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Reverse Epidemiology of Hypertension and Cardiovascular Death in the Hemodialysis Population

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Abstract—Maintenance hemodialysis patients in the United States have a high prevalence (≈80%) of systolic hypertension and a high mortality (≈20% per year). Some reports indicate a paradoxical association between hypertension and morality in hemodialysis patients (ie, a normal to low blood pressure is associated with poor outcome), whereas high pressure confers survival advantages, a phenomenon referred to as "reverse epidemiology." We hypothesized that malnutrition-inflammation complex syndrome may be a cause of this paradoxical association. We studied a 15-month cohort of 40 933 hemodialysis patients in the United States whose predialysis and postdialysis blood pressure values were recorded routinely during each hemodialysis treatment. Patients were 59.8±15.3 years old; 54% were women and 46% diabetics. Cox proportional hazard models were used for blood pressure categories (systolic <110, ≥190 mm Hg; diastolic <50, ≥110; and increments of 10 mm Hg in between). Unadjusted, case-mix and dialysis dose–adjusted, and additional malnutrition-inflammation–adjusted hazard ratios of all-cause and cardiovascular death showed progressively increasing all-cause and cardiovascular death risk for decreasing blood pressure values. The lowest mortality was associated with predialysis systolic pressure of 160 to 189 mm Hg, whereas normal to low predialysis pressure values were associated with significantly increased mortality. Adjustment for the malnutrition-inflammation mitigated only a small portion of paradoxical associations between the low blood pressure and mortality. Predialysis systolic hypertension remained a significant predictor of highest all-cause and cardiovascular survival rate. Although these associations may not be causal, they call into question whether treatment goals for the general population can be applied to dialysis patients or other similar populations. (***Hypertension*. 2005;45[part 2]:811-817.)**

Key Words: epidemiology ■ cardiovascular diseases

Eighty percent of a 250 000 maintenance hemodialysis (MHD) patients in the United States have systolic hypertension (HTN).[1] Approximately two thirds of American MHD patients die within 5 years of initiation of chronic dialysis treatment, mostly because of cardiovascular (CV) disease.[1] HTN is a known risk factor of CV disease in the general population.[2] Hence, HTN has been implicated as a major cause of poor clinical outcome and high mortality in MHD patients. However, efforts to treat conventional CV risk factors in MHD patients including HTN, hypercholesterolemia, and hyperhomocysteinemia have not resulted in significant improvement of their poor clinical outcome.[1] Surprisingly, several recent studies have indicated an inverse association between blood pressure (BP) values and death in MHD patients (ie, a high mortality rate has been paradoxically observed in MHD patients who have a low rather than a high predialysis BP, whereas high BP values have been shown to confer survival advantages).[3–5] Similar inverse associations have also been observed between mortality and body mass index (BMI),[6] serum concentrations of cholesterol,[7] homocysteine,[8] and advanced glycation end-products,[9] and other traditional risk factors. The phenomenon has been referred to as reverse epidemiology.[10] In addition to MHD patients, an estimated number of 20 to 40 million Americans may have a reverse epidemiology, including patients with advanced age, chronic heart failure (CHF), AIDS, and malignancies.[11] The occurrence of protein-energy malnutrition and inflammation, together also known as malnutrition-inflammation complex syndrome (MICS), which is frequently found in MHD patients, has been implicated as a main cause of the reverse epidemiology in MHD patients.[10,12] However, it is not clear whether MICS can explain the entire reverse epidemiology of HTN in MHD patients. We hypothesized that the reverse epidemiology of HTN is a robust phenomenon for all-cause and

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CV death and holds even after exhaustive multivariate adjustment in a large national database. In this article, we examine specifically whether MICS can explain a significant portion of this risk factor reversal.

Methods

Database Creation

The data warehouse of DaVita, Inc., the second largest dialysis care provider in the United States, with >500 dialysis facilities and ≈40 000 patients across the country at any given time, includes comprehensive information on virtually all of its patients. A 15-month cohort (April 2002 through June 30, 2003) of these patients was studied. This period was selected because patients' predialysis and postdialysis BP values during each 3× weekly hemodialysis session began to be registered electronically starting in early 2002. All repeated measures of every relevant variable for each patient within the entry quarter (during the first 13 weeks on the start of observation) were averaged to obtain 1 quarterly mean value for that variable. The study was approved by institutional review committees of Harbor-University of California, Los Angeles (UCLA) and DaVita.

