The prognostic value of heart rate response during vasodilator stress myocardial perfusion imaging in patients with end-stage renal disease undergoing renal transplantation

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Background. **In asymptomatic end-stage renal disease (ESRD) patients undergoing vasodilator stress myocardial perfusion imaging (MPI) prior to renal transplantation (RT), the impact of pre-transplant heart rate response (HRR) to vasodilator stress on post-RT outcomes is unknown.**

Methods. **We analyzed a retrospective cohort of asymptomatic patients with ESRD who underwent a vasodilator stress SPECT-MPI and subsequently received RT. Blunted HRR was defined as HRR <28% for regadenoson stress and <20% for adenosine stress. The primary endpoint was major adverse cardiac events (MACE), defined as cardiac death or myocardial infarction. Clinical risk was assessed using the sum of risk factors set forth by the AHA/ACCF consensus statement on the assessment of RT candidates.**

Results. **Among 352 subjects, 140 had an abnormal pre-transplant HRR. During a mean follow-up of 3.2 ± 2.0 years, 85 (24%) MACEs were observed. Blunted HRR was associated with increased MACE risk (hazard ratio 1.72; 95% confidence interval 1.12-2.63, P = 0.013), and remained significant after adjustment for gender, sum of AHA/ACCF risk factors, summed stress score, baseline heart rate, and β-blocker use. HRR was predictive of MACE in patients with normal MPI and irrespective of clinical risk. Blunted HRR was associated with a significant increase in post-operative (30-day) MACE risk (17.9% vs 8.5%; P = 0.009).**

Conclusion. **In asymptomatic ESRD patients being evaluated for RT, a blunted pre-transplant HRR was predictive of post-RT MACE. HRR may be a valuable tool in the risk assessment of RT candidates. (J Nucl Cardiol 2019;26:814–22.)**

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Abbreviations

ACCF	American College of Cardiology Foundation
AHA	American Heart Association
CI	Confidence interval
ESRD	End-stage renal disease
HR	Hazard ratio
HRR	Heart rate response
MI	Myocardial infarction
MPI	Myocardial perfusion imaging
RT	Renal transplantation
SPECT	Single-photon emission computed tomography

See related editorial, pp. 823–825

INTRODUCTION

Blunted heart rate response (HRR) to vasodilators stress agents during myocardial perfusion imaging (MPI) is independently associated with worse outcomes among patients with chronic kidney disease and end-stage renal disease (ESRD).[1-3] In this population, HRR was shown to have an incremental prognostic value and can improve risk stratification beyond clinical and MPI data.[4,5] However, all HRR studies in ESRD patients either censored events at renal transplantation (RT) or did not account for the impact of HRR on outcomes after RT.[1-5] This is important because significant hemodynamic changes occur after RT, including improvement in heart loading conditions and ejection fraction.[6] As a dynamic measure,[7] HRR may change after a drastic intervention, such as RT. Thus, the established prognostic value of HRR in ESRD may not extend to predict outcome after RT.[8]

Predicting post-operative and long-term prognosis of RT recipients prior to transplantation remains challenging. Although clinical risk factors and noninvasive imaging can help identify patients at risk,[8-12] additional risk stratification would be helpful. Many asymptomatic RT candidates undergo vasodilator stress MPI as part of a standard pre-transplant cardiac assessment.[8,10] In fact, MPI can help identify patients with obstructive CAD and those at risk for post-transplant major adverse cardiac events (MACE).[11] In patients undergoing pre-RT vasodilator stress MPI, the value of pre-transplant HRR in predicting post-transplant outcome is unknown. In this investigation, we sought to assess whether HRR in asymptomatic ESRD patients undergoing pre-RT vasodilator stress MPI can predict post-RT outcomes.

METHODS

Design and Patient Population

A retrospective cohort study design was implemented. The study population consisted of consecutive RT recipients (2005 through 2015) who underwent a vasodilator stress SPECT-MPI as part of pre-RT work-up. All subjects had ESRD (dialysis or glomerular filtration rate <15 $ml \cdot min^{-1}/1.73\ m^2$) at the time of MPI testing. When multiple MPI studies were performed prior to RT, the last pre-transplant MPI was used for the purpose of this investigation. No informed consents were obtained at the time of stress testing. However, all potential subjects were given the right to decline participation in the study via mail or phone surveys; those who declined were removed from the database. The study was approved by the institutional review board of Rush University Medical Center (Chicago, IL).

