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CLINICAL STUDY

Perfusion defects on real-time myocardial contrast echocardiography predict higher mortality in patients with end-stage renal disease – A 3-year follow-up

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Abstract

Aim: The aim of this study was to assess the prognostic significance of myocardial contrast echocardiography (MCE) in patients with end-stage renal disease (ESRD) on a 3-year follow-up and to compare the value of MCE with demographic, clinical, and laboratory parameters. *Methods:* Fifty-eight ESRD patients on regular dialysis were prospectively screened for coronary artery disease (CAD) using perfusion assessment on real-time MCE. We analyzed the following end points during the 3-year follow-up: death, cardiovascular complications, and combined end point, which consisted of adverse cardiac events mentioned above. All features were compared between the two groups with and without perfusion disturbances on MCE. *Results:* No adverse events related to MCE administration have been observed. Twenty-seven (47%) patients with ESRD demonstrated perfusion defects on MCE. The patients with perfusion defects on MCE comparison with those without perfusion disturbances were older ($p = 0.008$) and had lower ejection fraction (EF) ($p = 0.0001$) and higher wall motion index (WMSI) ($p = 0.0001$). After the 3-year follow-up, the incidence of death ($p = 0.00018$), cardiovascular end points, revascularizations [both percutaneous coronary intervention (PCI) and coronary artery bypass grafts (CABG) $p = 0.0016$ and $p = 0.004$, respectively], and composite end point ($p = 0.0015$) was significantly higher in patients with perfusion defect on MCE. *Conclusions:* In patients with ESRD, MCE appears to be a safe and useful tool for risk stratification. MCE facilitates decision for coronary angiography.

Keywords: myocardial contrast echocardiography, myocardial perfusion, coronary artery disease, ESRD, mortality, risk stratification

BACKGROUND

Cardiovascular risk stratification is extremely important in patients with end-stage renal disease (ESRD) as coronary artery disease (CAD) is a leading cause of death in this population accounting for about 40% of the total mortality. There is no optimal strategy for the assessment of cardiovascular risk in patients with ESRD. Routine screening for CAD in asymptomatic ESRD patients is usually done only for renal transplant candidates.[1] Many of these patients, despite severe CAD, are asymptomatic. In this challenging group of patients, clinical evaluation as well as noninvasive screening tests for CAD have numerous limitations. Most of the patients are unable to undergo exercise test because of fatigue. Accuracy of stress nuclear imaging as well as stress echocardiography (SE) depends on center experience. According to the different sources, sensitivity varies from 52 to 95%, and specificity from 71 to 94%.[2,3]

Multislice computed tomography demonstrates high sensitivity and specificity for the detection of significant coronary artery stenoses. However, ESRD patients are particularly prone to coronary calcifications, which make the interpretation of the vessel morphology extremely difficult.[4] Issues concerning radiocontrast agents and their volume should also be taken into account. Thus, there is a place for a novel, noninvasive first-line test in CAD that may be safely applied in ESRD patients.

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Myocardial contrast echocardiography (MCE) is a bedside technique recently applied for an assessment of myocardial perfusion. In patients with ESRD, utility of MCE was previously investigated only by our group.[5,6] There are no published data concerning risk stratification and prognostic utility of MCE in patients with ESRD.

AIM

The aim of this study was to assess the prognostic significance of MCE in patients with ESRD on a 3-year follow-up and to compare the value of MCE with demographic, clinical, and laboratory parameters.

METHODS

Between January 2005 and October 2007, 58 consecutive ESRD patients (21 women), mean age 59 ± 14 years, on regular dialysis were prospectively screened for CAD. Chest pain was a main indication for evaluation. Also patients with nonspecific chest pains were enrolled because many of the ESRD patients despite severe CAD have atypical clinical manifestation. However, asymptomatic persons were not investigated because of ethical reasons. At the study entry medical history was recorded and all patients underwent physical examination, resting ECG, and routine transthoracic echocardiography. Thirty-nine of the 58 patients underwent coronary angiography. The other patients did not give their informed consent for coronary angiography mainly because of the fear of invasive investigations and possible complications. The following laboratory tests were done: full blood count, C-reactive protein (CRP), troponin T, and CK-MB.

We analyzed the following end points during the 3-year follow-up: death, cardiovascular complications (cardiac arrest, myocardial infarction, stroke, hospitalization for cardiac reasons, revascularization), and combined end point, which consisted of death and all adverse cardiac events mentioned above.

