There is a broad spectrum of clinical sequelae associated with cardiac sarcoidosis (CS), a condition which accounts for 13% to 25% of deaths associated with sarcoidosis as a whole, but continues to present a significant diagnostic challenge. The current clinical standard for diagnosis of CS is the Japanese Ministry of Health and Welfare (JMHW) Criteria, last updated in 2006 (Figure 1), which incorporate histological findings with abnormalities on ECG and ambulatory monitoring as well as multiple imaging modalities such as Echocardiography, MRI, and nuclear imaging with Gallium, Technetium, and Thallium.

Clinical Perspective on p 626

Is There an Association Between Clinical Presentation and the Location and Extent of Myocardial Involvement of Cardiac Sarcoidosis as Assessed by 18F- Fluorodeoxyglucose Positron Emission Tomography?

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Background—Positron emission tomography using 18F-Fluorodeoxyglucose (FDG) is an emerging modality for diagnosis of cardiac sarcoidosis (CS). We compared the location and degree of FDG uptake in CS patients presenting with either advanced atrioventricular block (AVB) or ventricular tachycardia (VT).

Methods and Results—We included consecutive patients who presented with either AVB or VT with a diagnosis of CS. A cohort of patients with clinically silent CS was included as controls. FDG activity was quantified as standardized uptake values (SUV) and both the overall mean left ventricular (LV) SUV as well as the Maximum Mean Segmental SUV was recorded for each patient. Receiver operator characteristic (ROC) analysis was performed to identify cutoff SUV values that best identified patients with VT. A total of 27 patients with CS were included (13 females; mean age, 56±8 years; 8 VT, 12 AVB, and 7 controls). Both mean LV SUV and Max SUV in CS patients presenting with VT were significantly higher compared with those with AVB (mean SUV: VT median 5.33, range 4.7–9.35 versus AVB median 2.48, range 0.86–8.59, \( P=0.016 \); max SUV: VT median 11.07, range 9.24–14.4 versus AVB median 5.63, range 3.42–15.71, \( P=0.005 \)) and compared with controls. There was no significant difference in SUV values between AVB patients and controls. ROC analysis for identification of patients with VT showed AUCs of 0.93 and 0.895 for a mean LV SUV of >3.42 and a max SUV >8.56, respectively (\( P<0.001 \)).

Conclusions—CS patients with VT displayed significantly higher FDG uptake when compared with those with AVB and asymptomatic controls. Further prospective studies are required to evaluate this finding.

Key Words: fluorodeoxyglucose F18 ▪ positron emission tomography ▪ sarcoidosis

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In this study we compare the extent and location of abnormalities on FDG and rest perfusion PET in patients with CS presenting with either advanced atrio-ventricular block (AVB) or ventricular tachycardia (VT) as well as a control group of patients with clinically silent CS (ie, extracardiac sarcoidosis with clinical and imaging evidence of cardiac involvement without AVB, VT, or heart failure).

**Methods**

**Patient Population and Controls**

We analyzed the records of all patients who underwent PET scanning for evaluation for possible CS at our institution from September 2007 to October 2012 from our cardiac FDG-PET registry (CADRE) data.1 This is a database of all patients undergoing cardiac FDG PET in Ontario, the majority of whom were for assessment of myocardial viability in the setting of coronary artery disease, and has ethics approval from the Human Research Ethics Boards of participating centers.

We included all patients presenting with AVB or VT with diagnosed CS based on modified JMHW criteria who underwent PET scanning in this study. The original JMHW criteria include a positive Gallium scan as a major criterion but, because of its limited sensitivity, this is no longer performed at our institution. Therefore, similar to 2 previous studies,1,14 focal FDG uptake was used as an alternative imaging criterion. We also included rest perfusion defects on Rb-82 or 13-N-Ammonia PET as a minor criterion as an alternative to perfusion defect on Technetium or Thallium SPECT (Figure 1).

As controls, we included a cohort of patients with biopsy-proven extracardiac sarcoidosis and evidence of cardiac involvement on non-invasive testing or advanced imaging but without a history of AVB, VT, or heart failure. Again, patients with known or strongly suspected obstructive CAD or significant ongoing valve disease were excluded.

Results of all imaging studies for included patients were collected, including echocardiography, nuclear perfusion imaging, and MRI as well as ECG, and histology results. Where there was ambiguity over the diagnosis of CS or the clinical categorization of CS patients, the case was reviewed by two cardiologists (P.N. and D.B.) in conjunction with a Nuclear Medicine physician (E.L.) and a consensus was reached.

**Imaging Protocol**

All patients were instructed to adhere to a high-fat, low-carbohydrate diet on the day before, and fast for a minimum of 12 hours before scanning. Serum glucose was measured before scanning, as a baseline for comparison in cases where follow-up scanning may be performed. Low-dose intravenous heparin was administered to patients in whom there was no contraindication, to increase serum free fatty acids and further suppress background myocardial glucose uptake.

