Renal Denervation

Health-Related Quality of Life After Renal Denervation in Patients With Treatment-Resistant Hypertension


Abstract—Recent studies have demonstrated the effectiveness of radiofrequency ablation of the renal sympathetic nerves in reducing blood pressure (BP) in patients with resistant hypertension. The effect of renal denervation on health-related quality of life (QoL) has not been evaluated. Using the Medical Outcomes Study 36-Item Short-Form Health Survey and Beck Depression Inventory-II, we examined QoL before and 3 months after renal denervation in patients with uncontrolled BP. For baseline comparisons, matched data were extracted from the Australian Diabetes, Obesity, and Lifestyle database. Before renal denervation, patients with resistant hypertension (n=62) scored significantly worse in 5 of the eight 36-Item Short-Form Health Survey domains and the Mental Component Summary score. Three months after denervation (n=40), clinic BP was reduced (change in systolic and diastolic BP, −16±4 and −6±2 mm Hg, respectively; P<0.01). The Mental Component Summary score improved (47.6±1.1 versus 52±1; P=0.001) as a result of increases in the vitality, social function, role emotion, and mental health domains. Beck Depression Inventory scores were also improved, particularly with regard to symptoms of sadness (P=0.01), tiredness (P<0.001), and libido (P<0.01). The magnitude of BP reduction or BP level achieved at 3 months bore no association to the change in QoL. Renal denervation was without a detrimental effect on any elements of the 36-Item Short-Form Health Survey. These results indicate that patients with severe hypertension resistant to therapy present with a marked reduction in subjective QoL. In this pre- and post-hypothesis generating study, several aspects of QoL were improved after renal denervation; however, this was not directly associated with the magnitude of BP reduction.

Key Words: sympathetic nervous system ■ high blood pressure ■ ablation ■ depression
Anecdotal evidence from our initial series of patients treated by catheter-based renal denervation with independent reports of feeling calmer, more relaxed, as if a curtain was lifted, or the fast-forward button was no longer pressed encouraged us to study this aspect systematically. We therefore started to examine patient self-reported health-related quality of life before and 3 months after percutaneous radiofrequency renal denervation in a group of consecutive patients with treatment-resistant hypertension.

**Methods**

**Participants**

Data from 62 patients (40 men and 22 women, aged 61.0±1.4 years, ranging from 38 to 80 years) with resistant hypertension who were participating in our ongoing investigations into the effectiveness of renal denervation in controlling blood pressure form the basis of this report. All patients underwent a complete medical history and physical examination. All participants had been evaluated previously and treated at specialized clinics before being referred to our hypertension unit for further management. Hypertension was diagnosed based on the current European Society of Hypertension and European Society of Cardiology guidelines for the management of arterial hypertension.\(^1\) Patients had previously been screened for secondary forms of hypertension according to current guidelines.\(^1\)\(^2\) Resistant hypertension was defined according to the current statement of the American Heart Association.\(^3\) All medications were stable for 26 weeks before baseline assessment and the renal nerve denervation procedure and were continued until ≥3 months after the procedure. Medications were composed principally, in various combinations, of angiotensin receptor blockers (83% of participants), angiotensin-converting enzyme inhibitors (51%), \(\beta\)-blockers (51%), \(\alpha\)-blockers (21%), calcium channel blockers (73%), diuretics (85%), and centrally acting sympathoinhibitory agents (49%). Statins (61%), aspirin (32%), converting enzyme inhibitors (51%), and oral hypoglycemic agents (34%) were also used. Renal nerve ablation was achieved using a radiofrequency catheter (Simplicity; Medtronic Ardian Inc, Palo Alto, CA) that was introduced into each renal artery via the femoral access. All patients underwent an uncomplicated bilateral renal nerve ablation in 1 session with the catheter positioned in the lumen of the renal artery, as described previously.\(^1\)\(^3\)\(^4\) The procedure is approved in Australia by the Therapeutic Goods and Drug Administration, the research investigation was approved by the Institutional Ethics Committee, and written, informed consent was obtained from all participants.

