Effect of Hemodialysis on Traditional and Innovative Cardiac Markers

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The diagnostic approach to acute coronary syndrome (ACS) is challenging in patients with impaired renal function since most serum biomarkers are commonly increased in this clinical setting. Cardiac troponin T (cTnT), creatine kinase isoenzyme MB (CK-MB), myoglobin, and ischemia modified albumin (IMA), were assayed in 45 patients prehemodialysis (pre-HD) and posthemodialysis (post-HD), and results were adjusted for hemoconcentration. The pre-HD values of serum IMA and cTnT were above the respective diagnostic thresholds (IMA < 85 K units/L; cTnT < 0.03 ng/mL) in six (13%) and 27 (60%) patients undergoing chronic HD, respectively. A significant (105.0 vs. 79.0 K units/L, $P < 0.0001$) and variable (+38%; 95% confidence inter-

val [CI], 12–65%) increase of serum IMA was observed post-HD, whereas the other biomarkers significantly decreased (cTnT: 0.029 vs. 0.044 ng/mL, $P = 0.016$; CK-MB: 2.33 vs. 2.50 μ g/L, $P < 0.0001$; myoglobin: 128.1 vs. 148.7 μ g/L, $P < 0.0001$). Biomarkers of myocardial injury, especially cTnT and IMA, might be used in HD patients, provided that an appropriate diagnostic interpretation is guarantee, according to individual baseline value, metabolism, and time of sampling. Moreover, IMA might be reliably applied to stratify the long-term risk of these patients, but not for diagnosing an ACS during or immediately post-HD. J. Clin. Lab. Anal. 22:59–65, 2008.

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INTRODUCTION

Coronary artery disease (CAD) is commonplace in subjects with impaired renal function and cardiovascular disease (CVD) represents the leading cause of mortality in these patients (1). On overall, the cardiovascular mortality appears much higher in hemodialysis (HD) patients than in the general population (2,3), accounting for 50% of deaths (4).

Traditional biomarkers of myocardial necrosis, such as creatine kinase isoenzyme MB (CK-MB) and myoglobin are commonly increased in patients with chronic renal failure, even in the absence of clinically suspected myocardial ischemia (5,6). Moreover, cardiac biomarkers are more likely to be elevated in HD patients

than in those with renal failure not on dialysis and their value should hence be interpreted with caution (7). Although cardiac troponin T (cTnT) is a sensitive and specific marker of myocardial injury in the general population (8), this is less ascertained in patients undergoing chronic HD, who have frequently elevated baseline values of cTnT without any evidence of acute

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myocardial injury (9). Although controversy remains on the clinical usefulness of measuring troponins for the diagnosis of acute ischemic cardiac events in these subjects (10), the levels of both cardiac troponin I (cTnI) and cTnT are inversely related to renal function predialysis (11) and several clinical investigations have demonstrated that cTnT is an independent predictor of mortality in end-stage renal disease (ESRD) patients starting dialysis (12–14).

The causes of increased troponins in HD patients have not been fully elucidated. Some explanations that have been provided include accumulation of immunoreactive fragments of cardiac troponins due to reduced renal clearance (15,16) or continuous cardiac release from limited areas of clinically silent myocardial necrosis (17). Other possible hypotheses are the reexpression of cTnT isoforms in the skeletal muscle fibers during uremic-induced skeletal myopathy (18), the increase of left ventricular mass index (LVMI) (19), the loss of membrane integrity, constant outflow from the free cytosolic troponin pool (20), and uremic damage on myocardial cells (21). An additional drawback in the diagnostic use of traditional biomarkers of myocardial necrosis is the influence of the dialysis process itself on metabolism of cTnT, CK-MB, and myoglobin (22). The concentration of CK-MB and myoglobin is correlated with the creatinine clearance (23) and it is therefore difficult to interpret potential elevations of these markers in patients with impaired renal function.

The ischemia modified albumin (IMA) is increasingly regarded as a sensitive and early biochemical marker of ischemia (24–26). It has recently been suggested that IMA might be increased in patients with ESRD and its concentration would predict the prognosis of these patients (27). Nevertheless, previous studies were focalized on assessing baseline IMA levels and, to the best of our knowledge, no information is available on the influence of HD on this promising laboratory marker. Therefore, the aim of our study was to evaluate the effect of dialysis on IMA and to compare its metabolism during HD with that of the traditional biomarkers of cardiac ischemia.

