Heart rate variability (HRV) in kidney failure: measurement and consequences of reduced HRV

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Abstract
A common cause of death in end-stage renal disease (ESRD) patients on dialysis is sudden cardiac death (SCD). Compared to the general population, the percentage of cardiovascular deaths that are attributed to SCD is higher in patients treated by dialysis. While coronary artery disease (CAD) is the predominant cause of SCD in dialysis patients, reduced heart rate variability (HRV) may play a role in the higher risk of SCD among other risk factors. HRV refers to beat-to-beat alterations in heart rate as measured by periodic variation in the R–R interval. HRV provides a non-invasive method for investigating autonomic input into the heart. It quantifies the amount by which the R–R interval or heart rate changes from one cardiac cycle to the next. The autonomic nervous system transmits impulses from the central nervous system to peripheral organs and is responsible for controlling the heart rate, blood pressure and respiratory activity. In normal individuals, without cardiac disease, the heart rate has a high degree of beat-to-beat variability. HRV fluctuates with respiration: it increases with inspiration and decreases with expiration and is primarily mediated by parasympathetic activity. HRV has been used to evaluate and quantify the cardiac risk associated with a variety of conditions including cardiac disorders, stroke, multiple sclerosis and diabetes. In this narrative review, we will examine the association between HRV and SCD. This report explains the measurement of HRV and the consequences of reduced HRV in the general population and dialysis patients. Lastly, this review will outline the possible use of HRV as a clinical predictor for SCD in the dialysis population. The current understanding of SCD based on HRV findings among the ESRD population support the use of more aggressive treatment of CAD; greater use of angiotensin converting enzyme inhibitor (ACE-i)/angiotensin receptor blockers (ARBs) and β-blockers and more frequent and/or nocturnal haemodialysis to improve the survival of a patient with kidney failure.

Keywords: end-stage renal disease (ESRD); heart rate variability (HRV); sudden cardiac death (SCD)

Background
A common cause of death in end-stage renal disease (ESRD) patients on dialysis is sudden cardiac death (SCD). Compared to the general population, the percentage of cardiovascular deaths that are attributed to SCD is higher in patients treated with dialysis [1]. The many comorbidities and the presence of unique metabolic/physiologic alterations of the uraemic state make the management of coronary artery disease (CAD) and the prevention of SCD challenging in ESRD patients. These patients likely have risk factors such as hyperhomocysteinaemia, elevated lipoprotein a, oxidative stress, endothelial dysfunction, chronic inflammation and accelerated vascular calcification. In addition to the increased risk of CAD, dialysis patients are at risk of SCD that may be related to poor autonomic function with a significant decrease in heart rate variability (HRV) [2]. Factors that alter HRV include CAD, stress, sleep, age, gender and diabetes.

HRV provides a non-invasive method for investigating autonomic input into the heart. It quantifies the amount by which the R–R interval or heart rate changes from one cardiac cycle to the next. The autonomic nervous system transmits impulses from the central nervous system to peripheral organs and is responsible for controlling the heart rate, blood pressure and respiratory activity. In normal individuals, without cardiac disease, the heart rate has a high degree of beat-to-beat variability. HRV fluctuates with respiration: it increases with inspiration and decreases with expiration and is primarily mediated by parasympathetic activity. HRV has been used to evaluate and quantify the cardiac risk associated with a variety of conditions including cardiac disorders, stroke, multiple sclerosis and diabetes. In this narrative review, we will examine the association between ESRD and SCD and the role that reduced HRV...
Heart rate variability (HRV) in kidney failure

Table 1. Potential risk factors for SCD in ESRD

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may play in this high-risk population. This report explains the measurement of HRV and the consequences of reduced HRV in the general population and haemodialysis (HD) patients. Lastly, this review will outline the possible use of HRV as a clinical predictor for SCD in the dialysis population.

Sudden cardiac death in ESRD

SCD is defined as an unexpected natural death due to cardiac aetiology preceded by a sudden loss of consciousness and is the single greatest cause of mortality in ESRD patients on dialysis. The annual death rate for prevalent US dialysis patients for 2004 was 230 deaths per 1000 patient years [3,4]. Forty-three percent of all-cause mortality in HD and peritoneal dialysis (PD) patients was secondary to cardiac disease [3,4]. Arrhythmic mechanisms accounted for 58% of cardiac deaths among PD patients and 64% among HD patients [3]. The USRDS Cardiovascular Special Studies Center estimated the SCD rate among 2002 prevalent US dialysis patients to be ∼7% per year [3,4].

While CAD is the predominant cause of SCD in dialysis patients, left ventricular hypertrophy (LVH), electrolyte changes, myocardial structural changes, interstitial fibrosis, decreased perfusional reserve, decreased ischemic tolerance, decreased HRV and the intermittent nature of dialysis are other risk factors (Table 1) [5–7]. Diabetes mellitus (DM), hypertension (HTN) and hyperlipidaemia, conventional risk factors, were reported to have a low power to discriminate ESRD patients at risk for SCD [5–7]. Patients with chronic kidney disease have a higher probability of cardiac arrest as compared to patients without chronic kidney disease. The duration of chronic kidney disease increases the probability of cardiac arrest. Yet, the probability of cardiac arrest is lower in the chronic kidney disease population compared with those on dialysis, in whom the probability is 24% at 3 years (Figures 1 and 2) [3]. Despite the treatment of underlying coronary disease, the annual mortality of dialysis patients remains elevated implying that primary treatment of myocardial ischaemia may be an inadequate clinical strategy [3,4]. These findings suggest that other measures should be considered to improve our management of this high-risk population.

How to measure heart rate variability?

There are various ways of quantifying HRV including time domain, frequency domain, geometric and nonlinear analysis. Time-domain analysis measures normal R–R intervals. Various measurements are calculated from these intervals including standard deviation of all normal R–R intervals during a 24-h period (SDNN), standard deviation of 5-min average of normal R–R intervals (SDANN), average of 5-min SDNN (ASDNN), root-mean square of the difference of successive R–R intervals (rMSSD) and the number of instances per hour in which two consecutive R–R intervals differ by more than 50 ms over 24 h (pNN50). The accuracy of the SDNN can be affected by ectopic beats, artefact and missed beats; therefore, most labs will require at least 18 h of data. SDNN and its variables are thought to represent the sympathetic limb of the autonomic nervous system, whereas rMSSD, NN50 and pNN50, in the presence of normal sinus rhythm and atrioventricular-nodal (AV-nodal) function, represent the parasympathetic limb [8–12]. Frequency-domain analysis splits the heart rate signal into constituent frequency components. This is accomplished by using fast Fourier transformation that decomposes the signal into a set of sine and cosine waves. The different frequencies are as follows: very low frequency (VLF) <0.04 Hz that is thought to be influenced by the thermoregulation of vasomotor tone; low frequency (LF) 0.04–0.15 Hz that is affected by the baroreceptor reflex and is thought to reflect sympathetic and parasympathetic tone; high frequency (HF) 0.15–0.40 Hz that is influenced by respiratory frequency and thought to reflect parasympathetic tone. The LF/HF ratio is an index of sympathovagal activity.

Fig. 1. From USRDS database. Medicare data from 2004 showing the probability of cardiac arrest in the CKD population as compared to the non-CKD population.

Fig. 2. From USRDS database. Medicare data from 2004 showing the cumulative probability of cardiac arrest amongst the different populations.
balance and thus of autonomic status. Total power can be estimated with the sum of the frequencies [8–12]. Geometric analysis has been utilized to manage difficulties with ectopic complexes, missed beats and ‘noise’ in analysing electrocardiogram (ECG) recordings. This method creates histograms of intervals by sorting them into 7.8 ms bins and then calculating the triangular index (TI). However, one method has not been established as superior to another [8–12].

Consequences of decreased heart rate variability

Reduced HRV has been established as a significant independent risk factor for higher mortality and cardiac death in cardiovascular disease and healthy populations [8–12]. HRV was first studied in the general population in the 1970s by Wolf et al. in patients diagnosed with acute myocardial infarctions (MI) revealing that significant sinus arrhythmia (increased HRV) was associated with lower hospital mortality [13]. The Multicenter Postinfarction Research Group study [10,13] and the Autonomic Tone and Reflexes After Myocardial Infarction (ATRAMI) trial [8,10] report a correlation of decreased HRV to mortality. The Framingham study has also reported that low HRV in healthy subjects is a risk factor for adverse cardiac events [8].