BP Measures

Prehemodialysis and posthemodialysis BP values were measured routinely via automatically inflated cuffs using a digital monitor attached to each hemodialysis machine while patient was sitting on the dialysis station chair adjacent to the dialysis machine. Ten categories of systolic BP (<110 mm Hg, ≥190 mm Hg and 8 categories from 110 to 190 with 10 mm Hg increments) and 8 categories of diastolic BP (<50 mm Hg, ≥110 mm Hg and 6 categories from 110 to 190 with 10 mm Hg increments) were created. Patients with missing BP values in all quarters or with values below the 0.25th or above the 99.75th percentile levels were excluded.

Cohort Time, Dialysis Vintage, and Death

Cohort time included the number of days patients participated in the cohort and was a number between 1 and 457 days. Dialysis vintage was defined as the duration of time between first day of dialysis treatment and the first day that patients entered the cohort. Five categories of vintage were formed: (1) first 6 months, (2) between 6 and 24 months, (3) between 2 and 5 years, and (4) >5 years. The entry quarter was defined as the first quarter in which a patient's dialysis vintage was >3 months for at least half the duration of the quarter. By implementing this criterion, any patient who had not maintained in the cohort beyond the first 3 months of MHD was excluded. The causes of death, obtained from the computerized database, reflecting the reported information in the Cause of Death form (Form 2746), were obtained and summarized into 6 main categories: CV, infectious, gastrointestinal, cancer related, others, and unspecified/unknown.

Laboratory Data

Most blood samples were predialysis with the exception of postdialysis serum urea nitrogen to calculate urea kinetics. Blood samples were drawn using uniform techniques in all dialysis clinics across the nation and were transported to the Central DaVita Laboratory in Deland, Fla, within 24 hours. All laboratory values were measured via automated and standardized methods in DaVita Laboratory. Most laboratory values, including complete blood cell counts and serum levels of serum urea nitrogen, albumin, creatinine, ferritin, and total iron-binding capacity (TIBC), were measured monthly. Serum ferritin was measured quarterly. Hemoglobin was measured weekly to biweekly in most patients. Kt/V to reflect dialysis dose and normalized protein nitrogen appearance (nPNA), an estimation of daily protein intake, were measured monthly according to Daugirdas et al.[13]

Eight laboratory variables were selected to indicate the nutritional state and presence of inflammation, together also known as MICS:[12] (1) serum albumin, which has strong associations with inflammation and prospective mortality in MHD patients;[14,15] (2) nPNA as a marker of daily protein intake and an outcome predictor;[16] (3) serum TIBC, known to have a strong association with subjective global assessment of nutrition;[17,18] (4) serum ferritin, a possible inflammatory marker;[19,20] (5) serum creatinine, a marker of muscle mass;[21] (6) peripheral white blood cell count (WBC), which is reported to correlate with serum C-reactive protein (CRP) and to predict survival in MHD patients;[22,23] (7) Percent of lymphocytes in the WBC, a known nutritional marker that has been shown recently to have independent associations with mortality in MHD patients;[23,24] and (8) blood hemoglobin, an outcome predictor in MHD patients.[17,25]

Epidemiologic and Statistical Methods

Because the dialysis population is a dynamic cohort with a high turnover rate, a nonconcurrent cohort was formed to include all existing MHD patients of the first quarter (q1) and all new MHD patients of the subsequent quarters (q2 through q5). Hence, 5 quarterly data sets were merged using unique patient identifiers. A baseline value was created for each measure by left-truncating the first available 3-month averaged value of the entry quarter for each patient.

In addition to standard descriptive statistics, Cox proportional hazard regression for truncated and censored data was used to determine whether the 15-month survival was associated with baseline categories of BP. The reference category for all analyses was 130 to 149.9 mm Hg for systolic BP and 70 to 79.9 mm Hg for diastolic BP. These categories were chosen as the reference because they were the modal category (or adjacent to the modal category with similar sample size as the modal category) and because they had one of the highest numbers of death cases and allowed for most precise comparison with other BP categories. Five race/ethnic groups were generated: (1) whites (including non-Hispanic whites and Middle Easterners), (2) African Americans (including blacks and other Africans), (3) Asians (including Pacific Islanders), (4) American Indians, and (5) others.

