

The Challenge of Sudden Death in Dialysis Patients

Eberhard Ritz* and Christoph Wanner[†]

*Department of Internal Medicine, Division of Nephrology, University of Heidelberg, Heidelberg, and [†]Department of Internal Medicine, Division of Nephrology, University of Würzburg, Würzburg, Germany

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Case Presentation

A 60-yr-old patient with ESRD (82 kg/168 cm), hypertension for the previous 18 yr, and type 2 diabetes is found dead in bed by his wife at home on a Saturday morning. The patient's history is notable for having started dialysis 34 weeks previously. His last dialysis had been the previous day (on a Friday afternoon). Predialysis potassium had been 5.7 mmol/L, the dialysate K⁺ was 2.0 mmol/L, and Mg²⁺ was 0.5 mmol/L. Autopsy was not performed.

Before his morbid event, the patient had been doing well on dialysis. He had less than 6 episodes of hypotension (<100 mmHg) per month. His average predialytic weight gain was 4 kg, and, with fluctuations, his average predialysis BP was 155/65 mmHg. While continuing on gliquidone (an oral sulfonylurea hypoglycemic drug that does not accumulate in renal failure), he had no episodes of hypoglycemia, and his last glycosylated hemoglobin level was 7.2%. His medical history is of hypertension, type 2 diabetes, and left ventricular hypertrophy (LVH) with an ejection fraction of 55%. His electrocardiogram showed signs of LVH and flat T waves. He had no history of hypoglycemic episodes and no evidence of retinopathy. He reported no episodes of arrhythmia or precordial pain. A predialysis chest x-ray 2 wk before the terminal event had shown pulmonary congestion. His medications included 0.25 µg/d calcitriol, calcium carbonate, 10 mg of folate, 80 mg of verapamil, and no β blockers. In addition, he received varying doses of darbepoietin and iron gluconate as required. He did not receive a statin.

Dr. Eberhard Ritz: This case, unfortunately, is the usual presentation of patients on dialysis who succumb to sudden death: There are few, if any, specific premonitory symptoms or signs, cardiac standstill is usually the presenting symptom, and autopsy is not performed, so more specific information on underlying cardiac pathology, if any, is not available. The lack of pathoanatomic confirmation of the underlying pathology or pathologies—as in this case—continues to remain a problem that in the future should come onto the radar screen of nephrologists.

Nevertheless, this case presentation raises a number of un-

resolved issues and provides an occasion to discuss how the currently unsatisfactory results might be improved in the future. In this context, it is of interest to have a look at the recent 4D study. I have asked Dr. Christoph Wanner to discuss the issue of sudden death in the 4D study.

Dr. Christoph Wanner: One of the unexpected findings of the 4D study was the failure of atorvastatin to cause a significant decrease of an adjudicated composite cardiovascular end point and specifically of sudden death in type 2 diabetic patients on maintenance hemodialysis (1). The latter finding is pertinent to the present case presentation but may even have some more general significance for understanding sudden death of nondiabetic dialysis patients as well.

The 4D study was a prospective, randomized, controlled study of dialyzed type 2 diabetic patients in 178 German dialysis centers with a follow-up of 3.96 yr. LDL cholesterol was lowered by 10 or 20 mg of atorvastatin by 42% compared with 1.3% on placebo. The primary composite end point (comprising death from cardiac causes, fatal stroke, nonfatal myocardial infarction, or nonfatal stroke) was reduced by 8% (95% confidence interval [CI] 0.77 to 1.10), which was not statistically significant ($P = 0.37$). These results have recently been confirmed in a small Swedish study where atorvastatin had no significant impact on cardiovascular outcome in dialysis patients (2).

The main *post hoc* explanation for the negative outcome of the 4D study is the fact that adjudicated coronary death accounted only for 9% of deaths, while other cardiac causes accounted for 35%; among these, sudden death was the most frequent, accounting for no less than 26% of total deaths. This finding is in stark contrast to all other statin intervention trials in nonrenal patients, but the negative outcome may provide a useful hint, reminiscent of "The Adventure of Silver Blaze" of A. Conan Doyle (3):

(Inspector Gregory) "Is there anything you wish to draw my attention to?"

(Sherlock Holmes) "Yes, the curious incident of the dog in the nighttime."

(Inspector Gregory) "The dog did nothing in the nighttime!"