Clinical Data

Patients' baseline characteristics were collected before undergoing vasodilator stress test and were retrospectively tabulated for analysis. Dates of onset and end of dialysis therapy were tabulated based on detailed chart review. Baseline clinical risk in this population of kidney transplant candidates was determined according to the sum of risk factors (range 0-8) set forth by the American Heart Association (AHA)/American College of Cardiology Foundation (ACCF) consensus statement for the cardiac assessment of kidney transplant candidates. These risk factors include the following: age >60 years, hypertension, diabetes mellitus, hyperlipidemia, smoking, left ventricular hypertrophy, history of cardiovascular disease, and dialysis >1 year.[10] The AHA/ACCF scientific statement proposed the use of the simple summation of these risk factors to identify patients at risk who may benefit from noninvasive CAD surveillance testing prior to RT. Our group validated the sum of these risk factors for the prediction of obstructive CAD as well as post-operative and long-term MACE and demonstrated that patients with three or more of these risk factors are at increased risk.[11]

Cardiovascular disease was defined as a history of CAD, heart failure or left ventricular ejection fraction <50%, peripheral arterial disease, or cerebrovascular disease. CAD was defined as a history of coronary revascularization or myocardial infarction (MI). Left ventricular hypertrophy was defined by the presence of any of the following electrocardiographic criteria: Sokolov, Cornell, R in aVL > 11 mV, or Gubner–Ungerleider on pre-RT electrocardiographic tracings analyzed by observers blinded to other data.

Stress MPI

Subjects underwent one-day rest/vasodilator stress ^{99m}Tc-tetrofosmin (~10 mCi rest/~30 mCi stress) SPECT-MPI protocol, with the exception of a few obese patients who

underwent a two-day protocol (~30 mCi rest/~30 mCi stress), all conforming to the American Society of Nuclear Cardiology guidelines.[13,14] Caffeine and thioxanthenes were held 24 hours prior to the stress test. Vasodilator stress agent used was adenosine prior to July 1, 2009 or regadenoson on and after July 1, 2009. Patients received ^{99m}Tc-tetrofosmin intravenously at rest, followed by resting SPECT-MPI acquisition 30 minutes later. Afterwards, patients underwent a pharmacologic stress test with either regadenoson (0.4 mg administered intravenously over 10 seconds and was followed, 30 seconds later, by the stress dose of ^{99m}Tc-tetrofosmin intravenously) or adenosine (140 mcg·kg^{-1}·min^{-1} infused intravenously for 6 minutes and the stress dose of ^{99m}Tc-tetrofosmin was administered intravenously at midpoint of adenosine infusion). No concomitant low-level exercise was performed. Subsequently, patients underwent gated stress SPECT-MPI acquisition using conventional Siemens ECam^{TM} (Hoffman Estates, IL) dual-detector scintillation camera, using eight frames per cycle gating, according to accepted guidelines.[13] No attenuation correction was performed. Details of the protocol were previously published.[14,15]

MPI Interpretation

The 4DM-SPECT software (INVIA; Ann Arbor, MI) was used for image processing and analysis.[16] A semi-quantitative interpretation of all MPI scans was prospectively performed by a single expert reader (AA) who was blinded to clinical, hemodynamic, and outcomes data. Using a 17-segment model, each myocardial segment was scored according to the standard 5-point scale (0: normal; 1: equivocal; 2: moderate; 3: severe decrease in tracer uptake; 4: absence of detectable radiotracer activity). Summed stress scores (SSS) were obtained from the sum of the segmental scores of the stress MPI scans. Abnormal MPI was defined as SSS $\geq$ 4. The quantitative post-stress gated-SPECT left ventricular ejection fraction was tabulated for each subject.

Heart Rate Response

Patient heart rates were recorded at baseline and every 1 minute during vasodilator infusion and recovery phases of the stress test. The maximum heart rate during the stress protocol (infusion or recovery phase) was recorded. HRR was calculated as 100 × (peak stress heart rate − resting heart rate)/(resting heart rate).[4] Based on established HRR cut-off values,[1,3,4,7,17] the study cohort was divided into two study groups: *Normal HRR* ($\geq$28% for regadenoson or $\geq$20% for adenosine) and *Blunted HRR* (<28% for regadenoson or <20% for adenosine).

