Comparison of the prognostic value of dipyridamole and dobutamine myocardial perfusion scintigraphy in hemodialysis patients

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Screening for coronary artery disease (CAD) in hemodialysis patients is hampered by contraindications and/or limitations of the available techniques in this population. Myocardial perfusion scintigraphy (MPS) using dipyridamole has been considered inaccurate due to abnormally high basal levels of adenosine in uremia that could blunt the vasodilatory response. Since dobutamine may be more reliable, we directly compared the two in patients on hemodialysis. We performed MPS at rest and after separate dipyridamole or dobutamine stress in 121 chronic hemodialysis patients. More numerous, larger, and more intense reversible lesions were induced with dobutamine than with dipyridamole, mainly in the anteroseptal segments. Reversibility with dipyridamole but not dobutamine MPS was independently and strongly related with mortality associated with CAD and with fatal and non-fatal CAD. We hypothesize that the chronotropic action of dobutamine induced alterations of wall motion, leading to spurious perfusion defects, not unlike artifacts seen with left bundle branch block. Our study shows that even though dobutamine induced more pronounced myocardial ischemia than dipyridamole in chronic hemodialysis patients, dipyridamole MPS more accurately identifies patients at high risk for subsequent cardiac death or non-fatal CAD than dobutamine.

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Two recent observations rekindle the pursuit of the optimal coronary artery disease (CAD)-screening technique in chronic hemodialysis patients. First, the prevalence of asymptomatic CAD in hemodialysis patients seems to rise, commensurate with the increasing age and prevalence of diabetes in the hemodialysis population. In 1984, Rostand *et al.*[1] reported that 10% of asymptomatic dialysis patients had significant CAD, a prevalence not so different from that in the general population. In 2005, Ohtake *et al.*[2] performed a coronary angiography at the initiation of dialysis in 30 asymptomatic patients without cardiac history. Significant lesions were present in 53% of the population and in 83% of the patients with diabetes. In another report, significant CAD was present in 54% (7 of 13) of asymptomatic patients, just before initiation of dialysis.[3] Conversely, 75% of diabetic hemodialysis patients with angiographically documented CAD were asymptomatic.[4]

Second, coronary revascularization improves long-term prognosis in hemodialysis patients. In 1992, Manske *et al.*[5] had already shown that coronary revascularization, either by coronary artery bypass grafting (CABG) or by percutaneous coronary intervention (PCI), reduced cardiac morbidity and mortality in asymptomatic renal transplant candidates with diabetes and with at least one coronary artery stenosis greater than 75%, when compared with medical therapy alone. This observation was recently extended to the hemodialysis population in general. In a prospective cohort study of 259 hemodialysis patients with ischemic heart disease, the effects of PCI versus medical therapy were studied.[6] Both cardiac and all-cause death were significantly lower in the PCI group, regardless of the number of diseased vessels.

Although coronary angiography remains the gold standard, its high cost and potential adverse effects on residual renal function advocate the search for an adequate noninvasive screening test. A number of noninvasive techniques are available, but none of these has proved to be both practical and reliable in the hemodialysis population. Myocardial perfusion scintigraphy (MPS), with dipyridamole

to increase coronary flow, has been used as an alternative to exercise. Dipyridamole induces arteriolar vasodilation through inhibition of adenosine breakdown and inhibition of cellular uptake. Several studies have reported an increased relative risk for cardiac events in patients with abnormal versus those with normal test results.[7–13] Some of the studies that sought to validate dipyridamole MPS against coronary angiography, however, reported exceedingly low sensitivity.[14,15] The disappointing results have been attributed to abnormally high resting levels of adenosine in ESRD, resulting in a blunted vasodilatory response[14] or an altered vascular reactivity owing to diabetes[15,16] or left ventricular hypertrophy,[15] and the use of dipyridamole MPS has been considered to be unreliable in ESRD. Dobutamine is frequently used as an alternative pharmacological stressor, often in conjunction with echocardiography.[17] Dobutamine increases myocardial oxygen consumption by sympathetic stimulation, resulting in increased heart rate and contractility. The increased oxygen demand results in a secondary dilation of the coronary arteries. In addition, dobutamine has a minor direct vasodilatory effect on coronary vessels. In view of this mechanism of action, dobutamine MPS may be a more accurate predictor of CAD in hemodialysis patients. However, no direct comparisons with dipyridamole MPS have been reported in a hemodialysis population.

The present prospective study was therefore designed to make a head-to-head comparison of dipyridamole and dobutamine as cardiac stressors for MPS in patients on chronic hemodialysis. The ability of these two stressors to identify patients at risk for the subsequent development of a fatal or non-fatal cardiac event was studied. In addition, we assessed side effects and subjective tolerability.

RESULTS

Characteristics and tolerability of MPS

A total of 121 patients were enrolled and scheduled to undergo resting MPS, dipyridamole MPS, and dobutamine MPS. Ten patients eventually underwent no dobutamine MPS and one patient had no rest study, because of either logistic constraints or clinical problems. The quality of perfusion images was deemed insufficient in 3/120 rest MPS, 6/121 dipyridamole MPS, and 5/111 dobutamine MPS (NS). The left ventricular ejection fraction (LVEF) was judged unreliable in 5/120 rest MPS, 10/121 dipyridamole MPS, and in 8/111 dobutamine MPS (NS). As a left bundle branch block may induce false-positive septal perfusion defects in dobutamine rather than in dipyridamole MPS, we decided to exclude five patients who had a left bundle branch block at inclusion. The baseline characteristics of 102 patients who entered the final analysis are summarized in Table 1.