(Sherlock Holmes) "That was the curious incident."

In the 4D study, the dog that did not bark was the failure of sudden death to respond to a statin. Such negative outcome may suggest the following hypothesis: In nonrenal patients, coronary heart disease and cardiac ischemia from classical coronary atherosclerosis with plaque rupture is the main cause of

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Correspondence: Prof. Eberhard Ritz, Nierenzentrum, Im Neunheimer Feld 16, D60120 Heidelberg, Germany. Phone: 0049-6221-601705; Fax: 0049-6221-603302; E-mail: prof.e.ritz@t-online.de

sudden death. In contrast, in dialysis patients, classical coronary heart disease is either not responsible for sudden death or is not responsive to statins. We are not able to solve this issue, but in the following we try to go beyond simplistic explanations and to provoke discussion, reflection, and planning of future studies.

Dr. Eberhard Ritz: Let us first discuss the epidemiologic magnitude of the problem of sudden death on dialysis. In the general population, Myerburg and colleagues (4–6) found a rate of “sudden death” of 0.36 to 1.28‰ per year, and this has been confirmed in more recent series. With respect to the elderly dialysis population, a key observation is that, in the background population, the rate in males age 60 to 69 yr is as high as 8/1000/yr (7). In the general population, sudden cardiac death accounts for approximately 50% of cardiovascular deaths, and the majority, based on first recorded rhythms, is ventricular fibrillation in 75 to 80%; bradyarrhythmia accounts for most of the rest (5). Most cases are accounted for by ischemic heart disease and myocardial infarction (MI). In one autopsy study on coronary patients dying from sudden death, 59 of 113 patients had acute coronary thrombosis and 54 of 113 patients had severe narrowing of the coronary by a stable atherosclerotic plaque without acute thrombosis (8). Two further autopsy studies found ischemic heart disease in 59 and 62% respectively; nonischemic heart disease accounted for 7.5% and other pathologies (*e.g.*, pulmonary embolism, rupture of the aorta, intracerebral hemorrhage for 27.6% [9,10]). Other possibilities to consider—for which epidemiologic information is less reliable—include suicide, seizures, primary hypoventilation, and massive pulmonary embolism (which was extremely rare in the distant past, but this may have changed with the use of erythropoietin).

In contrast, in the dialysis population, Herzog (11) found a 100-fold higher rate (93‰ per year) accounting for 60% of cardiac deaths: 47 presented as “cardiac arrest” (cause unknown) and 13% as “arrhythmia.” It has long been known that sudden death accounts for the majority of deaths in dialysis patients, particularly in diabetics, and sudden death was also identified as the most frequent cause of death in two national random samples of hemodialysis patients (12,13). It is of note that the frequency of cardiac arrest on dialysis increases with time on dialysis, almost doubling within 4 yr. It is also significantly higher, by a factor of 1.6, in diabetic compared with nondiabetic patients (11). In view of this excessive rate in dialyzed patients, it is quite surprising that a recent task force report on sudden death does not mention dialysis as a predisposing factor, illustrating the need for more interaction between specialties (5). Much of the information on dialysis patients is difficult to interpret: In nonrenal patients, the link between “sudden death” and structural cardiac disease or malfunction of ion channels (“channelopathy”) is usually straightforward; in dialysis patients, however, many confounding factors—uncommon in the general population but unrelated to heart disease—may also cause death fulfilling the criteria of sudden death (*e.g.*, hyperkalemia, suicide, air embolism [5,6,14]). The causes of sudden death in dialysis patients may also vary between countries: One autopsy controlled study in

Japan found stroke as the most frequent cause of sudden death (25.8%), followed by cardiac disease (19.4%), infectious disease (17.2%), and others (15).

The European and worldwide experience suggests that the frequency of cardiac death in the dialysis population varies in parallel with its frequency in the background population: 27% of the variation in the frequency of cardiac death in the dialysis population is explained by the mortality in the general population (16,17). This observation would suggest that the dialyzed patients largely die as the result of the same cardiovascular causes as individuals in the general population. This conclusion, however, conflicts with some of the above data and would also not explain the failure of atorvastatin in the 4D study to significantly affect sudden death (1). One cannot exclude the possibility, however, that advanced and calcific coronary heart disease of dialysis patients responds less well to statin treatment but is still causally related to sudden cardiac death. The outcome of (presumably observed) cardiac arrest in dialysis patients is abysmal: 30 d survival is 32%, and 1 yr survival is 15% (11).