MATERIALS AND METHODS

Patient Population

A total of 45 HD patients, 21 males and 24 females, mean age 65 ± 17 years, were recruited from the dialysis unit of the University Hospital of Verona. All were outpatients and free of acute illness. Only patients with at least a 6-month duration of stable maintenance HD treatment were included in the study. None of the patients had overt inflammatory disease within the past 2 months or showed evidence of cancer, liver abnor-

malities, or hypothyroidism. Out of the 45 patients, eight had diabetes mellitus (18%), 31 hypertension (69%), 14 peripheral artery occlusive disease (PAOD) (31%), 10 ischemic cerebral disease (22%), and 13 ischemic heart disease (IHD) (29%). Patients were considered to have diabetes if they had a fasting plasma glucose above 126 mg/dL (7.0 mmol/L) or were treated with insulin or an oral antidiabetic agent (28). Hypertension was defined as current systolic or diastolic blood pressure $\geq 140/90$ mmHg or current treatment with antihypertensive drugs (29). Diagnosis of PAOD was confirmed or excluded by clinic evaluation and Doppler ultrasound measurement of the ankle-arm index, i.e., the ratio of ankle to arm systolic blood pressure, performed according to a standard protocol by trained physicians (30). Patients were considered to have had previous ischemic cerebral disease when they had either a history of transitory ischemic attack (TIA) or ictus. Patients were considered to have previous IHD if they had history of myocardial infarction, coronary revascularization, or more than 70% stenosis and/or occlusion of at least one coronary artery if a coronary angiogram was performed before sampling.

Patients received no other medications except vitamins, phosphate binders, and calcitriol. In hypertensive HD patients, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers, or combined therapy were given; all patients were on erythropoietin treatment. The patients had HD for 3.5–4 hr three times a week using unfractionated heparin for anticoagulation. Each patient gave an explicit and written informed consent for being enrolled in this study. All patients were followed up for 1 year. Reference ranges for innovative and traditional biomarkers of myocardial injury and ischemia were also assessed on 65 healthy controls volunteers, matched for sex and age.

Laboratory Methods

Blood samples were drawn immediately before (pre-HD) after an overnight fast, and 5 min after the end of the HD session (post-HD) by antecubital venipuncture. Blood was collected directly into siliconized vacuum tubes containing no additives (Becton-Dickinson, Oxford, UK).

Blood was centrifuged at 1,500 g for 10 min at room temperature, serum was separated, stored in aliquots, and kept frozen at -70°C until measurement. IMA was determined by a colorimetric assay (31) (Ischemia Technologies, Denver, CO) on the Modular System P (Roche Diagnostics GmbH, Mannheim, Germany). The following formula was applied to correct IMA values for serum albumin: [(individual serum albumin concen-

tration/median albumin concentration of the population)* IMA value] (32). Age- and sex-adjusted diagnostic threshold is <85 K units/L, as recommended by the manufacturer. Serum albumin and creatinine were measured on the Modular System P, using proprietary reagents (Roche Diagnostics GmbH), whereas cTnT, CK-MB, and myoglobin were assayed on an Elecsys 2010 platform (Roche Diagnostics GmbH). Although the detection limit for cTnT is 0.01 ng/mL, the recommended diagnostic threshold for myocardial injury is >0.03 ng/mL, which corresponds to the lowest TnT concentration associated with a 10% total imprecision in the assay (33). Threshold retained for CK-MB was 6 µg/L. Total imprecision, as expressed by the coefficient of variation, was comprised between 3 and 6% for creatinine and albumin, lower than 3% for CK-MB and myoglobin, and lower than 10% for cTnT and IMA, as quoted by the manufacturers. The post-HD values of cTnT, myoglobin and CK-MB were

adjusted for hemoconcentration due to ultrafiltration during dialysis using the formula: adjusted postdialysis value of marker = unadjusted postdialysis of marker * (predialysis albumin/postdialysis albumin).

Results of measurements and relative distributions of values were compared by Mann-Whitney U test. Pre- and post-HD measurements were compared using the Wilcoxon matched-pairs test and data are reported as medians and 95% confidence intervals (CIs). The level of statistical significance was always established at $P < 0.05$.

RESULTS

The baseline characteristics of the patient population pre-HD are presented in Table 1. Out of the 45 patients tested, 27 (60%) and six (13%) had cTnT and IMA values above the relative diagnostic thresholds, respectively. The number of patients with values above the relative diagnostic thresholds post-HD was substantially comparable for cTnT (22, 49%), though all the patients (45, 100%) displayed values of IMA exceeding the recommended diagnostic cutoff for myocardial ischemia. A significant correlation was observed between IMA levels pre-HD and post-HD ($r = 0.45$, $P = 0.0017$). Main results of cardiac markers measurement pre-HD and post-HD are shown in Table 2. A significant variation of all the biomarkers tested was observed post-HD. In particular, the post-HD values of cTnT, CK MB, and myoglobin were significantly lower than the pre-HD values, whereas a significant increase was observed for IMA (mean increase: +38%, 95% CI, 12–65%). TnT, IMA, CK-MB, and myoglobin values in patients with and without IHD, diabetes mellitus, and peripheral vascular disease are shown in Tables 3, 4, and 5. No significant difference in any of the parameters tested was observed between patients with or without previous history of ischemic disorders. Table 4.

DISCUSSION

The genesis and progression of CAD in HD patients is multifaceted, with a large coronary extension and high rate of coronary calcifications (34). The increased

TABLE 1. Characteristics of the study population at baseline*

	Patients (n = 45)
Age (years)	65 ± 17
Male sex (%)	21 (47)
Diabetes (%)	8 (18)
Hypertension (%)	31 (69)
Peripheral vascular disease (%)	14 (31)
Ischemic heart disease (%)	13 (29)
Ischemic cerebral disease (%)	10 (22)
Antihypertensive drugs (%)	21 (47)
Length of time on dialysis (months)	56 ± 58
Predialysis weight (kg)	67 ± 14
Predialysis cardiac frequency	72 ± 12
Predialysis systolic pressure (mm Hg)	146 ± 23
Predialysis diastolic pressure (mm Hg)	139 ± 31
CRP (mg/L)	8.3 ± 11.9
Creatinine (mg/dL)	756 ± 221
Albumin (g/L)	33.7 ± 5.2
Predialysis cTnT >0.03 ng/mL [no. of patients (%)]	27 (60)
Predialysis IMA >85 K units/L [no. of patients (%)]	6 (13)

*Results are reported as mean values and standard deviations (SDs), or absolute number (%).

TABLE 2. Values of cardiac Troponin T (cTnT), ischemia modified albumin (IMA), creatine kinase isoenzyme MB (CK MB), and myoglobin in all patients predialysis compared to values postdialysis*

	Predialysis	Postdialysis	P
cTnT (ng/mL)	0.044 (0.037–0.071)	0.029 (0.032–0.059)	0.016
IMA (K units/L)	79.00 (75.19–80.50)	105.0 (103.4–109.5)	<0.0001
CK-MB (µg/L)	2.50 (2.58–3.25)	2.33 (2.33–2.97)	<0.0001
Myoglobin (µg/L)	148.7 (148.5–229.2)	128.1 (120.9–186.4)	<0.0001

*Pre- and postdialysis measurements were compared using the Wilcoxon matched-pairs test and data are reported as median (95% CI).

TABLE 3. Mean values and SDs of cardiac Troponin T (cTnT), ischemia modified albumin (IMA), creatine kinase isoenzyme MB (CK MB), and myoglobin in patients with and without previously reported ischemic heart disease (IHD)*

	Patients with IHD (n = 13)	Patients without IHD (n = 32)	P
Predialysis cTnT (ng/mL)	0.063 ± 0.052	0.051 ± 0.058	n.s.
Postdialysis cTnT (ng/mL)	0.056 ± 0.059	0.041 ± 0.039	n.s.
Predialysis IMA (K units/L)	76.0 ± 8.9	78.5 ± 8.9	n.s.
Postdialysis IMA (K units/L)	104.3 ± 9.9	107.4 ± 10.1	n.s.
Predialysis CK-MB (μg/L)	2.92 ± 0.96	2.91 ± 1.19	n.s.
Postdialysis CK-MB (μg/L)	2.73 ± 0.99	2.62 ± 1.09	n.s.
Predialysis myoglobin (μg/L)	142.33 ± 71.63	207.75 ± 149.72	n.s.
Postdialysis myoglobin (μg/L)	115.10 ± 56.68	169.37 ± 121.41	n.s.

*Differences were evaluated by Mann-Whitney U-test.

n.s., not significant; SDs, standard deviation.

TABLE 4. Mean values and SDs of cardiac Troponin T (cTnT), ischemia modified albumin (IMA), creatine kinase isoenzyme MB (CK MB), and myoglobin in patients with and without previously reported diabetes mellitus (DM)*

	Patients with DM (n = 8)	Patients without DM (n = 37)	P
Predialysis cTnT (ng/mL)	0.044 ± 0.024	0.056 ± 0.061	n.s.
Postdialysis cTnT (ng/mL)	0.030 ± 0.025	0.049 ± 0.048	n.s.
Predialysis IMA (K units/L)	75.2 ± 9.5	78.3 ± 8.8	n.s.
Post-dialysis IMA (Kunits/L)	102.6 ± 7.5	107.3 ± 10.4	n.s.
Predialysis CK-MB (μg/L)	2.59 ± 0.83	2.99 ± 1.17	n.s.
Postdialysis CK-MB (μg/L)	2.40 ± 0.81	2.71 ± 1.10	n.s.
Predialysis myoglobin (μg/L)	147.45 ± 67.65	197.80 ± 143.99	n.s.
Postdialysis myoglobin (μg/L)	106.72 ± 56.19	163.85 ± 115.37	n.s.

