IJKD KIDNEY DISEASES

Hemodynamic Response to Exercise for Prediction of Development of Kidney Failure

Revealing a Cardiorenal Secret Cross Talk

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Original Paper

Introduction. Kidney disease increases the risk of cardiovascular disease. The corollary of that observation should be that cardiovascular disease would not only increase the risk of kidney dysfunction, but also cause kidney damage, a concept not previously proposed.
Materials and Methods. Hemodynamic response to a graded exercise stress test was measured in 70 candidates to evaluate the association of heart rate and blood pressure change, heart rate reserve, chronotropic incompetence (percentage of achievement of maximal predicted heart rate), and circulatory power with development of kidney failure (glomerular filtration rate < 30 mL/min/1.73 m^2) during 123 months of follow-up period.
Results. Kidney failure was more likely to develop in patients with lower heart rate change, heart rate reserve, percentage of achievement of maximal predicted heart rate, and circulatory power (P = .002, P = .01, P = .02, and P = .008, respectively), even after adjustment for age, resting pulse pressure, hypertension, diabetes mellitus, and exercise test result (hazard ratios, 5.9, 2.9, 3.3, and 2.9, respectively). A resting pulse pressure of 60 mm Hg and higher was accompanied by 7.4 times (95% confidence interval, 1.8 to 30.9) greater risk of developing kidney failure, independent of age and resting systolic blood pressure (P = .006).
Conclusions. Hemodynamic responses to a standard graded exercise stress test independently predicted the development of kidney failure. Also, arterial stiffness (represented by resting pulse pressure) could be a factor linking ventricular and kidney function. Early diagnosis of kidney disease should include a cardiovascular assessment and vice versa.

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INTRODUCTION

It has become very clear, particularly over the past few years, that chronic kidney disease (CKD) is a powerful cardiovascular (CV) risk factor, even in patients with mild CKD.[1-3] However the mechanism by which CKD leads to CV damage cannot be accounted for simply by the increased incidence of hypertension or even hypercholesterolemia.[4] It is probable that the relationship between the heart and the kidney is close since that the heart and the kidney were called "fatal twins" in a recent publication.[5] This relationship is not just due to known links including the renin-angiotensin-aldosterone system and is possibly best illustrated by an evaluation of patients with severe cardiac failure where the degree of CKD had a stronger

correlation with subsequent mortality than other comorbidities, including the cardiac ejection fraction.[6] Therefore, as a corollary to the observed increase in CV disease with decreasing kidney function, the development of kidney dysfunction might be expected in patients with impaired CV function. Cardiovascular diseases not only share many risk factors with CKD, but also may have direct effects on the kidney, although no direct evidence supporting this hypothesis has yet been published.

Since the cardiac response to exercise is a predictor for cardiac events including sudden death,[7] mortality,[8,9] and coronary artery disease,[10] patients undergoing an exercise stress test for possible coronary artery disease were evaluated and the test results correlated with the individual's kidney function. Furthermore, all patients were then followed up during several years and their kidney function was evaluated. We hypothesised that early presentations of CV dysfunction, as manifested in the exercise test, may predict future kidney function.

MATERIALS AND METHODS

Study Population

One hundred patients were randomly selected from candidates undergoing a standard cardiac exercise test in a tertiary care hospital in Australia. Patients with severe kidney failure or a transplanted kidney, smokers and those taking a beta-blocker medication were excluded from the study. Consequently, this cohort study evaluated 70 patients (mean age, 60 ± 8 years) who were classified into 2 groups based on their heart rate (HR) response to the exercise. The patients' baseline characteristics are presented in Table 1. The test indication included a diagnosis of cardiac ischemia or assessment of exercise tolerance in 60, postinfarction analysis in 7, and coronary artery bypass graft assessment in 3 cases.