Associated Factors and Pathogenesis

It has recently been stated that (in nonrenal) patients, virtually all sudden death from cardiac causes is secondary to underlying coronary disease (18). This statement is certainly correct, but while coronary heart disease is a potential cause in uremic patients, cardiac abnormalities unrelated to coronary disease are also likely to be causal, or at least aggravating, factors in the genesis of sudden death (5,6,19). Unfortunately, only scant autopsy information is available, and the few available studies fail to clarify the issue of which proportion of dialysis patients dying from sudden death have coronary disease as a causal factor.

Potential Factors Increasing the Risk for Sudden Death in Dialysis Patients (Table 1)

Cardiac Hypertrophy and Heart Failure

As shown in the Framingham Heart Study, the hazard ratio for sudden death is higher by a factor of 1.45 (95% CI 1.1 to 1.93; $P < 0.008$) for each 50-g/m increase in left ventricular mass,

Table 1. Potential factors increasing the risk for sudden death in dialysis patients

LVH and heart failure
Abnormal myocardial structure and function (fibrosis, microvessel disease, reduced ischemia tolerance)
Electrolyte shifts and hypervolemia (related to dialysis sessions)
Hyperphosphatemia
Obstructive sleep apnea?
QT dispersion
QT prolonging medication
Sympathetic overactivity and autonomic nerve dysfunction
AngII-induced electric remodeling?

and this relation is more pronounced in men than in women (20).

Both concentric and eccentric LVH are frequent in dialysis patients and are related to lower rates of survival, but there is no information to what degree LVH predicts sudden death in dialysis patients, and, because of the high prevalence of LVH, this would presumably also not be helpful (21). In hypertensive patients with LVH, however, arrhythmias are known to contribute to the increase in cardiovascular mortality (22).

Systolic dysfunction (*i.e.*, a low ejection fraction) is common in dialysis patients and has the worst survival prognosis (21). The criterion of low ejection fraction may underestimate the frequency of systolic dysfunction in uremic patients, which may be better reflected by fractional midwall shortening (23).

Sympathetic Overactivity

The norepinephrine spillover technique uses labeled norepinephrine to quantitate the proportion of norepinephrine released from sympathetic nerve endings into the circulation after having escaped local reuptake (24). Using this technique, high total norepinephrine turnover but, more important, cardiac norepinephrine spillover (450% higher than in controls) was found in nonrenal patients with heart failure who had survived episodes of spontaneous sustained ventricular tachycardia or ventricular fibrillation (25). Such cardiac sympathetic overactivity might be particularly relevant in the arrhythmogenesis of patients with renal failure given the fact that their background sympathetic activity is already elevated (26).

Cardiac Fibrosis and Microvessel Disease

Cardiac fibrosis has both mechanical and electrical sequelae that impact on cardiovascular prognosis (27). Fibrosis reduces the ventricular compliance so that higher left atrial filling pressures are required for adequate diastolic LV filling. The result is a higher propensity to develop pulmonary edema when the patient with LV fibrosis is hypervolemic and, conversely, a higher propensity to develop hypotension when this patient experiences hypovolemia (*e.g.*, during rapid ultrafiltration). Fibrosis also promotes arrhythmia. If fibrous tissue with high electrical resistance is interposed between cardiomyocytes, it will cause local delay in the spread of the action potential favoring the development of reentry types of arrhythmia, both ventricular and atrial (28,29).

A further typical abnormality of cardiac structure in uremia is microvessel disease (*i.e.*, wall thickening of the intramyocardial arteries and capillary deficit [30]). Wall thickening of intramyocardial arteries restricts compensatory vasodilation. The capillary deficit (capillary/cardiomyocyte mismatch) results from inadequate capillary growth in response to cardiac hypertrophy despite increased expression of vascular endothelial growth factor (VEGF), presumably pointing to VEGF hyporesponsiveness as suggested by low VEGF receptor expression. Inadequate capillary density will restrict the ability of the heart to cope with increased oxygen demand. Finally, after ligation of the left coronary, infarcts are larger in animals with experimental uremia, pointing to reduced ischemia tolerance (31).

Electrolyte Shifts and Hypervolemia Related to Dialysis Sessions

Bleyer *et al.* (32) observed that sudden death is particularly frequent hours after the start of dialysis on the one hand and during the hours preceding the next dialysis session on the other hand. Furthermore, sudden death is particularly frequent after the long weekend (33,34). These observations suggest a potential role of electrolyte shifts and hypervolemia, respectively. Proof of this hypothesis would be a diminished risk for sudden death in patients on long slow or daily dialysis.

Role of Hyperphosphatemia

It came as a surprise that two large national studies identified high predialysis serum phosphate not only as a powerful predictor of coronary death but specifically also of sudden death, the relative risk being 1.06 compared with 1.08 for coronary artery disease and cerebrovascular accident (13). One explanation for this unexpected finding may be that in experimental studies, hyperphosphatemia is a permissive factor for the above structural abnormalities, specifically interstitial fibrosis and thickening of intramyocardial arteries (35). It is also conceivable that hyperphosphatemia affects intracellular handling of calcium and thus interferes with electrical stability.

It is remarkable that a relation between serum phosphate and cardiac events is even found in nonrenal patients with cardiac disease (36). Unfortunately, it is unknown whether this is also true for sudden death.

A Role of Obstructive Sleep Apnea?

We speculate that obstructive sleep apnea may be a potent cause of cardiac arrest in dialysis patients. In nonrenal individuals, the most frequent time of sudden death is the morning hours (9 to 12 h) (37). In contrast, in patients with obstructive sleep apnea, sudden death is most frequent from midnight to 6 a.m. (38). In the 4D study, approximately 40% of sudden deaths were reported as "in the morning found dead in bed." Could such inversion of the circadian rhythm point to a causal role of obstructive sleep apnea?

Sleep-disordered breathing is known to be associated with nocturnal arrhythmia (39). This association may be relevant for renal patients as well: In symptomatic dialysis patients (restless sleep, morning headaches, daytime sleepiness, personality changes), Kimmel *et al.* (40) found obstructive sleep apnea in no less than 73% of patients. In the overall dialysis population, a prevalence of 21 to 47% was found compared with only 2 to 4% in the general population (41,42). More direct evidence comes from the observation that in a small sample of dialysis patients, cardiovascular events are actually predicted by nocturnal episodes of arterial oxygen desaturation, although no sudden deaths occurred in this study (43). An impressive reduction of sleep apnea has been observed by the Toronto group using quotidian dialysis (44). This issue certainly deserves more rigorous investigation.

QT Dispersion and QT Prolonging Medication (Acquired Long-QT Syndrome)

As found by Stewart and others (45,46), a prolonged QT interval and QT dispersion are common in advanced chronic kidney

disease (CKD), particularly in patients with LVH and other echocardiographic abnormalities. Further frequently investigated indicators of the risk for sudden death in the past were heart rate variability (reflecting autonomic dysfunction) and altered baroreflex sensitivity or sensitivity index, respectively (an index of baroreflex dysfunction) (47). These tests were found to be more frequently abnormal in dialysis patients who later experienced cardiac events and specifically cardiac arrest. The drawback of these tests is their complexity, which prevents routine use.

An underappreciated aspect of sudden death is the acquired long-QT syndrome (14). It is known that on the one hand the repolarization reserve is diminished by the presumed reduction of K^+ channels in uremia (14). On the other hand, the smaller number of remaining K^+ channels exhibit increased sensitivity to inhibition (acquired long-QT syndrome). Such inhibition may come about either by drugs that directly inhibit the outward K^+ channel I_{Kr} and prolong QT (e.g., sotalol, erythromycin, antidepressants, antihistamines, antipsychotics, antifungals, pentamidine) or, alternatively, by administration of drugs that interfere with the elimination of these QT-prolonging drugs and increase their plasma concentration (48). The most common clinical manifestation is the provocation of *torsades de pointes* (i.e., polymorphic ventricular tachycardia [for details, go to <http://www.torsades.org> or <http://www.heartjnl.com/>]) (19). Another factor predisposing to sudden death are unrecognized genetic variants of ion channels ("channelopathies"), which may be suspected from a family history of sudden death (49).

That dialysis sessions can trigger sudden death in a patient with a genetic form of long-QT syndrome with malfunction of ion channels, so-called "channelopathy," is illustrated by the tragic case of a female patient with—at that time undiagnosed—genetic long-QT syndrome: The first two hemodialysis sessions caused cardiac standstill, which was fatal on the second occasion; the family investigation showed a genetic cause (50). Dialysis may trigger such episodes by causing electrolyte shifts, presumably depleting transiently intracellular K^+ and Mg^{2+} (14). Similarly, dialysis sessions presumably also trigger sudden death in patients with acquired long-QT syndrome.

Autonomic Nerve Dysfunction and Sympathetic Overactivity

Dialysis patients with their shrunken kidneys in place but not nephrectomized dialysis patients have striking sympathetic overactivity, as documented by microneurography (51). Sympathetic overactivity is an established indicator of cardiac risk. The plasma norepinephrine concentration is a predictor of death and cardiovascular events in dialysis patients without congestive heart failure (52). Sympathetic overactivity may certainly be a causal factor in the genesis of sudden death, but prospective evidence is lacking. The risk may be further increased by autonomic polyneuropathy and patchy denervation of sympathetic fibers with consequent catecholamine receptor upregulation in the remnant fibers and by lesser bioavailability of nitric oxide, which antagonizes many effects of catecholamines (53).

The response of the heart to sympathetic stimulation is mod-

ulated by the protein Semaphorin 3a (54). Semaphorin 3a-transgenic mice show catecholamine suprasensitivity and prolonged QT; they die from sudden death. Whether this molecule, obviously an interesting candidate, is altered in uremia is currently unknown.

Angiotensin II–Induced Electric Remodeling?

High mortality from sudden death is seen in animal models characterized by overexpression of angiotensin II (AngII; e.g., the double-transgenic dTGR rat expressing human angiotensinogen and renin). These animals die suddenly between weeks 7 and 8. Recently, Fischer *et al.* (55) reported in this high AngII model abnormal "electrical remodeling" in the left ventricle with reduced expression of the potassium channel subunit $Kv4.3$ and gap junction protein $Cx43$, as well as prolonged and inhomogeneous depolarization and repolarization. These abnormalities and the induction of ventricular tachycardia were prevented by treatment with the angiotensin receptor blocker (ARB) losartan, of interest because of recent preliminary reports of reduced cardiovascular mortality in dialysis patients on ARB (56).

Outlook

Animal experiments have recently shown that an endogenous noncoding micro-RNA (miR-1) that mediates posttranscriptional gene silencing is overexpressed in patients with coronary heart disease. This is of interest because mice overexpressing miR-1 are characterized by arrhythmogenesis, which is specifically eliminated by an antisense inhibitor (57). This molecule may well open a new perspective in arrhythmogenesis and is an obvious candidate for investigation in uremia.

Therapeutic Approaches

Primary Prevention

In principle, strategies to reduce sudden death either aim at reducing the occurrence of cardiac arrest (primary prevention) or imply measures to improve the likelihood of survival in case of cardiac arrest (secondary prevention).

β Blockers. In one observational study on hemodialyzed type 2 diabetic patients, Koch *et al.* (58) observed that 4% of the patients who died from cardiovascular causes but no less than 12% of those who survived had been on β blockers, suggesting a benefit from β blockers. Consequently, we had strongly argued for the more widespread use of β blockers in dialyzed patients, particularly in diabetics (59). Meanwhile, some evidence has come forward from a small, prospective, randomized, controlled study: Dialyzed patients with dilated cardiomyopathy were randomized to receive placebo or the β blocker carvedilol on top of appropriate treatment for heart failure (60). Cardiovascular death at 2 yr was 29.3% in the patients on carvedilol and 67.9% in the patients on placebo (a reduction of risk by 43.7%), impressive when compared with the effects of other interventions on survival, such as statins, erythropoietin, and calcium free phosphate binders. In this study, not only all-cause and cardiovascular mortality were reduced but also the risk for sudden death (3.4 *versus* 10.6% on placebo), although, as a result of limited biostatistical power, it was not

statistically significant. Because of the small size of the study and the high patient dropout rate, it would be highly desirable to see its results confirmed by an independent study. In the CAPRICORN and COPERNICUS studies, survivors of MI who happened to have mild to moderate CKD also showed marked reduction of cardiovascular mortality from carvedilol, so the cardiovascular risk from sympathetic overactivity apparently starts early in the course of CKD (61,62).

How about the effect of β blockers on the prognosis of cardiac arrest? In a large study on 43,200 prevalent hemodialysis patients, β blockers increased the odds of surviving cardiac arrest by 40% (62).