Outcomes

Patients were retrospectively followed for events of death, cardiac death, and MI. Outcome events and their corresponding dates were ascertained using the social security death index, death certificates, medical records, mailed surveys, and telephone interviews by adjudicators blinded to clinical, hemodynamic, and MPI data. Patient-reported events were validated by reviewing internal or external medical records. Cardiac death was determined if a fatal cardiac condition (tachyarrhythmia, heart failure, or MI) was listed on the death certificate or in medical records as the primary or secondary cause of death. Non-fatal MI was defined based on the clinical determination of the managing cardiologist or having a troponin elevation >threefold above the assay's upper limit of normal which is set by the manufacturer at 99th percentile of normal population.

The primary endpoint was MACE defined as cardiac death or MI. The secondary endpoints included the following: (1) post-operative MACE occurring within 30 days after RT, and (2) all-cause death.

Statistical Approach

Continuous data were expressed as means ± standard deviations and were compared using the two-tailed Student's *t* test for normally distributed data, and the Wilcoxon test for skewed data. Categorical data were displayed as frequencies and percentages, and were compared using the Pearson's χ^2 test.

Kaplan–Meier curves and the log-rank test were used to compare cumulative event rates. Outcome analyses treated the date of renal transplantation as ''time 0''. Follow-up time was defined by the date of a qualifying outcome event, date of last clinical encounter (health record documentation or date of survey), or a maximum follow-up period of 6 years, whichever occurred first.

Risk associated with blunted HRR was expressed as hazard ratio (HR) with 95% confidence interval (CI), calculated using univariate or multivariate Cox regression models, adjusting for clinically relevant variables. We built a multivariate Cox regression models that included HRR status (normal vs blunted) as the variable of interest and adjusted for the sum of AHA/ACCF risk factors (range 0-8) as a single ordinal covariate (to avoid over-fitting), gender, baseline heart rate, and the sum stress score (Model 1). Furthermore, we built another multivariate Cox regression model (Model 2) by adding β-blocker use to Model 1 as an additional covariate (Model 2 = Model 1 + β-blocker use). In addition, we re-ran the analyses using HRR as a continuous variable. We also assessed for possible interaction between HRR and each of the following: the sum of the AHA/ACCF risk factors, SSS, and lag-time between MPI and RT. The proportional hazards assumption with respect to Cox regression modeling was confirmed using ''log *minus* log'' survival plots. To test for the incremental value of blunted HRR, we determined the global chi-square value in stepwise Cox models without and with blunted HRR variable; the change in the χ^2 was calculated and the *P* value was obtained using one degree of freedom. Moreover, we performed sensitivity analyses looking at the association between blunted HRR and MACE among patients with normal MPI, those with no prior MI, and without history of revascularization. All tests were 2-tailed, and a *P* value <0.05 was considered statistically significant. All statistical analyses were carried out using SPSS version 23 software package (IBM, Inc., Armonk, NY).

RESULTS

Among 352 subjects who had vasodilator stress MPI prior to RT, 140 (40%) had an abnormal pre-transplant HRR. The baseline characteristics of the study cohort and those with normal and blunted HRR are summarized in Table 1. Notably, the mean time-gap between MPI and renal transplant was 1.3 ± 1.3 years [median (25th-75th percentile), 0.82 (0.42-1.72) years]. Compared to patients with normal HRR, those with blunted HRR were more commonly men and had a greater burden of comorbidities, cardiovascular disease, AHA/ACCF risk factors, and abnormal stress MPI (Table 1).

During a mean follow-up of 3.2 ± 2.0 years, there were 35 (10%) deaths of any cause and 85 (24%) MACEs of which 43 (12%) occurred in the 30-day post-operative period (Supplement Table 1). There were no events during the period between MPI and renal transplant. Blunted HRR was associated with increased MACE risk (Figure 1A), which persisted after adjusting for relevant clinical and imaging covariates in Models 1 and Model 2 (Table 2, Supplemental Table 2). Blunted HRR was associated with a significant increase in MACE rate in patients with normal MPI, but not among patients with abnormal MPI (Figure 2). Moreover, as shown in Figure 3, blunted HRR was associated with an increased MACE rate in the subgroup of patients with low pre-transplant clinical risk (sum AHA/ACCF risk factors $\leq$2) and a trend towards increased MACE rate in patients with high pre-transplant clinical risk (sum AHA/ACCF risk factors $\geq$3 risk factors). In sensitivity analyses, blunted HRR was associated with increased MACE among patients with normal MPI (HR 1.81; CI 1.11-2.96; P = 0.018), without prior MI (HR 1.66; CI 1.05-2.63; P = 0.031), and without history of coronary revascularization (HR 2.07; CI 1.32-3.25; P = 0.002).

Patients with blunted HRR had a significant increase in post-operative MACE (17.9% vs 8.5%; log-rank P = 0.009), as shown in Figure 1B. The increase in post-operative MACE risk remained significant after multivariate adjustments in Model 1 and Model 2 (Table 2). On the other hand, blunted HRR was associated with an insignificant increase in the rate of all-cause death in univariate and multivariate analysis (Figure 1C, Table 2).

HRR, as a continuous variable, was associated with a significant increase in the risk of MACE and post-operative MACE and a trend towards an increased risk of all-cause death in univariate and multivariate analyses (Table 3). Moreover, there was no significant interaction between HRR (as a categorical or a continuous variable) and the sum of the AHA/ACCF risk factors (HRR * AHA/ACCF risk factors) or between HRR and SSS (HRR * SSS) impacting any of the study outcomes (Tables 2, 3). This indicates that the impact of HRR on outcomes was consistent irrespective of perfusion abnormality burden (SSS) or pre-transplant clinical risk (sum of AHA/ACCF risk factors). Finally, to account for the possible effect of the time-gap between stress MPI and RT on outcomes, we tested for an interaction between this time-gap and HRR impacting the study primary outcome, and found no significant interaction (P = 0.45). This indicates that the impact of HRR on outcomes was consistent irrespective of the time-gap between MPI and the kidney transplant.

DISCUSSION

To our knowledge, this is the first study to assess the prognostic value of HRR to vasodilator stress in ESRD patients selected to undergo kidney transplantation. We found that blunted HRR to vasodilator stress prior to RT was predictive of post-RT outcomes. These findings were consistent after adjusting for clinical risk, baseline heart rate, β-blocker use, MPI finding, and after performing several sensitivity analyses.

Patients with ESRD are at increased risk for cardiovascular events; this is in-part due to higher burden of comorbidities, particularly cardiovascular disease.[18] ESRD patients who are being considered for RT often undergo pharmacologic stress MPI as part of their RT evaluation to rule out significant ischemic heart disease.[8-12,19-22] One of the parameters derived from the vasodilator stress test is HRR, which is often expressed as percent change in heart rate from baseline to peak during vasodilator stress.[2] Prior studies have shown that blunted HRR is prevalent in nearly one-half of ESRD patients,[2,5] which is confirmed in this study. Failure to mount appropriate HRR was shown to be predictive of all-cause mortality and cardiac specific endpoints, and provide incremental risk stratification beyond clinical and MPI findings.[2,5] While the cause of blunted HRR in ESRD patients is not well understood, it has been postulated that it may be a marker of autonomic dysfunction in diabetic patients.[1,17,18,23] The independent and incremental prognostic value of HRR, whether considered as a continuous or dichotomous variable, has been well established in multiple patient populations, including those with diabetes, chronic kidney disease, ESRD, and others.[1,4,7,24] However, none of the HRR studies in ESRD were dedicated to RT candidates or RT recipients. Moreover, all studies

