The increasing emphasis on patient-centered care has refocused research interests, and hemodialysis patients have identified symptom management as a top research priority.1,2 A recent study analyzed the top 3 prioritized physical symptoms of insomnia, muscle cramps, and fatigue from the standpoint of their current state, barriers, and knowledge gaps impeding progress and a possible path forward.3 In keeping with the importance of this topic, a survey of our dialysis center patients was conducted to characterize the frequency, severity, and timing of dialysis-related cramps. Dialysis-related cramps can be extremely painful and can compromise the efficacy of hemodialysis therapy, but their pathophysiology is unclear.4,5 The central role of volume removal as the trigger for susceptible patients seems evident from the fact that intradialytic cramps are usually associated with hypotension and that prompt correction of hypotension by saline administration and discontinuation of ultrafiltration often improve the cramping. Here we propose a central role of relative angiotensin II deficiency as the cause of decreased muscle blood flow during dialysis and therefore a key contributor to this painful complication of dialysis.

Of the 149 participants surveyed, 79 (53%) self-identified as diabetic. In all, 79% of the participants (117 of 149) reported having experienced cramps at least once during dialysis (Table 1). Of these 117 patients, 63 (54%) stated that cramps occurred during only dialysis days, whereas 54 (46%) reported cramps during both dialysis and nondialysis days. None of the patients reported cramps on nondialysis days only. A total of 73% (85 of 117) reported cramps during the last hour and 26% (30 of 117) in the middle of dialysis (Table 1). Severity of cramps was rated using a scale from 1 to 10 and then classified in 3 categories: minor (1–3), moderate (4–6), and severe (7–10). Two patients were not able to estimate the severity of their cramps. Among the 117 participants who experienced cramps, 14% (n = 16) rated the pain as minor and 38% (n = 44) as moderate, whereas almost half (47%, n = 55) reported severe cramps (Table 2). Patients who reported severe pain were subcategorized for the analysis into moderately severe (pain scale rating of 7–8) and extremely severe (pain scale rating of 9–10). In all, 41 of the 55 patients (75%) reporting severe pain scored the pain as moderately severe, and 14 of 55 patients (25%) scored the pain as extremely severe.

Most patients surveyed (76%) reported that fluid removal by dialysis was decreased, was stopped, and/or fluid was given back as the main intervention used to alleviate their cramps (Table 2). Half of the patients stated that “bringing the toes up” was tried as a way to ameliorate the cramps. When asked about all interventions to alleviate dialysis cramps, the most frequent response (29%) was a combination of decreasing fluid removal, raising the lower extremities, and massaging the extremities. Stopping dialysis prematurely was 1 of the measures reported by some (22 of 117), either alone or in combination with other measures (19%). Pain from intradialytic cramps was frequently reported as severe and a cause for premature termination of dialysis in 19% of the cramping patients we surveyed, a percentage similar to the 17.9% termination rate previously reported.4

Among the 117 patients with cramps, 15 (12.8%) were receiving angiotensin II receptor blockers (ARBs), and 21 (17.9%) were receiving angiotensin-converting enzyme (ACE) inhibitors (Figure 1). In total, the 2 classes of renin–angiotensin system (RAS) blockers...
were used by 36 of the 117 patients with cramps (30.7%) and only 4 of the 32 patients without cramps (12.5%). This difference was statistically significant by the Fisher exact test \( (P = 0.028) \). There were no significant differences in the percentage of cramping and noncramping patients who received \( \beta \)-blockers or calcium channel blockers (Figure 1).

Attempts to develop a rational approach for treating muscle cramps are clearly hampered by an incomplete understanding of its pathophysiology. The efficacy of fluid replacement as a palliative measure supports the key role of fluid removal as the initiating event. Yet, for similar degrees of fluid removal, some patients experience severe cramps whereas others do not. This suggests that an abnormal response to fluid removal is involved in those patients who experience cramps. Our survey also revealed that some patients experience cramps on nondialysis days, which may suggest a predisposition unrelated to fluid removal. A delayed effect of fluid removal during dialysis, however, may be responsible for their cramping much in the same way that some patients experience a delayed hypotensive response after hemodialysis.5

Mechanisms that have been proposed to be responsible for dialysis-related cramps include hypoxia caused by hypotension and vasoconstriction, osmotic shifts, hyponatremia, hypomagnesemia, and carnitine deficiency.4 A clue to the nature of the pathogenesis of cramps was provided by using a tilt table to study the hemodynamic response of cramping and noncramping dialysis patients to postural change.6 From this study, it was concluded that intradialytic skeletal muscle cramps result at least in part from a sympathetic nervous system response to dialysis-induced volume stress.

We now propose a key role of angiotensin II as a main contributor to muscle cramping during dialysis. Specifically, we hypothesize that the lack of an appropriate increase in angiotensin II activity during fluid removal by hemodialysis results in decreased muscle blood flow, which in turn causes cramps. Normally, within seconds of changing from a recumbent to a standing position, hemorrhage, or other stress that causes a perceived reduction in intravascular volume, such as fluid removal during dialysis, there is release into the circulation of renin secreted by the kidney juxtaglomerular apparatus.7 This leads to the rapid formation of angiotensin I by cleavage of angiotensinogen by renin and concurrent angiotensin II formation. When appropriately regulated during volume removal by hemodialysis, angiotensin II may ensure adequate muscle blood flow and helps to prevent cramping. In support of the proposed angiotensin II hypothesis of cramping during dialysis is the key finding of Fliser et al.,8 that infusions of angiotensin II caused a marked increase in skeletal muscle blood in normal volunteers, which has been confirmed by others. The action of angiotensin II on muscle blood flow is in contrast to the vasoconstrictive properties of this peptide and the decreased renal blood flow consistently reported after infusions of this peptide.