For each analysis, 3 models were examined based on the level of multivariate adjustment. (1) Unadjusted model included BP categories and mortality data as well as the entry quarter indicators because of the nonconcurrent nature of the constructed cohort; (2) Case-mix– and dialysis dose–adjusted models also included age, gender, race and ethnicity, diabetes mellitus, vintage categories, primary insurance (Medicare, Medicaid, private, and others), marriage status (married, single, divorced, widowed, and others), standardized mortality ratio of the dialysis clinic during entry quarter as calculated by the US Renal Data System (USRDS),[1] residual renal function during the entry quarter (Kru), and the Kt/V (single pool); and (3) Case-mix– and MICS-adjusted models included all the above-mentioned covariates as well as 9 indicators of nutritional state and inflammation, including nPNA and serum albumin, TIBC, ferritin and creatinine, WBC, lymphocyte percentage, hemoglobin level, and BMI (ie, the postdialysis dry weight [kg] divided by height squared [m^2]), that correlate with outcome.[6] Missing covariate data (<5%) were imputed by the mean or median of the existing values. All descriptive and multivariate statistics were performed via SAS, version 8.02 (SAS Institute).

Results

The original 15-month national database of all MHD patients included 63 592 subjects. After implementing the above-mentioned selection and merging criteria, including deleting patients who did not maintain beyond 3 months of MHD or who had inadequate or overtly missing data, the resulting cohort included 48 987 MHD patients, of whom 32 873 (67%) originated from the q1 data set and the rest from q2 through q5. Of these 48 987 MHD patients, 40 933 had ≥1

TABLE 1. Baseline Data of the Nonconcurrent (Left Truncated) Cohort of 40 933 MHD Patients, Including 32 873 Patients (67%) From the q1 and 8080 (32%) From q2–q5

Variable	Mean±SD or %
Age, years	59.8±15.3
>65 years old, %	41.2
Sex, % women	53.9
Diabetes mellitus, %	45.6
Race and ethnicity	
Caucasians, %	35.0
Blacks, %	33.4
Asians, %	3.2
Hispanics, %	16.0
Vintage, time on dialysis	
3–6 months, %	26.2
6–24 months, %	26.8
2–5 years, %	30.1
>5 years, %	16.9
Primary insurance	
Medicare, %	62.2
Medicaid, %	5.8
Causes of death	
CV, %	48.4
Infectious, %	11.9
Cancer, %	2.9
Gastrointestinal, %	2.0
Others, %	9.0
Unknown/unspecified, %	25.8
Standardized mortality ratio	0.8±0.2
Cohort time, months	9.6±8.5
Post-HD weight, kg	74.5±20.0
BMI, kg/m^2	26.3±6.2
Kt/V, single pool	1.6±0.3
nPCR or nPNA, g/kg per day	1.0±0.3
Serum albumin, g/dL	3.8±0.4
Creatinine, mg/dL	9.1±3.2
Ferritin, ng/mL	570±444
TIBC, mg/dL	199.7±40.4
Blood hemoglobin, g/dL	12.1±1.2
WBC, per fL	7178±2202
Lymphocyte, % of total WBC	21.2±7.6
Predialysis systolic BP, mm Hg	153±23
Predialysis diastolic BP, mm Hg	79±13
Postdialysis systolic BP, mm Hg	141±22
Postdialysis diastolic BP, mm Hg	73±12

HD indicates hemodialysis; nPCR, normalized protein catabolic rate.

3-month–averaged measure of BP during the 5 quarters and formed the final cohort. Table 1 shows baseline demographic, clinical, and laboratory characteristics of the nonconcurrent cohort. CV cause of death was documented in 48% of all expired patients. Table 2 shows the predialysis systolic and diastolic BP categories and the all-cause and CV mortality among them. Low BP categories had the highest 15-month mortality rates.