*Differences were evaluated by Mann-Whitney U-test.

n.s., not significant; SDs, standard deviation.

TABLE 5. Mean values and SDs of cardiac Troponin T (cTnT), ischemia modified albumin (IMA), creatine kinase isoenzyme MB (CK MB), and myoglobin in patients with and without previously reported peripheral vascular disease (PVD)*

	Patients with PVD (n = 14)	Patients without PVD (n = 31)	P
Predialysis cTnT (ng/mL)	0.056 ± 0.052	0.053 ± 0.059	n.s.
Postdialysis cTnT (ng/mL)	0.047 ± 0.057	0.045 ± 0.040	n.s.
Predialysis IMA (Kunits/L)	78.3 ± 6.7	77.5 ± 9.8	n.s.
Postdialysis IMA (Kunits/L)	106.7 ± 10.0	106.4 ± 10.2	n.s.
Predialysis CK-MB (μg/L)	2.96 ± 1.13	2.90 ± 1.13	n.s.
Postdialysis CK-MB (μg/L)	2.72 ± 0.98	2.62 ± 1.10	n.s.
Predialysis myoglobin (μg/L)	162.00 ± 106.45	200.98 ± 145.28	n.s.
Postdialysis myoglobin (μg/L)	124.67 ± 64.57	166.80 ± 122.66	n.s.

*Differences were evaluated by Mann-Whitney U-test.

n.s., not significant; SDs, standard deviation.

burden of CVD in asymptomatic dialysis patients (1) is only partially explained by an increased prevalence of traditional risk factors, such as hypertension, diabetes mellitus, dyslipidemia, smoking, obesity, and physical inactivity (35), whereas additional risk may be conferred by hyperhomocysteinemia, anemia, abnormal calcium/phosphate metabolism, inflammation, malnutrition, oxidative stress, and elevated lipoprotein (a) (36).

Therefore, an appropriate stratification of risk and a timely detection of cardiac ischemia by sensitive and specific biomarkers might improve the outcome of these patients.

Although elevated serum concentrations of cardiac troponins are sensitive and specific markers of myocardial damage in the general population, some earlier studies demonstrated that the baseline levels might be

higher than normal in a significant proportion of chronic HD patients without any evidence of acute myocardial injury (37). The influence of impaired renal function and HD on troponin metabolism is hence acknowledged as a major source of diagnostic uncertainty in uremic patients, since both the sensitivity and specificity of this marker might be substantially reduced. Neither other common cardiac markers, such as lactate dehydrogenase, CK, and CK-MB, are sensitive or specific as in the general population (38). Regardless of this potential drawback in the diagnostic interpretation of values, the level of cardiac troponin seems to predict mortality and cardiovascular events in HD patients (13,39), representing a valuable tool to identify high-risk asymptomatic HD patients. Roberts et al. (11) observed that the levels of cTnI and cTnT are inversely correlated with the renal function in pre-HD and transplant patients, but were not related to time on HD for those receiving dialysis therapy. Moreover, Hojs et al. (40) reported that patients with elevated cTnT are characterized by advanced asymptomatic atherosclerosis in carotid arteries. A variety of potential underlying mechanisms have been proposed to explain the increased prevalence of diagnostic values of troponins in HD patients, including diffuse myocardial necrosis, proteolysis, or leakage of cytoplasmatic cTnT with no irreversible damage to the contraction complex of heart-muscle cells. cTnT is more frequently elevated than cTnI among these patients and this could be due to the relatively higher levels of an unbound cytosolic pool of cTnT and its higher molecular weight (41).

