Myocardial microvascular disease and major adverse cardiovascular events in patients with end-stage renal disease: rationale and design of the MICROCARD study

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Abstract

Background. Myocardial ischaemia, a consequence of coronary artery disease, is a major cause of death in patients with end-stage renal disease (ESRD). The pathophysiology and clinical presentation of coronary artery disease in ESRD patients seem to differ from non-ESRD patients with higher implication of myocardial microvascular disease (MMD), higher mortality, fewer myocardial infarctions, less significant coronary stenosis and low efficacy of well-established drugs such as statin and angiotensin-converting enzyme inhibitors. No study has investigated the presence of MMD and its clinical impact in ESRD patients.

Methods. We designed an observational prospective cohort study to investigate the prevalence of MMD and its association with major adverse cardiovascular events (MACE) in ESRD patients with a positive non-invasive test for myocardial ischaemia. Patients eligible for inclusion are those >18 years old receiving dialysis and/or undergoing investigation for kidney transplantation, who are referred to our renal clinic and meet all the inclusion criteria but none of the exclusion criteria. Patients with a positive test for myocardial ischaemia will be enrolled in the ‘invasive group’. They will be further examined to detect simultaneously epicardial coronary stenosis by coronary angiography and MMD using pressure wire measurement of fractional flow reserve and coronary flow reserve followed by calculation of the index of microcirculatory resistance. Patients with a negative test for myocardial ischaemia will be enrolled in a ‘control group’ designed to verify whether the invasive group is indeed at high risk for MACE. Both groups will be followed up for 2 years to compare the incidence of MACE.

Conclusion. The MICROCARD study will phenotype MMD and will investigate its relation with the incidence of MACE in ESRD patients with myocardial ischaemia. Clinicaltrial.gov NCT01291771.
Introduction

Cardiovascular disease is the major cause of mortality in patients with end-stage renal disease (ESRD) [1]. Half of the patients with ESRD who require dialysis or kidney transplantation will die from cardiovascular causes [2]. Myocardial ischaemia, detected by stress myocardial perfusion single-photon emission computed tomography (SPECT) or dobutamine stress echocardiography, is frequently detected in patients with ESRD and is a strong predictor of future major cardiac adverse events and death [3, 4]. De Lima et al. prospectively evaluated the predictive value of non-invasive testing and coronary angiography on adverse cardiac events in renal transplant candidates. They concluded that the presence of significant coronary stenosis was a better and independent predictor of cardiac events than non-invasive testing [5, 6].

In contrast, in the study by Hage et al. [3], the presence and severity of coronary artery disease by angiography in the subset of patients with positive non-invasive testing or with known coronary artery disease that underwent angiography were not predictive of survival. In an unpublished pilot study comparing epicardial coronary arteries angiographic abnormalities in ESRD (n = 20) and non-ESRD (n = 31) patients with positive non-invasive test for myocardial ischaemia, we found 20% significant coronary stenosis (>70%) in ESRD patients versus 48% in non-ESRD patients (P < 0.05). Although they had no significant stenosis, the majority of ESRD patients with a positive non-invasive test for myocardial ischaemia had coronary calcifications and non-significant coronary atheroma. Of note, previously published observational studies reported various proportions of significant coronary artery disease in ESRD patients invasively examined after non-invasive testing ranging from 40 to 68% [5, 7]. In patients with positive non-invasive testing and non-significant coronary artery stenosis, myocardial ischaemia may be related to myocardial microvascular disease (MMD) resulting from calcium and phosphate disorder, inflammation, anaemia, uraemic toxin and hypertension [8].