For baseline comparisons, control data were extracted from the population-based Australian Diabetes, Obesity, and Lifestyle (AusDiab) database.\(^5\) The Australian Diabetes, Obesity, and Lifestyle study is a longitudinal study examining the natural history of diabetes mellitus, prediabetes, heart disease, and kidney disease. Data matching from the Australian Diabetes, Obesity, and Lifestyle study was well matched for age, sex, and BMI. There were 6 cases that had to be matched on a broader category of hypertension according to current guidelines.\(^1\)\(^2\)\(^3\)\(^4\) Furthermore, patients had previously been screened for secondary forms of hypertension according to current guidelines.\(^1\)\(^2\) Resistant hypertension was defined according to the current statement of the American Heart Association.\(^3\) All medications were stable for 26 weeks before baseline assessment and the renal nerve denervation procedure and were continued until ≥3 months after the procedure. Medications were composed principally, in various combinations, of angiotensin receptor blockers (83% of participants), angiotensin-converting enzyme inhibitors (51%), \(\beta\)-blockers (51%), \(\alpha\)-blockers (21%), calcium channel blockers (73%), diuretics (85%), and centrally acting sympathoinhibitory agents (49%). Statins (61%), aspirin (32%), converting enzyme inhibitors (51%), and oral hypoglycemic agents (34%) were also used. Renal nerve ablation was achieved using a radiofrequency catheter (Simplicity; Medtronic Ardian Inc, Palo Alto, CA) that was introduced into each renal artery via the femoral access. All patients underwent an uncomplicated bilateral renal nerve ablation in 1 session with the catheter positioned in the lumen of the renal artery, as described previously.\(^1\)\(^3\)\(^4\) The procedure is approved in Australia by the Therapeutic Goods and Drug Administration, the research investigation was approved by the Institutional Ethics Committee, and written, informed consent was obtained from all participants.

**Blood Pressure**

At each clinical visit before renal denervation, average sitting office blood pressure was measured in both arms after ≥5 minutes of rest, calculated as the average of 3 consecutive measurements within a 1-minute interval using a validated device (Omron HEM-907, Omron Healthcare Singapore PTE Ltd). The arm with higher blood pressure readings was used for subsequent measures.

**Medical Quality of Life Assessment**

The Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) is a self-report questionnaire that has been used to assess quality of life in various populations.\(^6\) The questionnaire contains 36 items that yield 8 category scales: (1) physical functioning, (2) role limitations caused by physical problems, (3) bodily pain, (4) general health, (5) vitality, (6) social functioning, (7) role limitations caused by emotional problems, and (8) mental health. Scale scores range from 0 to 100, with higher scores indicating better health. The 8 category scores can be aggregated into 2 summary scales, the Physical Component Summary scale and the Mental Component Summary scale. The summary scores were calculated as \(t\) scores based on general Australian population norms,\(^6\) with a mean of 50 and an SD of 10. The SF-36 has demonstrated excellent psychometric properties in both patient and healthy control populations.\(^6\) Additionally, in the resistant hypertension patients, the Beck Depression Inventory (BDI-II)\(^7\) and Spielberger State and Trait Anxiety inventories\(^8\) were used to assess symptoms of depression and levels of anxiety, respectively. Participants completed the self-report questionnaires either at home or at the clinic before any laboratory investigations. Questionnaires were completed at baseline in all subjects, and in 40 participants (65%) repeat testing was performed 3 months after renal denervation.

**Statistics**

Statistical analysis was performed using SigmaStat Version 3.5 (Systat Software, Point Richmond, CA). Group data are reported as mean±SEM. Comparisons between groups were performed using a 1-way ANOVA. Post hoc testing was performed using Dunn test. The effects of renal denervation on SF-36 category scales and summary scores, BDI, and anxiety state and trait were assessed using 1-way ANOVA for repeated measures. Analysis was performed on ranks for non-Gaussian data. Data are presented as mean with 95% confidence intervals. Associations between the Physical and Mental Component Summary scores and physiological variables were examined using stepwise multiple regression analysis with cumulative \(R^2\) values shown. A value of \(P<0.05\) (with Bonferroni adjustments for multiple comparisons when required) was considered significant.