Taken together, these previous clinical evidences do not attribute a definite role to cTnT, myoglobin, and CK-MB testing in HD patients, especially for the diagnosis of acute coronary syndrome (ACS), and additional or complementary biomarkers might be helpful to the diagnostic and clinical reasoning. Results of our investigation confirm that in the absence of an acute coronary event, pre-HD levels of cTnT are commonly increased in patients undergoing chronic HD (up to 60% of the cases) and they are only marginally decreased by HD, since 49% of the patients still have post-HD values above the recommended diagnostic threshold. This is in disagreement with results of previous studies (37,42), which reported a significant rise in cTnT following HD. It should be considered that a variety of confounding factors should not be overlooked when interpreting results of troponin testing in this peculiar clinical setting (37), including the choice of an accurate diagnostic cutoff, the sampling time, and the influence of hemoconcentration. In the present investigation blood samples were drawn immediately before and 5 min after the end of the HD session. Therefore, due to the specific release pattern of troponin following

myocardial injury (HD lasted less than 4 hr and troponin concentrations in blood increase only from 4 to 6 hr after onset of chest pain) (43), the changes observed could be most conceivably attributed to HD. At variance with previous investigations that used the lower limit of the analytical sensibility of the assay, we applied a more reliable diagnostic threshold, corresponding to the lowest cTnT concentration associated with a 10% total imprecision (33). Finally, we could rule out any bias from hemoconcentration, since results of each biomarker were adjusted for the plasma volume changes.

Due to its high negative predictive value, myoglobin has been included earlier in diagnostic algorithms for the early stratification of the cardiovascular risk (44). However, myoglobin metabolism is substantially impaired by impaired renal clearance (6,45), and we observed that its mean levels in pre-HD patients are significantly higher than those of healthy controls subjects matched for sex and age (188.9 $\mu\text{g/L}$ vs. 35.77 $\mu\text{g/L}$; $P < 0.0001$). In agreement with previous indications, we confirm that the slight but significant decrease observed post-HD (153.7 $\mu\text{g/L}$, $P < 0.0001$), which is likely due to low molecular weight solutes removal by the HD membrane, would make the variation of myoglobin values in HD patients of questionable diagnostic interpretation (23).

The IMA is a biological marker licensed by the U.S. Food and Drug Administration (FDA) for diagnostic use in suspected myocardial ischemia (46). The combination of IMA with myoglobin, CK MB, and cardiac troponins increases the diagnostic sensitivity for myocardial infarction in the general population up to 97%, with a negative predictive value of 92% (26). Although the definitive mechanism of action for producing IMA during ischemia is unclear, the metal binding capacity of albumin for transition metals like cobalt is reduced as a consequence of the generation of reactive oxygen species that modify the metal binding capacity of the albumin moiety (31). A variety of heterogeneous ischemic conditions, including endothelial and extracellular hypoxia, acidosis, free radical injury, and sodium and calcium pump disruptions, have been associated with rapid modifications of the cobalt binding properties (47–49). Therefore, IMA should not be regarded as a specific cardiac marker, especially in patients suffering from diseases associated with enhanced oxidative stress, such as uremia (50), where the balance between prooxidant and antioxidant capacities is conventionally shifted toward an increased oxidative stress (51,52). Moreover, HD is often associated with adverse ischemic effects, such as arteriovenous (AV) access-related ischemia and hypoperfusion (53), which results from dialysis-induced alterations in oxygen delivery and

myocardial oxygen consumption. Ischemic steal syndrome (ISS) is an additional complication of AV access creation for HD and occurs in approximately 10% of cases (54). The pathophysiological basis of this condition is a marked decrease or reversal of flow in the arterial segment distal to the AV fistula or graft, induced by the low resistance of the fistula outflow (54).

It has been reported that baseline IMA levels might predict mortality in patients with ESRD, since higher levels are frequently associated with larger left ventricular size, decreased systolic function, and greater estimated left ventricular filling pressures (27). Moreover, patients with an IMA rise >20 K units/L during dobutamine stress echocardiography have significantly worse survival (55). Although the assessment of pre-HD IMA levels might thus appear a valuable tool for stratification of the cardiovascular risk in these patients, no information is available on the acute variation of this marker during HD. The results of our investigation demonstrate that baseline IMA levels in HD patients are mostly below the recommended diagnostic cutoff for the general population. However, we have also observed a significant and unpredictable increase post-HD, which was not accompanied by biochemical or clinical symptoms of skeletal muscle and myocardial ischemia. This is consistent with the conclusion that HD-induced oxidative stress and damage are commonplace and the IMA increase might be attributable to the hemobiocompatibility of the dialysis system that plays a critical role in the production of free oxygen radical species (56). Moreover, since IMA values rise within minutes after the onset of ischemia, remain elevated for 6 to 12 hours, and return to baseline within 24 hr (57), our findings support the hypothesis that baseline pre-HD values might be used to predict long-term mortality and morbidity, whereas the heterogeneous and unpredictable increase post-HD would not be useful for the diagnosis of an ACS occurred during or immediately after HD.

In conclusion, we suggest that biomarkers of myocardial injury, especially cTnT and IMA, might be used in HD patients, provided that an appropriate diagnostic interpretation according to individual baseline value, metabolism, and time of sampling is guaranteed.

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