TABLE 2. Predialysis Systolic and Diastolic BP Groups and 15-Month Mortality

	Sample Size (%)	All-Cause Death (%)	CV Death (%)
Predialysis systolic BP, mm Hg			
<110	1015 (2.5)	398 (39.2)	190 (18.7)
110–119	1686 (4.1)	435 (25.8)	218 (12.9)
120–129	3132 (7.7)	608 (19.4)	273 (8.7)
130–139 (base group)	5443 (13.3)	852 (15.7)	407 (7.5)
140–149	6917 (16.9)	941 (13.6)	458 (6.6)
150–159	7452 (18.2)	955 (12.8)	480 (6.4)
160–169	6436 (15.7)	709 (11.0)	353 (5.5)
170–179	4481 (11.0)	537 (11.9)	268 (5.9)
180–189	2452 (6.0)	296 (12.1)	135 (5.5)
≥190	1907 (4.7)	285 (14.9)	131 (6.9)
All patients	40 921	6016 (14.7)	2913 (7.1)
Predialysis diastolic BP, mm Hg			
<50	317 (0.8)	139 (43.9)	54 (17.0)
50–59	2236 (5.5)	692 (31.0)	344 (15.4)
60–69	7186 (17.6)	1415 (19.7)	676 (9.4)
70–79 (base group)	12132 (29.6)	1708 (14.1)	841 (6.9)
80–89	10 945 (26.7)	1236 (11.3)	604 (5.5)
90–99	5519 (13.5)	548 (9.9)	268 (4.9)
100–109	1919 (4.7)	195 (10.2)	92 (4.8)
≥110	678 (1.7)	88 (13.0)	36 (5.3)
All patients	40 932	6021(14.7)	2915 (7.1)

Table 3 shows the hazard ratios of all-cause mortality for different predialysis systolic and diastolic BP categories. The baseline predialysis systolic BP group of 180 to 189 mm Hg was associated with the lowest adjusted prospective mortality. Predialysis diastolic BP in range of 70 to 99 mm Hg exhibited the lowest death rates. The Figure shows the hazard ratios of CV death for all 4 groups of predialysis and postdialysis (systolic and diastolic) BP values. Trends were similar to those seen for all-cause mortality (Table 3). Stepwise addition of some of the case-mix covariates to the unadjusted model showed that the age contributed substantially to the observed difference between the 2 models. Sensitivity analysis, including constructing the same multivariate models using the subcohort of 32 873 MHD patients from q1, resulted in similar hazard ratios (data not shown). Further subgroup evaluation of the elevated mortality risk associated with low predialysis systolic BP indicated similar patterns for diabetic and nondiabetic patients and for MHD patients at different age and race groups, as well as dialysis dose, vintage, and serum albumin categories (data not shown).

Discussion

The role of HTN as a CV risk factor in the general population is indisputable. Even high-normal BP confers a significantly greater risk of cumulative incidence of CV events.[2] Several

TABLE 3. Hazard Ratios of All-Cause Death for Predialysis Systolic and Diastolic BP Categories Based on Cox Regression Models

	Unadjusted		Case-Mix and Kt/V Adjusted		Case-Mix and MICS Adjusted	
All-Cause Death	Hazard Ratio (95% CI)	*P* Value	Hazard Ratio (95% CI)	*P* Value	Hazard Ratio (95% CI)	*P* Value
Systolic BP range						
<110	2.11 (1.87–2.38)	<0.0001	1.95 (1.73–2.2)	<0.0001	1.60 (1.42–1.81)	<0.0001
110–119	1.40 (1.25–1.57)	<0.0001	1.36 (1.21–1.53)	<0.0001	1.20 (1.07–1.35)	0.002
120–129	1.22 (1.10–1.35)	0.20	1.22 (1.1–1.36)	0.0002	1.17 (1.05–1.3)	0.004
130–139 (base)	1.00	N/A	1.00	N/A	1.00	N/A
140–149	0.87 (0.80–0.96)	0.10	0.89 (0.81–0.97)	0.012	0.90 (0.82–0.99)	0.02
150–159	0.82 (0.74–0.89)	0.02	0.85 (0.77–0.93)	0.0004	0.88 (0.8–0.96)	0.005
160–169	0.74 (0.67–0.82)	0.0006	0.77 (0.7–0.85)	<0.0001	0.81 (0.73–0.9)	<0.0001
170–179	0.79 (0.71–0.88)	0.04	0.82 (0.74–0.91)	0.0003	0.88 (0.79–0.98)	0.02
180–189	0.76 (0.67–0.87)	0.0006	0.74 (0.65–0.85)	<0.0001	0.81 (0.71–0.92)	0.002
≥190	0.96 (0.84–1.09)	0.39	0.98 (0.86–1.12)	0.77	1.06 (0.92–1.21)	0.43
Diastolic BP range						
<50	2.52 (2.11–3.00)	<0.0001	2.26 (1.9–2.7)	<0.0001	2.00 (1.68–2.39)	<0.0001
50–59	1.92 (1.76–2.10)	<0.0001	1.67 (1.53–1.83)	<0.0001	1.46 (1.33–1.6)	<0.0001
60–69	1.37 (1.28–1.47)	<0.0001	1.25 (1.17–1.35)	<0.0001	1.19 (1.1–1.27)	<0.0001
70–79 (base)	1.00	N/A	1.00	N/A	1.00	N/A
80–89	0.85 (0.79–0.91)	0.003	0.97 (0.9–1.04)	0.38	1.00 (0.93–1.07)	0.92
90–99	0.73 (0.67–0.81)	<0.0001	0.93 (0.84–1.03)	0.16	0.97 (0.88–1.07)	0.55
100–109	0.78 (0.67–0.90)	0.008	1.06 (0.91–1.23)	0.47	1.10 (0.94–1.29)	0.22
≥110	0.84 (0.67–1.03)	0.04	1.28 (1.03–1.6)	0.026	1.30 (1.04–1.62)	0.02

