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Influence of Age-Related Versus Non-Age-Related Renal Dysfunction on Survival in Patients with Left Ventricular Dysfunction

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Abstract

Normal aging results in a predictable decline in glomerular filtration rate (GFR) and low GFR is associated with worsened survival. If this survival disadvantage is directly caused by the low GFR, as opposed to the disease causing the low GFR, the risk should be similar regardless of the underlying mechanism. Our objective was to determine if age related declines in estimated GFR (eGFR) carry the same prognostic importance as disease attributable losses in patients with ventricular dysfunction. We analyzed the Studies Of Left Ventricular Dysfunction (SOLVD) limited data set (n=6337). The primary analysis focused on determining if the eGFR mortality relationship differed by the extent the eGFR was consistent with normal ageing. Mean eGFR was 65.7 ± 19.0 ml/min/1.73m². Across the range of age in the population (27 to 80 years), baseline eGFR decreased by 0.67 ml/min/1.73m² per year (95% CI 0.63 to 0.71). The risk of death associated with eGFR was strongly modified by the degree to which the low eGFR could be explained by aging (p interaction <0.0001). For example, in a model incorporating the interaction, uncorrected eGFR was no longer significantly related to mortality (adjusted HR=1.0 per 10 ml/min/1.73m², 95% CI 0.97–1.1, p=0.53) whereas a disease attributable decrease in eGFR above the median carried significant risk (adjusted HR=2.8, 95% CI 1.6–4.7, p<0.001). In conclusion, in the setting of LV dysfunction, renal dysfunction attributable to normal aging had a limited risk for mortality, suggesting that the mechanism underlying renal dysfunction is critical in determining prognosis.

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Keywords

Cardio-renal syndrome; Age related renal dysfunction; Prognosis; Heart failure

Introduction

Renal dysfunction (RD) has emerged as one of the strongest prognostic indicators in patients with heart failure (HF).¹ However, it is unclear if these poor outcomes are the direct result of adverse effects of a reduction in glomerular filtration rate (GFR), or if the RD is primarily a surrogate for greater HF disease severity. There are multiple theoretical mechanisms which would implicate the decline in GFR itself as a primary culprit mechanism.² However, recent human observational data have suggested that not all declines in renal function are prognostically equivalent.^{3–8} An accessible approach toward this question of causality may be studying the effect of “normal” aging. After a peak in GFR in the third decade of life of approximately 130 ml/min/1.73 m², renal function progressively declines on the order of 0.8 ml/min/1.73 m² per year.^{9–12} Notably, in studies of the general population, the relative risk for death associated with any given eGFR progressively diminishes as age increases.^{13–15} Although thought to be part of the “normal” aging process, the resultant reduction in GFR that occurs with aging is a true loss of GFR and physiologically indistinguishable from that produced by pathologic reductions in GFR.^{9,16} As a result, if the adverse outcomes associated with RD stem from the reduction in GFR, it should be irrelevant whether the low GFR is the result of a “benign” cause such as the aging process or a pathologic process such as HF-induced RD. However, if RD is primarily acting as an indicator of otherwise unmeasured disease severity, the risk for mortality attributable to RD should be much greater in patients that have a reduction in GFR primarily as a result of a pathologic cause. As such, the focus of the study was determining if the eGFR mortality relationship differed by the degree to which low eGFR was driven by normal aging.

Methods

The Studies Of Left Ventricular Dysfunction (SOLVD) prevention and treatment trials were National Heart, Lung and Blood Institute (NHLBI) sponsored, randomized, double-blind, placebo controlled trials of the effect of enalapril in patients with asymptomatic and symptomatic left ventricular dysfunction and comprise the overall SOLVD population. Methods and results have been previously published.^{17,18} Briefly, 4,228 patients were enrolled in the prevention trial and 2,569 patients in the treatment trial at 23 international centers (total n= 6797). Inclusion in either trial required an ejection fraction $\geq$ 35% and age between 21 and 80 years. Exclusion criteria included a baseline creatinine level >2.5 mg/dL. Patients with data available to estimate baseline GFR (n=6782) were included in the current analysis.