This study complies with the declaration of Helsinki. The study protocol was approved by local ethics committee, and an informed consent was obtained from all subjects participating in the study. Baseline characteristics of this group is shown in Table 1.

Table 1. Patients' characteristics

Age (years)	59.56 ± 13
Male/female (*n*)	37/21
Risk factors *n* (%)	
Hypertension	58 (100)
DM	15 (38.5)
History of myocardial infarction	3 (5.1)
Renal disease, *n* (%)	
Glomerulonephritis	18 (31.0)
Diabetic nephropathy	16 (28)
Duration of dialysis (months)	42 ± 24
LVEF (%)	53.66 ± 10.75

Note: DM, diabetes mellitus; LVEF, left ventricular ejection fraction.

Transthoracic echocardiography

All studies were performed using the Philips Ultrasound System Sonos 5500 equipped for harmonic imaging and 3.6-MHz transducer. Basic measurements including left ventricle (LV) size, left atrium (LA) size, interventricular septum thickness, posterior wall of LV thickness, and right ventricular size were taken in every patient. Baseline fundamental imaging, including two parasternal (long and short axes) views, was used to evaluate baseline global and regional wall motion score indices using the 17 segment model before MCE according to the recommendations of the American and European Societies of Echocardiography.[7] For each wall segment, motion was scored as 1 (normal), 2 (hypokinetic), 3 (akinetic), and 4 (dyskinetic). LV ejection fraction (LVEF) and wall motion score index (WMSI) were obtained for all echo scans. WMSI was obtained by dividing the sum of the segment scores by the number of segments scored.

LVEF was derived using the biplane method, from orthogonal apical long-axis projections (four-chamber- and two-chamber views). All measurements were derived in blinded fashion by two experienced operators. The mean three measurements of the best-visualized cardiac cycles were calculated for each echo study.

Myocardial contrast echocardiography

Echocardiographic examinations with MCE were done before coronary angiography. Instrument setting for MCE was optimized to have maximum sensitivity and ideal conditions for visual myocardial contrast detection. The recommended dynamic range was in the medium or midrange (45–55 dB); focal zone depth was set at approximately two-thirds of the image; gain was adjusted so that myocardial tissue speckle details could be seen on the baseline images (this resulted in homogenous gray backscatter throughout the entire wall of the LV). Thereafter, all settings were kept constant during the acquisition of the images. The heart was visualized using harmonic imaging in either four- or two-chamber view.

MCE was performed using a modality of real-time perfusion imaging with low mechanical index (MI: 0,1). Optison (Amersham, Princeton, New Jersey, USA) or SonoVue (Bracco, Milan, Italy) contrast agent was administered through a peripheral vein. We used two kinds of contrast agents because Optison was temporarily withdrawn from the market during patients' enrolment. A dose of 1 mL for each echocardiographic view was followed by 10-mL saline flushed through. The criterion for MCE was defined as homogenous enhancement in 50% of wall thickness in each segment. Perfusion assessment was qualitative (two perfusion patterns: 0 and 1). Adequate myocardial perfusion was

scored when the segment showed homogenous opacification in at least one view. Lack of opacification was scored as low myocardial enhancement and regarded as myocardial perfusion defects. Perfusion assessment was performed using harmonic imaging in either four- or two-chamber apical view.

Echocardiographic images were digitally stored in a sine loop format for off-line analysis by two experienced observers. Discrepancies were resolved by consensus. Before the study started, investigators agreed that results of MCE would not influence the clinical decision about coronary angiography and revascularization.

Coronary angiography

Coronary angiography was performed by hand injection of contrast medium (low osmolarity, low viscosity) through 6F catheters after 200 μg of ICGTN, filmed at 12.5 frames/s. The procedure was done through femoral route by standard Judkins technique. Luminal stenosis more than 75% by diameter was regarded as significant (visual assessment).

Correlations between MCE and coronary angiography results are not the topic of this study. Mentioned correlations were presented by our group earlier.[5]

Statistical analysis

Descriptive statistics (percentages for discrete variables and mean ± SD for continuous variables) was done for baseline characteristics. Student's *t*-test was performed to reveal possible differences in data between groups. Chi-square test was used to analyze the differences between the group with and without perfusion defects on MCE. A p-value ≤0.05 was considered statistically significant. The statistic software NCSS 2007 was used.