Table 1. Baseline characteristics stratified by heart rate response

	All patients N = 352	Normal HRR N = 212	Blunted HRR N= 140	P value
Demographics				
Age (years)	53 ± 12	52 ± 12	54 ± 12	0.080
Age ≥ 60 years	108 (31%)	55 (26%)	53 (38%)	0.018
Male gender	218 (62%)	119 (56%)	99 (71%)	0.006
African American	172 (49%)	111 (52%)	61 (43%)	0.039
Body mass index (kg/m^2)	28 ± 5	28 ± 5	29 ± 5	0.147
Comorbidities				
Hypertension	330 (94%)	195 (92%)	135 (96%)	0.092
Diabetes mellitus	156 (54%)	71 (34%)	85 (61%)	<0.001
Dyslipidemia	185 (53%)	103 (49%)	82 (59%)	0.066
Cardiovascular disease	157 (45%)	92 (43%)	65 (46%)	0.575
Old myocardial infarction	21 (6%)	9 (4.2%)	12 (8.6%)	0.094
Coronary artery bypass graft	22 (6.3%)	12 (5.7%)	10 (7.1%)	0.574
Prior percutaneous angioplasty	43 (12%)	22 (10%)	21(15%)	0.195
Cerebrovascular accident	41 (12%)	17 (12%)	24 (11%)	0.814
Left ventricular hypertrophy (ECG)	126 (36%)	74 (35%)	52 (37%)	0.668
Active smoker	40 (11%)	28 (13%)	12 (8.6%)	0.180
End-stage renal disease				0.023
No dialysis	18 (5%)	15 (7%)	3 (2%)	
Hemodialysis	306 (87%)	176 (83%)	130 (93%)	
Peritoneal dialysis	28 (8%)	21 (10%)	7 (5%)	
Dialysis ≥1 year	280 (80%)	157 (74%)	123 (88%)	0.002
Dialysis duration (years)	4.4 ± 3.4	4.6 ± 3.8	4.1 ± 2.8	0.233
Sum AHA/ACCF risk factors	4.0 ± 1.5	3.7 ± 1.5	4.4 ± 1.4	<0.001
AHA/ACCF ≥3 risk factors	292 (83%)	166 (78%)	126 (90%)	0.004
β-blockers	208 (59%)	118 (56%)	90 (64%)	0.107
Vasodilator stress MPI				
Stress test indication				0.211
Preop-operative risk assessment and/or asymptomatic	287 (82%)	168 (79%)	119 (85%)	
Chest pain, exertional dyspnea or abnormal ECG	65 (18%)	44 (21%)	21 (15%)	
Time between stress and RT (years)	1.3 ± 1.3	1.2 ± 1.2	1.5 ± 1.5	0.039
Regadenoson	240 (68%)	146 (69%)	94 (67%)	0.734
Baseline heart rate (bpm)	72 ± 13	69 ± 11	76 ± 14	<0.001
Summed stress score	2.3 ± 4.2	2.2 ± 4.2	2.6 ± 4.3	0.375
Summed rest score	1.9±3.4	1.8±3.2	2.2±3.7	0.261
Summed difference score	1.2±2.5	1.2±2.7	1.3±2.2	0.92
Abnormal myocardial perfusion (SSS ≥ 4)	72 (20%)	38 (18%)	34 (24%)	0.144
Transient ischemic dilation	1.01±0.18	1.00±0.20	1.03±0.15	0.129
Ejection fraction (%)	64 ± 12	65 ± 10	61 ± 13	0.004
Ejection fraction <50%	46 (13%)	24 (11%)	22 (16%)	0.231
Heart rate response (%)	35 ± 20	48 ± 20	16 ± 9	<0.001

AHA/ACCF risk factors: age ≥60 years, hypertension, diabetes, hyperlipidemia, smoking, left ventricular hypertrophy, history of cardiovascular disease, dialysis ≥1 year. Continuous variables are presented as means ± standard deviations. Categorical variables are presented as frequencies (percentages). All patients who underwent coronary angiogram had the procedure prior to renal transplant