Exercise and Response

A symptom-limited standard graded cardiac exercise test protocol was applied either by treadmill or cycle ergometer. Prior to testing, a brief history and a standard 12-lead electrocardiography were obtained and blood pressure (BP) and heart rate (HR) at rest recorded. Blood pressure and electrocardiography monitoring was performed during the test and during recovery. The chronotropic incompetence was assessed as a failure to achieve 85% of the maximal predicted HR (MPHR) for the patient's age,[8] and HR reserve (HRR) was calculated using the below formula[11]:

HRR = [(peak HR - HR at rest)/(220 – age - HR at rest)] × 100

Exercise load was assessed by estimated oxygen cost (mL/kg/min), based on a standard normogram.[12] Circulatory power was calculated as the product of oxygen and maximal systolic BP (SBP) at exercise, and the rate-pressure product as maximal HR multiplied by maximal SBP per 100.[9,13] Exercise-induced changes in HR and SBP

Table 1. Baseline patient characteristics By Level of Changes in Heart Rate

Characteristic	Change in Heart Rate		*P*
	Low	High	
Number of patients	35	35	
Male sex, %	51	43	.47
Age, y	61.7 ± 9.1	59.1 ± 8.4	.21
Follow-up duration, y	10.0 ± 3.1	8.5 ± 3.1	.07
Resting heart rate, bpm	76.4 ± 13.5	71.9 ± 12.8	.16
Systolic blood pressure, mm Hg	139.5 ± 25.8	149.6 ± 27.1	.12
Diastolic blood pressure, mm Hg	80.0 ± 14.9	89.5 ± 14.9	.007
Resting pulse pressure, mm Hg	59.4 ± 18.9	60.1 ± 20.9	.89
Hypertension	16	18	.78
Hyperlipidemia	15	18	.67
Diabetes mellitus	6	6	> .99
Test positive	10	10	> .99
Serum creatinine, mg/dL	1.18 ± 0.25	1.04 ± 0.38	.13
Baseline glomerular filtration rate, mL/min/1.73 m^2	60.9 ± 16.8	68.6 ± 20.9	.09
Final glomerular filtration rate, mL/min/1.73 m^2	41.9 ± 22.1	58.1 ± 21.4	.003

were calculated by subtraction of the HR and BP at rest from maximal values of these variables.

Follow-up

Serum creatinine levels for each year were reviewed after the exercise test and at the closing date of the study. Creatinine clearance was calculated using the Modification of Diet in Renal Disease equation.[14] The given outcome was developing severe kidney failure, defined as an estimated glomerular filtration rate (GFR) less than 30 mL/min.

Statistical Analysis

Patients were classified into 2 groups for each hemodynamic variable of SBP change, HR change, MPHR, HRR, and circulatory power with 35 mm Hg, 65 bpm, 85%, 70%, and 3000 mm Hg.mL/min/kg as cutoff points, respectively. Also, the cohort was grouped based on their resting pulse pressure with 60 mm Hg as the positivity criterion. The difference between patients' characteristics for cohort subgroups was then evaluated by the chi-square test, and finally the development of severe kidney failure was separately compared between each couple of comparison groups by survival analysis and log-rank test. The impacts of covariants were adjusted using the Cox proportional hazard analysis. The analyses were performed using the Stata (version 8.1, StataCorp LP, College Station, TX, USA).

RESULTS

Seventy patients whose average age was 60 years at baseline (range, 37 to 77 years) were followed up for 123 months (range, 33 to 179 months). During the follow-up period, 20 kidney failure events occurred (28%). Partial correlation analysis showed that while estimated GFR had the expected negative relationship with age, it was also inversely associated with HR change (P = .003). However an association between GFR and SBP change was not significant after adjustment for age (P = .19; Figure 1).

The patients were initially categorized based on their HR response to the exercise and their characteristics are summarized in Table 1. There was no significant difference in age, sex, SBP, resting HR, baseline estimated GFR, positive exercise test result, and frequency of major comorbidities including hypertension, diabetes mellitus (DM), and hyperlipidemia between the two groups. However, individuals with a smaller change in HR demonstrated a lower diastolic BP and a lower GFR during the follow-up (P = .007 and P = .003, respectively).

The patients were also classified according to their development of a kidney failure (estimated GFR ≤ 30 mL/min/1.73 m^2). Those with the event had a lower exercise tolerance and cardiac function than individuals with a higher GFR (Table 2). The proportion of positive results for ischemia with the exercise test was not different in the patients with and without kidney failure (P = .33). However, not surprisingly, diabetic patients were more likely to develop kidney failure (P = .01).

The results of the survival analysis method

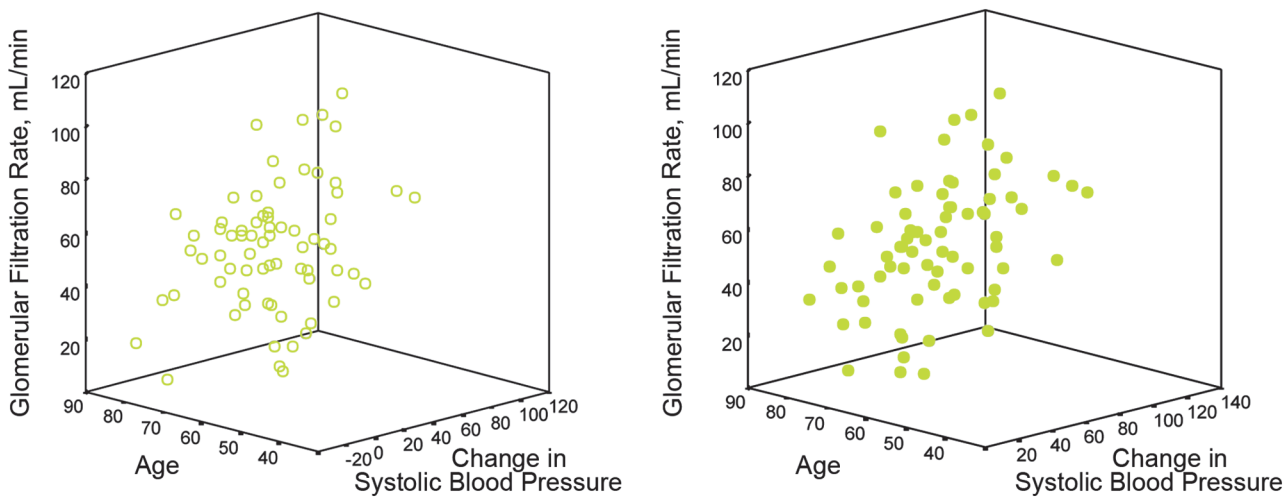

Figure 1. Partial correlation of glomerular filtration rate with age and systolic blood pressure (left) and heart rate (right) exercise response.

Table 2. Baseline Patient Characteristics by Kidney Function After Follow-up

Characteristic	Glomerular Filtration Rate, mL/min		*P*
	< 30	≥ 30	
Number of patients	20	50	
Male sex, %	50	54	.76
Age, y	69.7 ± 9.2	72.1 ± 9.0	.33
Resting heart rate, bpm	74.3 ± 13.2	74.1 ± 13.6	.95
Systolic blood pressure, mm Hg	144.1 ± 25.5	144.8 ± 27.5	.92
Diastolic blood pressure, mm Hg	77.8 ± 9.7	87.5 ± 15.5	.01
Resting pulse pressure, mm Hg	66.5 ± 20.6	57.4 ± 19.1	.09
Hypertension	45.0	50.0	.70
Hyperlipidemia	55.0	44.0	.40
Diabetes mellitus	28.0	10.0	.02
Oxygen cost, mL/min/kg	16.1 ± 6.7	22.2 ± 8.8	.008
Rate-pressure product, mm Hg × bpm	22171.8 ± 7206.6	18874 ± 12136.4	.27
Circulatory power, mmHg × mL O_2/min/kg	3041.9 ± 1666.4	4029.9 ± 1803.6	.04

demonstrated that a lower hemodynamic exercise response was accompanied by a greater development of severe kidney failure. The observed difference was significant for HR change, HRR, percentage of MPHR, and circulatory power (P = .002, P = .01, P = .02, and P = .008, respectively; Figure 2) but not for SBP change (P = .21), when analysed by log-rank test for equality of survivor function (preserved kidney function). Also, the exercise test result for ischemia was not a determinant factor for the given outcome (P = .49), neither was sex, history of hypertension, or hyperlipidemia (P = .86, P = .97, and P = .26, respectively). Of particular interest, having a resting pulse pressure of 60 and higher was accompanied by a 7.4-time greater risk (95% confidence interval, 1.8 to 30.9) of developing kidney failure, independent of age and SBP at rest (P = .006).