RESULTS

Demographic, clinical, and laboratory parameters were compared between the groups (with and without perfusion disturbances). Overall, out of 58 patients, 27 (46.6%) of them with ESRD demonstrated perfusion defects on MCE. The patients with perfusion defects on MCE compared with those without perfusion disturbances were older (64 ± 10 vs. 54 ± 14 years; $p = 0.008$) and had lower EF (48 ± 12 vs. 59 ± 6%; $p = 0.0001$) and higher WMSI (1.3 ± 0.3 vs. 1.06 ± 0.2; $p = 0.0001$). No adverse events related to MCE administration have been observed.

Mortality

Twenty-two (37.9%) of 58 patients died during the 3-year follow-up: 5 (16.1%) from the group without perfusion defects and 17 (63.0%) from the group with perfusion defects. The difference was statistically significant ($p = 0.00018$).

Causes of death in the patients without perfusion defect on MCE were as follows: 1 – sudden cardiac death; 1 – lung cancer; 1 – pneumonia; and 2 – sepsis. Causes of death in the patients with perfusion defect on MCE were as follows: 3 – stroke; 2 – chronic heart failure; 1 – myocardial infarction; 1 – complication after coronary artery bypass grafts (CABG); 1 – sudden cardiac death; 1 – infective endocarditis; 1 – pulmonary embolism; 1 – pneumonia; 1 – sepsis; 2 – cancer; and 3 – cause of death not certain.

In univariant analysis, following features were associated with death: age, perfusion defect on MCE, LVEF, WMSI, CRP level (Table 2). Multiple linear regression analysis was performed to predict composite end point. Only perfusion disturbances (OR 1.385, CI 1.018–1.883, $p = 0.0304$) were associated with death.

Cardiovascular complications

There were eight episodes of cardiac arrest successfully resuscitated, six (22.2%) in the group with perfusion defects and two (6.5%) in the group without perfusion defects ($p = 0.078$). In univariant analysis, only diabetes mellitus (DM) was associated with cardiac arrest (OR 11.66, CI 1.119–121.6, $p = 0.035$).

Five (18.5%) episodes of myocardial infarction not followed by death were observed in the group with perfusion defects and none in the other group ($p = 0.00421$) (Figure 1). In multiple linear regression analysis, perfusion defect on MCE (OR 4.85, CI 0.99–23.74, $p = 0.045$) and elevated concentration CRP (OR 1.08, CI 1.001–1.165, $p = 0.038$) were associated with myocardial infarction.

There was also statistical difference in the incidence of hospitalizations because of cardiovascular reasons. Seventeen patients (63.0%) of 27 with perfusion defects were hospitalized whereas only 4 (12.9%) patients of 31 in the group without perfusion defects ($p = 0.00005$) (Figure 1).

Statistical difference in the incidence of stroke (three episodes of stroke in the group with perfusion defect vs. one in the other group, $p = 0.23039$) was not observed.

Only 39 patients of 58 underwent coronary angiography. Nineteen patients did not give their informed consent because of negative attitude to invasive diagnostics and treatment. Eleven (40.7%) patients of 27 from the group with perfusion defects underwent revascularization procedure, 6 (22.2%) had percutaneous

Table 2. Univariant analysis showing features associated with death.

Feature	OR	CI	p-Value
Age	1.138	1.077–1.020	0.0056
Perfusion defect on MCE	1.503	1.212–1.863	0.000146
LVEF	0.913	0.857–0.972	0.0037
WMSI	1.335	1.038–1.718	0.002133
CRP	1.0562	0.009–0.118	0.0497

Note: OR, odds ratio; CI, confidence interval; MCE, myocardial contrast agent; LVEF, left ventricular ejection fraction; WMSI, wall motion score index; CRP, C-reactive protein.