Estimated glomerular filtration rate (eGFR), uncorrected for aging, was calculated using the 4 variable Modified Diet and Renal Disease equation (MDRD).¹⁹ The normal GFR that would be expected with healthy aging was calculated by the equation [age predicted GFR = $130 \text{ ml/min/1.73 m}^2 - ((\text{age in years} - 30) * 0.8)$] given that normal GFR in adults prior to age 30 years is approximately 130 ml/min/1.73 m² after which time it is reported to decline on the order of 8 ml/min/1.73 m² per decade.^{9–11} Given that heart failure is not known to protect against age-related declines in renal function, to account for normal decline that would be expected in the population, an age corrected eGFR was calculated by the equation [age corrected eGFR = MDRD eGFR + $((\text{age in years} - 30) * 0.8)$]. Disease attributable decrease in eGFR (i.e., the decline in eGFR beyond that expected for normal aging) was calculated by subtracting the age corrected eGFR from 130 ml/min/1.73 m². The

same parameter could be calculated by subtracting the eGFR from the age predicted GFR. The entire SOLVD population was analyzed as a whole to maximize power given the lack of interaction across the prevention vs. treatment trials in the primary analysis (3 way interaction $p=0.38$).

The primary analyses in this study focused on determining if the risk for death associated with eGFR was modified by the degree to which the low eGFR was the result of disease vs. normal aging. As such, the primary endpoint was the interaction between eGFR, the disease attributable decrease in eGFR, and mortality. Values reported are mean $\pm$ standard deviation, median (quartile 1 - quartile 4), and percentile. Independent Student's t-test or the Mann-Whitney U test was used to compare continuous parameters. Pearson's Chi Square was used to evaluate categorical variables. Linear regression was used to estimate the decline in renal function across the age range of the population. Proportional hazards modeling was employed to evaluate time to event associations with all-cause mortality. To determine if effect modification was present between disease attributable decrease in eGFR and the eGFR-mortality association, a model incorporating the main effect of eGFR, the main effect of disease attributable decrease in eGFR, and the two way interaction of these terms was constructed. Candidate covariates for multivariable modeling were obtained by screening all baseline variables for a univariate association with mortality ($p \leq 0.2$). Covariates were removed using backwards elimination (likelihood ratio test), and variables with a $p < 0.2$ were retained.²⁰ Loess approach with span 5 was used to estimate the trends of eGFR and age corrected eGFR (Figure 1). Using a weighted proportional hazard model of overall survival with independent variables such as eGFR, disease attributable decrease in eGFR, and their interaction, we estimated the hazard ratio with respect to eGFR=106.5 and with zero disease attributable decrease in eGFR. A reference value of 106.5ml/min/1.73m² was employed as this is the median age predicted GFR in the population. Specifically, the hazard ratio at a value of (eGFR, disease attributable related decrease in eGFR) in Figure 2 is calculated as the hazard rate at the value of (eGFR, disease attributable related decrease in eGFR) divided by the hazard rate at (eGFR, disease attributable decrease in eGFR)=(106.5, 0). Significance was defined as 2-tailed $p < 0.05$ for all analyses excluding tests of interaction where p values < 0.1 were considered significant. Statistical analysis was performed with IBM SPSS Statistics for Windows, Version 19.0. (IBM Corp., Armonk, NY), Statistical Analysis System (SAS), Version 9.3, (SAS Institute, Cary, NC), and Matrix Laboratory (MATLAB), Version R2012, (The MathWorks, Inc., Natick, MA).

Results

Baseline characteristics of patients in this analysis are presented in Table 1. The age of the population ranged from 27 to 80 years with a mean of 59 ± 10 years. The mean eGFR was 65.7 ± 19.0 ml/min/1.73m² which is 51.0 % (41.3% – 59.2%) below a truly normal GFR of 130ml/min/1.73m² (Figure 1A). In the overall population, 35.1% (27.2% – 43.6%) of this deviation from true normal was consistent with expected age related loss and 62.9% (54.4% – 70.3%) was consistent with a disease attributable decrease in eGFR. However, this differed across the age range of the population where the absolute degree of disease attributable decrease in eGFR remained relatively stable but progressive age related loss accrued over time (Figure 1B). Interestingly, the loss in eGFR with progressive age in the population was not greater than that described in healthy populations (shaded areas in Figure 1A and 1B) as eGFR decreased linearly at a rate 0.67 ml/min/1.73m² per year (95% CI 0.63 to 0.71). Consistent with the above, correction of eGFR for the reported age related decline in eGFR found in other populations (0.8 ml/min/1.73m² per year over the age of 30 years) resulted in a relatively stable baseline eGFR across the range of age in the population (Figure 1B).