Heart rate and blood pressure before starting were not different for dipyridamole and dobutamine MPS (Table 2). Despite specific instructions to withdraw β-blocking agents and the use of atropine in addition to dobutamine, more than one-third of patients did not achieve the target heart rate (85% of maximum) during dobutamine infusion (Table 2). Significantly more patients developed electrocardiographic signs of ischemia and arrhythmia during the dobutamine test than during dipyridamole infusion. Dobutamine infusion was interrupted in one patient due to severe chest pain. The scoring of subjective discomfort was not significantly different between both stressors (Table 2).

Table 1 | Baseline characteristics of the study population (*N*=102)

	Mean (s.d.) or % (*n*)
Age (years)	64.3 (10.8)
Male sex (%)	59.8% (61/102)
Dialysis vintage (number of years in dialysis)[a]	0.89 (0.32–2.42)
Cardiovascular history	
Acute myocardial infarction (%)	7.8% (8/102)
Percutaneous coronary intervention (%)	8.8% (9/102)
Coronary artery bypass grafting (%)	15.7% (16/102)
Cerebrovascular disease (%)	27.4% (28/102)
Peripheral vascular disease (%)	21.6% (22/102)
History of cardiovascular disease (%)	50.0% (51/102)
History of coronary artery disease (%)	22.6% (23/102)
Cardiovascular risk factors	
Positive familial history (%)	14.8% (13/88)
Hypertension (%)	80.4% (82/102)
Hypercholesterolemia (%)	51.0% (52/102)
Diabetes (%)	32.4% (33/102)
Current smoking (%)	11.8% (12/102)
Clinical characteristics	
Body mass index (kg/m^2)	26.2 (4.4)
Predialysis systolic pressure (mm Hg)	145.8 (20.3)
Predialysis diastolic pressure (mm Hg)	77.2 (11.2)
Baseline ECG alterations	
Supraventricular arrhythmias (%)	3.9% (4/102)
Left ventricular hypertrophy	
Present (%)	66.3% (59/89)
Left ventricular mass index (g/m^2)	135.6 (48.0)

ECG, electrocardiogram.
[a]Median (interquartile range).

LVEF was significantly lower at dobutamine MPS than at dipyridamole MPS (Table 3). Although a comparable number of irreversible lesions were observed, more reversible lesions were seen during dobutamine MPS. These were also larger and/or more marked, reflecting in the summed difference and summed stress scores being significantly higher with dobutamine MPS. As a result, the subgroup of patients with both normal functional and perfusion results was significantly smaller at dobutamine compared with dipyridamole MPS.

In 43 of the 97 patients evaluated, the semi-quantitative analysis was identical for dobutamine and dipyridamole stress studies. In 18 patients, one of the stress studies was normal, whereas the other was abnormal: dipyridamole normal and dobutamine reversible defects ($n=14$), dipyridamole reversible defects and dobutamine normal ($n=3$), or dipyridamole irreversible defect and dobutamine normal ($n=1$). In the remaining 36 patients, different perfusion defects were detected in both studies: in the same vascular territories

Table 2 | Characteristics of dobutamine and dipyridamole stress testing

Mean (s.d.) or % (*n*)	Dobutamine	Dipyridamole	Significance[a]
Heart rate rest (beats/min)	76.6 (13.7)	77.8 (17.2)	*P*=0.39
Systolic blood pressure rest (mm Hg)	151.4 (30.7)	150.5 (29.2)	*P*=0.77
Diastolic blood pressure rest (mm Hg)	78.5 (16.7)	79.4 (15.6)	*P*=0.38
Heart rate peak (beats/min)	132.8 (15.7)	—	—
Systolic blood pressure peak (mm Hg)	169.6 (37.8)	—	—
Diastolic blood pressure peak (mm Hg)	75.8 (16.7)	—	—
Heart rate achieved (% maximum)	85.6 (10.3)	—	—
Heart rate achieved <85% maximum	44.3% (43/97)	—	—
Ischemia on ECG (%)	20.6% (21/102)	7.8% (8/102)	*P*=0.0008
Angina (%)	8.9% (9/101)	6.9% (7/101)	*P*=0.56
Arrhythmia (%)	28.4% (29/102)	15.7% (16/102)	*P*=0.009
Subjective score (scale 0–10)[b]	1 (0–3)	1 (0–2)	*P*=0.19

ECG, electrocardiogram.
[a]According to the Wilcoxon's signed-rank test or the McNemar's test.
[b]Median (interquartile range).

Table 3 | Characteristics of MPS

Rest			
LVEF, mean (s.d.)	54.4 (14.1)		
LVEF <45%, % (*n*)	22.2% (22/99)		
Summed rest score: mean, median (IR[a])	2.31, 1 (0–4)		
Categories, % (*n*): 0	50.5% (51/101)		
1–3	20.8% (21/101)		
⩾4	28.7% (29/101)		
Stress	**Dipyridamole**	**Dobutamine**	**P-value[b]**
LVEF, mean (s.d.)	57.6 (13.0)	53.9 (12.4)	*P*<0.0001
<45%	16.0% (15/94)	21.3% (20/94)	*P*=0.06
Global perfusion result, % (n)[c]			
N	41.8% (41/98)	31.6% (31/98)	
R	16.3% (16/98)	28.6% (28/98)	'R or I or R/I' vs 'N': *P*=0.02
I	23.5% (23/98)	19.4% (19/98)	'R or R/I' vs 'N': *P*=0.008
R/I	18.4% (18/98)	20.4% (20/98)	'I or R/I' vs 'N': *P*=0.48
Summed stress score: mean, median (IR[a])	3.88, 1 (0–5)	4.42, 2 (0–6)	*P*=0.009
Categories, % (*n*): 0	41.4% (41/99)	31.3% (31/99)	
1–3	25.2% (25/99)	26.3% (26/99)	
⩾4	33.3% (33/99)	42.4% (42/99)	
Summed difference score: mean, median (IR[a])	1.63, 0 (0–2)	2.11, 0 (0–3)	*P*=0.02
Categories, %(*n*): 0	65.3% (64/98)	51.0% (50/98)	
1–3	17.4% (17/98)	26.5% (26/98)	
⩾4	17.4% (17/98)	22.4% (22/98)	
SDS ⩾4 or LVEF <45%, % (*n*)	26.9% (25/93)	37.6% (35/93)	*P*=0.02