An unadjusted estimation of cause-specific mortality rates in ESRD patients was reported by the United States Renal Data System (USRDS) in 2010 [9]. It showed that cardiovascular diseases accounted for 38% of total mortality with myocardial infarction only accounting for 5%, and sudden cardiac arrest being the most frequent cause of death (22%). The French registry analysing cardiovascular risk factors and causes of death in ESRD patients showed that cardiovascular diseases accounted for 30% of total mortality. In this registry, 10% of ESRD patients died of sudden or unexpected death which were likely to be of cardiovascular cause. Despite a high-risk profile for coronary diseases (25% with established coronary disease, 80% with hypertension and 40% with diabetes), myocardial infarction accounted only for 3.7% of total mortality [10]. Interestingly, therapeutic strategies such as statin and angiotensin-converting enzyme (ACE) inhibitors successful in reducing cardiac death in non-ESRD, high-risk patients, appeared less efficient in clinical trials specifically performed in ESRD patients [11–14]. It has been suggested that the low efficacy of statins in reducing cardiac event in ESRD patients may be related to the specific physiopathology of myocardial disease in these patients such as microvessel disease and interstitial fibrosis [15].

MMD is known to be responsible for chronic and acute myocardial ischaemia in patients with no significant coronary stenosis [16]. Combined measurement of coronary fractional flow reserve (FFR) and coronary flow reserve (CFR) completed by calculation of the index of microcirculatory resistance (IMR) was shown to be an effective and reliable method to investigate MMD [17, 18]. No study has investigated the presence of MMD and its clinical impact in ESRD patients. There are no guidelines regarding the management of myocardial ischaemia without epicardial coronary stenosis in ESRD patients.

We hypothesized that MMD was highly prevalent in ESRD patients with a positive non-invasive test for myocardial ischaemia and that it was associated with a higher incidence of major adverse cardiovascular events (MACE).

In this article, we will introduce the study design and the rationale of the MICROCARD study.

Materials and methods

Study objectives

The primary objective of the present study is to show that the presence of proven MMD is a predictor of MACE in ESRD patients with positive non-invasive test for myocardial ischaemia prospectively followed up for 2 years. The secondary objective is to show that MMD is highly prevalent in ESRD patients with myocardial ischaemia detected on non-invasive testing.

Study design

This is an observational prospective cohort study. All ESRD patients scheduled for kidney transplantation in Lyon University Hospital Centre are being referred to our cardio renal clinical unit for cardiovascular evaluation.

Study population

ESRD patients >18 years old receiving dialysis and/or undergoing investigation before kidney transplantation, referred to our cardio renal clinic, who meet all the inclusion and none of the exclusion criteria are eligible (Table 1).

Experimental groups and organization

Patients will be enrolled in one of the experimental groups after non-invasive detection of myocardial ischaemia by stress myocardial perfusion SPECT and/or dobutamine stress echocardiography. Patients with a positive test for myocardial ischaemia will be enrolled in the ‘invasive group’. Patients with a negative test for myocardial ischaemia will be enrolled in the ‘control group’. The control group is designed to verify whether our population of ESRD patients with positive non-invasive test for myocardial ischaemia is at high risk for MACE compared with ESRD patients with a negative test.

Patients enrolled in the invasive group will undergo invasive detection of MMD performed at the time of coronary angiography. Patients from both groups will be followed up annually for 2 years.

Enrolment began in January 2011 and is expected to be completed by January 2012. Follow-up for the primary end point will be completed in...
January 2014. The study is being conducted entirely by the principal investigator. All data analysis will be performed by the biostatistician involved in the study design. Events will be adjudicated by an independent end point committee.

A study flow chart is displayed in Figure 1.

Measurements

Baseline data recorded at the time of patient enrolment include aetiology of chronic kidney disease, dialysis duration, prior kidney transplantation, prior parathyroidectomy, cardiovascular risk factors (hypertension, dyslipidaemia, active smoking, diabetes and family history of coronary artery disease), prior cardiac events and current use of medication. Present cardiac status including New York Heart Association functional class, physical examination, electrocardiogram (ECG), echocardiographic data and results of non-invasive test for myocardial ischaemia are also recorded. Baseline biological parameters include: caecaemia, phosphatemia, parathormonemia, total cholesterol, high-density lipoprotein cholesterol, triglycerides, low-density lipoprotein cholesterol (calculated), haemoglobin, HbA1c, Brain Natriuretic Peptide, Troponin I, fibrinogen and C-reactive protein.