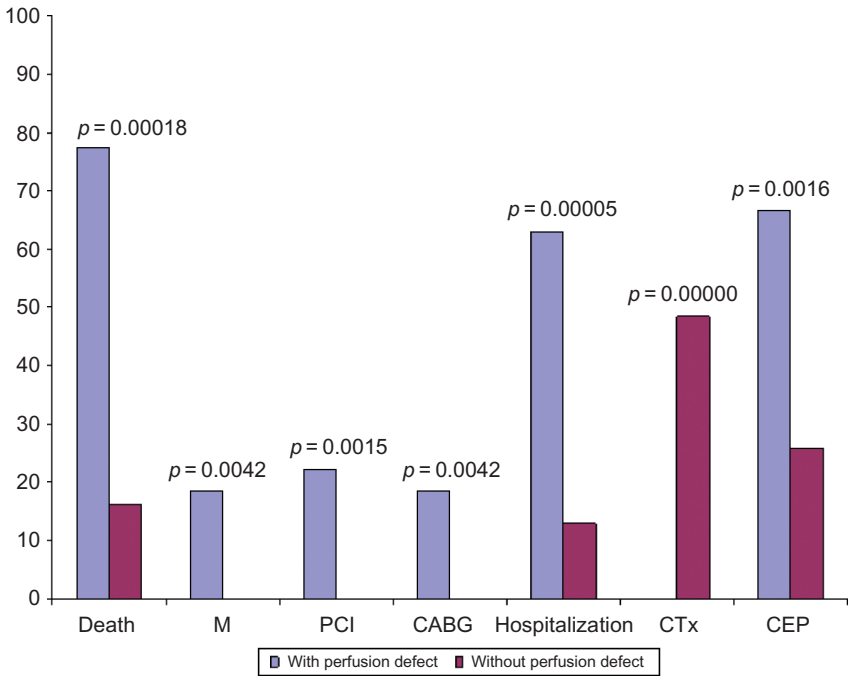

Figure 1. Comparison of the incidence of death, PCI, CABG, hospitalizations because of cardiovascular causes, CTx, and CEP between the group with perfusion defects on MCE and the group without perfusion defects on MCE.

Note: MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafts; CTx, renal transplantation; CEP, combined end point; MCE, myocardial contrast agent.

coronary intervention (PCI) and 5 (18.5%) had CABG (Figure 1). All PCIs were carried out with bare metal stent implantation. There were no cases of drug-eluting stent implantation. In every case of CABG, cardiopulmonary bypass was used.

None from the group without perfusion defects had revascularization procedure ($p = 0.0016$ and $p = 0.004$, respectively). In univariant analysis, the following features were associated with PCI: DM, LV size, interventricular septum size, LA size, and LVEF (Table 3). In multiple linear regression analysis, it turned out that only DM (OR 17.883, CI 1.020–313.519, $p = 0.043$) and LVEF (OR 0.893, CI 0.806–0.990, $p = 0.028$) were associated with percutaneous revascularization. In univariant analysis, only perfusion defect on MCE was significantly associated with CABG (OR 1.366, CI 1.012–1.843, $p = 0.036$).

Table 3. Univariant analysis showing features associated with PCI.

Feature	OR	CI	*p*-Value
DM	15.909	1.583–159.833	0.016
LV size	1.147	1.000–1.315	0.044
Interventricular septum width	0.869	1.037–3.367	0.033
LA size	1.168	1.007–1.370	0.048
LVEF	0.915	0.849–0.986	0.017

Note: OR, odds ratio; CI, confidence interval; DM, diabetes mellitus; LV, left ventricle; LA, left atrium; LVEF, left ventricular ejection fraction.

Composite end point

Composite clinical end point included cardiac death, cardiac arrest, acute myocardial infarction (AMI), myocardial revascularization, hospitalization for cardiac cause, and stroke over the 3-year follow-up. During follow-up, 26 of 58 patients (44.8%) reached composite end point (Figure 1). Eighteen (66.7%) of them demonstrated perfusion defects on MCE, whereas 8 (25.8%) had no perfusion defects (χ^2 test; $p = 0.0015$). In univariant analysis, the following features were associated with combined end point: age, perfusion defect on MCE, LVEF, WMSI, size of LA, presence of DM, and higher weight (Table 4). Multiple linear regression analysis was performed to predict composite end point. Perfusion disturbances (OR 1.37, CI 95% 1.01–1.86, $p = 0.035$), lower LVEF (OR 1.18, CI 95% 1.03–1.35,

Table 4. Univariant analysis showing features associated with combined end point.