LVEF, left ventricular ejection fraction; SDS, summed difference score.
[a]IR=interquartile range.
[b]According to the Wilcoxon's signed-rank test or the McNemar's test.
[c]N=normal perfusion; R=presence of reversible defect; I=presence of irreversible defect; R/I=presence of both reversible and irreversible defects.

($n=29$), an additional territory with dipyridamole ($n=3$), an additional territory with dobutamine ($n=3$), or in different territories ($n=1$). Figure 1 details the distribution of reversible perfusion defects over the 17 myocardial segments. Reversible perfusion defects occurred significantly more frequent in the anteroseptal segments in the dobutamine tests.

Diagnostic accuracy

In the patients who underwent a prospectively scheduled coronary angiography independently of the results of MPS, sensitivity, specificity, and accuracy for detection of significant stenoses were 57, 59, and 58% for dipyridamole, and 57, 24% ($P=0.03$ vs dipyridamole), and 39% ($P=0.03$ vs dipyridamole) for dobutamine.

Prognostic power

Patients were prospectively followed up for 4.4 years on an average. Kidney or combined kidney–pancreas transplantation was performed in 30 and 2 patients, respectively, but the recording of end points continued uninterrupted. Forty-three

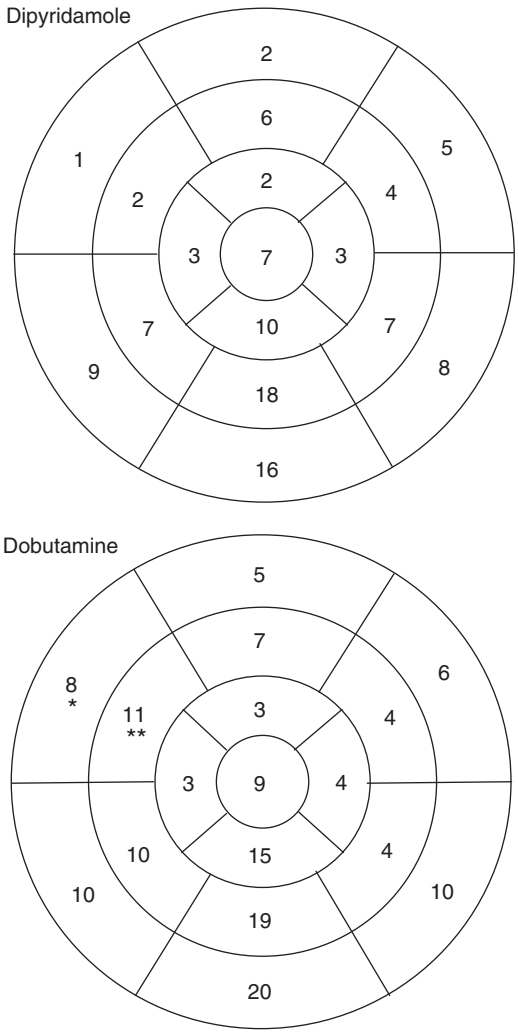

Figure 1 | Bull's eye representation of segments with reversible defects in 97 patients. *$P = 0.04$ versus dipyridamole by McNemar's test; **$P = 0.01$ versus dipyridamole by McNemar's test.

patients (42%) died during follow-up, 11 of which were due to CAD (six fatal acute myocardial infarctions and five heart failure). Sudden death occurred in four patients. In addition, 28 patients (26%) developed non-fatal CAD (three had non-fatal acute myocardial infarction, eight were hospitalized for heart failure, 25 underwent CABG, PCI, or additional medical treatment for a documented coronary stenosis, and three had non-fatal arrhythmia). This resulted in a total CAD incidence of 143 per 1000 person-years.

Low LVEF at rest ($<45\%$) was an independent predictor of total mortality, CAD mortality, and fatal and non-fatal CAD (Tables 4–6). Most functional parameters were strongly related to fatal and non-fatal CAD for dipyridamole MPS, but not for dobutamine MPS. For dipyridamole MPS, the hazard ratios for CAD death associated with a high ($\geqslant 4$) summed stress score (SSS) and summed difference score (SDS) were 5.48 and 7.16, respectively. For both dobutamine and dipyridamole MPS, the presence of an irreversible defect in the absence of a reversible defect was not predictive of future events, even when only large defects were considered (SRS $\geqslant 4$).

The better distinction by dipyridamole MPS than by dobutamine MPS of patients at high versus low risk is graphically illustrated in the Kaplan–Meier curves (Figure 2 for CAD mortality and Figure 3 for all CAD-related events). Patients with pronounced ischemia on dipyridamole MPS (SDS $\geqslant 4$) have a shorter time course to a fatal CAD event (Figure 2a) and a shorter survival free of CAD-related events (Figure 3a) than those without pronounced ischemia on dipyridamole MPS. In contrast, patients with a comparable degree of ischemia on dobutamine MPS (SDS $\geqslant 4$) do not seem to fare worse than those without such ischemia on dobutamine MPS (Figures 2b and 3b).