Two years follow-up data regarding MACE and renal events will be recorded in collaboration with the nephrology department that referred the patient to our cardio renal clinic.

Major end points

MACE will be recorded at 2 years: death, cardiovascular death, non-cardiovascular death, new onset of stable angina, acute coronary syndrome [ST elevation myocardial infarction (STEMI), non-ST elevation myocardial infarction (NSTEMI) and unstable angina], stroke, severe ventricular arrhythmia, new onset of atrial fibrillation and new onset or worsening of congestive heart failure.

Secondary end points

**FFR, CFR and IMR measurements.** Invasive detection of MMD will be performed in patients of the invasive group during coronary angiography. After the completion of the diagnostic coronary angiography, assessment of FFR and thermodilution-derived CFR will be performed in the left anterior descending, the circumflex and the right coronary arteries as follow. A 0.014-inch coronary pressure wire (Radi Medical Systems) will be calibrated outside of the body and then advanced through a 6-French guider catheter to position the pressure sensor at the ostium of the guiding catheter, where equal pressure readings by the guiding catheter and the pressure wire will be confirmed. The wire will then be positioned in the distal portion of the coronary artery. The shaft of the pressure wire acts as a proximal thermistor and the pressure sensor acts as a distal thermistor. Room temperature saline will be injected down the coronary artery in 3 mL aliquots three times and the resting mean transit time of the saline will be recorded and averaged. Maximal hyperaemia will then be induced by administration of intracoronary adenosine (150 μg) via the guiding catheter and the hyperaemic mean transit time will be determined by averaging the transit times after three injections of 3 mL of saline. FFR will be measured by dividing the mean distal pressure by the mean aortic pressure during maximal hyperaemia. The mean transit time is inversely proportional to flow; thermodilution-derived CFR will be calculated by dividing the resting mean transit time by the hyperaemic mean transit time [19]. IMR will be calculated by dividing pressure by flow—in this case, the distal pressure by the inverse of the hyperaemic mean transit time or, more simply, distal pressure multiplied by the hyperaemic mean transit time [17].

**Adverse events**

All expected and unexpected adverse events will be recorded for safety evaluation (Table 2). Expected adverse events are related to patients’ ESRD status. Unexpected adverse events are those that may result from invasive detection of MMD. All listed adverse events will be notified to
expected patients with optimal preventive combination therapy. For ESRD patients with MMD and non-significant epicardial coronary stenosis, we propose to phenotype MMD in ESRD patients. We propose to correlate this disease with usual cardiovascular risk factors and markers.

Discussion

In the MICROCARD study, we will investigate whether myocardial ischaemia detected on non-invasive testing is related to MMD and predicts major cardiovascular events in ESRD patients. We propose to phenotype MMD in ESRD patients and to correlate this disease with usual cardiovascular risk factors and markers.

Patients will be enrolled in our cardio renal clinic which collaborates with the nephrology department of our institution to perform cardiovascular evaluation in ESRD patients under dialysis and/or scheduled for kidney transplantation. We chose to exclude patients with prior acute coronary syndrome and/or prior coronary revascularization because they were more likely to have abnormal non-invasive tests for myocardial ischaemia.

Treatment with disease-modifying therapy which is proved to reduce rates of myocardial infarction or death (e.g. aspirin, beta adrenergic receptor blockers, ACE inhibitors or statins) is used less frequently in patients with ESRD than in the general population [20]. Although there are no guidelines regarding the management of ESRD patients with MMD and non-significant epicardial coronary stenosis, we propose to treat them as high-risk patients with optimal preventive combination therapy.