Why would a blunted angiotensin II response be involved in dialysis cramping? An appropriate response of angiotensin II to fluid removal is dependent on several factors: namely, renin secretion, which is often decreased in patients with end-stage kidney disease as a result of chronic volume overload and sclerosis of the juxtaglomerular apparatus in some cases.7 What we are hypothesizing is that the more impaired the RAS response is, the more likely it is that cramping occurs as a result of inappropriately low angiotensin II levels. When dogs with intact kidneys were dialyzed, they exhibited a normal RAS response to fluid removal as shown by an increase in plasma renin activity and did not exhibit capillary

### Table 1. Reported muscle cramps frequency and characteristics

| Survey question                                      | Response, n (%) | Response, n (%) | Response, n (%) | Response, n (%) |
|-------------------------------------------------------|-----------------|-----------------|-----------------|-----------------|
| Have you ever had muscle cramps during dialysis?      | Yes             | No              |                 |                 |
|                                                       | 117 of 149 (78) | 32 of 149 (21)  |                 |                 |
| Which days do you usually experience muscle cramps?   |                 |                 |                 |                 |
|                                                       | Dialysis days   | Nondialysis days | Both            |                 |
|                                                       | only            |                 |                 |                 |
|                                                       | 63 of 117 (54)  | 0 of 117 (0)    | 54 of 117 (46)  |                 |
| When you have cramps during dialysis, when do they usually occur? | Initiation (first h) | Middle | End (last h)  |                 |
|                                                       | 1 of 117 (1)    | 30 of 117 (26) | 85 of 117 (73)  |                 |
| Has the dialysis session sometimes been interrupted because of the cramps? | Yes | No |                 |                 |
|                                                       | 92 of 117 (79)  | 24 of 117 (21)  |                 |                 |
| How often does dialysis interruption occur?           | More than 50%a  | Less than 50%a  |                 |                 |
|                                                       | 15 of 92 (16)   | 77 of 92 (84)   |                 |                 |

*aAs many as 10% of the patients (9 of 92) reported that they almost always had the session interrupted because of cramps.  
*bThe majority (64%) of the patients (59 of 92) reported that interruptions in the dialysis session happened rarely.

### Table 2. Reported muscle cramps frequency and characteristics

| Survey question                                      | Response, n (%) | Response, n (%) | Response, n (%) | Response, n (%) |
|-------------------------------------------------------|-----------------|-----------------|-----------------|-----------------|
| How severe are the cramps?                            | Mild            | Moderate        | Severe          | Unable to estimate |
|                                                       | 16 of 117 (14)  | 44 of 117 (38)  | 55 of 117 (47)  | 2 of 117 (2)      |
| What treatment is usually being done for dialysis cramps? | Decrease fluid removal/Infuse fluid back | Bring toes up fluid back | Massage or squeeze the extremities | Stop dialysis prematurely |
|                                                       | 89 of 117 (76)  | 60 of 117 (51)  | 56 of 117 (48)  | 22 of 117 (19)    |
Peripheral vasoconstriction from sympathetic activation is likely to occur in all patients during hemodialysis, leading to derecruitment of skeletal muscle capillaries. Muscle cramping is more likely in patients whose sympathetic system activation during hemodialysis is not accompanied by an appropriate activation of the RAS during fluid removal and the attendant increase in renin and therefore plasma angiotensin II. Our survey findings moreover are consistent with the angiotensin II hypothesis of dialysis cramping proposed here, as patients treated with RAS blockers experienced cramps more often than those who were not treated with these agents (Figure 1).

Weaknesses of our survey that should be noted include an open recall period (from initiation of dialysis to the survey period), which creates variability in the intervals being surveyed. Another weakness is the lack of data on blood pressure during dialysis. Lack of validation of our questionnaire and our use of the Stanford Pain Scale, which is not specific to dialysis-related cramps pain, are additional limitations. Further studies are needed to confirm our observations from larger databases before it can be recommended that RAS blockers be avoided in patients with cramps. Now that angiotensin II is commercially available for treating patients with shock that is refractory to norepinephrine infusions, it may be possible to study whether infusions of this natural peptide or novel agonists may be effective in preventing intradialytic skeletal muscle cramps.

**DISCLOSURE**

AJA holds U.S. patent number 9,919,022 relating to the use of All receptor agonists to prevent or reduce hemodialysis-associated skeletal muscle cramps. DB is a co-inventor of U.S. patent number 10,443,049 relating to the use of ACE2 truncates and also the founder of Angiotensin II therapeutics Inc. All the other authors declared no completing interests.

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**Figure 1.** Antihypertensive medications in patients with and without cramps. *P = 0.028, one-way Fisher’s exact test, otherwise not significant.

ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker.