Sudden Cardiac Death in Haemodialysis Patients: Assessment of Risk Factors and Prevention

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IZNENADNA SRČANA SMRT BOLESNIKA NA HEMODIJALIZI: PROCENA RIZIKA I PREVENCIJA
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INTRODUCTION
Sudden cardiac death (SCD) is unexpected death due to cardiac causes occurring within one hour of symptom onset (1). Although the most frequent cause of SCD is coronary artery disease, other contributing factors in maintenance haemodialysis (HD) patients include left ventricular remodelling, volume overload, disturbed electrolyte balance, rapid electrolyte and fluid shifts and secondary hyperparathyroidism (1, 2). The annual mortality rate from SCD in HD patients is 5-7% (2).

Aetiopathogenesis of sudden cardiac death
Risk factors and cardiovascular diseases
Uraemia in general and HD in particular carry numerous risk factors for the development of cardiovascular disease. These include high arterial blood pressure, multiple lipid abnormalities, oxidative stress, microinflammation, hyperhomocysteinaemia, anaemia, high shunt blood flow and secondary hyperparathyroidism (3-5). All these factors are responsible for the development of atherosclerosis, arteriosclerosis and cardiomyopathy (5).

Atherosclerosis occurs when fatty plaques build up in the intimal layer of arterial walls, narrowing the lumen of the vessel. Atherosclerosis of the coronary arteries causes ischemic heart disease (6). Arteriosclerosis is a condition in which the artery wall thickens due to media thickening, calcification and remodelling of the smooth muscle cells of the tunica media into osteoblasts-like cells. Hardening of the arterial walls in arteriosclerosis decreases their elasticity and causes pressure overload to the left ventricle (3-7). Cardiomyopathy occurs due to left ventricular wall thickening, decreased myocardial vasculari-
sation, myocardial scarring and alterations of the small blood vessels in the myocardial interstitium. Clinical manifestations of cardiomyopathy include heart failure, myocardial hypersensitivity to ischaemia, prolonged ventricular repolarisation (prolonged QT interval), increased risk for ventricular arrhythmias and SCD (5, 8, 9). Left ventricular hypertrophy, coronary artery disease and disturbed systolic function of the left ventricle (left ventricular ejection fraction < 35%) represent major risk factors for SCD in maintenance HD patients (5, 8, 9).

Risk factors for sudden cardiac death related to haemodialysis

Rapid electrolyte shift

Haemodialysis per se is a risk factor for arrhythmias due to rapid the electrolyte shifts and cardiovascular instability (intradialytic hypotension) that can occur with this treatment (10-13). Rapid potassium and calcium shifts during HD sessions and low levels of electrolytes in the dialysate increase the risk for cardiac arrhythmia (10-13). The use of potassium-free or low-potassium dialysates ([K+]d = 1.0 mmol/L), particularly at the beginning of a dialysis session, removes potassium quickly, causing a rapid decline in the patient’s serum potassium concentration, which may lead to a disturbance of ventricular myocardial repolarisation, an increase in the corrected QTc interval (QTd) dispersion and increased risk for ventricular arrhythmias (10-13).

Calcium ions, however, play an important role in myocardial and arterial contractility. The use of low-calcium ([Ca++]d = 1.25 mmol/L) dialysates decreases ionised serum calcium and prolongs and increases the dispersion of the QTc interval, thus contributing to ventricular arrhythmias and SCD (10-13).

Educating patients to maintain an optimum predialysis potassium level of 4.6-5.3 mmol/L and individual adjustment of dialysis parameters decreases the risk of SCD death in HD patients (13).

Rapid fluid shifts (haemodynamic instability)

Dialysis-induced hypotension is represented by a sudden drop of systolic blood pressure below 90 mmHg or of at least 30 mmHg during HD (13, 14). Acute intradialytic hypotension reduces coronary blood flow and may lead to myocardial ischaemia, disturbances of regional myocardial motility and ventricular arrhythmia even in the absence of coronary heart disease (15). Haemodynamic instability during HD sessions can be prevented by the early identification of patients at higher risk for hypotension and by the individual adjustment of dialysis parameters. Patients at risk are those with malnutrition and hypoalbuminaemia, left ventricular hypertrophy, diabetes and diseases of the autonomous nervous system. Individualised dialysis strategies to obtain haemodynamic stability include the adequate choice of dialysers, adjusting the dialysate temperature, the use of sodium-modelling profiles, the careful adjustment of ultrafiltration and sequential dialysis (13-15).

Interdialytic restriction of fluid and dietary sodium intake (recommended maximum intake 2.0 g/24 h) and an interdialytic weight gain of less than 4% of the dry body weight decrease left ventricular overload, haemodynamic stress and the risk for ventricular arrhythmias (16).

Identifying patients at risk for sudden cardiac death

All HD patients have increased risk for SCD (17-19). The plan for the early detection of patients at risk for SCD should include the following: clinical assessment of the patient (anamnesis and physical examination), echocardiographic examination (measuring QT/QTc interval, measurement of QTc interval dispersion, variation of T wave amplitude and duration), measuring heart rate variability (HRV) and determining serum troponin T and troponin I concentrations (20-24).

The QT interval is easily measured and enables the identification of patients at higher risk for SCD. The QT interval is a measure of the time between the start of the Q wave and the end of the T wave on an electrocardiogram (ECG). It represents the time required for the completion of both ventricular depolarisation and repolarisation. The standard clinical correction is to use Bazett’s formula to calculate the heart rate-corrected QT interval. Bazett’s formula is QTc = QT / √RR, where RR is the interval from the onset of one QRS complex to the onset of the next QRS complex, measured in milliseconds. In HD patients, a QTc interval longer than 500 ms suggests an increased risk for ventricular dysrhythmia (24, 25). Furthermore, increased QTc dispersion, as measured on standard ECG, is a useful and reliable predictor of susceptibility to life-threatening ventricular arrhythmias in HD patients. QTc interval variability is the difference between the longest and the shortest QTc interval registered on a standard ECG (25, 26); normal QTc variability is 40 - 50 ms. QTc variability over 50 ms in HD patients suggests higher risk for ventricular arrhythmias and SCD (26).

Heart rate variability is an electrocardiographic parameter of sympathetic and parasympathetic control of the heart rate. A decrease or loss of HRV is associated with increased risk for ventricular arrhythmias and SCD (27, 28). Drugs that induce parasympathetic activity also decrease the rate of SCD in HD patients. ACE inhibitors and beta-blockers enhance the parasympathetic influence on the heart, increase HRV and decrease the risk for SCD in HD patients (27, 28). Nocturnal HD, performed for 8 to 10 hours, 6 times/week, decreases sympathetic activity and increases HRV and the partial pressure of arterial blood overnight compared to the standard HD scheme of 3 times for 4 hours each week (20).

Treatment plan

The plan to reduce the risk for SCD in maintenance HD patients includes primary and secondary measures (29-32). The primary plan requires medicamentous therapy and
individual adjustment of HD parameters, while secondary intervention includes coronary revascularisation and the placement of an implantable cardioverter defibrillator (ICD) (29-32).

**Primary treatment plan**

**Medicamentous therapy**

Medicamentous therapy to control risk factors for SCD in maintenance HD patients includes beta-blockers, angiotensin convertase inhibitors, angiotensin receptor blockers, vitamin D active metabolites, calcimimetics and erythropoietin. Beta-blockers decrease the risk for SCD in HD patients by decreasing myocardial sympathetic activity, lowering the rate of ventricular arrhythmias and increasing HRV and baroreceptor sensitivity (28-33). Carvedilol improves left ventricular ejection fraction and survival in heart failure patients with NYHA II and NYHA III on maintenance HD (34, 35). Other treatments are focused on increasing HRV (beta-blockers, angiotensin convertase inhibitors), stabilising arteriosclerotic plaques (anti-aggregation agents and statins) and controlling left ventricular hypertrophy (beta-blockers, angiotensin convertase blockers and erythropoietin) (28-33).