HRR, heart rate response; *LV*, left ventricular; *RT*, renal transplant

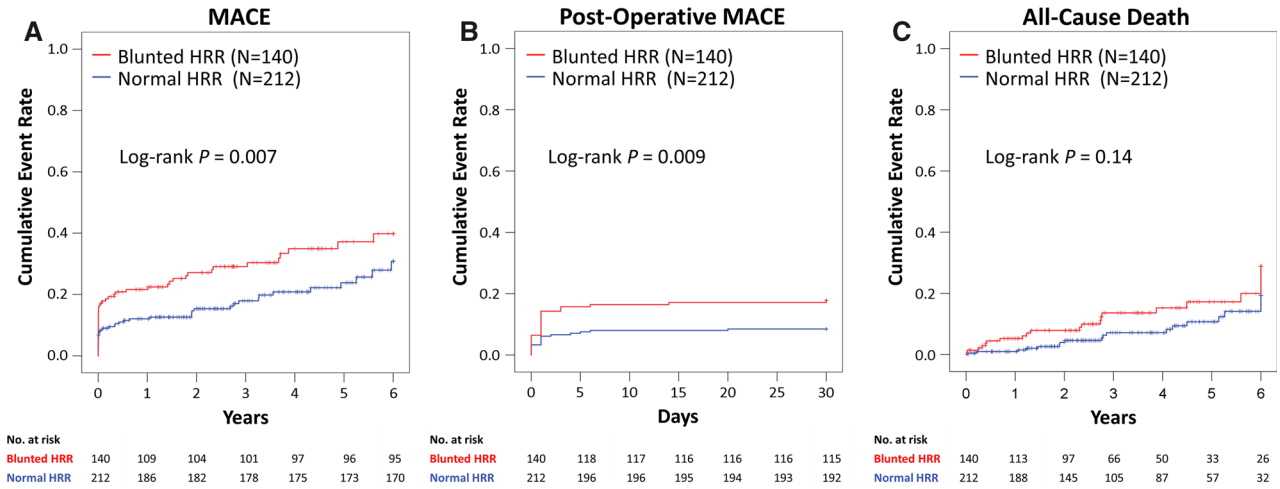

Figure 1. Impact of blunted HRR on outcomes after renal transplant. Kaplan–Meier survival plots of cumulative event rates according to heart rate response groups. *HRR*, heart rate response; *MACE*, major adverse cardiac events (cardiac death or myocardial infarction); post-operative MACE, MACE within 30 days after renal transplant.

censored events at RT or did not account for the impact of HRR on outcome subsequent to RT. To our knowledge, no study has assessed the value of pre-RT HRR in predicting post-operative or long-term outcomes after RT. In this study, we found that pre-RT HRR was a valuable tool in the prediction of post-transplant MACE risk. Importantly, blunted HRR was predictive of MACE risk in patients with normal MPI and those with low clinical risk (≤3 AHA/ACCF risk factors), suggesting that HRR can be particularly helpful in patients who otherwise seem to be at low risk.

Notably, there is a sharp and early increase in MACE following RT (Figure 1). These events are driven by post-operative non-fatal MI (42 out of 43 post-operative events). We speculate that these are type-II MI events, caused by increased myocardial oxygen demand due to intra-operative and peri-operative stress, fluid shifts, bleeding, blood pressure fluctuation, fluid overload, etc. Thus, the value of HRR in predicting post-RT outcome seems to be primarily derived from predicting 30-day post-operative events, namely non-fatal MI, as the survival curves of the HRR groups quickly separate in the post-operative period and remain parallel during the remainder of follow-up. On the other hand, the study failed to demonstrate a significant association between blunted HRR and all-cause death events, which were dominated by non-cardiac deaths. Notably, the hazard ratio for mortality with blunted HRR seems lower than previously reported in HRR literature.[2,25] One may speculate whether HRR is ''reset'' among survivors of RT, thus attenuating the impact of pre-transplant HRR on post-RT survival. Larger studies are needed to further investigate the impact of blunted HRR on all-cause mortality following RT. Moreover, blunted HRR was not associated with a significant increase in MACE risk among patients with abnormal MPI. Intensification of medical therapy and optimal revascularization pre- and post-RT in patients with abnormal MPI may, in-part, explain this finding.

It remains unclear how to use HRR data in guiding decision-making in RT candidates. Can coronary revascularization, aggressive medical therapy, or strict dialysis therapy in the peri-operative period modulate the risk predicted by HRR? Prospective controlled studies can address these questions.

Recent work by our group demonstrated that clinical risk identified by the sum of the AHA/ACCF risk factors and MPI findings can help identify patients at risk for MACE after RT, demonstrating that patients with three or more AHA/ACCF risk factors have not only higher likelihood of obstructive CAD, but are also at increased post-operative and long-term MACE risk following transplantation.[11] Moreover, MPI findings provided additional diagnostic and prognostic value, particularly among patients with intermediate clinical risk (3-4 AHA/ACCF risk factors). The present investigation, complements our recent findings by showing that HRR is predictive of post-transplant MACE irrespective of clinical risk and MPI findings; and it is particularly useful among those with normal MPI and low clinical risk (≤3 AHA/ACCF risk factors).

Table 2. Impact of blunted HRR on outcomes

	MACE		Post-operative MACE[a]		All-cause death	
HRR adjustment	**HR[b] (95% CI)**	***P***	**HR[b] (95% CI)**	***P***	**HR[b] (95% CI)**	***P***
HRR, unadjusted	1.72 (1.12–2.63)	0.013	2.18 (1.19–3.99)	0.012	1.69 (0.84–3.42)	0.144
HRR, adjusted Model 1	1.64 (1.04–2.60)	0.034	2.27 (1.19–4.33)	0.013	1.55 (0.74–3.25)	0.248
HRR, adjusted Model 2	1.60 (1.02–2.51)	0.042	2.23 (1.17–4.25)	0.015	1.75 (0.90–3.40)	0.101