As previously reported, eGFR had a strong association with worsened survival in the overall SOLVD population (HR=0.84 per 10 ml/min/1.73m² increase in eGFR, 95% CI 0.82–0.87, $p<0.0001$).⁴ This association weakened slightly but remained significant after adjustment for baseline characteristics (age, sex, race, ejection fraction, heart rate, blood pressure, New York Heart Association class, baseline medications, study drug assignment, prevention vs. treatment trial, diabetes, hypertension, and history of myocardial infarction or stroke; HR=0.92 per 10 ml/min/1.73m² increase in eGFR, 95% CI 0.89–0.95, $p<0.0001$). Notably, there was a highly significant interaction ($p<0.0001$) between eGFR and the disease attributable decrease in eGFR where the risk for death was greatly attenuated in patients where the low eGFR was consistent with normal aging (Figure 2). For example, in a model incorporating the interaction, eGFR was no longer significantly related to mortality (adjusted HR=1.0 per 10 ml/min/1.73m², 95% CI 0.97–1.1, $p=0.53$) when the decrease in eGFR was fully explained by aging. In contrast, a disease attributable decrease in eGFR above the median carried significant risk (adjusted HR=2.8, 95% CI 1.6–4.7, $p<0.001$). The interaction remained significant with adjustment for baseline characteristics (p interaction=0.009). Similarly, in a sensitivity analysis using age directly, rather than the deviation from the GFR predicted for age, also produced a significant interaction ($p=0.009$). Furthermore, in sensitivity analyses varying the predicted age related decline in renal function between 0.5 ml/min/1.73m² per year and 1.0 ml/min/1.73m² per year, in addition to the population derived value of 0.67ml/min/1.73m² per year, also produced a highly significant interaction ($p<0.001$ for all comparisons).

Discussion

The principal finding of this analysis is that the association between a low eGFR and survival appears to be significantly modified by whether the low eGFR was consistent with the normal aging process. Notably in patients with a lower eGFR that was consistent with that which could be found with normal aging, eGFR demonstrated a weak association with mortality. However, patients with a low eGFR that could not be explained by normal age-related losses (i.e., disease attributable loss in GFR) had a substantial burden of mortality associated with the low eGFR. These data provide additional support for the notion that the strong association between mortality and RD is more complicated than a simple cause and effect relationship between low glomerular filtration and adverse outcomes.

We and others have previously described that the clinical context in which a reduction in eGFR occurs is a strong determinate of the prognostic importance, even when the decrement in renal function is similar. For example, worsening renal function in the setting of aggressive decongestion, titration of vasodilators, or initiation of a renin-angiotensin-aldosterone antagonist has a much more benign prognosis compared to that of a non-provoked decline in renal function.^{3,5–7,21–23} Similarly, we and others have reported that an improvement in renal function can have a similar or worse prognosis to that of a worsening in kidney function.^{8,24,25} Furthermore, in the setting of HF essentially all the risk associated with a low eGFR clusters in patients with an elevated blood urea nitrogen to creatinine ratio, a marker of “pre-renal” pathophysiology such as HF-induced RD.^{4,8} However, the problem with interpretation of much of the above data is it is difficult to disassociate the cause for the change in renal function from the reduction in GFR itself (i.e., the relative benefit of initiation of an ACE inhibitor from the relative harm from the resultant lowering of GFR). To do this, a specific phenotype of renal dysfunction whose cause would not be expected to offer a survival advantage to offset the reduction in GFR must be identified. Age related declines in GFR may offer such a scenario. As a result, we believe the current findings, in conjunction with the above referenced data, argues strongly that the mortality risk associated

with moderate degrees of RD is largely the result of its surrogacy for disease severity rather than a direct cause and effect relationship.

Despite the strong possibility that RD is primarily a marker rather than cause of adverse outcomes, and age related declines in renal function may have a limited prognostic importance, this does little to reduce the overall importance of the kidney in HF. Although risk prediction algorithms that include renal function may be improved by incorporating interaction with the underlying mechanism, the fact remains that renal function influences almost all aspects of HF care. Even an age-related decline in GFR will affect the sodium and fluid balance, limit our ability to maintain euolemia, in addition to altering the clearance, efficacy, and tolerance to multiple medications. Furthermore, if RD is identifying a distinct and particularly virulent HF phenotype, this likely represents a much greater therapeutic opportunity than if the low GFR was directly causing the adverse outcomes given the irreversibility of many forms of RD (i.e., age-related loss in GFR is not likely reversible/treatable). As such, research efforts to better understand the mechanisms underlying RD in HF, identify specific phenotypes, and develop therapeutic strategies to correct the underlying pathophysiology could offer great advantage to these very high-risk patients.