Heart rate variability and end-stage renal disease (ESRD)

Studies of HRV and ESRD patients have shown a decrement in HRV. Vita et al. [14] demonstrated in 30 uraemic patients that 53% of patients had autonomic dysfunction, in which 40% was isolated to the parasympathetic limb and 13% had combined parasympathetic and sympathetic damage. On multivariate analysis 63% had moderate-severe autonomic neuropathy. On power spectral analysis (PSA), a significant reduction of LF in the supine uraemic group compared to normal controls was noted, indicating that there is early sympathetic involvement that traditional autonomic tests were unable to detect. Axelrod et al. noted a decrease in power from control to uraemics in the 0.1–0.2 Hz and 0.2–0.3 Hz (17) frequency indicating dysfunction in both parasympathetic and sympathetic function. A decrement in autonomic function was seen in both HD and PD patients that was more than compared with patients not yet on dialysis. This work by Vita et al. [14] supports the use of PSA as a tool to detect autonomic dysfunction.

Changes in HRV during dialysis treatments

ESRD patients have been shown to have changes in HRV associated with exposure to HD. Rubinger et al. [15] evaluated patients who had intradialytic hypotension (unstable group) and found that while on dialysis, RR (mean of mean 5 minute RR intervals between normal beats) increased in both stable and unstable patients. Significant decreases in SD (mean of 5 minute RR SD’s) during dialysis as compared to night period and in SDANN (SD of mean 5 minute RR intervals) during dialysis as compared to both day and night were observed in all patients. LF/HF was significantly lower during dialysis than during night in the unstable group. Both groups of patients demonstrated a decrease in sympathetic activity during dialysis. They also noted that LF/HF ratio was significantly lower in unstable women compared with unstable men. A study by Tong and Hou [16] further demonstrated that some HRV parameters are particularly sensitive to the HD procedure. Thirty-five HD patients (excluded diabetics, HTN, intradialytic hypotensive patients, patients with established autonomic dysfunction, cardiac disease, Kt/V < 1 and patients taking medications that could affect autonomic function) had an ECG performed 1 h before dialysis, during dialysis and 2 h post dialysis. No significant changes in BP before, during or after HD were noted. SDNN and LF/HF ratio were significantly reduced during the 3 h of dialysis and recovered 2 h after HD to values similar to pre-dialytic period. The ultrafiltration rate (UF) and Kt/V were main determinants of LF/HF ratio; LF/HF was negatively correlated with the UF rate and positively correlated with Kt/V suggesting that better HD adequacy can improve HRV.

While the treatment of kidney failure with dialysis impacts HRV, the CAD burden and other comorbid illnesses of the HD patient may also influence HRV. Diabetic patients on HD have a greater cardiovascular mortality than do non-diabetic ESRD patients, which is thought to be secondary to further impairment of the autonomic nervous system due to the co-occurrence of uraemic and diabetic neuropathy [17]. HRV parameters in non-diabetic ESRD were compared to those in diabetic ESRD patients on HD immediately before dialysis, during dialysis and post dialysis in a study done by Giordano et al. [17]: 40 patients (20 ESRD: 11 non-diabetic, 9 diabetic; 10 with type 2 DM and 10 healthy controls) were studied. Controls were noted to have the lowest LF and LF/HF ratio and the highest value for RR mean, total power (TP) and HF components. Pre-dialytic values of RR mean, total power and HF were significantly higher in the pre-dialytic period than in the dialytic period in both diabetic and non-diabetic ESRD groups. The LF (p < 0.01) and LF/HF (p < 0.001) components increased during the dialytic period. However, these results contradict the findings by Rubinger et al. [15] and Tong and Hou [16] in which a decrease in LF/HF and sympathetic activity during dialysis was observed. Post-dialytic values of HRV in diabetic patients gradually returned to pre-dialytic (p < 0.01) levels; no significant difference between the values were noted (p < 0.10). Non-diabetic ESRD patients had a RR mean, TP and HF values that were significantly higher and LF and LF/HF components that were significantly lower during the post-dialytic period than during the pre-dialytic period (p < 0.01); the LF (p < 0.01) and LF/HF ratio (p < 0.01) were significantly lower compared with the pre-dialysis values. Significant differences in HRV parameters were seen when the diabetic and non-diabetic groups were compared. The pre-dialytic RR mean, TP and HF were significantly higher in the non-diabetic ESRD patients than in the diabetic ESRD group. In contrast, LF and LF/HF had an opposite trend that is a similar pattern seen in controls. No significant difference between the diabetic and
Heart rate variability (HRV) in kidney failure

Several studies have demonstrated that decreased HRV can be predictive of survival in the ESRD population. Hayano et al. [21] studied 30 HD patients who underwent coronary angiography due to signs/symptoms of CAD and underwent 24 h ECG monitoring between dialysis sessions to assess prognostic value of HRV. Multivariate Cox proportional hazard model revealed a triangular index (TI) < 22 and TINN (baseline width of the least square triangular fitting of the highest peak of the histogram of NN intervals) < 328 ms were independently associated with increased risk for all-cause death and SCD. Kaplan Meier survival curves revealed 5-year mortality for all patients with HRV TI ≥ 22 or TI < 22 to be 15% and 67%, respectively. Five-year mortality for patients with CAD and HRV TI ≥ 22 and TI < 22 were 33 and 88%, respectively. If no CAD was present the five-year survival with a TI ≥ 22 and TI < 22 were 0% and 50%, respectively. With these results it is evident that a reduced HRV has an independent prognostic value in chronic HD patients and identifies patients with an increased risk for all-cause mortality and SCD. However, one cannot deduce from this study why some patients had a reduced HRV compared to others. This study suggests that a reduced HRV cannot only be a part of a mechanism that increases mortality but could also be a marker for poor prognosis. The predictive value of a decreased HRV independent of left ventricular ejection fraction (LVEF), multi-vessel stenosis and ventricular tachycardia suggests that a combination of factors in addition to a decreased HRV could exert a cumulative effect on the risk of mortality. Limitations to these findings include a small sample size and a very high-risk population. The same group moved forward to conduct another study with a larger sample size of medically stable patients. One hundred and twenty patients from an outpatient dialysis unit had both time and frequency-domain HRV analysis over a period of 26 ± 10 months. During that time period 21 died, 10 cardiac (4 MI, 4 progressive heart failure, 2 SCD) and 11 were secondary to non-cardiac

non-diabetic ESRD patients was observed during dialysis. However, the post-dialytic period revealed that RR, TP and HF were significantly higher and LF and LF/HF were significantly lower in the non-diabetic group compared to the diabetic group. Significant changes in HRV were observed up to 24 h post dialysis.

Beneficial effects of HD on HRV have been shown to be the most pronounced during the first day of the inter-dialytic period. The study of Tong and Hou [16], with a similar population, also contradicts these results in that LF/HF ratio decreased during the 3-h HD procedure and recovered to pre-dialytic levels 2 h after dialysis, whereas in this study post dialytic HRV parameters were improved compared with pre-dialytic values and persisted for up to 24 h post dialysis in non-diabetics. This study shows that there is a prevalence of cardiac sympathetic activity in ESRD patients compared to non-ESRD patients, there is prevalence of cardiac sympathetic activity in the pre-dialytic period in diabetics compared with non-diabetic patients, there is a further increase in cardiac sympathetic activity during dialysis compared with pre-dialysis in both groups and diabetic patients do not represent changes in the autonomic nervous system in the post-dialytic period when compared to non-diabetic patients. This may be secondary to the co-occurrence of uraemic and diabetic neuropathy.

The improved HRV seen 24 h post-dialysis may explain the timing and characteristics of SCD in a dialysis population. Bleyer et al. [18] examined a group of patients undergoing conventional thrice weekly HD showing a bimodal distribution of death with a 1.7-fold increased death risk occurring in the 12-h period at the start of dialysis and a 3-fold increase risk of death 12 h before the first dialysis session after the weekend. The increase in SCD in the first few hours of dialysis may be secondary to the increased LF and LF/HF ratio and decrease in HF that is reported in the prior study. The lowest ratio of observed to expected death was noted in the 12–24 h and 24–36 h intervals that may represent the beneficial effects of improved HRV after dialysis.

Longitudinal HRV findings among dialysis populations

Although there seem to be conflicting results on the changes of HRV during a single dialysis session, HRV appears to improve with duration of therapy. There has been a correlation between HRV indices and Kt/V suggesting that adequacy of dialysis was associated with changes in the autonomic nervous system. A retrospective analysis of the autonomic system was done by Laaksonen et al. [19] on HD and continuous peritoneal dialysis (CAPD) patients by looking at changes in HRV. HRV was measured using time-domain analysis on 16 patients on HD and PD. The adequacy of dialysis was assessed by Kt/V in the HD group; however, PD adequacy was measured subjectively by patients’ well-being and nutritional status. HRV parameters (SDNN/RMSM and rMSSD) were obtained from 5-min supine ECGs. The improvement in HRV time-domain parameters occurred only in patients who had a mean Kt/V > 1.2 (p < 0.002), progressive deterioration of autonomic neuropathy was associated with a Kt/V < 0.87. During CAPD, a similar trend was seen but was not significant (p = 0.18). Diabetic patients (n = 4) were noted to have a severely abnormal HRV at the beginning of the study that did not improve over 2.9 years of the study. This study was limited by small sample sizes and did not have objective measures in PD adequacy. In another longitudinal study with a healthy control group, 20 ESRD patients (13 HD, 7 CAPD) compared to 15 healthy controls were evaluated by Demircioglu et al. [20] to assess the effect of dialysis on autonomic function. HRV, by 24-h EKG-Holter, was done at the time the patient was initiated on dialysis and then 12 months later. ESRD patients, prior to the initiation of dialysis, were noted to have a significant decrease in all parameters of time-domain HRV. After 12 months of dialysis, a significant improvement was observed in time-domain analysis that was found in the CAPD group compared to the HD group. This study suggested that dialysis for 12 months can cause a significant improvement in autonomic dysfunction, especially in CAPD patients.
death. Compared with survivors, non-survivors secondary to cardiac death were noted to be older and had lower levels of albumin, no significant difference between survivors and non-cardiac death were noted. Survivor, cardiac and non-cardiac death compared with the healthy population demonstrated a decrease in all time- and frequency-domain HRV parameters. No significant difference was seen between survivors and non-cardiac death. Among time- and frequency-domain HRV, a decrease in TI, VLF, ULF and LF/HF ratio were significantly predictive of cardiac death, none was able to predict non-cardiac death. Albumin, age and CAD were also predictors of cardiac death. The mortality rate for a TI < 23.5 (median value) was 13.3%, ULF < 9 (median value) was also 13.3%. Therefore, HRV is decreased in HD and decreased TI has prognostic value in the general ESRD population not just in angiographically proven CAD ESRD population.

**HRV and nocturnal haemodialysis**

It may be that increasing the frequency and duration of HD would provide a more physiologic homeostasis that will lead to a more normal sympathovagal balance and decrease incidence of SCD. A small cohort study by Chan et al. [23] on ESRD patients assessed whether nocturnal HD would lower the sympathetic drive, as measured by HRV, during sleep and that this decrease would be associated with an improvement in nocturnal hypoxaemia. It was found that the apnoea–hypopnoea index, nocturnal hypoxaemia and RR interval were significantly higher in the dialysis population on conventional HD (4 h, three times per week) as compared to the control population. However, after they were converted to nocturnal HD (8–10 h, six times per week) decreases in the apnoea–hypopnoea index, nocturnal hypoxaemia and a fall in heart rate were noted. It is important to understand the risk factors involved in ESRD-related SCD, so interventions can be made to decrease the incidence of SCD in this population.

HRV not only reflects the severity of underlying cardiac pathology, but it may also reflect factors that directly affect the heart. Increased vagal activity decreases the heart rate and cardiac work resulting in a decreased myocardial oxygen demand. However, increased sympathetic activity seen in patients with a decreased HRV results in higher levels of norepinephrine, which can be directly toxic to the heart [8,19]. High levels of norepinephrine can result in cytotoxic effects leading to apoptosis of the beta-receptor and hypertrophic affects of the alpha-receptor [8,19]. Sympathetic activity is increased in patients with renal insufficiency or ESRD from a direct effect of the diseased kidneys [8,19]. However, Chan et al. [23] revealed a reduction in daytime plasma norepinephrine concentrations after conversion from conventional HD to nocturnal HD secondary to increased frequency and dose of dialysis.