Statistical considerations

Sample size calculation. In our cardio renal clinical experience, 50% of ESRD patients have a positive test for myocardial ischaemia. We hypothesized that 40% of these patients will have a MACE within 2 years versus 20% in patients with negative test for myocardial ischaemia. A sample size of 105 patients per group achieves a power of 90% at a significance level of 0.05 to detect this difference. Among ESRD patients with positive test for myocardial ischaemia, we expect 80% without significant epicardial coronary stenosis.

Statistical analysis

All analysis will be performed on R Software. For baseline data, continuous variables with normal distribution will be presented as mean (±SD), non-normally distributed variables as median (with 25th and 75th percentile) and dichotomous variables will be presented as absolute numbers and percentages. Comparison of continuous variables between groups will be made by independent t-tests or the Mann-Whitney U-test, depending on their distribution. For the comparison of dichotomous variables, we will use the χ² test or Fisher exact test, where applicable.

The major end point at 2 years will be analysed using survival curves. Group’s comparisons will be performed using a log-rank test. FFR, CFR and IMR will be compared between coronary arteries perfusing ischaemic and non-ischaemic territories on non-invasive test for myocardial ischaemia using bilateral t-tests. Multivariate analysis (logistic regression) will be performed to identify the predictive factors of MMD: age, sex, hypertension, diabetes, significant epicardial coronary stenosis, calcaemia, phosphataemia, parathormonaemia, total cholesterol and haemoglobin. Multivariate analysis using a Cox model will be performed to identify predicting factors of major cardiovascular event (including MMD). For all analysis, P-value <0.05 will be considered significant.

Ethical considerations

The study is conducted according to the principles of the Declaration of Helsinki and in accordance with the French law relating to the protection of patients participating in biomedical research. The study design, all research aims, and the specific measurements in the MICROCARD study have been approved by the regional ethical committee. New measurements will only be embedded in the study after approval of the ethical committee. All participants are asked for their written informed consent after having received written and oral information about the study. All patients will be followed and treated according to the highest standard of care recommendations.

The sponsor and to an independent data safety monitoring board (DSMB).

Statistical and ethical considerations

Expected
- Death
- Acute coronary syndrome
- New onset of stable angina
- New onset or worsening of congestive heart failure
- Stroke
- Severe ventricular arrhythmia
- New onset of atrial fibrillation
- Worsening of glomerular filtration rate or need for dialysis in patients not previously under dialysis
- Kidney transplantation
- Severe bleeding from the site of arterial puncture for coronary angiography requiring blood transfusion and/or prolonged hospitalization and/or surgery

Unexpected
- Sustained atrioventricular block requiring specific care
- Iatrogenic coronary artery dissection
- Iatrogenic coronary artery occlusion
- Iatrogenic acute coronary syndrome
- Any iatrogenic coronary event leading to coronary revascularization
- Acute decompensated heart failure or cardiogenic shock
- Any adverse event occurring at the time of FFR and CFR measurements

ST elevation myocardial infarction, Non-ST elevation myocardial infarction, unstable angina.
Future clinical trials evaluating these therapeutic strategies in ESRD patients with MMD are needed. Non-invasive detection of myocardial ischaemia either by SPECT and/or dobutamine stress echocardiography are routinely used to investigate high-risk ESRD patients. They both show significant sensitivity and specificity although their performance remains controversial. They allow detection, localization and extension of ischaemia within the myocardium. They do not show coronary lesions which may be related both to epicardial coronary stenosis and/or microvascular disease. FFR/CFR performed at the time of coronary angiography is a validated invasive method allowing detection of both epicardial and microvascular disease [16, 17].

The risk to benefit ratio of ESRD patients enrolled in our study was carefully evaluated. As previously demonstrated, the risk associated with advancing a sensor-tipped guide wire in a coronary vessel is extremely low [21–23]. Intracoronary injection of high dose of adenosine was shown to be safe [24, 25]. All serious adverse events will be recorded and followed up by a DSMB. Because ESRD patients are known to be at high risk for cardiovascular events, they will all receive optimal preventive therapy according to the standards of care, whatever the results of the coronary angiography.