The 2-year CAD-free survival in patients with normal-stress MPS, defined as MPS not showing reversibility and an LVEF of at least 45%, was 84.6% for dipyridamole and 85.6% for dobutamine.

An additional analysis was performed to evaluate a potential confounding effect of left ventricular hypertrophy on the occurrence of reversible lesions during MPS. When differential ischemia between dobutamine and dipyridamole MPS, as measured by the difference of the corresponding SDS, was compared in three tertiles of the left ventricular mass index, no trend of an increased difference between dobutamine and dipyridamole MPS for a higher left ventricular mass was observed.

The relative likelihood of undergoing PCI or CABG within 2 months after MPS in the group with SDS $\geqslant 4$ versus that with SDS <4 was 4.34 (1.66–11.31) for dipyridamole and 2.06 (0.74–5.70) for dobutamine.

DISCUSSION

This study was designed to determine whether either dobutamine or dipyridamole is the optimal cardiac stressor in a hemodialysis population, with respect to tolerability and prognostic power.

Both dobutamine and dipyridamole have been reported to be generally well tolerated in a hemodialysis population,[18,19] but no direct comparisons are available. The chronotropic incompetence that contributes to submaximal exercise testing in hemodialysis patients was also evident during dobutamine testing. More than one-third of patients failed to achieve the target heart rate (85% of maximum) during dobutamine infusion, which is in agreement with previous reports.[20] Nevertheless, more patients developed ischemic changes on ECG or experienced arrhythmias during dobutamine infusion than during dipyridamole stress. Dobutamine stress also induced more, larger, and more intense reversible perfusion defects than did dipyridamole infusion. Despite these differences, subjective tolerance was similar for both pharmacological agents. This may be in keeping with the high prevalence of asymptomatic CAD in current hemodialysis populations.

The diagnostic accuracy of both stressors was studied in a subset of patients in whom coronary angiography was

Table 4 | Prognostic value of functional and perfusion parameters: total mortality

	Rest					
	HR (95% CI)[a]	χ^2	P			
LVEF <45%	3.35 (1.74–6.48)	12.98	P=0.0003			
SRS: 1–3 vs 0	1.57 (0.60–4.08)	0.85	P=0.36			
SRS: ⩾4 vs 0	2.00 (0.77–5.20)	2.01	P=0.16			
	Dipyridamole			Dobutamine		
	HR (95% CI)[a]	χ^2	P	HR (95% CI)[a]	χ^2	P
LVEF <45%	2.07 (0.88–4.89)	2.78	P=0.10	1.81 (0.81–4.04)	2.08	P=0.15
R or I or R/I vs N[b]	1.67 (0.82–3.41)	1.99	P=0.16	0.85 (0.40–1.80)	0.18	P=0.68
R vs N	1.99 (0.86–4.60)	2.61	P=0.11	0.39 (0.14–1.08)	3.27	P=0.07
I vs N	1.25 (0.40–3.94)	0.15	P=0.70	0.69 (0.22–2.16)	0.41	P=0.52
SSS: 1–3 vs 0	1.40 (0.61–3.20)	0.62	P=0.43	0.71 (0.29–1.75)	0.55	P=0.46
SSS: ⩾4 vs 0	2.08 (0.86–5.01)	2.67	P=0.10	1.00 (0.42–2.35)	0.01	P=0.99
SDS: 1–3 vs 0	1.16 (0.47–2.89)	0.11	P=0.74	0.52 (0.22–1.26)	2.09	P=0.15
SDS: ⩾4 vs 0	2.20 (0.99–4.89)	3.71	P=0.06	1.03 (0.48–2.23)	0.01	P=0.94
SDS 4 or LVEF <45%	2.00 (0.98–4.10)	3.60	P=0.06	1.65 (0.87–3.16)	2.32	P=0.13

CAD, coronary artery disease; LVEF, left ventricular ejection fraction; SDS, summed difference score; SRS, summed rest score; SSS, summed stress score.
[a]Hazard ratios (95% CI) adjusted for age, sex, history of CAD, diabetes, hypertension and center (Cox proportional hazards regression analysis).
[b]N=normal perfusion; R=presence of reversible defect; I=presence of irreversible defect; R/I=presence of both reversible and irreversible defects.

Table 5 | Prognostic value of functional and perfusion parameters: CAD mortality

	Rest					
	HR (95% CI)[a]	χ^2	P-value			
LVEF <45%	7.13 (2.02–25.15)	9.32	P=0.002			
SRS: 1–3 vs 0	3.02 (0.44–20.86)	1.26	P=0.26			
SRS: ⩾4 vs 0	7.93 (1.04–60.50)	3.99	P=0.04			
	Dipyridamole			Dobutamine		
	HR (95% CI)[a]	χ^2	P-value	HR (95% CI)[a]	χ^2	P-value
LVEF <45%	3.50 (0.94–13.05)	3.47	P=0.06	3.10 (0.87–11.07)	3.02	P=0.08
R or I or R/I vs N[b]	3.28 (0.81–13.23)	2.78	P=0.10	2.25 (0.54–9.32)	1.25	P=0.26
R vs N	14.68 (1.87–115.30)	6.52	P=0.01	1.65 (0.23–11.61)	0.25	P=0.62
I vs N	0.74 (0.02–25.39)	0.03	P=0.87	2.51 (0.13–48.88)	0.37	P=0.54
SSS: 1–3 vs 0	1.77 (0.29–10.96)	0.38	P=0.54	1.92 (0.37–9.98)	0.60	P=0.44
SSS: ⩾4 vs 0	5.48 (1.12–26.85)	4.40	P=0.04	2.67 (0.52–13.63)	1.39	P=0.24
SDS: 1–3 vs 0	1.12 (0.12–10.52)	0.01	P=0.92	1.38 (0.29–6.52)	0.17	P=0.68
SDS: ⩾4 vs 0	7.16 (1.80–28.55)	7.78	P=0.005	1.64 (0.38–7.17)	0.44	P=0.51
SDS ⩾4 or LVEF <45%	5.20 (1.37–19.75)	5.87	P=0.02	2.43 (0.73–8.12)	2.08	P=0.04