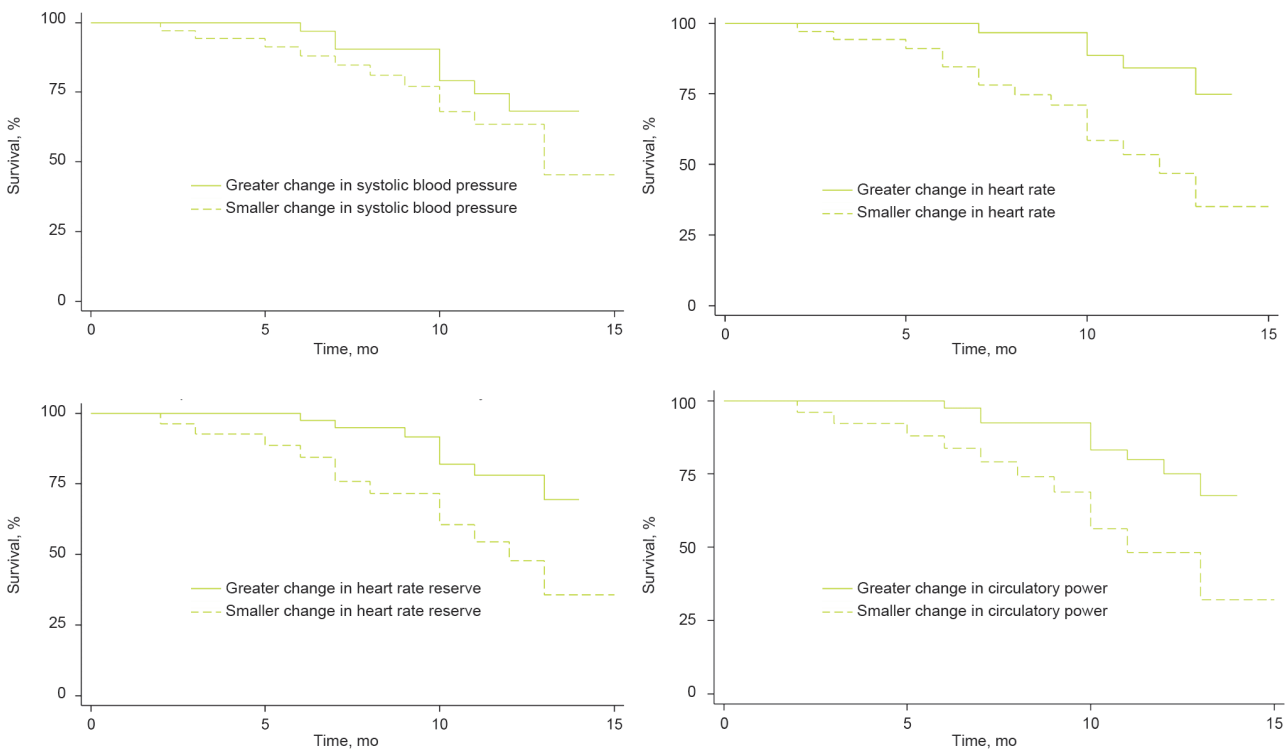

Figure 2. Cumulative frequency of patients without severe renal insufficiency in subgroups based on the degree of the response to the exercise test.

Diabetes mellitus reduced the chance of preserving kidney function (GFR > 30 mL/min) by 68% during a 10-year follow-up. Multivariable analyses demonstrated the DM effect to be independent of age, hypertension, hyperlipidemia, and the exercise test result (hazard ratio, 3.6; $P = .02$), but dependent on resting pulse pressure and the hemodynamic response (as represented by circulatory power and each HR indexes). It may be concluded that the impact of DM on renal deterioration is mediated by arterial and cardiac impairment. On the other hand, the predictive value of the HR response indexes to exercise for kidney failure remained significant after multivariable adjustment and did not change after eliminating diabetic patients from the analysis.

Adjustment for DM, hypertension, age, exercise test result, HR, and pulse pressure at rest demonstrated that the probability of development of kidney failure increased by approximately 6-fold when a patient was classified into the lower HR response category (hazard ratio, 5.9, 95% confidence interval, 1.6 to 21.3). When HR change was taken as a continuous variable, each beat per minute increase in HR reduced the risk by 3% (95% confidence interval, 1% to 6%). Likewise, the impact of HRR (hazard ratio, 2.9; 95% confidence interval, 1.1 to 7.9), MPHR (hazard ratio, 5.9; 95% confidence interval, 1.6 to 21.3) and circulatory power (hazard ratio, 2.9; 95% confidence interval, 1.1 to 7.8) remained markedly significant after the abovementioned adjustment ($P = .03$, $P = .02$, and $P = .04$, respectively). The circulatory power ($P = .02$) and HR change ($P = .04$) were also independent of the baseline GFR. Furthermore, stratification of the data to levels of initial GFR with 10 mL/min increments showed that in all participants with a GFR greater than 50 mL/min, HR change remained a significant determinant for progression towards kidney failure ($P = .008$).

Our findings also demonstrated that HRR was superior to MPHR in predicting kidney function deterioration (chi-square, 6.49 versus 5.75). In contrast, rate-pressure product had no predictive value and was not associated with other indexes of cardiac or kidney function in this study.

DISCUSSION

The novel finding in this long-term follow-up study was that the hemodynamic response to an exercise stress test, in particular HR and circulatory power, independently predicted further development of kidney failure. Most importantly, resting pulse pressure (a surrogate of arterial stiffness) was also a significant predictor for progression to kidney failure. While an impaired cardiac response could be due to cardiac ischemia, the proportion of patients with a positive exercise test result was comparable between the groups. Also, there was no significant difference in the proportion of conventional risk factors between the two groups.

Among individuals with severe CKD, the risk of cardiovascular disease is 10 to 20 times higher than the general population with an increased risk even in mild CKD.[2,3,15] Kidney failure also worsened postinfarction prognosis in a large cohort of 14527 participants and each 10 unit reduction in GFR (below 81 mL/min/1.73 m^2) was associated with a 10% increase in death and nonfatal outcomes.[3] Furthermore, several studies have reported increased CV events and mortality in microalbuminuria, and an inverse association of GFR and mortality.[16] In large cross-sectional studies of hypertensive patients, a lower GFR was associated with higher prevalence of left ventricular hypertrophy, after adjustment for age, sex, body mass index, DM, BP, and smoking.[17-19] Henry and coworkers also reported an association of left ventricular hypertrophy and mild CKD in a community-based male elderly population and suggested arterial stiffness as the linking factor between heart and kidney.[20] Therefore, although mechanisms by which renal insufficiency worsens prognosis in patients with heart disease are not clear, it seems logical that the patient's vascular disease affects both heart and kidney circulation. Therefore, patients with coronary artery disease and renal insufficiency have more diffuse and more severe vascular disease when compared with patients with normal kidney function. This accelerated vascular disease may be caused by diverse factors including increased lipoprotein(a), fibrinogen, D-dimer, and prothrombin fragments.[21]

Although the predictive value of the exercise HR response for GFR may indicate the causal effect of underlying cardiac pathologies on kidney function, it may also be associated with subclinical kidney damage and a consequent change in arterial compliance before a substantial increase in serum

creatinine has occurred. In 1290 untreated patients with low plasma creatinine levels, an elevated pulse wave velocity was associated with a reduced GFR and was more important in younger (< 55-year-old) patients.[22] As further support, Thambyrajah and colleagues suggested that endothelial dysfunction is already present early in the kidney failure process.[1] In a recent longitudinal study, the baseline creatinine level was the most important factor affecting the relationship between age and pulse wave velocity.[23] Our previous report demonstrating a significant impact of resting pulse pressure on the hemodynamic response to exercise,[24] and our current result indicating the predictive value of resting pulse pressure for kidney function support the idea of a pivotal role of arterial stiffness in the heart and kidney association.

Despite reports suggesting association of cardiac and kidney function, there is no original study to confirm the impact of mild to moderate heart dysfunction on CKD. Nevertheless it is not unreasonable to consider a reciprocal interaction between heart and kidney such that subtle impaired cardiac function leads to kidney dysfunction with time. Considering the association of left ventricular hypertrophy and CKD, it is likely that the reduced SBP change represents an inability of heart to increase BP in parallel to exercise,[9] and therefore, should predict the further development of kidney disease. However we were unable to show a statistically significant impact of the change in SBP, possibly due to unaccounted sources of BP response variation to exercise such as non-beta-blocker medications. In other words, the failure to achieve a significant difference in development of ESRD between the low and high changes in SBP despite the trends was likely due to a lack of statistical power rather than a lack of difference. Additionally, circulatory power was a significant determinant of kidney survival after follow-up in a multivariate analysis. Although this finding supports the above mentioned hypothesis (association of ventricular and kidney function), it is noteworthy that the circulatory power index is not recommended for use as a single index of ventricular function and must be interpreted in the context of other values.[25]

A Framingham study subset showed that established CV risk factors, including age, body mass index, smoking, and DM are associated with new-onset kidney disease.[15] The impact of smoking, DM and fibrinogen levels on declining kidney function were also discussed in a large cohort of elderly.[26] Not surprisingly, DM had a significant impact on developing kidney failure in our study and our estimated odds ratio (3.6, adjusted for comorbidities) was comparable to larger studies.[26] Nevertheless, the relationship of kidney failure incidence and HR response to exercise remained significant after excluding the DM subjects as well as in multivariate analyses. On the other hand, the impact of DM was not independent from resting pulse pressure and the response to exercise which supports the concept that arterial and cardiac function plays an important role in DM kidney damage.

Estacio and colleagues reported that individuals with normal albuminuria had a significantly higher peak oxygen volume than patients with microalbuminuria. They found that the relationship of microalbuminuria and exercise capacity was independent of age, sex, duration of DM and hypertension, body mass index, and haemoglobin.[27] Considering the association of an increased urinary albumin excretion with kidney disease and LV dysfunction in type 2 DM reported by Kelbaek and Sampson,[28,29] it could be concluded that cardiac and kidney changes may be related and may develop in parallel with arterial compliance playing a linking role in this process.

Since peak exercise capacity was the strongest predictor of all cause mortality among both normal subjects and those with CV disease,[9] our finding of lower peak VO_2 and circulatory power in patients who developed kidney failure could be expected. Furthermore, while previous reports indicate a predictive value of HR response to exercise for sudden death,[7] mortality,[8,9] and coronary artery disease,[10] our present results have demonstrated for the first time that it is also predictive for kidney failure. However the mechanisms by which chronotropic incompetence predicts kidney function is not clear. Whereas the impaired response could not be explained by impaired myocardial perfusion, our finding of a lower diastolic BP in the impaired HR response to exercise as well as the event positive group suggests that altered autonomic tone may play a role, a factor with a known cardiac risk association.[30] In addition, our findings demonstrated that HRR is superior when

compared to 85% MPHR in predicting kidney function deterioration, supporting previous studies about CV events, presumably because 85% MPHR only takes age into account, while HRR considers HR and age which can increase its predictive value.[11,31]

Given the abovementioned evidence, we describe our finding by a model linking heart and kidney function (Figure 3). Increased arterial stiffness may damage kidney and heart simultaneously. This damage is present earlier in the heart than in the kidney. Ventricular impairment stimulates the renin-angiotensin system for preserving tissue perfusion which in turn increases blood pressure and arterial stiffness. While kidney damage progresses it accentuates arterial damage and also causes anaemia which can worsen cardiac disease in a vicious cycle composed of heart, kidney and arteries. However, it is hard to define the origin of the primary damage. It could originate in autonomic nervous imbalance or disturbed vasodilatory responses, eg, impaired bioavailability of nitric oxide. Alternatively, extracellular matrix of vascular and renal cells might be involved as a common factor, interacting between the kidney and large arteries.

Our study has some limitations. Firstly, our sample may not be representative of the general population; though they were a non-selected group from a large number of subjects who underwent an exercise stress test in a tertiary care referral hospital. Secondly, knowing the effect of beta-blockers on exercise responses and the impact of smoking on the incidence of renal insufficiency and exercise tolerance, we excluded subjects who were smokers or on beta-blocker medication but we could not record body mass index and hemoglobin data and also could not exclude the potential confounding effect of other medications including calcium channel blockers, angiotensin-converting enzyme inhibitors and nitrates. Thirdly, while our study subjects were free from kidney failure, they

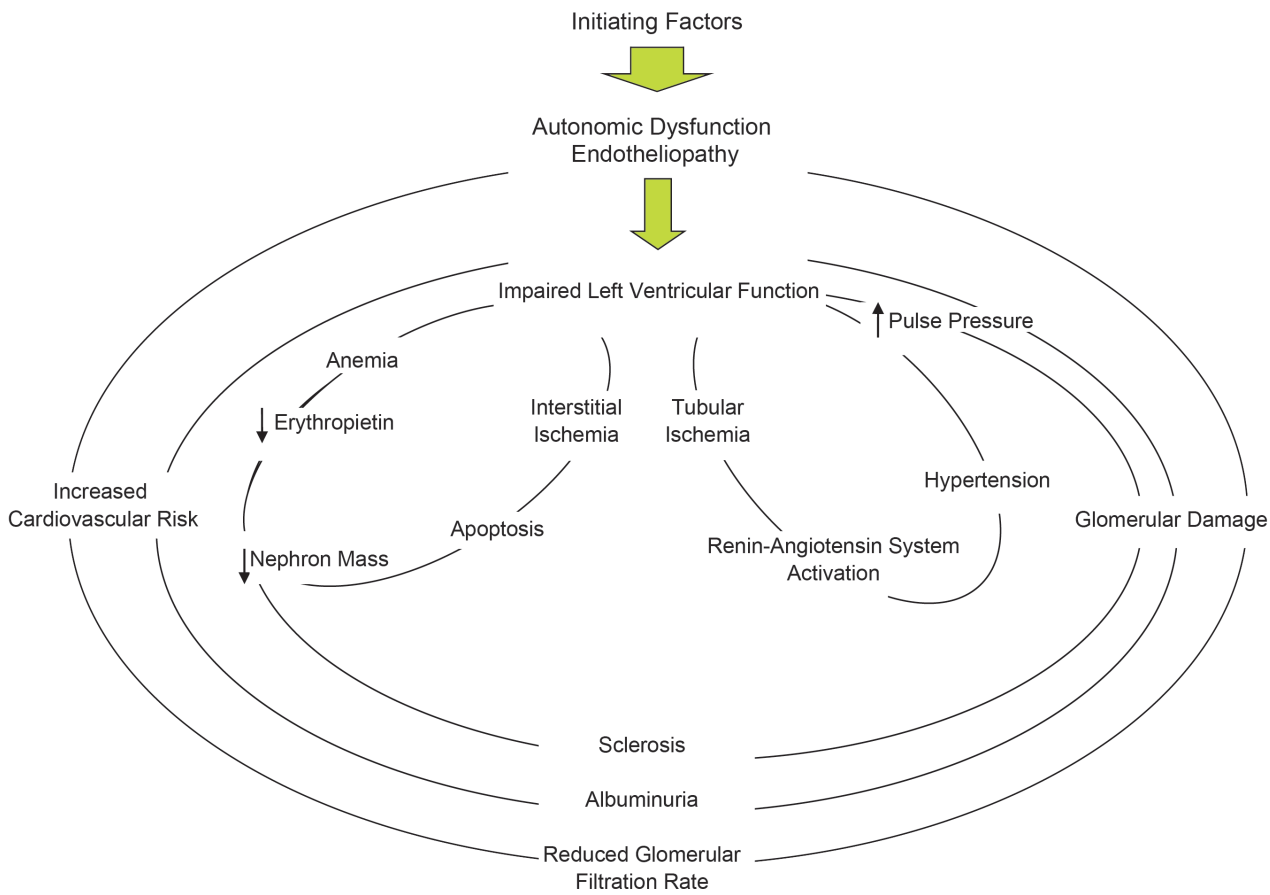

Figure 3. A hypothetical cardiorenal model.

had different GFR levels (though nonsignificant) at study entry which could not be excluded as a factor. Nevertheless, even this difference at the entry suggests the relationship between exercise response and kidney function. Moreover, we eliminated this potential confounder in multivariate analyses and by stratification.

CONCLUSIONS

This longitudinal study demonstrated the predictive value of the hemodynamic exercise response for the development of severe CKD. Based on the result of this study and other available evidence, we conclude that the early diagnosis and prevention of kidney disease requires a complementary examination of the CV system and vice versa which should include the assessment of hemodynamic responses to exercise, estimated GFR and probably arterial compliance and microalbuminuria. This approach should lead to improved risk stratification and encourage a more aggressive treatment in high risk patients. In turn, this should facilitate the primary and secondary prevention of kidney as well as cardiac disease.

CONFLICT OF INTEREST

None declared.

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