**Haemodialysis treatment**

A biocompatible high-flux membrane, ultrapure dialysate (bacteria < 0.1 CFU/mL and endotoxin < 0.03 EU/mL) and an optimal dialysis dose (Kt/V ≥ 1.4) significantly contribute to lowering the mortality rate in HD patients (34). Haemodiafiltration (HDF) achieves optimal transfer for both small (<5 kDa) and mid-size (5-50 kDa) molecules, including mediators of inflammation, complement factor D and other molecules involved in the development of heart disease (36). The optimal treatment with standard HD or HDF (≥3 times per week for ≥4 h), with blood flow ≥ 300 mL/min, adequate dietary intake, interdialysis weight gain < 4% and adequate medica
tmentous treatment (phosphate binders, vitamin D active metabolites, calcimimetics, iron supplements and erythropoietin), should provide a Kt/V ≥ 1.4, mean arterial pressure ≤ 105 mmHg, predialysis serum potassium concentration of 4.6-5.3 mmol/L, serum phosphate concentration of 0.8-1.6 mmol/L, serum calcium concentration of 2.2-2.5 mmol/L, solubility product ≤ 4.4 mmol²/L², parathormone levels of 150-300 pg/mL, bicarbonate level ≥ 20 mmol/L, transferrin saturation of 30-50%, serum ferritin concentration of 200-500 ng/mL, haemoglobin concentration of 100-120 g/L and serum albumin concentration ≥ 35 g/L (37).

In patients with disturbed left ventricular systolic function, hypotension and haemodynamic instability limit the achievement of optimal ultrafiltration during an HD session. These patients are candidates for peritoneal dialysis because it provides better haemodynamic stability (38). The treatment plan for haemodynamically unstable patients should also include some of the new HD modalities, such as short daily haemodialysis (SDHD) or nocturnal home haemodialysis (NHD). SDHD is performed 5 to 6 days per week for 1.5-2 hours, whereas NHD is performed while sleeping, usually for 6-8 hours, 4-6 nights per week (38).

**Secondary treatment plan**

**Coronary revascularisation**

According to coronaryographic findings, HD patients are at either high risk (coronary disease of the main left ventricular artery; three-vessel coronary disease, mild symptoms and decreased left ventricular function; two-vessel disease involving the proximal left coronary artery) or low risk for acute coronary syndrome (single-vessel coronary disease - only one vessel involved and preserved myocardial function) (6, 39, 40). Coronary artery bypass grafting (CABG) decreases the risk of acute coronary syndrome in the high-risk group, whereas patients at low risk are usually treated with drugs, percutaneous transluminal angioplasty (PTCA) or coronary artery stenting (CAS) (6, 39, 40). HD patients have a significantly higher inhospital mortality rate in the first 30 days following CABG and are at significantly higher risk for postoperative complications (sepsis, respiratory insufficiency and gastrointestinal complications) compared to HD patients after CAS and nonrenal patients (41, 42). More studies are needed to determine the criteria for selecting HD patients and adequate coronary revascularisation procedures (41, 42).

**Implantable cardioverter defibrillator**

ICDs decrease mortality risk by 42% in HD patients surviving cardiac arrest (19, 23, 43). However, only 8% of maintenance HD patients who survive cardiac arrest actually have preventively placed ICDs (19, 23, 42). ICD implantation is associated with a high risk of bleeding, infection and venous suboclusion and occlusion. Therefore, it is typically placed on the side opposite to the vascular access for HD (43). ICDs are placed in HD patients with a left ventricular ejection fraction < 35% following cardiac arrest caused by ventricular dysrhythmias (ventricular tachycardia or fibrilation). More clinical studies are needed to define the criteria for choosing patients for this procedure and to assess its validity, cost-effectiveness and budget impact in a manner similar to other health technologies (43-47).

**CASE REPORT**

Patient CR, born in 1955, started regular haemodialysis therapy in 1994. (Insuffitientia renalis chronica terminalis, Status post-nephrectomiam lat. dex. pp calculus, Haemodialysis chronica regularis). As a part of uncontrolled secondary hyperparathyroidism (Secondary hyperparathyroidism, Osteodystrophia chronica renalis, iPTH = 1500 pg/ml), the patient developed significant vascular (coronary artery) and
valvular calcification, which called for triple aorto-coronary by-pass and implantation of a synthetic mitral valve (Status post-lM inferolateralis aa III, Status post-by-pass AC triplex et implantationem valvulae mitralis aa III). The patient received regular haemodialysis therapy, erythropoietin, statins and anti-aggregation and anticoagulant therapy with adequate laboratory monitoring. Sudden and rapid deterioration of chronic heart insufficiency (Myocardio-pathia chronica ischaemica decompensata) and the development of cardiogenic shock (Shock cardiogenes) resulted in the patient’s death (Exitus letalis).

CONCLUSION

Early identification of maintenance HD patients at risk of ventricular dysrhythmias and SCD enables timely and adequate treatment to decrease the risk for SCD mortality and improve survival.

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