CAD, coronary artery disease; LVEF, left ventricular ejection fraction; SDS, summed difference score; SRS, summed rest score; SSS, summed stress score.
[a]Hazard ratios (95% CI) adjusted for age, sex, history of CAD, diabetes, hypertension and center (Cox proportional hazards regression analysis).
[b]N=normal perfusion; R=presence of reversible defect; I=presence of irreversible defect; R/I=presence of both reversible and irreversible defects.

performed subsequent to the MPS studies. To avoid selection bias, only those patients who were designated to undergo coronary angiography independently of the result of MPS were included in the analysis. Although sensitivity was similar, specificity was markedly lower for dobutamine than for dipyridamole. Multiple factors intervene between stenosis of the epicardial coronary arteries, as visualized on coronary angiography, and diminished blood flow, as visualized on MPS. These include the functional severity of stenosis, the presence of a collateral circulation, as well as the status of the distal vascular bed and the microcirculation. Coronary angiography may therefore not be the best standard to assess MPS. The ability to predict CAD-related events may be a more relevant criterion to judge non-invasive tests.

The novel observation of this study is that myocardial perfusion defects revealed by dipyridamole stress are stronger multivariate predictors of fatal and non-fatal CAD in chronic hemodialysis patients than defects induced by dobutamine infusion. Reversible defects on dobutamine MPS, although being more numerous and more marked, do not convey a significant risk for future events. In agreement with previous studies of dipyridamole MPS,[12,21] we found that only reversible and not fixed defects independently predict fatal and non-fatal CAD. Using stepwise logistic regression analysis, Brown *et al.*[8] found that only irreversible defects

Table 6 | Prognostic value of functional and perfusion parameters: CAD

	Rest		
	HR (95% CI)[a]	χ^2	*P*-value
LVEF <45%	2.03 (0.97–4.25)	3.54	*P*=0.06
SRS: 1–3 vs 0	0.91 (0.31–2.68)	0.03	*P*=0.86
SRS: ⩾4 vs 0	3.14 (1.21–8.13)	5.56	*P*=0.02

	Dipyridamole			Dobutamine		
	HR (95% CI)[a]	χ^2	*P*-value	HR (95% CI)[a]	χ^2	*P*-value
LVEF <45%	1.96 (0.84–4.62)	2.40	*P*=0.12	2.20 (1.02–4.70)	4.09	*P*=0.04
R or I or R/I vs N[b]	2.14 (1.02–4.51)	4.01	*P*=0.04	1.48 (0.67–3.28)	0.94	*P*=0.33
R vs N	3.16 (1.20–8.36)	5.41	*P*=0.02	1.19 (0.43–3.26)	0.11	*P*=0.74
I vs N	1.27 (0.35–4.60)	0.13	*P*=0.72	1.12 (0.24–5.12)	0.02	*P*=0.88
SSS: 1–3 vs 0	1.21 (0.46–3.16)	0.15	*P*=0.70	1.10 (0.41–2.94)	0.04	*P*=0.84
SSS: ⩾4 vs 0	2.90 (1.25–6.75)	6.11	*P*=0.01	1.82 (0.74–4.48)	1.71	*P*=0.19
SDS: 1–3 vs 0	1.08 (0.40–2.94)	0.02	*P*=0.88	1.94 (0.88–4.26)	2.74	*P*=0.10
SDS: ⩾4 vs 0	3.66 (1.69–7.91)	10.86	*P*=0.001	1.57 (0.63–3.89)	0.95	*P*=0.33
SDS ⩾4 or LVEF <45%	2.60 (1.25–5.41)	6.54	*P*=0.01	2.08 (1.02–4.22)	4.10	*P*=0.04

CAD, coronary artery disease; LVEF, left ventricular ejection fraction; SDS, summed difference score; SRS, summed rest scores; SSS, summed stress score.
[a]Hazard ratios (95% CI) adjusted for age, sex, history of CAD, diabetes, hypertension, and center (Cox proportional hazards regression analysis).
[b]N=normal perfusion; R=presence of reversible defect; I=presence of irreversible defect; R/I=presence of both reversible and irreversible defects.

on thallium MPS and left ventricular dysfunction on radionuclide ventriculography were independent predictors. In contrast, other authors reported that both reversible and fixed defects were prognostic of cardiac events.[22,23]

We can only speculate with regard to the causes of the better predictive ability of dipyridamole versus that of dobutamine. It remains to be seen whether it would hold when echocardiography, instead of MPS, would be used with one or both of the stressors. In this respect, it should be emphasized that the detection of ischemia by echocardiography relies on the induction of wall motion abnormalities, whereas MPS measures myocardial perfusion in a more direct way. It is known that the presence of a left bundle branch block may be associated with false-positive septal perfusion defects with dobutamine rather than with dipyridamole MPS. A large proportion of patients with left bundle branch block may thus skew the results to the disadvantage of dobutamine. We therefore have excluded five patients with a left bundle branch block from the final analysis to eliminate this possibility. We suspect that the chronotropic action of high-dose dobutamine, albeit somewhat blunted in the dialysis population, may induce alterations of wall motion that may lead to spurious perfusion defects, similar to the artifacts seen with left bundle branch block. An argument in favor of this hypothesis is that the higher number of reversible defects with dobutamine in our study can be largely attributed to the anteroseptal wall, similar to the left bundle branch block artifacts. Our data do not support the hypothesis that left ventricular hypertrophy is a major determinant of the enhanced ischemia seen with dobutamine versus dipyridamole, because we did not observe an increased difference between dobutamine and dipyridamole MPS in those patients with the highest left ventricular mass. Finally, it should be emphasized that we used a higher dose of dipyridamole than in all previous studies of dipyridamole MPS in ESRD. It is unclear whether this may have influenced the results substantially.