**Implications and conclusions**

Other predictors of risk for ESRD-related SCD are needed and further characterization of the causal pathways of SCD in the dialysis population can help identify patients at higher risk and determine targeted interventions to decrease the likelihood of SCD in this population. However, there appears to be a reluctance to recommend aggressive cardiac intervention in this population. This had been referred to as ‘therapeutic nihilism’ or ‘renalism’ by Chertow et al. [25]. They looked at a population of patients with chronic kidney disease and noted that younger patients, men and white individuals were more likely to undergo coronary interventions than were older patients, women and blacks. Among 7783 patients who were considered to be appropriate candidates for angiography and had a GFR <30ml/min, only 28.1% underwent the procedure. The unadjusted one-year mortality for the chronic kidney disease patients who underwent the procedure was 30.2% compared with 60.2% for those who did not [25]. Yasuda et al. [26] prospectively assessed 259 HD patients to see if percutaneous coronary interventions are beneficial for HD patients. The five-year cardiac survival rate for the medically-managed group was 41.6%, 77.1% in the intervention group and 84.5% in the non-stenosis group. The effects of percutaneous interventions on cardiac and all cause death remained significant after adjusting for other risk factors. These data suggest that percutaneous intervention can improve the prognosis of dialysis patients with CAD [26].

Medications can increase vagal tone that may in turn decrease SCD. ACE-inhibitors (ACE-i), beta-blockers (β-blocker) and spironolactone have been shown to enhance cardiac parasympathetic control [8,18]. Studies in post-MI and CHF patients have shown that treatment with ACE-i results in a significant increase in HRV [8]. The AIRE study showed that there was a 30% reduction in SCD in patients treated with ramipril [8]. The Randomized Aldactone® Evaluation Study (RALES) showed a reduction in mortality in CHF patients treated with spironolactone [8]. The beneficial effects of spironolactone were thought to be secondary to inhibiting the aldosterone system, as this has been shown in animals and human studies to affect cardiac autonomic control [8]. Pun et al. [24] conducted a study using a cohort from the Gambro Healthcare System to identify modifiable factors associated with survival after an in-unit cardiac arrest. They found a benefit in survival after cardiac arrest associated with the use of ACE-i/angiotensin receptor blockers (ARB), β-blockers and calcium channel blockers [24]. A positive correlation between dosage and survival benefit was noted for β-blockers and ACE-i/ARBs.

In this review we have presented the literature supporting the position that impaired HRV can be a surrogate marker to predict SCD. However, at this point there are insufficient data showing that normalization of HRV would improve clinical outcomes and patient survival in the ESRD population. HRV does offer potential for improving our basic understanding of the sympathetic and parasympathetic influences in this population at high risk for autonomic dysfunction. Our group has been particularly focused on the changes in HRV with sleep since cardiac parasympathetic tone increases from wake to sleep and with the sleep cycle cardiac vagal tone is higher during non-rapid eye movement (NREM) sleep than during rapid eye movement (REM) sleep. Even within NREM sleep there is a progressive
increase in vagal tone from Stage 1 to Stage 4 and a noted reduction in vagal activity during Slow Wave Sleep. While it is expected that HRV increases with NREM sleep, does the spectral analysis of the ECG vary across the night for those with kidney failure? Further work in this area can be expected to increase our understanding of the autonomic tone of patients with ESRD. In clinical applications of HRV findings, it is thought that both medical and non-medical strategies can be used to improve HRV. In both animal data and in limited studies of the general population, ACE-i/ARBs and β-blockers may have a role in improving HRV; however, it has not been shown in the ESRD population. Other literature in the general population has suggested that HRV may serve as a therapeutic guide for the benefits of physical activity. In the limited literature examining interventions to improve HRV in the dialysis population, the data from nocturnal dialysis suggest that optimisation of uremic clearance may also offer improvements. Given these current limitations of HRV, physicians should aggressively address underlying cardiovascular disease in patients with ESRD and re-evaluate the need for a cardiac workup in the dialysis population. Currently, more aggressive treatment of CAD, greater use of ACE-i/ARBs and β-blockers and more frequent and/or nocturnal HD show promise for decreasing the incidence of SCD in ESRD. HRV is a promising surrogate marker for SCD that also lends itself as a potential modifiable outcome measure. In the future, more robust trials and data are needed to substantiate our hypothesis.

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