**Participant Demographics**

The baseline clinical characteristics of the patients with resistant hypertension are presented in Table 1. These subjects tended to be overweight or obese (range, 21.9–52.7 kg/m\(^2\)), and their blood pressure remained substantially elevated despite being on \(4.8±0.3\) antihypertensive drugs. Control groups were well matched for age, sex, and BMI.

**Table 1. Baseline Demographic Data**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Resistant Hypertension</th>
<th>Normotensive Control</th>
<th>Controlled Blood Pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (% male)</td>
<td>65</td>
<td>63</td>
<td>68</td>
</tr>
<tr>
<td>Age, y</td>
<td>61.9±1.4</td>
<td>62.0±0.8</td>
<td>65.4±1.5</td>
</tr>
<tr>
<td>BMI, kg/m(^2)</td>
<td>31.9±0.7</td>
<td>30.8±0.6</td>
<td>31.6±0.9</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>166±3*</td>
<td>122±1</td>
<td>122±3</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>88±2*</td>
<td>69±1</td>
<td>68±2</td>
</tr>
<tr>
<td>No. of antihypertensive medications</td>
<td>4.8±0.3</td>
<td>0</td>
<td>1.3±0.1</td>
</tr>
</tbody>
</table>

BMI indicates body mass index.

\(\ast P<0.01\).

\(†\) Data obtained from the AusDiab database.
Baseline Quality-of-Life Assessment

Patients with resistant hypertension scored significantly worse in 5 of the eight SF-36 domain scores and the Mental Component Summary score when compared with both the control groups (Figure). Role physical ($P=0.02$), role emotional ($P=0.05$), and the physical component score ($P=0.04$) also tended to be worse in the resistant hypertension patients. There was no difference in the body pain domain score between groups ($P=0.61$). The SF-36 domain scores and summary scores did not differ between the 2 control groups.

Within the resistant hypertension group, forward stepwise regression analysis revealed that a lower Physical Component Summary score could be predicted by a combination of female sex ($r=0.53$, $P<0.001$), increasing age ($r=0.36$, $P=0.004$), BMI ($r=0.31$, $P=0.02$), and systolic blood pressure ($r=0.28$, $P=0.03$), with the combination of these factors accounting for 45% of the variance in Physical Component Summary score. The Mental Component Summary score bore no relationship to any of these physical parameters. The SF-36 domain and summary scores in the resistant hypertension patients were not related to the number of medications that the patients were taking. In the control subjects, a lower Physical Component Summary score could be predicted by a combination of BMI ($r=0.30$, $P<0.001$) and age ($r=0.19$, $P=0.003$), with these 2 variables accounting for 17% of the variance. Sex and systolic blood pressure did not significantly add to the ability to predict the Physical Component Summary score in the control population. The Mental Component Summary score in the control subjects was related only to BMI ($r=-0.22$, $P<0.001$).

The baseline BDI-II score in the resistant hypertension patients was 8.9±1.1 (range, 0–49). The majority of participants (79%) presented with minimal signs of depression. Nine patients presented a score indicative of mild depression, 3 moderate depression, and 2 severe depression. Spielberger anxiety state and trait scores were not elevated, being 31±1 and 35±1, respectively.

Three Months Postrenal Denervation

After the denervation procedure, all participants remained under the care of their individual specialist and general physicians but had 3 to 6 monthly study follow-up visits, at which time medications and adverse events were recorded. Follow-up psychometric questionnaires were completed in 65% of subjects. There were no adverse events reported that could account for loss to follow-up. Three months after the renal denervation procedure, clinic blood pressure was significantly reduced (change in systolic and diastolic blood pressure, $-16±4$ and $-6±2$ mm Hg, respectively; $P<0.01$ for both). Medications were not changed.

Renal denervation was without a detrimental effect on any elements of the SF-36. The SF-36 Mental Component Summary score had improved significantly after 3 months (Table 2). The increase in Mental Component Summary score was driven largely by increases in the vitality, social function, role emotion, and mental health domains. There was no significant change in the Physical Component Summary score. BDI scores improved. Of particular note were improvement in symptoms of sadness ($P=0.01$), tiredness ($P<0.001$), and libido ($P<0.01$). There was no change in state or trait anxiety levels (Table 2).

### Table 2. Psychometric Assessment After Renal Denervation

<table>
<thead>
<tr>
<th>Psychometric Test</th>
<th>3 Months Postrenal Denervation</th>
<th>Change From Baseline (95% CI)</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SF-36 domains</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical function</td>
<td>75±4</td>
<td>+9 (1.1 to 15.7)</td>
<td>0.03</td>
</tr>
<tr>
<td>Role physical</td>
<td>68±2</td>
<td>+10 (−4.8 to 24.8)</td>
<td>0.19</td>
</tr>
<tr>
<td>Body pain</td>
<td>73±2</td>
<td>+3 (−2.8 to 8.8)</td>
<td>0.32</td>
</tr>
<tr>
<td>General health</td>
<td>59±4</td>
<td>+4 (−1.4 to 8.8)</td>
<td>0.20</td>
</tr>
<tr>
<td>Vitality</td>
<td>57±4</td>
<td>+8 (1.0 to 15.8)</td>
<td>0.04</td>
</tr>
<tr>
<td>Social function</td>
<td>84±5</td>
<td>+10 (1.7 to 17.6)</td>
<td>0.02</td>
</tr>
<tr>
<td>Role emotion</td>
<td>91±4</td>
<td>+26 (7.5 to 42.0)</td>
<td>0.008</td>
</tr>
<tr>
<td>Mental health</td>
<td>80±2</td>
<td>+7 (1.7 to 11.3)</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>SF-36 Summary Scores</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical component</td>
<td>44±2</td>
<td>+1 (−1.3 to 3.8)</td>
<td>0.35</td>
</tr>
<tr>
<td>Mental component</td>
<td>52±1</td>
<td>+6 (2.5 to 8.7)</td>
<td>0.001</td>
</tr>
<tr>
<td>Beck Depression Inventory</td>
<td>5.5±1.2</td>
<td>−2.6 (−5.0 to –0.2)</td>
<td>0.03</td>
</tr>
<tr>
<td>Spielberger Anxiety Rating</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>State</td>
<td>29±2</td>
<td>−0.5 (−3.4 to 2.4)</td>
<td>0.37</td>
</tr>
<tr>
<td>Trait</td>
<td>32±1</td>
<td>−1.5 (−4.0 to 1.0)</td>
<td>0.26</td>
</tr>
</tbody>
</table>

SF-36 indicates 36-Item Short-Form Health Survey.
The magnitude of the reduction in blood pressure at 3 months or the blood pressure level achieved bore no association to the baseline or change in SF-36 component or summary scores or the BDI-II and state and trait anxiety levels.

Discussion
Recent reports documenting the effectiveness of catheter-based renal denervation in reducing blood pressure, improving glucose metabolism and insulin sensitivity, and in reducing left ventricular hypertrophy highlight the importance of the sympathetic nervous system in cardiovascular and cardiometabolic diseases. In this report, we noted that subjective health-related quality of life was markedly diminished in patients with treatment-resistant hypertension and document that, in these patients, ablation of renal sympathetic nerves not only resulted in a significant reduction in blood pressure but also in an improvement in health-related quality of life. In particular, the Mental Health Component Summary score of the SF-36 and symptoms of the BDI were significantly improved 3 months after renal sympathetic nerve ablation. This was independent of the blood pressure changes observed or the blood pressure level reached. Whether there is a biological basis for the improvement in health-related quality of life after renal denervation remains to be determined. This was an observational study and we cannot exclude the possibility that, after years of frustration with controlling their blood pressure, patients’ health perceptions improved as a result of being involved in a successful clinical trial and told that their blood pressure was improved.

Although a number of studies indicate that the health-related quality of life in patients with hypertension is diminished, the actual effect of elevated blood pressure, as opposed to the medications used, on the assessment of quality of life is not well understood. Studies by Croog et al and Testa et al highlight the variable effects that different medications, even within the same class, may exert on health-related quality of life. In the present study, given the large and variable nature of the medications used, it is difficult to meaningfully evaluate the impact of current pharmacotherapy on quality of life in our patients with resistant hypertension. Previous reports also indicate that the diagnosis of hypertension itself may be sufficient to illicit a detrimental effect on health-related quality of life. Importantly, the presence of comorbidities, such as diabetes mellitus or cardiovascular disease, significantly worsens the subjective assessment of health quality of life in hypertensive subjects. In the present investigation, we found no difference in SF-36 individual domain or summary scores between the normotensive individuals and hypertensive subjects with well-controlled blood pressure who were on ≤2 antihypertensive medications and who, presumably, were aware of their condition. This observation is consistent with some, but not all, previous reports. In a recent meta-analysis, Trevisol et al concluded that health-related quality of life in patients with hypertension was slightly worse than in normotensive individuals but highlighted the large heterogeneity of studies with regard to selection criteria and comparison groups.

In contrast, patients with resistant hypertension and uncontrolled blood pressure despite treatment with an average of 4.8 drugs had markedly diminished health-related quality of life compared with both control groups. Although we cannot delineate the potential impact of elevated blood pressure, per se, nor the potential influence of the multiple antihypertensive drugs being used, it is noteworthy that the improvements in several domains observed at 3 months of follow-up occurred in the absence of changes in the antihypertensive regimen, suggesting that the medication, per se, is not a major driver of diminished health-related quality of life in our study cohort. Although assessments were made before any hospital intervention in the treatment-resistant group, we cannot discount that the impending procedure may have influenced the baseline subjective assessment of health-related quality of life.

The SF-36 is widely used to evaluate subjective health-related quality of life. Normative data are available for healthy subjects stratified by age and sex and for a range of patient groups, including diabetes mellitus, renal disease, and congestive heart failure. The influence of severe obesity and the remedial effect of substantial and sustained weight loss on SF-36 scores have also been documented. The SF-36 category and summary scores that we observed in our subjects with uncontrolled hypertension were markedly reduced, particularly in those categories related to mental health. Vitality, social functioning, and mental health were all significantly diminished in these patients. Vitality is indicative of a person’s energy level and degree of fatigue, social functioning reflects the effect of health or emotional problems on the quality and quantity of a person’s social interactions, and mental health indicates the amount of time a person experiences feelings of nervousness, anxiety, depression, and happiness.

Importantly, although the Physical Component Summary score was not significantly diminished in these patients before the procedure, largely because the experience of pain or the extent to which pain interfered with normal activities was not increased, they did demonstrate a marked reduction in the physical functioning and general health dimensions of the SF-36 scale. Taken together, these observations paint a picture of a patient group experiencing a high degree of impairment with regard to the subjective assessment of health-related quality of life.

After renal denervation, we found no deterioration in any of the SF-36 component or summary scores and noted improvement in the SF-36 mental health summary score and the BDI-II score. Similarly, although using different assessment tools, Grimm et al found an improvement in the subjective assessment of quality of life in patients with mild hypertension 3 months after the initiation of pharmacotherapy. The incremental rise in quality of life was most prominent in indices related to mental health and general and social functioning and was related not only to the magnitude of blood pressure reduction but also to the amount of weight loss and increase in physical activity. Wiklund et al, in an analysis of the Hypertension Optimal Treatment cohort, found greater improvement in well-being in those patients that achieved the lowest diastolic blood pressure target. We found no association between the magnitude of blood pressure reduction and improvement in health-related quality of life after renal denervation.
Given the severity of hypertension and the complexity of medications used in our patients, this is perhaps not surprising. After renal denervation, the change in SF-36 was driven by the incremental elevation in the vitality, social function, role emotion, and mental health domains, whereas changes in the BDI-II occurred largely in relation to symptoms, including sadness, fatigue, and libido. The improvement in libido in our patients contrasts with the findings of the Hypertension Optimal Treatment study, where the more intensive blood pressure reduction was associated with deterioration in sex life, particularly in males.35

In conclusion, patients with severe hypertension resistant to therapy present with a marked reduction in subjective health-related quality of life. Renal denervation is accompanied by an improvement in health-related quality of life, particularly in aspects related to mental health, 3 months after the procedure.

Perspectives

Although we cannot exclude the possibility of a placebo effect, with patients’ subjective health-related quality of life being influenced by the added attention given them through their involvement in an intensive clinical trial, the combined improvement in SF-36 Mental Health Component Summary score and the BDI-II rating after renal denervation is intriguing. Sensory renal afferent nerves do project to the hypothalamus36 and have been shown to influence the firing rate of medullary and hypothalamic units in the cat.37 In rats with chronic renal failure, renal afferent denervation prevents the development of hypertension and, importantly, in the context of the present report, an increase in norepinephrine turnover rate in the posterior and lateral hypothalamic nuclei and the locus ceruleus (A6 region).38 The majority of brain norepinephrine is located in the locus coeruleus,39 which, together with its hypothalamic and amygdala projections, is functionally linked with behavioral responses involving autonomic activation.39,40 Whether the improvement in SF-36 and BDI-II that occurred after renal denervation is sustained and has a biological basis associated with reduction in sympathetic tone remains unknown but does merit further attention.

Acknowledgment

The authors thank Kevin Lambert for data management and database development. Professors Gavin Lambert, Murray Esler, Jonathan Shaw, John Dixon, Markus Schlaich are supported by National Health and Medical Research Council of Australia fellowships. Dr Hering has been supported by a Research Fellowship from the Foundation for Polish Science (KOLUMB/2010-1).

Sources of Funding

This work was supported by grants from the National Health and Medical Research Council of Australia, from Medtronic, and from Ardan before its acquisition by Medtronic. The Baker IDI Heart and Diabetes Institute is supported in part by the Victorian Government’s OIS Program. The funding organizations played no role in the design and conduct of the study, collection, management, analysis, or interpretation of the data, nor preparation, review, or approval of the article.

Disclosures

The laboratories of Gavin Lambert, Murray Esler, and Markus Schlaich currently receive research funding from Medtronic, Abbott Pharmaceuticals, Servier Australia, and Allergan. Gavin Lambert has acted as a consultant for Medtronic and has received honoraria or travel support for presentations from Pfizer, Wyeth Pharmaceuticals, Servier, and Medtricron. Murray Esler serves on scientific advisory boards of Abbott (formerly Solvay) Pharmaceuticals and Medtricron. Markus Schlaich serves on scientific advisory boards for Abbott (formerly Solvay) Pharmaceuticals, Novartis Pharmaceuticals, and Medtricron and has received honoraria and travel support from Medtricron, Servier, Novartis, and Medtricron. Henry Krum receives research support from Medtricron, Novartis, Pfizer, Alere, and Bayer. John Dixon is a consultant for Allergan Inc, Bariatric Advantage, and Scientific Intake and is a member of the Optifast Medical Advisory Board for Nestle Health Australia. J. Shaw has received honoraria and lecture fees from Sanofi Aventis, Eli Lilly, Novo Nordisk, Merck Sharp and Dohme, and Pfizer. David Barton has received honoraria or travel support from Pfizer, Servier, Astra Zeneca, Lilly, Novartis, Janssen Cilag, and Lundbeck. Acknowledgment for support of the Australian Diabetes, Obesity, and Lifestyle study is listed in reference 15. The other authors have no conflicts to report.

References


Health-Related Quality of Life After Renal Denervation in Patients With Treatment-Resistant Hypertension


Hypertension. 2012;60:1479-1484; originally published online October 15, 2012; doi: 10.1161/HYPERTENSIONAHA.112.200865

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2012 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/60/6/1479

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at:
http://hyper.ahajournals.org/subscriptions/