Dipyridamole MPS provides information incremental to clinical data and accurately identifies patients at increased odds for fatal and non-fatal CAD-related events, who therefore need more aggressive treatment. Conversely, an optimal risk stratification discriminates patients who do not require further intervention. A normal dipyridamole MPS was associated with a 2-year CAD-free survival of 85%. Re-testing of patients with normal studies every 2–3 years thus seems to be a reasonable strategy. However, the risk for CAD-related events despite a normal MPS remains much higher in patients with ESRD than that in the general population. ESRD is a powerful modifier of the prognostic value of a normal MPS.[24] Clinical suspicion should therefore continue to be high.

A limitation of the study is that clinicians were not blinded to the results of MPS that was performed as part of the study, because this was considered unethical. They were free to use the information gained to define the therapeutic strategy deemed optimal. A positive MPS may have led to a coronary angiography and a subsequent revascularization procedure, and may therefore have introduced a detection bias. We have partly corrected for this bias by censoring events occurring within 2 months of MPS. It has been demonstrated that coronary revascularization reduces the risk of coronary events in chronic hemodialysis patients.[5,6] The execution of an MPS may thus have decreased the risk at further events. Therefore, all relative risks obtained should be regarded as conservative estimates. It could be argued that the larger number of reversible lesions revealed by dobutamine led to a higher number of revascularization procedures, with a subsequent protection of these patients from further events. This mechanism would then falsely make dobutamine seem less predictive of CAD. However, the relative likelihood of undergoing a PCI or CABG within 2 months of MPS in

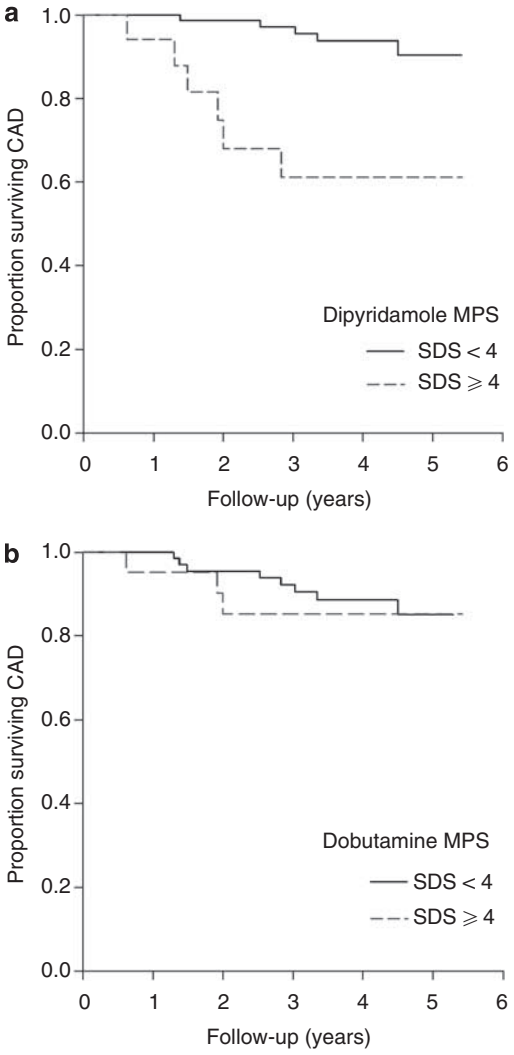

Figure 2 | Kaplan–Meier survival curves for patients who had a summed difference score <4 (solid line) or ⩾4 (dashed line) at myocardial perfusion scintigraphy, with dipyridamole (a) or dobutamine (b). CAD, coronary artery disease.

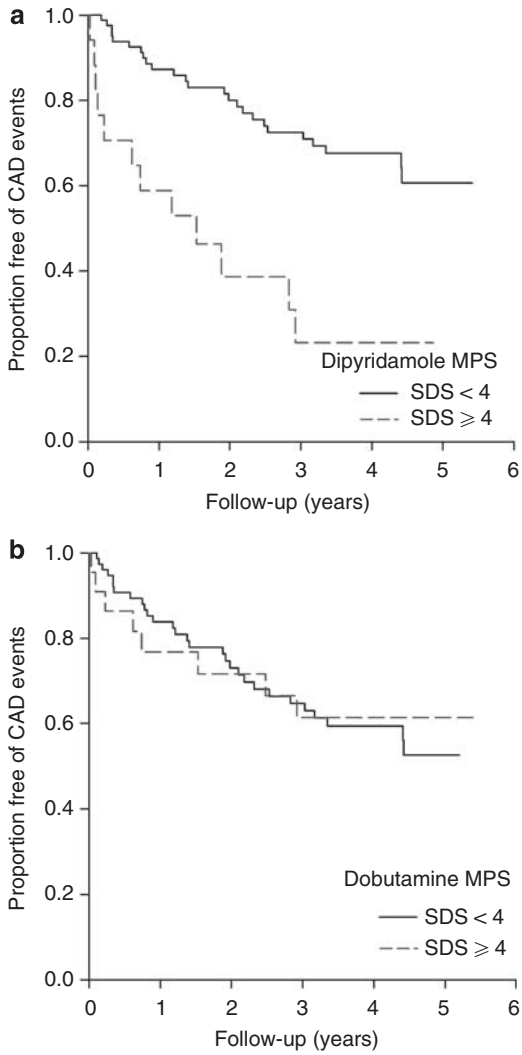

Figure 3 | Kaplan–Meier curves for freedom from fatal or non-fatal CAD events in patients who had a summed difference score <4 (solid line) or ⩾4 (dashed line) at myocardial perfusion scintigraphy, with dipyridamole (a) or dobutamine (b). CAD, coronary artery disease.

