arrhythmias during dialysis which occurred within the CICU, and hence was unlikely to miss this component of the arrhythmia event rate. The protective effect of hemodialysis on some cardiac arrhythmias likely relates to the correction of volume-overload electrolyte disturbances such as hyperkalemia.

Study Limitations

We acknowledge the limitations of this study, as it was a retrospective analysis of prospectively collected data. Misclassification bias concerning the exposure, renal function, was an important issue. Since we did not have body weight in the database, we used a measure that takes into account age, gender, and serum creatinine level measured on the first blood draw in the emergency department. Since the unit of measure was mL/kg/min/72 kg, we recognize the value will underestimate renal function for individuals > 72 kg, and underestimate for those < 72 kg. We would expect that a Cockroft-Gault value, another calculation such as the Modification in Diet in Renal Disease equation, or actual measurement of glomerular filtration, would have reduced variance, and by eliminating random misclassification bias, would have elevated the RRs reported in the tables and figure of this article. We did not have detailed information about the use of antiarrhythmics, the clinical response to an arrhythmia event, or the use of devices such as pacemakers or implantable defibrillators. In addition, we did not have critical electrolyte information such as pH, potassium, calcium, magnesium, or phosphorus at the time of the arrhythmia event collected in the database, and we anticipate electrolyte disturbance likely played a major role. Although acute renal failure and the initiation of dialysis was not an event captured on our registry, we expect this factor may have influenced group 4, a predialysis group, but not the other groups, where new dialysis was an unlikely clinical issue. Lastly, we did not have a detailed ECG analysis, and information such has the QT interval, QT dispersion, and other variables would have been of considerable interest in explaining our findings. The multivariate analysis could have been strengthened by temporal capture of data, which was not possible given the retrospective study design. For example, in the immediate time of the arrhythmia several important critical care events such as intubation, acid-base status, electrolytes, fever, and other contributors could be noted. We acknowledge that with a large database, small differences in characteristics, *eg*, serum sodium, across the groups may not be clinically significant, but are found to be statistically significant.

Conclusion

Baseline CorrCrCl derived from the serum creatinine, age, and gender is a significant, independent risk factor for acute arrhythmic complications in critically ill patients. We conclude that renal dysfunction is integrally related to the occurrence of arrhythmias and death, hence, further research into the clinical and biological mechanisms, as well as potential preventative and curative measures, for this relation are warranted.

References

1 McCullough PA, Wolyn R, Rocher LL, et al. Acute renal failure after coronary intervention: incidence, risk factors, and relationship to mortality. Am J Med 1997; 103:368–375

2 McCullough PA, Soman SS, Shah SS, et al. Risks associated with renal dysfunction in patients in the coronary care unit. J Am Coll Cardiol 2000; 36:679–684

3 Chertow GM, Lazarus JM, Christiansen CL, et al. Preoperative renal risk stratification. Circulation 1997; 95:878–884

4 Mangano CM, Diamondstone LS, Ramsay JG, et al. Renal dysfunction after myocardial revascularization: risk factors, adverse outcomes, and hospital resource utilization: The Multicenter Study of Perioperative Ischemia Research Group. Ann Intern Med 1998; 128:194–203