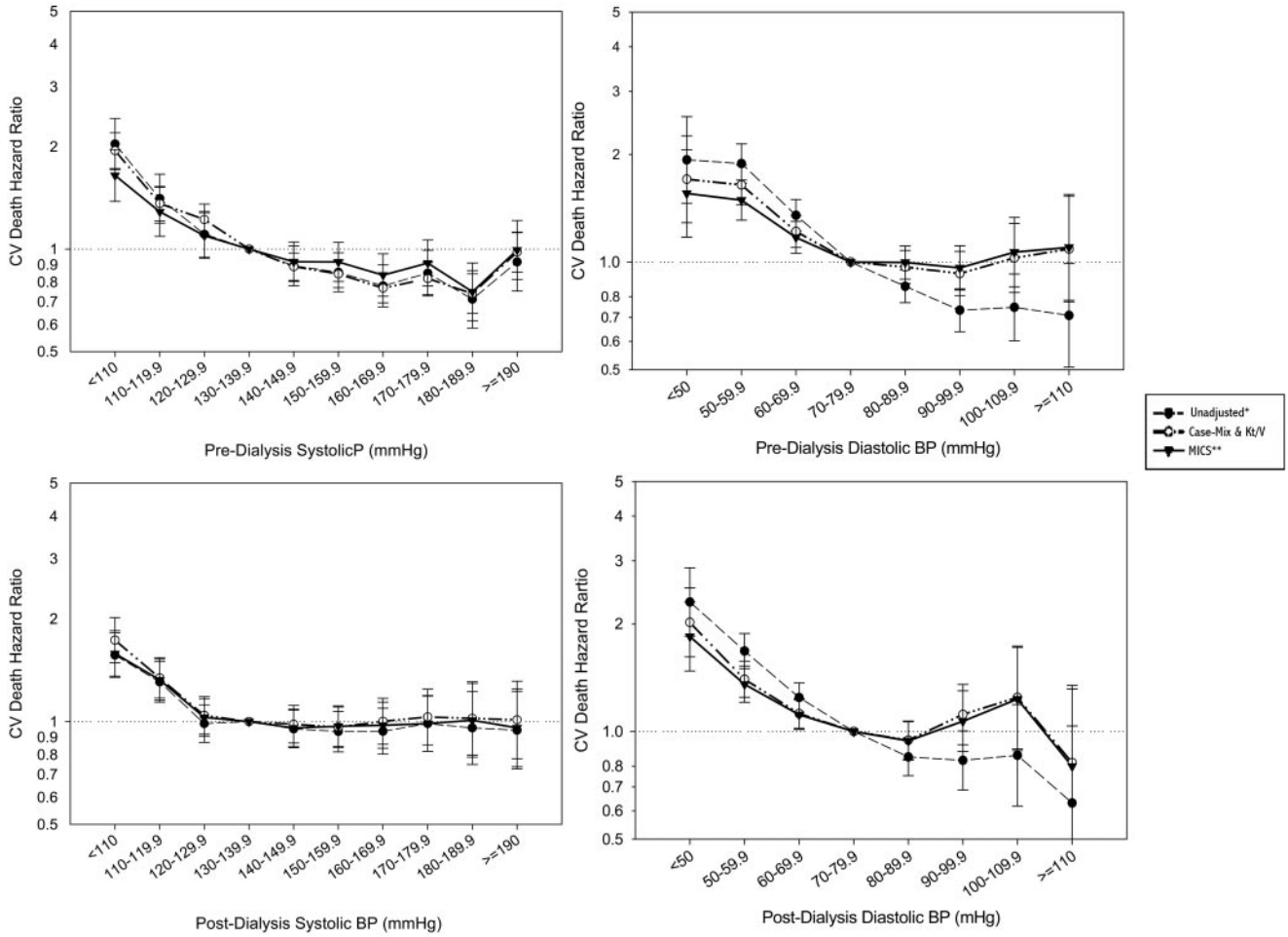
CI indicates confidence interval.

reports have shown an HTN prevalence of 70% to 90% among MHD patients.[1,26] Similar to the general population, some studies have also suggested that HTN in MHD patients is associated with increased mortality risk.[27] This has led several advisors to advocate tight control of predialysis BP (eg, systolic BP >140 mm Hg) as an indicator of quality of care by dialysis facilities.[28]

However, recent studies with large sample sizes have failed to find that high BP is an independent mortality risk factor in MHD patients. In a cross-sectional study of 936 MHD patients in the HEMO study, Cheung et al[29] reported no significant association between predialysis systolic BP and any of the CV disease end points. Indeed, recent studies of MHD patients point to a paradoxical link between low BP and poor survival, whereas high BP appears to confer survival advantages. Although the adverse consequences of low BP are not a new concept, its impact on dialysis outcome and on CV mortality has been underappreciated. In our current study, the death risk is most prominent when systolic and diastolic BP values are <120 and 70 mm Hg, respectively. Iseki et al[30] showed a strong association between low diastolic BP and risk of death in a cohort of 1243 MHD patients who were followed up for 5 years. Zager et al,[3] in a study of 5433 MHD patients followed up for a mean of 2.9 years, noted that the relative death rate for patients with predialysis or postdialysis hypotension (systolic BP <110 mm Hg) increased to 4× normal or >2.5× normal, respectively. Port et al[4] analyzed data from 4839 MHD patients in the USRDS Case Mix Adequacy Study and found that when predialysis systolic BP decreased below the reference group (120 to 149 mm Hg), the relative mortality risk increased at BP measurements <110 mm Hg. Fleischmann et al[31] found that the cumulative hazard for dying was strongly associated with the predialysis BP tertiles, with the lowest survival in the lowest third and the best survival in the upper third. Klassen et al[5] studied a 12-month cohort of 37 069 MHD patients and confirmed the reverse association between all-cause mortality and predialysis systolic BP as well as pulse pressure. The negative (reverse) association between pulse pressure and death became partially positive only after controlling for systolic BP. However, systolic BP and pulse pressure correlated strongly (R^2=0.72);[5] hence, such overadjustment may remove a substantial amount of the natural contribution of pulse pressure on mortality. A correlation of low predialysis systolic BP with increased mortality has also been reported by Lowrie et al,[32] Duranti et al,[33] and Salem et al.[34]

Similar to MHD patients, a reverse epidemiology of HTN has also been observed in CHF patients.[35] Ghali et al[36] showed that systolic and diastolic BP were lower in the deceased CHF patients compared with the survivors. Rihal et al[37] and Cowie et al[38] showed that low systolic BP was independently predictive of subsequent mortality in CHF. Similarly, in the Rotterdam Study, a higher BP conferred a more favorable prognosis in CHF patients.[39] In another study, systolic BP was among very few independent predictors of better survival in 1033 elderly CHF patients.[40] Similar findings were reported by Muntwyler et al[41] and Poole-Wilson et al[42] for paradoxical effect of systolic BP on mortality in CHF patients.