An additional interesting finding from this analysis is that age-related declines in eGFR did not appear to be accelerated by the presence of cardiac dysfunction, or the comorbidities that accompany and cause HF. Notably, in this population the rate of decline was 0.67 ml/min/1.73m² per year which was actually less than the frequently cited figure of 0.8ml/min/1.73m² per year described in non-diseased populations.⁹⁻¹¹ Furthermore, the non-age related/disease attributable decline in eGFR was quite similar across the population. Given that it is highly unlikely that heart failure somehow protects the kidney from the effects of normal aging seen in healthy populations, these data suggest that despite a lower mean eGFR in elderly patients with heart failure, they may have a very similar burden of “cardio-renal syndrome” compared to younger patients.

This study was a post hoc retrospective analysis of a clinical trial and as a result residual confounding cannot be excluded. The SOLVD trials were not designed to evaluate associations with renal function. Specifically, patients with severe renal insufficiency (creatinine >2.5 mg/dL) were excluded from SOLVD limiting generalization to patients with more extreme degrees of renal dysfunction. Although the SOLVD trials included a large number of patients spanning over 50 years of age, the majority of patients were within 30 years and there was not a substantial number of very elderly participants. As a result, the number of patients with more severe degrees of renal dysfunction that could be entirely attributable to normal aging was small limiting the precision of the findings. The limited number of patients with severe heart failure, who might be more susceptible to direct effects of a low GFR, also limits generalization. However, the lack of interaction of our findings between the prevention and treatment populations argues against this possibility. The accuracy of creatinine based GFR estimation equations with increasing age has not been thoroughly studied in heart failure. However, the consistency of these results with those found in normal populations provides reassurance that inaccuracy of the equations is unlikely to primarily explain these observations. Additionally, the SOLVD trial was conducted in an era before evidence based neurohormonal antagonists were standard of care. Given that these therapies may modify the risk profile of cardio-renal interactions; our findings need to be replicated in a contemporary cohort employing these interventions. Given the above limitations, these hypothesis generating findings should primarily serve as proof of concept and motivate future research.

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Figure 1.

Renal function across the spectrum of age in the general population as predicted with normal aging (panel A) and in the SOLVD population (panel B)

Shaded areas represent the decline in GFR reported to occur with normal aging (~8 ml/min/1.73m² decline in eGFR per decade over the age of 30 years). Correction of eGFR for the predicted decline in eGFR with normal aging eliminates the trend toward lower eGFR with greater age in the population (panel B). (GFR: Glomerular filtration rate eGFR: Estimated glomerular filtration rate).

Figure 2.

Relationship between eGFR and mortality stratified by the difference between age predicted GFR and eGFR.

Note that the risk of death associated with any given eGFR is significantly greater if it is beyond what is expected for normal aging. GFR: Estimated glomerular filtration rate.

Difference between eGFR and GFR predicted with normal aging calculated as $[130 \text{ ml/min/} 1.73\text{m}^2 - (((\text{age in years} - 30) * 0.8) - \text{eGFR})]$.

Table 1

Baseline Characteristics

Characteristic	(n=6782)
Age (years)	59.3 ± 10.2
White	5982 (88%)
Men	5866 (86%)
Hypertension	2645 (39%)
Diabetes Mellitus	1309 (19%)
Coronary heart disease	5066 (75)
Heart rate (beats/minute)	76 ± 12
Systolic blood pressure (mmHg)	119 ± 17
Enalapril	3391 (50%)
Beta blocker	1207 (18%)
Digoxin	2245 (33%)
Loop diuretic	2204 (33)%
Serum sodium (mmol/L)	140 ± 3
Creatinine (mg/dL)	1.2 ± 0.3
Uncorrected estimated glomerular filtration rate (mL/min/1.73m ²)	66 ± 19
Estimated glomerular filtration rate corrected for normal aging (mL/min/1.73m ²)	88 ± 17
Disease attributable decrease in estimated glomerular filtration rate (mL/min/1.73m ²)	42 ± 17
Left ventricular ejection fraction (%)	27 ± 6
New York Heart Association class	1.7 ± 0.7