ESRD population has additional cardiovascular risk related to non-traditional factors including microalbuminuria, uraemia, hyperuricaemia, calcaemia and phosphataemia disorder associated calcification, inflammation and hyperhomocysteinaemia [26]. Even if kidney transplantation improves ESRD patients’ outcomes, risk factors often persist after transplantation and can worsen in the post-transplantation period resulting in accelerated atherosclerosis [27]. Anti-rejection therapy used in the post-transplant period such as steroids, calcineurin inhibitors and sirolimus increase the development of or worsening of pre-existing hypertension, dyslipidaemia, hyperuricaemia, weight gain and glucose intolerance. All these factors make ESRD patients a unique population that may require a different cardiovascular risk screening strategy as well as management. Several studies have evaluated the combination of non-invasive tests for myocardial ischaemia, coronary angiography, ECG abnormalities and clinical risk score to identify ESRD patients at high risk for cardiovascular events [28, 29].

Our study protocol was built to investigate MMD in ESRD patients with a pathophysiological approach. We intend to study the discrepancy between positive non-invasive tests and the absence of significant epicardial coronary stenosis. Since we will not investigate epicardial coronary artery disease and MMD in patients with negative non-invasive testing, our design will not allow us to calculate the incidence of MMD in all ESRD patients. In addition, pressure wire-based investigation of MMD in ESRD patients is restricted to experienced centres and is not likely to replace non-invasive tests.

MICROCARD is the first study that will carefully phenotype coronary artery disease including MMD in ESRD patients with positive non-invasive testing for myocardial ischaemia contributing to the amelioration of risk screening strategy and clinical management.

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Contrast-enhanced ultrasound with SonoVue could accurately assess the renal microvascular perfusion in diabetic kidney damage

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Abstract

Objective. The aim of this study was to investigate the clinical significance of real-time gray-scale contrast-enhanced ultrasound (CEUS) through evaluating renal microvascular perfusion in diabetic kidney damage.

Methods. Diabetic patients (aged: 62.5 ±7.2, n = 33) were divided into Group A with chronic kidney disease (CKD) Stages I and II (n = 19) and Group B (n = 14) with CKD Stages IV and V. Twenty-one healthy adults were selected as control group. The real-time and dynamic imaging from renal cortex was performed using contrast-enhanced ultrasound with SonoVue. The outflow time-intensity curves (TICs) with >85% goodness-of-fit index were chosen for the analysis of basic intensity, intensity increment (A1), arriving time (AT), time to peak (TTP), mean transit time, peak intensity (PI) and total area under the curve (AUC).

Results. (i) After intravenous injection of a contrast agent, the renal artery, cortex, pyramid and renal vein were clearly displayed in sequence. (ii) TIC of renal cortical Perfusion in all groups showed an asymmetrical single-peak curve, which has an obvious ascending slope, peak and descending slope. The ascending slope was steep, whereas the descending slope was flat. However, the ascending slope in Group A and B was steeper than that in the control group. (iii) Compared to the control group, AT and TTP were all markedly prolonged but A1 and PI were significantly decreased in Group A and B (P < 0.05). In Group A, the AUC had a trend of increase; however, the area under the ascending slope (AUC1), area under the descending slope (AUC2) and AUC were all decreased in Group B (P < 0.05). (iv) AUC positively correlated with glomerular filtration rate (GFR) (r = 0.472, P = 0.01), but TTP did not correlate well with GFR (r = 0.262, P = 0.177).

Conclusions. CEUS could accurately assess renal microvascular perfusion in a real-time and dynamic manner. PI, TTP and AUC could be used for the diagnosis of the renal microvascular damage in early and late stage diabetic patients. CEUS is a safe, noninvasive and simple technique to detect the severity of kidney microvascular perfusion deficits.