Historically, HTN is associated with concentric left ventricular hypertrophy, ventricular dilatation, ischemic



Association between BP and 15-month CV death in 40 933 MHD patients (95% confidence interval bars are depicted). Note that the unadjusted models also include entry quarter. **MICS-adjusted models also include all covariates in the previous models.

heart disease, and CHF. However, after development of cardiac failure, low BP predicts mortality and is a potential marker for severity of cardiac disease.[27,43] Hence, it is possible that low BP in MHD patients is preceded by HTN and its CV consequences during early stages of chronic kidney disease; although mechanisms that maintain elevation of BP may fail gradually by the time the end-stage renal disease is reached, the impaired CV system may persist. In addition, patients presenting with baseline predialysis hypotension may possess such subclinically significant risk factors or comorbidities as heart failure or ischemic cardiomyopathy.[30] However, even if we assume that the reverse association between BP and mortality in MHD patients is attributable to coexistence of CHF in these patient populations, the question as to why the reverse epidemiology exists in CHF patients remains to be answered. Low BP may also be a reflection of autonomic neuropathy that, in turn, is a marker for more severe uremic complications. Because antihypertensive drug therapy may contribute to low predialysis systolic BP, one may hypothesize that either overmedication (perhaps specific antihypertensive agents) or cardiac pump failure is the major contributor to the observed associations. We did not have the medication data for this cohort, and to our knowledge, virtually no other study has examined the potential role of medications as a cause of low BP and increased mortality in such large populations of dialysis patients.

The concept of reverse epidemiology may appear counterintuitive, especially because HTN is an established risk factor for CV disease and poor outcome in the general population. Nonetheless, given the consistency of the observations among MHD patients, there must be population-specific conditions, which render these populations more susceptible to a poor outcome when low BP is present while protecting them when HTN coexists. Several explanations have been suggested, including a more stable hemodynamic status and neurohormonal alterations in obese and hypertensive individuals,[44] endotoxin–lipoprotein interaction,[45] reverse causation,[46] survival bias,[10] time discrepancies among competitive risk factors (overnutrition versus undernutrition),[10] and the overwhelming effect of MICS on traditional CV risk factors.[12] Moreover, normal to low predialysis BP may increase the risk of ischemic injury during the hemodialysis and ultrafiltration procedures leading to increased mortality in MHD patients.[47] Because most MHD patients die within 5 years of commencing dialysis treatment, the long-term effects of conventional CV risk factors on future mortality might be overwhelmed by

the short-term effects of these or other risk factors intrinsic to dialysis populations, such as undernutrition and inflammation, together known as MICS. Hence, dialysis patients do not live long enough to die of the consequences of HTN. If that is true, the wisdom of aggressive antihypertensive therapy in the setting of poor short-term outcome should be re-evaluated.

Our study lacked data on the history of CV comorbidity, heart rate, and medications in our MHD patients. However, data concerning the presence or absence of diabetes mellitus were available and were adjusted for in all multivariate models. Moreover, many other covariates included in the models are known to have strong associations with comorbid conditions. Hence, we suspect that the associations would not have been very different if additional adjustments had been made for other comorbidities. Limited comorbidity data used in some previous studies by others usually originate from the dialysis initiation form (Form 2728), in which comorbid conditions are significantly under-reported[48] and which is outdated for prevalent MHD patients with higher vintage periods. Another limitation of our study may be lack of explicit laboratory markers of inflammation such as CRP. We did use data on serum albumin, ferritin, and TIBC and WBC, and lymphocyte percentage tend to vary significantly with inflammation.[17–20,22] Another limitation of our analysis is that it is based on only a 15-month follow-up, rather than a longer period of observation, and so may not apply to long-term survival. Nonetheless, two thirds of MHD patients die within the first 5 years of initiation of dialysis.[1] The narrow time window of our study ensures that confounding by changes in practice or technology is minimal. Our study has by far the largest sample size to date, and our data originate from 1 dialysis care provider that has uniform patient management practices; all laboratory measurements are performed in 1 single facility, and most data are means of several measures. Hence, measurement variability is minimized. Moreover, we specifically studied CV death in addition to all-cause mortality that was the sole focus of previous studies. We found that the inverse trend persisted even after exhaustive multivariate adjustment. Hence, other mechanisms are likely to be involved.

Perspective

Although these paradoxical associations may not be causal, the reverse epidemiology of HTN and its relative survival advantage in MHD and CHF patients or other similar populations may have major clinical and public health implications. Extrapolation of data from studies in the general population and imposing their guidelines to 20 to 40 million Americans with a reverse epidemiology may be inappropriate if additional studies confirm our findings. Studies targeting unique characteristics of these distinct populations are urgently needed to find answers to these questions and, if indicated, to modify and tailor HTN guidelines for such individuals as MHD and CHF patients.

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