Feature	OR	CI	*p*-Value
Age	1.06	01.01–1.12	0.017
Perfusion defect on MCE	1.64	1.24–2.18	0.00038
LVEF	1.17	1.060–1.291	0.0013
WMSI	2.22	1.35–3.67	0.0014
LA size	1.16	1.04–1.29	0.00775
DM	6.81	1.58–29.27	0.00824
Higher weight	1.21	1.02–1.43	0.0189

Note: OR, odds ratio; CI, confidence interval; DM, diabetes mellitus; LVEF, left ventricular ejection fraction; WMSI, wall motion score index; LA, left atrium; MCE, myocardial contrast agent.

$p = 0.014$), and presence of DM (OR 12.87, CI 95% 1.86–89.21, $p = 0.00796$) were associated with poor clinical outcome.

Fifteen (48.9%) patients from the group without perfusion defects underwent renal transplantation whereas none from the other group had such procedure ($p = 0$).

DISCUSSION

Increased cardiovascular mortality begins with mild kidney disease and rises further with more advanced renal failure. Various methods such as clinical status, laboratory parameters, and imaging techniques are used to evaluate cardiovascular risk in ESRD patients. We present MCE as a completely new method of risk stratification in this challenging population. According to our knowledge, we were the first to publish the preliminary results regarding the application of MCE in perfusion assessment in ESRD patients.[5,6]

MCE

Echocardiographic intravenous contrast agents (EICA) are nowadays widely used in cardiology especially after the publication of evidence-based recommendations by European Association of Echocardiography.[8] According to its recommendations, contrast echocardiography significantly improves the image quality during rest and SE (LV opacification, endocardial border delineation) and at the same time provides additional information on myocardial perfusion. Furthermore, contrast echocardiography reduces the need for additional, costly, and more hazardous invasive tests.[9]

EICA contain gas microbubbles that cross pulmonary circulation, have similar properties as blood cells, and may be assumed as blood flow tracers. In our study we used two contrast agents: SonoVue containing sulfur hexafluoride and Optison containing perfluorocarbon were encapsulated in a phospholipid and albumin shell, respectively. Such contrast agents, poorly soluble, not undergoing metabolism, remaining totally in the intravascular space, are eliminated during expiration, not eliminated by kidneys, thus not contraindicated in patients with renal failure. In the literature, the incidence of side effects is low (0.01%), which is mainly limited to allergic reactions.[8,10]

Nonrenal elimination is of great importance in patients with kidney disease; however, there is a little experience in this population. In our study group, we did not observe any adverse events related to EICA.

MCE and cardiovascular risk in population with CAD

Recently, EICA was applied for the perfusion exploration particularly after AMI.[11,12] In this setting, MCE provides additional information concerning infarct extension, no-reflow phenomenon, and tissue viability. It has demonstrated excellent correlation between perfusion abnormalities detected by MCE and Technetium-99m Sestamibi single photon emission computed tomography (SPECT).[3] Furthermore, according to Dwivedi et al.,[13] the extent of residual myocardial viability after AMI at rest was superior to nitrate-enhanced SPECT for the prediction of unfavorable cardiac events after AMI and was an important determinant of the outcome.[13–15] In our study, impaired myocardial perfusion was detected in as much as 46.6% of our patients. Compared with those with normal perfusion, patients with abnormalities on MCE were at higher risk for cardiovascular events during the 3-year follow-up time, including death, myocardial infarction, cardiac revascularizations, and hospitalizations because of cardiovascular causes. Of the clinical, biochemical, and echocardiographic markers of prognosis, perfusion defect as determined by MCE was a good predictor of cardiac death, AMI, CABG, and combined end point.

Despite the initial statement that MCE results will not influence decision-making, in our study population only the patients with perfusion defect on MCE had coronary revascularization either PCI or CABG (22.5% and 18.5% of patients with perfusion defect, respectively). Although 11 patients with perfusion defect had coronary revascularization, none of them underwent renal transplantation, whereas 15 (48.9%) of 27 from the group without perfusion defects underwent renal transplantation. In our study, after the diagnosis of CAD, especially confirmed on coronary angiography, the patients' names were withdrawn from the waiting list for renal transplantation. Even after successful revascularization, their names were never entered into the list again. Unfortunately, neither PCI nor CABG influenced the decision about renal transplantation and in this sense both types of procedures did not help the patients to benefit from transplantation.