Is there a rationale to explain the efficacy of β blockers? Experimental studies documented that stimulation of renal baroreceptors and chemoreceptors leads to afferent stimulatory traffic through the spinal cord and increasing norepinephrine turnover in the hypothalamic cardiovascular centers, thus increasing efferent sympathetic traffic. The relevance of this observation for dialysis patients has been shown in studies using the methodological gold standard (*i.e.*, microneurography), which documented excessive sympathetic efferent nerve traffic (51,63). Interestingly, after successful renal transplantation, removal of the recipient's own anuric kidneys normalized sympathetic nerve activity, which had remained elevated after transplantation, illustrating the role of the damaged kidney in triggering sympathetic overactivity (63). A novel aspect is introduced by the recent demonstration that the kidneys produce a circulating aminooxydase ("renalase"), which catabolizes catecholamines (64). If the results are confirmed, then one would anticipate that catecholamine concentrations increase in parallel with the decrease in the renal production of renalase. The impact of sympathetic overactivity may be amplified by the fact that the counterbalancing effect of the parasympathetic system is attenuated in renal disease; furthermore, target organs are sensitized to catecholamine action by diminished availability of nitric oxide (53).

The hypothetical argument that obstructive sleep apnea plays a role in sudden death of dialysis patients would provide a further argument for the use of β blockers, since β blockers seem to be effective in sleep disordered breathing (65).

Blockade of the Renin-Angiotensin System. In hemodialyzed patients, a prospective controlled trial with the angiotensin-converting enzyme (ACE) inhibitor fosinopril had no significant impact on mortality, although the per-protocol analysis showed a borderline effect (66). Recently, however, some small, underpowered studies showed improved mortality and reduction of cardiovascular events in dialysis patients on candesartan and on different ARB in an unpublished further small multicenter study (56). In the context with cardiac arrest on dialysis, it is of interest that in 43,200 dialysis patients, the use of ACE inhibitors and ARB was also associated with better survival of patients with cardiac arrest (62). It is known that the availability of AngII in tissues is greater in individuals with the genotype D of the ACE gene; it is therefore of interest that a Dutch study showed that among incipient hemodialysis patients with genotype D, the risk for cardiovascular death is higher, consistent

with the notion that AngII plays a role in cardiovascular death, including sudden death (67).

Role of Spironolactone or Eplerenone? The RALES Study showed that spironolactone significantly reduced cardiovascular death in patients with heart failure, and aldosterone blockade was found specifically also to reduce sudden death (68,69). This drug had not been studied in dialysis patients because of the suspected risk for hyperkalemia. A recent study with a crossover design in few patients ($n = 8$) with a high dose of spironolactone (50 mg 2 \times daily) *versus* placebo showed significant lowering of BP without any significant effect on predialytic serum potassium (70). Obviously, such BP effect is independent of the diuretic effect of spironolactone. If confirmed, then it will also raise the issue of whether spironolactone might be useful to prevent sudden death similar to what was found in nonrenal patients in anuric dialysis patients as well. Further studies to document the safety of this hypothetical approach are necessary, however.

Active Vitamin D. It has recently been documented that 1,25(OH)₂ vitamin D₃ is a potent suppressor of the secretion of renin (71). In this context, it is of interest that 1 α -calcitriol caused regression of LVH in hemodialysis patients concomitant with a decrease of AngII and atrial natriuretic peptide (72). More recently, reduction of QTcmax and QTc was observed with the same maneuver. It deserves consideration whether the survival benefit of active vitamin D seen in observational studies may not in part be the result of reduced cardiac death, including sudden death.

Secondary Prevention

With sound reasoning, Herzog (73) has proposed that every dialysis unit have a automatic external defibrillator to cope with the emergency of cardiac arrest. This advice is not negated by the result of an observational study that the availability of automatic external defibrillator did not significantly impact on the outcome of cardiac arrest in dialysis units—absence of evidence is not evidence of absence (74). If defibrillators work in airports, in airplanes, and when operated by police, then they might also save at least some lives in dialysis units when the personnel is adequately trained, although the chances in the high-risk dialysis patients are admittedly less (5).