Model 1 included HRR, AHA/ACCF risk factors, gender, baseline heart rate, and summed stress score. Model 2 included variables in Model1 + β-blocker use. Interaction P values for blunted HRR × summed stress score for MACE, post-operative MACE, and all-cause death were 0.89, 0.96, and 0.98, respectively. Interaction *P* values for blunted HRR × AHA/ACCF risk factors for MACE, post-operative MACE, and all-cause death were 0.58, 0.57, and 0.95, respectively

HRR, heart rate response; *MACE*, major adverse cardiac events (cardiac death or myocardial infarction); *HR*, hazard ratio, *CI*, confidence interval

[a] MACE within 30 days post-transplant

[b] HR of blunted HRR relative to normal HRR. HR > 1 portrays increased risk

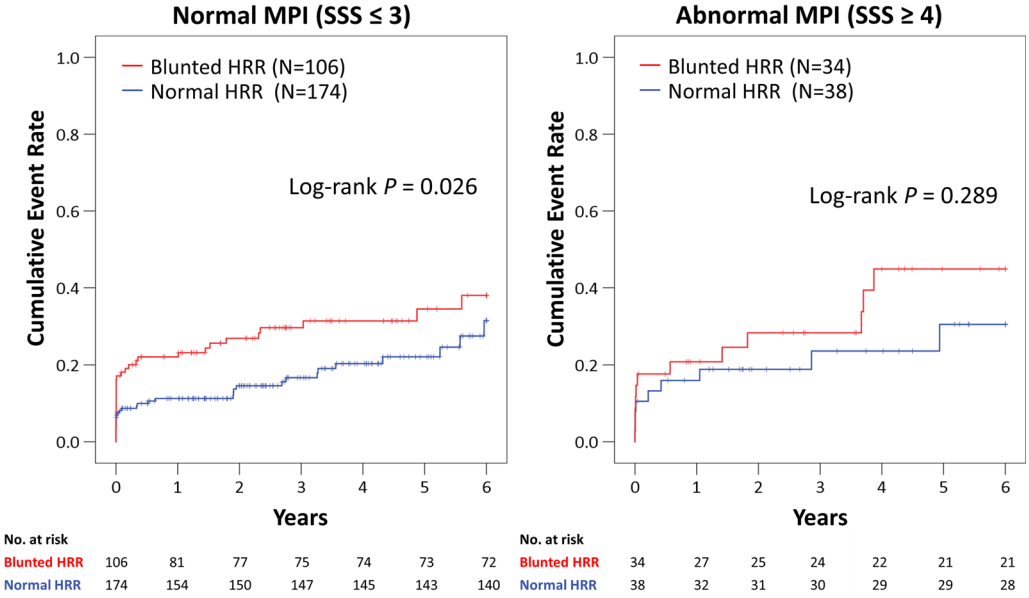

Figure 2. Impact of blunted HRR on post renal transplant MACE according to myocardial perfusion imaging. Kaplan–Meier survival plots of cumulative event rates according to heart rate response groups, stratified based on normal and abnormal myocardial perfusion imaging. *HRR*, heart rate response; *MPI*, myocardial perfusion imaging; *SSS*, summed stress score.

Limitations

The non-controlled, single-center design is a clear limitation. In addition, there was a significant difference in time-gap between MPI and renal transplant that could have influenced the results, despite the lack of interaction between gap-time and blunted HRR. Moreover, although patient outcomes, electrocardiographic findings, and MPI interpretations were prospectively tabulated, clinical history data were collected retrospectively, leaving out some unmeasured confounders such as patient frailty and medications other than beta-blockers. It is also plausible that patients or their families failed to recall some events. Additionally, the number of events was relatively small, thus we could not adjust for all relevant covariates. We also could not adjust for post-RT medications and post-RT steroid-induced diabetes, and we lacked post-RT HRR assessment. Finally, data on revascularization and medical therapy following MPI is not available for analysis. Therefore, there is a need for external and prospective validations of our results.