patients with SDS ⩾4 versus those with SDS <4 actually tended to be higher with dipyridamole than with dobutamine, which excludes this possibility.

In conclusion, we found that in hemodialysis patients, a high-dose dipyridamole MPS is a better predictor for future CAD-related events than is dobutamine MPS. Dipyridamole should be the preferred cardiac stressor in the noninvasive screening of ESRD patients for CAD.

METHODS

Study population

The study was conducted at two tertiary care hospitals in the Belgian cities of Bruges and Ghent. All patients aged more than 18 years and in chronic hemodialysis for more than 1 month were eligible, except those with recent (<3 months) myocardial infarction or revascularization. Exclusion criteria were pregnancy, breastfeeding, and contraindications to dipyridamole (unstable angina, severe chronic obstructive pulmonary disease or asthma, treatment with methylxanthines, predialysis systolic blood pressure below 90 mm Hg) or dobutamine (unstable angina, severe aortic stenosis, hypertrophic obstructive cardiomyopathy, atrial tachyarrhythmia with uncontrolled ventricular response, ventricular tachycardia, predialysis blood pressure of more than 200/100 mm Hg, aortic dissection and large aortic aneurysm) administration. All patients who fulfilled the inclusion and exclusion criteria and provided informed consent were included. At inclusion, a full medical history, including risk factors for coronary artery disease, was recorded. Positive familial history was defined as a first-degree relative with premature cardiovascular disease.

Physical examination was performed and a blood sample was taken for risk factor determination. Hypertension was defined as ⩾140 mm Hg systolic and/or ⩾90 mm Hg diastolic pressure on more than one occasion and/or antihypertensive drug treatment. Diabetes mellitus was diagnosed according to the World Health Organization criteria. Hypercholesterolemia was defined as plasma total cholesterol >190 mg/100 ml and/or treatment with cholesterol-lowering drugs. An ECG and a chest X-ray were performed.

A two-dimensionally guided M-mode echocardiographic study was carried out in resting conditions for atrial and left ventricular measurements, including interventricular septal thickness at end-diastole ($IVST_d$), left ventricular internal dimension at end-diastole ($LVID_d$), and posterior wall thickness at end-diastole (PWT_d). Measurements were made in accordance with the recommendations of the American Society of Echocardiography. Left ventricular mass (g) was calculated using the formula $0.80 \times [1.04 \times (IVST_d + LVST_d + PWT_d)^3 - LVID_d^3] + 0.6$ g. Left ventricular mass index was derived by dividing the left ventricular mass by body surface area. Left ventricular mass index >116 g/m^2 in men and >104 g/m^2 in women was the criterion for left ventricular hypertrophy. The study protocol was approved by the Institutional Review Board at both institutions involved. All patients gave written informed consent.

Myocardial perfusion scintigraphy

Patients were scheduled to undergo three MPS on separate days, but within a 3-week period: at rest, after dipyridamole infusion, and after dobutamine infusion. The order of the tests was determined by logistic considerations. β-blockers were withdrawn 24 h before MPS. Phylline-containing drugs, beverages or foods were prohibited 24 h before dipyridamole MPS. Patients were fasting for at least 4 h. MPS was always performed on a midweek dialysis day, after the dialysis session.

Dobutamine was infused at a dose of 10 μg/kg per min, with 10 μg/kg per min increments at 3 min intervals, up to a maximal rate of 40 μg/kg per min. Atropine (4×0.25 mg at 1 min intervals) was allowed to achieve the target heart rate. ^{99m}Tc-Sestamibi was administered at a dose of 925 MBq when at least 85% of the predicted maximal heart rate (220–patient's age) was achieved. Dobutamine infusion was continued for 2 min after administration of the perfusion tracer. Dipyridamole was infused at a dose of 0.84 mg/kg over 6 min. ^{99m}Tc-Sestamibi was administered at a dose of 925 MBq 2 upto 5 min after completion of the dipyridamole infusion.

After MPS, patients were asked to score subjective discomfort caused by dipyridamole or dobutamine on a visual analog scale (0–10).

Acquisition was started at least one-half hour after tracer administration for stress studies and 45 min for rest studies. Imaging was performed using a three-headed γ camera (Multispect3, Siemens, Erlangen, Germany at Bruges; Prism3000, Marconi, Picker, Cleveland, Ohio at Ghent) fitted with low energy collimators. The patients were in supine position, if possible with the arms out of the field of view. Images were acquired from 96 (Bruges) to 120 (Ghent) detector positions over a 360-degree noncircular contour. The dwell time on each position was 40 to 20 s, respectively. The energy window was 15%, centered around 141 keV. The matrix size was 64×64, with the original pixel size being 7.12 mm on the Siemens Multispect and 5.01 mm on the Picker Prism; a zoom factor of 1.23 was used on the Siemens system to obtain a pixel size of 5.79 mm. Gated images were acquired into eight time bins. The gating window center was set manually.

Images were reconstructed using a Butterworth filter (cutoff 0.35 cycles/cm, order 5). The volume was reoriented along the long axis. This was carried out by one observer (PF) for the three imaging sets together, in order to align the datasets as good as possible. The perfusion images as well as the functional parameters derived from the gated study were judged as adequate or inadequate. Stress/rest couples were presented to the readers in a random order so as to blind the readers to the result of the other stress study for the same patient and to the nature of the stressor used in a particular study. Three experienced nuclear physicians, also blinded to the clinical data, scored myocardial perfusion on the ungated image sets, by consensus and using a 17-segment ventricular model and a semi-quantitative scoring system from 0 to 4: 0 = normal tracer accumulation, 1 = mild defect, 2 = moderate defect, 3 = severe defect, 4 = absent perfusion. Stress myocardial perfusion scintigraphies were categorized as 'normal' when all segments were scored as 0, as 'reversible' if any segmental score of 1 or higher at stress decreased at the rest study, or as 'irreversible' if none of the abnormal segmental scores at stress decreased at the rest study. The use of gated images was limited to the differentiation between attenuation defects and fixed real perfusion defects. Summed stress scores, summed rest scores (SRS), and reversibility scores (summed difference scores, SDS) were calculated as the sums of all segmental scores in each of the myocardial segments. LVEF was calculated using Quantitative Gated SPECT software version 4.0, commercially obtained from the camera vendors.

Coronary angiography

Patients with stable angina and patients evaluated for kidney transplantation ($n = 35$) were prospectively designated to undergo coronary angiography, independently from the result of MPS. Coronary angiography and left ventriculography were performed using a standard approach with six French catheters. Ventriculography was performed in the 30° right anterior oblique and 60° left anterior oblique views. Coronary arteries were selectively injected in multiple views. End-diastolic cine frames were selected for optimal stenosis visualization. Stenoses were evaluated in two orthogonal views. A normal arterial segment was identified immediately proximal and distal to the lesion and measured with an electronic caliper. The minimal stenosis diameter was also measured and severity was expressed as percent reduction of the normal diameter. Significant CAD was considered present in the case of a reduction of 70% or more in the luminal diameter of at least one major epicardial vessel or 50% or more in the left main coronary. Coronary angiography was performed on an average of 46 days (s.d. 31 days, median 37 days) after inclusion. Two patients were excluded from the analysis because of intercurrent clinical problems in the interval between coronary angiography and MPS. Two additional patients were excluded owing to the presence of a left bundle branch block on the baseline ECG. For the comparison of MPS results with those of coronary angiography, MPS was considered abnormal when any reversible or irreversible defect was detected.

Patient follow-up

After enrollment, patients were followed up 3-monthly, on the basis of medical history, physical examination, and blood tests. Six-monthly ECGs and chest X-rays were taken and echocardiography was repeated every year. End points were recorded at each visit.

Fatal end points were all-cause mortality and CAD mortality. CAD mortality included death due to cardiac arrhythmia, congestive heart failure, or myocardial infarction. Sudden death was recorded separately and not included in the analysis of CAD mortality, to avoid confounding by cardiac arrest due to hyperkalemia in the absence of structural heart disease. Non-fatal CAD included the following:

- Non-fatal acute myocardial infarction, documented by at least two of the following: a clinical history suggesting acute

myocardial infarction, ECG changes suggestive of myocardial infarction, and a significant rise of myocardial enzymes (according to WHO criteria issued in 1995).

- New or increasing angina (new-onset exertional angina, accelerated or rest angina, or both) requiring upgrading of medical therapy, treatment by PCI or CABG.
- Angiographic findings of one or more epicardial vessel stenosis of at least 70% or of at least 50% in the left main coronary, which were treated by PCI or CABG. If a coronary arteriography had been performed before enrollment, only new lesions were taken into account.
- Hospitalization for congestive heart failure, defined as the presence of symptoms or signs of left or right heart failure such as auscultatory rales or peripheral edema, in the presence of documented ventricular dysfunction. Fluid overload due to inadequate adjustment of dry weight was not considered to be an end point.
- New-onset ventricular or supraventricular arrhythmias resulting in hemodynamic compromise.

The physicians of the dialysis units were not blinded to the results of MPS. To avoid confounding introduced by the performance of coronary angiography after MPS, non-fatal end points occurring within 2 months of enrollment were censored from the analysis.

Statistical analysis

The distributions of study variables were characterized according to means, s.d., medians, interquartile ranges, and proportions. Differences in the characteristics of dipyridamole MPS and dobutamine MPS were evaluated using Wilcoxon's signed rank test for quantitative variables or McNemar's test for dichotomous variables. Differences in differential ischemia of dobutamine versus dipyridamole MPS, according to the degree of left ventricular hypertrophy, were assessed using the Kruskal–Wallis test. The estimation of CAD-free survival in patients with normal dipyridamole MPS was carried out according to the Kaplan–Meier method.[25] Hazard ratios and their 95% confidence intervals were estimated according to Cox proportional hazard modeling, with age, sex, history of CAD, diabetes, hypertension, and recruitment center as covariates.[25] The model assumption of proportionality of hazards was checked by plotting log $[-\log(S(t))]$ against time, where $S(t)$ represents the Kaplan–Meier survival estimate.[25] *P*-values were obtained through Wald χ^2 statistics. All statistical analyses were performed using SAS software (The SAS system, Release 9.1.3, Cary, NC, USA: SAS Institute Inc.).

DISCLOSURE

All the authors declared no competing interests.

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