It has been argued that the indication for implantation of cardioverter defibrillators (ICD) deserves further study in patients who survived cardiac arrest or have a high risk for cardiac arrest (11). Although the results of a pilot study were positive, the uncontrolled experience with ICD in nondialyzed patients with CKD admittedly had not been too encouraging (75). In a small observational study, major complications were more frequent in CKD patients, but, in this study, mortality was not elevated when compared with nonrenal controls with comparable cardiac disease (76). In a single-center, retrospective, cohort study, the few (3.2%) patients with ESRD had significantly shorter survival (3.2 ± 0.6 *versus* 7.4 ± 0.5 yr) (77). Cuculich *et al.* (78) also reported a relatively poor prognosis of CKD patients with ICD provided for primary prevention of sudden death: 1-Yr survival was 96.3% in patients with normal renal function compared with 61.2% in patients with a serum

creatinine >2 mg/dl or on dialysis. The hazard ratio for renal patients was 10.5 (95% CI 4.8 to 23.1). The outcome may be improved by β blockers and renin-angiotensin system blockade, however. In patients without CKD who had received an ICD, administration of β blockers and ACE inhibitors was associated with improved survival—a note of hope (79).

Remaining Challenges

In the 4D Study, the frequency of sudden death was not significantly affected by treatment with statins. This observation suggests but does not prove that pathomechanisms unrelated to the growth of coronary plaques play a more important role in the genesis of sudden death of dialyzed patients compared with the general population. Adjudicated death from coronary heart disease constituted only a relatively minor proportion of cardiac deaths (9% of overall death), however; the majority of patients died from sudden death (26%) and heart failure (6%). In the absence of autopsy data, it is impossible to decide whether sudden death was associated with coronary heart disease that had possibly advanced to a stage unresponsive to statins because of calcification or inflammation. Alternatively, the noncoronary mechanisms discussed may have become the major perpetrators. This alternative is further supported by the recent observation that in patients with advanced CKD 4 or 5, intensified multiple risk factor intervention for 2 yr compared with conventional care failed to modify significantly vascular abnormalities (carotid intima media thickness and endothelial function as evaluated by brachial artery reactivity); it also failed to affect cardiovascular events (80). It remains sensible, however, to start intervention with statins in early stages of CKD, when they are still effective (81).

Let us come back to the above case: What is the best guess for what caused his sudden death? As a type 2 diabetic, he was certainly at high risk for an MI, and this possibility is by no means excluded by the fact that before the event he was completely asymptomatic. This is the rule, rather than the exception, in diabetics with uremia and advanced autonomic neuropathy. A further good possibility is hyperkalemia, usually the consequence of dietary indiscretion with or, in this case, without insufficient dialysis.

A more theoretical possibility is a potential adverse role of his treatment with a sulfonyleurea compound. Sulfonyleureas target ATP-dependent K^+ channels in the pancreatic β cells, but an isoform of these receptors is also present in the heart sarcolemma and mitochondria. Inhibitors of the opening of these cardiac K_{ATP} channels interfere with ischemic preconditioning of the heart and have been claimed to increase cardiac risk, although recent observational data appear reassuring (82,83).

Possibly the absence of β blocker therapy might have been a predisposing factor, although in nonrenal patients, verapamil (which the patient received) was equivalent to β blockers in diabetic patients with coronary heart disease patients (84). So I cannot see what else in the management of this case could have prevented this all-too-common catastrophe.

Question and Answers

1. Dr. Ajay K. Singh (Renal Division, Brigham and Women's Hospital, Associate Professor of Medicine, Harvard Medical School): Professor Ritz, thank you for your case discussion and the comprehensive review on the syndrome of sudden death. I would like to ask you to elaborate on the potential role that automated defibrillator devices play in preventing sudden death. What do we know about the benefits? What type of patients should receive these devices?

Prof. Ritz: Certainly the results with ICD in patients with CKD are worse than in nonrenal patients. I agree with the strong but so far unsuccessful plea of Charles Herzog, however, that to be sure about the real value in dialysis patients, one has to conduct a controlled prospective trial—and, I add, accompanied by optimal conservative treatment in the intervention and control arms including β blockers. In the absence of definitive evidence, the cardiologist/nephrologist team must make decisions with clinical common sense.

2. Dr. Colm Magee (Renal Division, Brigham and Women's Hospital, Assistant Professor of Medicine, Harvard Medical School): Professor Ritz, my impression is that an ST segment elevation MI (or, to put it another way, acute coronary artery occlusion due to plaque rupture and thrombosis) is a relatively uncommon phenomenon in dialysis patients. Is this true?