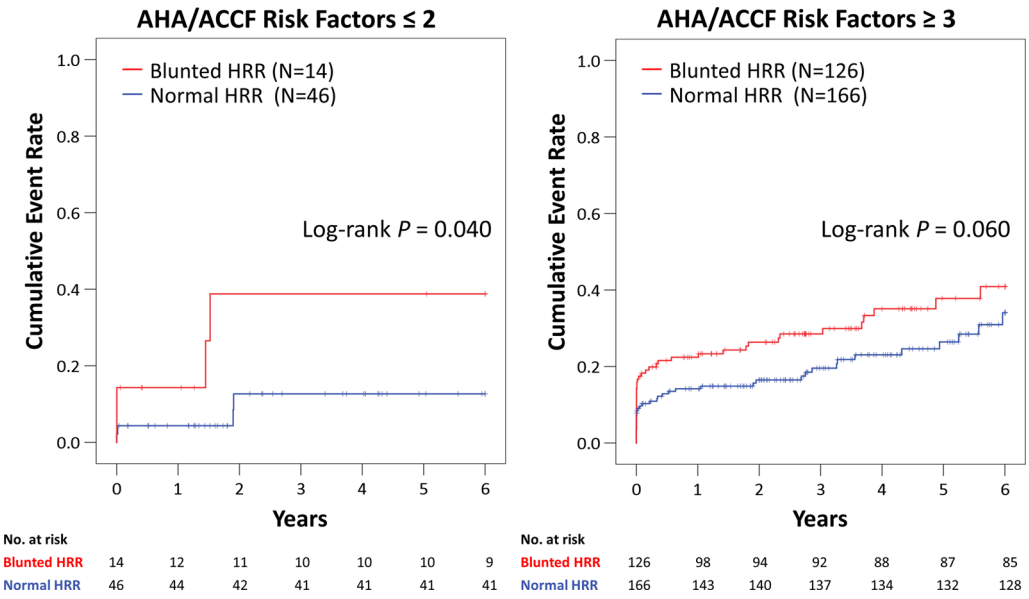

Figure 3. Impact of blunted HRR on post renal transplant MACE according to AHA/ACCF risk factors. Kaplan–Meier survival plots of cumulative event rates according to heart rate response groups, stratified based on the sum of AHA/ACCF risk factors. AHA/ACCF risk factors: age ≥60 years, hypertension, diabetes, hyperlipidemia, smoking, left ventricular hypertrophy, history of cardiovascular disease, dialysis ≥1 year.

Table 3. Impact of Pre-Transplant HRR, as a Continuous Variable, on Outcomes

	MACE		Post-operative MACE[a]		All-cause death	
HRR Adjustment	**HR[b] (95% CI)**	***P***	**HR[b] (95% CI)**	***P***	**HR[b] (95% CI)**	***P***
HRR, unadjusted	0.987 (0.977–0.997)	0.010	0.988 (0.973–1.002)	0.091	0.986 (0.970–1.002)	0.082
HRR, adjusted Model 1	0.986 (0.974–0.998)	0.026	0.984 (0.967–1.001)	0.067	0.983 (0.963–1.003)	0.097
HRR, adjusted Model 2	0.987 (0.975–0.999)	0.048	0.984 (0.967–1.002)	0.082	0.983 (0.964–1.004)	0.105

Model 1 included HRR, AHA/ACCF risk factors, gender, baseline heart rate, and summed stress score. Model 2 included variables in Model1 + β-blocker. Interaction *P* values for HRR * summed stress score for MACE, post-operative MACE, and all-cause death were 0.89, 0.96, and 0.98, respectively. Interaction *P* values for HRR * AHA/ACCF risk factors for MACE, post-operative MACE, and all-cause death were 0.58, 0.57, and 0.95, respectively

HRR, heart rate response; *MACE*, major adverse cardiac events (cardiac death or myocardial infarction); *HR*, hazard ratio, *CI*, confidence interval

[a] MACE within 30 days post-transplant

[b] HR depicts risk per 1%-point increment in HRR. HR <1 portrays increased risk

NEW KNOWLEDGE GAINED

The main findings of our study were as follows: (1) blunted HRR was prevalent (>40%) among ESRD patients selected for RT; (2) patients with blunted HRR experienced 60% increase in the risk of MACE following RT, and double the risk of post-operative MACE; (3) blunted pre-RT HRR was associated with worse post-RT outcomes, independent of pre-transplant risk factors, baseline heart rate, and MPI findings; (4) blunted HRR allowed for additional risk stratification in patients perceived to be at low risk based on clinical and MPI findings.

CONCLUSION

In asymptomatic ESRD patients being evaluated for RT, a blunted pre-transplant HRR was predictive of post-RT MACE and post-operative MACE, independent of traditional risk factors. HRR seems to be a valuable tool in the risk assessment of RT candidates.

Disclosure

Rami Doukky receives research funding grants and serves on an advisory board for Astellas Pharma Global Development (Northbrook, IL). The other authors have nothing to disclose.

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