Imaging techniques markers

In the literature, there are no data concerning applying echocardiographic contrast agents in ESRD patients; that is why our results cannot be compared with the results of other authors. Nevertheless, we try to compare the significance of the new method with other well-established clinical, laboratory, and echocardiographic markers.

Prognostic value of echocardiographic and nuclear imaging techniques in ESRD patients was largely investigated but with nonuniform results. LV systolic function indicators such as EF and fractional shortening are independently associated with the incidence of fatal and nonfatal cardiovascular events. The prediction power of LV function indicators was independent of traditional and novel risk factors in ESRD such as CRP. Additionally, myocardial contractility by echocardiography provides prognostic information independently of LV mass and other risk factors in ESRD.[9]

In our study, the patients with perfusion defects on MCE compared with those without perfusion disturbances had lower EF and higher WMSI. Both LVEF and WMSI were associated with death whereas PCI was associated not only with EF but also with LV size, LA size, and interventricular septum thickness. According to our data, LVEF, WMSI, and size of LA were associated with combined end point.

LA volume (LAV) has recently emerged as a new biomarker for risk stratification and risk monitoring in patients with ESRD.[16] In our study, a size of LA was associated only with composite end point.

Numerous investigated echocardiographic parameters are based on transthoracic echocardiography scans which quality might be poor. That is why the application of MCE in transthoracic echocardiography enhances objective information not only about LV size and function, but also about myocardial perfusion and viability at the same time.

The predictive accuracy of SE for adverse cardiac events has been variable in the population with ESRD undergoing renal transplantation. A positive SE predicts a sevenfold higher risk of cardiovascular events regardless of the need for revascularization before the transplant.[17] Nevertheless, SE is strongly dependent on the center's experience and might have doubtful value in cases with suboptimal echocardiographic views.

Both carotid intima media thickness (IMT) and aortic pulse wave velocity are also independent predictors of cardiovascular events in both the general population and among those with ESRD, but changes in IMT and large arteries stiffness did not predict cardiovascular outcomes.[18,19]

Despite the data that traditional laboratory-based outcome measures in dialysis are improving over time, population-based data indicate that mortality rates are not improving in parallel. Identifying markers that are useful in profiling cardiovascular risk and enabling stratification of early mortality is an important goal in the treatment of ESRD patients.

Perfusion defect on MCE was better in predicting end points than any other factors; for example, demographic variables (age, body weight, and presence of DM), laboratory findings (CRP), and echocardiography findings (LVEF, WMSI, LA size, LV size, and interventricular septum size). Various echocardiographic features were associated with death and composite end points but only in univariant analysis. MCE results like no other factor correlated with mortality, myocardial infarction, CABG, and composite end point at the same time in both univariant and multivariant analyses. In multivariant analysis, perfusion defect on MCE was the only factor that predicted death and CABG. In our opinion, MCE contribute much more than the standard echocardiography to the risk assessment in ESRD patients.

In this study, 19 patients did not give their informed consent for coronary angiography because of negative attitude to invasive diagnostics and treatment. Especially in such group MCE may give useful additional information and help to assess cardiovascular risk.

This is the first study assessing MCE significance in ESRD patients during long-term follow-up; that is why the decision on coronary angiography was made without taking into account perfusion defects on MCE. According to our results, we think that in ESRD patients with chest pains and perfusion defect on MCE, doctors should suggest coronary angiography more insistently.

This article examines the potential clinical role of a novel cardiovascular marker in risk stratification and selection of the patients with ESRD at highest risk of cardiovascular death. MCE might be one of the most valuable noninvasive imaging methods in cardiovascular risk stratification in patients with ESRD. Its portability, rapid acquisition and interpretation of data, and the absence of radiation exposure make it an ideal bedside technique.

STUDY LIMITATIONS

Our study has some limitations. Sample size is rather small; however, it consisted of more than 60% of our hemodialyzed population (all symptomatic patients). In addition, our study population came from a single dialysis center, belonging to the same medical University. We applied a visual assessment of the perfusion defect on MCE. During the study period, Optison was temporarily withdrawn from the marked. That is why we were obliged to switch to SonoVue contrast agent, which is nowadays widely applied in Europe. However, we assume that both contrast agents were not compared for perfusion assessment. Finally, we did not investigate asymptomatic patients.

CONCLUSIONS

In patients with ESRD, MCE appears to be a safe and useful tool for risk stratification. MCE facilitates the decision of coronary angiography.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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