

## Sudden Death, A Common Cause of Death in Japanese Hemodialysis Patients

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See article vol. 27: 306-318

There is a large difference in the reported cause of cardiac death in dialysis patients between Japan and other countries. In Japan, 26% of deaths are due to heart failure and only 2.5% of deaths are caused by sudden cardiac death (SCD)<sup>1)</sup>, whereas in the United States, 28% of deaths are caused by SCD and only 4% of deaths are due to heart failure<sup>2)</sup>, according to the national data in both countries. Thus, the major cause of cardiac death in Japan is heart failure, whereas it is SCD in the United States, one of the leading countries for dialysis medicine in the world. One of the reasons for this big difference may be no currently established and accepted definition of SCD in the clinical setting. A recent meta-analysis<sup>3)</sup> analyzing the incidence of SCD in patients with end-stage kidney disease clearly showed a complicated situation, wherein the definition of SCD varied among the 43 included studies. In these studies, there was no obvious definition of SCD in 26 studies and the remaining 17 studies included time in their definition of SCD. The most common definitions of SCD were “death occurring within 1 h of symptom onset with no clinical support for another cause” and “death occurring within 24 h of symptom onset with no clinical support for another cause”<sup>4)</sup>.

Several recent articles have suggested that the incidence of SCD in Japanese dialysis patients is higher than was previously thought<sup>5, 6)</sup>. Hiyamuta *et al.*<sup>7)</sup> performed a multicenter longitudinal observational cohort study and reported a notable finding about sudden death in Japanese hemodialysis (HD) patients on this issue. They focused on a search for the incidence and associated factors of sudden death in their study, which included 3505 Japanese HD patients. During the 10-year follow-up period, 1735 patients died, including 227 (13%) cases of sudden death, which is defined as witnessed death within 24 h

of the onset of acute symptoms and unwitnessed unexpected death within the interval between dialysis sessions, excluding causes such as trauma, suicide, and suffocation. Taking these studies into account, it would appear that SCD is more common in the Japanese dialysis clinical setting than was previously thought, and its incidence in Japan appears to be still low, but close to that in other countries.

Two major questions regarding SCD in Japanese HD patients remain unanswered. We have believed and accepted the common sense theory that fatal arrhythmia is the central cause of sudden death in HD patients because of the high prevalence of latent coronary artery disease<sup>8)</sup> and cardiac functional morphological abnormalities<sup>9)</sup> in them and because they have a high rate of triggers for ventricular arrhythmias, such as volume expansion and electrolyte shifts, which occur routinely. According to the findings from an autopsy study<sup>10)</sup>, only one-fourth of sudden deaths are due to a suspected fatal arrhythmic event, which includes acute myocardial infarction, arrhythmia, and hyperkalemia. Thus, fatal arrhythmia as a cause of sudden death in HD patients might be fewer than was previously thought. In the study of Hiyamuta *et al.*<sup>7)</sup>, it is of interest that about 25% of sudden deaths, which is almost the same percentage as that reported in an autopsy study<sup>10)</sup>, were found to develop on Monday, after a long interval day of HD schedule that fatal arrhythmia is most likely to develop.

In general, most SCD events are believed to be due to fatal ventricular arrhythmias, ventricular tachycardia, or ventricular fibrillation. The second question is whether this ordinary concept is applicable to HD patients. A recent clinical study by an Australian group has shown an impressive finding that all SCD events in HD patients were caused by bradycardia and asystole, such as sudden cardiac arrest (SCA) without ventricular arrhythmia and advanced atrioventricular block<sup>11)</sup>. Even though their study had a small sample size, they explored the cause of death using a loop

recorder, which is an implanted monitor used to identify the cause of syncope in clinical practice. During a 1-year follow-up period, they confirmed five SCD events, and fatal bradyarrhythmia was recorded at the time of each event in four patients; this means that no fatal ventricular tachyarrhythmias were observed in the four HD patients with SCD<sup>11</sup>). In addition, it has been reported that SCD was more often seen in the long interdialytic period in HD week<sup>11</sup>). A similar finding was confirmed by a study from a Brazilian group, which showed a high frequency of fatal bradyarrhythmia monitoring using loop recorders in 100 chronic HD patients<sup>12</sup>). The two key words “bradyarrhythmia” and “long interdialytic period” remind us that severe bradyarrhythmia due to hyperkalemia may lead to sudden death. Unfortunately, potassium levels were not added to the risk analysis for sudden death in the study of Hiyamuta *et al.*<sup>7</sup>). On the other hand, high phosphorus levels associated with sudden death in the study may be explained via bradyarrhythmia. Although it is not beyond the hypothesis, hyperphosphatemia might induce the calcification of myocardial conduction system and cause fatal bradyarrhythmia. Several autopsy case reports in dialysis patients have demonstrated the association of degenerated calcification of the atrioventricular (AV) node with sudden death due to bradyarrhythmia<sup>13, 14</sup>). These findings do not necessarily imply that fatal ventricular tachyarrhythmias are not one of the underlying cause of SCD in HD patients, however, we need to pay more attention to bradyarrhythmias, such as advanced AV block and SCA, as a cause of SCD.

Even in Japanese dialysis patients, who have a better prognosis than dialysis patients in the other countries of the world, further study is necessary to know whether the incidence SCD due to fatal arrhythmia is actually high and whether it is mainly due to ventricular tachyarrhythmia.

### Conflict of Interest

NJ, YT, and TH declare having received honoraria as a speaker from Chugai Pharmaceutical and Kyowa Kirin.

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