Prof. Ritz: You are right, and you are wrong: The *relative proportion* of dialyzed patients dying from ST segment elevation is small relative to the patients dying without clinical signs of coronary disease from sudden death or heart failure. To be absolutely sure, one would of course wish to have solid autopsy data. On the other hand, if you calculate the *absolute* rates per 1000 patient-years, then you will certainly find that it is higher than in the background population.

3. Dr. Joseph V. Bonventre (Director, Renal Division, Brigham and Women's Hospital, Robert Ebert Professor of Medicine, Harvard Medical School): Coronary disease is common in patients with CKD. Could you elaborate on the contribution of myocardial ischemia to the syndrome of sudden death in patients with CKD?

Prof. Ritz: In the absence of solid clinical data, the best approach is to analyze the available experimental data. In the subtotally nephrectomized rat, we found with Dr. Amann less capillaries in the heart, thicker intramyocardial arteries (both causing presumably less coronary perfusion reserve in response to increased demand, as in syndrome X), and finally with Dikow we found that ischemia tolerance was reduced and infarct size bigger. Information on the hypoxia sensor HIF1 α might clarify the underlying pathomechanisms, but as of today we don't have the smoking gun to identify the culprit for diminished ischemia tolerance. We also don't know the relative importance of vascular *versus* metabolic factors reducing ischemia tolerance. The problem has, however, extreme clinical relevance, since interventions must be targeted to relevant culprit mechanisms (currently ongoing experiments in MI concerning organoprotection use, for instance, erythropoietin, but also glucose-insulin infusion, etc.).

4. Dr. J. Kevin Tucker (Renal Division, Brigham and Women's Hospital, Assistant Professor of Medicine, Harvard Medical

School): Do you have information on the syndrome of sudden death among patients on daily or nocturnal dialysis?

Prof. Ritz: I don't have information. Given the small numbers of patients on this procedure and given the fact that they are not representative for the current dialysis population, even if we had data, they would be difficult to interpret. The ongoing trial might in the future give at least a hint. Intuitively, I would say the chances are excellent that the patients on these forms of dialysis do better with respect to sudden death: They have lower BP, less electrolyte fluctuations, less sympathetic overactivity, etc.

5. Dr. Huong Tran (Renal Division, Brigham and Women's Hospital, Research Fellow, International Society of Nephrology Fellow): Dr. Ritz, could you please discuss the role of hypertension as a risk factor for sudden death in dialysis patients?

Prof. Ritz: We know that LVH and cardiac interstitial fibrosis predispose to sudden death, so one can be sure that hypertension, which not only causes LVH but also promotes progression of LVH and fibrosis in experimental models such as the subtotally nephrectomized rat, will presumably increase the risk for sudden death.

Dr. Stefan G. Tullius (Chief, Division of Transplant Surgery, Brigham and Women's Hospital, Associate Professor of Medicine, Harvard Medical School): Could you please address the influence of secondary and tertiary hyperparathyroidism as a risk factor for the syndrome of sudden death? Is the rate of sudden death reduced following subtotal parathyroidectomies?

Prof. Ritz: I don't know. One reason why this is an appropriate and important question is the finding by Block which I mentioned that hyperphosphatemia is associated with increased sudden death. Is it phosphate *per se*? Is it parathyroid hormone, or is it some third culprit, like FGF23? We don't know.

Dr. Julie Lin (Renal Division, Brigham and Women's Hospital, Assistant Professor of Medicine, Harvard Medical School): I am interested in whether β blockers modulate the risk for developing sudden death in this population. More specific, are dialysis patients who are not taking β blockers at higher risk for sudden death?

Prof. Ritz: There is only one relatively small trial available from Naples concerning dialysis patients with cardiomyopathy (60). Carvedilol caused in this study a dramatic reduction of death with a suggestion of less sudden death (which was not statistically significant, however). Whether this finding in cardiomyopathic dialysis patients can be generalized is uncertain. It is equally uncertain, if not unlikely, that all β blockers are created equal. Given the extreme sympathetic overactivity in uremia, I assume that β blockers will affect sudden death.

What observational data (a study of ours and apparently never fully published URREA data [85]) suggest is that the risk for cardiovascular death and overall death, respectively, is less in dialysis patients on β blockers (58,59). There are, to the best of my knowledge, no specific data available on sudden death.

Disclosures

None.

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