5 Paganini EP, Halstenberg WK, Goormastic M. Risk modeling

in acute renal failure requiring dialysis: the introduction of a new model. Clin Nephrol 1996; 46:206–211
6 Ramirez G, Brueggemeyer CD, Newton JL. Cardiac arrhythmias on hemodialysis in chronic renal failure patients. Nephron 1984; 36:212–218
7 de Lima JJ, Vieira ML, Lopes HF, et al. Blood pressure and the risk of complex arrhythmia in renal insufficiency, hemodialysis, and renal transplant patients. Am J Hypertens 1999; 12:204–208
8 Morales MA, Gremigni C, Dattolo P, et al. Signal-averaged ECG abnormalities in haemodialysis patients: role of dialysis. Nephrol Dial Transplant 1998; 13:668–673
9 Fortescue EB, Bates DW, Chertow GM. Predicting acute renal failure after coronary bypass surgery: cross-validation of two risk-stratification algorithms. Kidney Int 2000; 57:2594–2602
10 Demers RY, Chapman RA, Flasch MH, et al. The Henry Ford Health System. Cancer 1998; 82:2043–2046
11 Kress L. Henry Ford Health System medical information management system: strategy for creating a community-wide health information system. Medinfo 1995; 8:1531–1532
12 Whitelaw N, Warden G, Wenzler MR. Current efforts toward implementation of an urban health strategy: the Henry Ford Health System. J Urban Health 1998; 75:356–366
13 Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976; 16:31–41
14 Baracskay D, Jarjoura D, Cugino A, et al. Geriatric renal function: estimating glomerular filtration in an ambulatory elderly population. Clin Nephrol 1997; 47:222–228
15 Levey AS, Bosch JP, Lewis JB, et al. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation; Modification of Diet in Renal Disease Study Group. Ann Intern Med 1999; 130:461–470
16 Robert S, Zarowitz BJ, Peterson EL, et al. Predictability of creatinine clearance estimates in critically ill patients. Crit Care Med 1993; 21:1487–1495
17 Levin A, Singer J, Thompson CR, et al. Prevalent left ventricular hypertrophy in the predialysis population: identifying opportunities for intervention. Am J Kidney Dis 1996; 27:347–354
18 Kaplinsky E. Significance of left ventricular hypertrophy in cardiovascular morbidity and mortality. Cardiovasc Drugs Ther 1994; 8:549–556
19 Savage T, Giles M, Tomson CV, et al. Gender differences in mediators of left ventricular hypertrophy in dialysis patients. Clin Nephrol 1998; 49:107–112
20 Takeda K, Nakamoto M, Baba M, et al. Echocardiographic evaluation in long-term continuous ambulatory peritoneal dialysis compared with the hemodialysis patients. Clin Nephrol 1998; 49:308–312
21 Gruppo Emodialisi e Patologie Cardiovasculari. Multicentre, cross-sectional study of ventricular arrhythmias in chronically haemodialysed patients. Lancet 1998; 2:305–309
22 Saragoca MA, Canziani ME, Cassiolato JL, et al. Left ventricular hypertrophy as a risk factor for arrhythmias in hemodialysis patients. J Cardiovasc Pharmacol 1991; 17: S136–S138
23 Parfrey PS, Harnett JD, Griffiths SM, et al. The clinical course of left ventricular hypertrophy in dialysis patients. Nephron 1990; 55:114–120
24 Tamura K, Tsuji H, Nishiue T, et al. Determinants of ventricular arrhythmias in hemodialysis patients: evaluation of the effect of arrhythmogenic substrate and autonomic imbalance. Am J Nephrol 1998; 18:280–284
25 Lubbecke F, Steudle V, Schutterle G, et al. Catecholaminergic and muscarinergic receptors in chronic experimental uremia. Clin Physiol Biochem 1989; 7:149–160
26 Dhein S, Rohnert P, Markau S, et al. Cardiac β-adrenoceptors in chronic uremia: studies in humans and rats. J Am Coll Cardiol 2000; 36:608–617
27 Lubbecke F, Steudle V, Schaper J, et al. Experimental uremic cardiomyopathy: fact or fiction? Contrib Nephrol 1986; 52: 134–145
28 Lubbecke F. Myocardial alterations in chronic experimental renal failure. Contrib Nephrol 1994; 106:7–12
29 Mann JF, Jakobs KH, Riedel J, et al. Reduced chronotropic responsiveness of the heart in experimental uremia. Am J Physiol 1986; 250:H846–H852
30 McMahon AC, Vescovo G, Dalla Libera L, et al. Contractile dysfunction of isolated ventricular myocytes in experimental uraemia. Exp Nephrol 1996; 4:144–150
31 Kreusser W, Rambausek M, Klooker P, et al. Hemodynamics and cardiac metabolism in experimental uremia. Contrib Nephrol 1984; 41:262–265
32 Rambausek M, Mann JF, Mall G, et al. Cardiac findings in experimental uremia. Contrib Nephrol 1986; 52:125–133
33 Weisensee D, Schnaars Y, Schoeppe W, et al. Potential uremic toxins modulate energy metabolism of cardiac myocytes *in vitro*. Exp Nephrol 1997; 5:194–200
34 Weisensee D, Low-Friedrich I, Riehle M, et al. *In vitro* approach to 'uremic cardiomyopathy.' Nephron 1993; 65: 392–400
35 Tun A, Khan IA, Wattanasauwan N, et al. Increased regional and transmyocardial dispersion of ventricular repolarization in end-stage renal disease. Can J Cardiol 1999; 15:53–56
36 Donohoe P, McMahon AC, Walgama OV, et al. L-type calcium current of isolated rat cardiac myocytes in experimental uraemia. Nephrol Dial Transplant 2000; 15:791–798
37 Druml W, Kelly RA, England BK, et al. Effects of acute and chronic uremia on active cation transport in rat myocardium. Kidney Int 1990; 38:1061–1067
38 Rambausek M, Amann K, Mall G, et al. Structural causes of cardiac dysfunction in uremia. Ren Fail 1993; 15:421–428
39 Rambausek M, Kollmar S, Klug D, et al. Regulation of myocardial isomyosin V1 in uraemic rats. Eur J Clin Invest 1991; 21:64–71
40 Mall G, Huther W, Schneider J, et al. Diffuse intermyocardiocytic fibrosis in uraemic patients. Nephrol Dial Transplant 1990; 5:39–44
41 Roithinger FX, Punzengruber C, Rossoll M, et al. Ventricular late potentials in haemodialysis patients and the risk of sudden death. Nephrol Dial Transplant Proc 1992; 7:1013–1018
42 Amann K, Breitbach M, Ritz E, et al. Myocyte/capillary mismatch in the heart of uremic patients. J Am Soc Nephrol 1998; 9:1018–1022
43 Amann K, Munter K, Wessels S, et al. Endothelin A receptor blockade prevents capillary/myocyte mismatch in the heart of uremic animals. J Am Soc Nephrol 2000; 11:1702–11
44 Chhabra SC, Sandha GS, Wander GS. Incidence of cardiac arrhythmias in chronic renal failure, especially during hemodialysis. Nephron 1991; 57:500–501
45 Kinoshita O, Kamakura S, Kimura G, et al. Increased ventricular vulnerability during haemodialysis. Lancet 1991; 338: 1333–1334
46 Cupisti A, Galetta F, Caprioli R, et al. Potassium removal increases the Q-Tc interval dispersion during hemodialysis. Nephron 1999; 82:122–126
47 Cupisti A, Galetta F, Morelli E, et al. Effect of hemodialysis on the dispersion of the QTc interval. Nephron 1998; 78:429–432