Patients were positioned in the 64-slice PET/CT scanner (either Discovery RX or Discovery 690 PET/VCT; GE Healthcare, Canada) in the supine position. The PET imaging protocol included sequential transmission scans and 3-minutes PET images in transaxial, coronal, and sagittal planes with a resolution of 2.5 mm (three-dimensional reconstruction). The acquisition was performed with a 64-slice PET/CT scanner (Discovery RX; GE Healthcare, Canada) in the supine position. The PET imaging protocol included sequential transmission scans and 3-minutes PET images in transaxial, coronal, and sagittal planes with a resolution of 2.5 mm (three-dimensional reconstruction).

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Afterwards 5 MBq/kg \(^{18}F\)-FDG was administered intravenously. After an uptake phase of 60 minutes, a whole body scan was performed with a CT scan from the femoral region to the head for attenuation correction. This was followed by a dedicated cardiac scan from which the myocardial SUV values were measured.

Perfusion and FDG images were reconstructed in standard transaxial plane orientation and proper alignment of PET and CT data were assessed and corrected visually. Images were manually reoriented to standard short-axis, horizontal-long axis, and vertical long axis views and using the standard ASNC 17 segment model of the LV. Perfusion within each segment was scored visually and a total summed rest score (SRS) was calculated. FDG uptake was also assessed visually within each segment and the uptake pattern was recorded as either: normal, metabolism-perfusion matched defect consistent with scar, or metabolism-perfusion mismatch defect consistent with inflammation with or without scarring. The number of abnormal segments (ie, that were found to have either: abnormal perfusion, abnormal FDG uptake, or both) was recorded for each patient. Furthermore, visual analysis was used to identify the presence or absence of RV uptake on transaxial images for all patients. Ejection fraction was estimated from gated images.

Next the FDG/CT coregistered images were analyzed visually in three orientations using hybrid imaging software and regions of interest (ROI) were used to identify the maximum mean segmental SUV values for each patient, which was calculated by dividing the standard deviation of segmental SUV values by the mean overall SUV value. This parameter is an indicator of the heterogeneity of FDG uptake in the myocardium, which is expected to be higher in CS, and has been recently shown by Tahara et al to be an accurate quantitative means of identifying disease activity in patients with CS.

Statistical Analysis

Mean values with 95% confidence intervals for baseline clinical characteristics were calculated for each patient presentation group and compared using a 2-tailed \(t\) test for independent samples. Nonparametric methods were used for comparing mean LV SUV, max LV SUV, rest EF, SRS, coefficient of variation (COV), and septal/lateral wall SUV ratio. In particular, the Kruskal–Wallis one-way analysis of variance was used to compare all 3 groups simultaneously (AVB versus VT versus clinically silent CS patients), and pairwise comparisons were conducted using the Wilcoxon rank-sum test. For the pairwise comparisons, significance was determined by comparing the probability value to the Bonferroni corrected probability value of 0.0166 to correct for multiple comparisons.

The relationship between SUV values and the number of abnormal LV segments on visual analysis as well as left ventricular ejection fraction (LVEF) was evaluated using Spearman’s rank correlation coefficient for non-normally distributed data.

The diagnostic performance for predicting patients with VT, of both the mean overall LV SUV and the max SUV, was analyzed using ROC curves, displaying sensitivity and specificity at different cutoff values. Analysis was performed using MedCalc (MedCalc Software Inc., Mariakerke, Belgium) statistical software.

Results

Baseline Demographics

A total of 134 patients underwent FDG-PET scanning at our institution between September 2007 and September 2012 with the indication of evaluation for cardiac sarcoidosis. Of these, 90 patients were excluded because they had no positive histological or imaging evidence of sarcoidosis. Of the remaining 44 patients, there were 26 patients who met modified JMHW criteria for diagnosis of CS, of whom 12 had advanced AVB, whereas 8 had documented sustained
VT. Five patients had a history of cardiomyopathy without documented AVB or VT and therefore were not included, and 1 patient with AVB was excluded because of the finding of obstructive CAD on angiography. Six of the 20 patients in our final CS cohort were included in a prior meta-analysis of the diagnostic accuracy of FDG-PET in CS.³

There were another 18 patients with abnormal PET results. Of these, 7 patients had a histological diagnosis of extracardiac sarcoidosis without a history of VT, AVB, or heart failure, and the control comprised these patients.

The remaining 11 patients (4 AVB, 3 VT, 4 asymptomatic) had insufficient evidence for a diagnosis of CS and were therefore excluded. The inclusion and exclusion processes are outlined in Figure 2.

The baseline characteristics of the 27 included patients are summarized in Table 1, and their clinical criteria for diagnosis of CS are outlined in Table 2. Overall, 10 of 12 AVB patients and 5 of 8 VT patients underwent PET scanning within 1 month of first clinical presentation. The remaining 5 patients had a prior diagnosis of CS (2 AVB, 3 VT) and underwent scanning >2 years after initial presentation to assess disease activity.

All of these patients had ICDs in situ at the time of scanning with device interrogation revealing no sustained VT in the AVB patients. Two of the 3 VT patients with secondary prevention ICDs had received an appropriate shock from their ICD within 1 year of PET scan, whereas the other had documented runs of nonsustained VT.

Half of the included patients were female with no significant difference in age between groups. In total, 5 patients underwent cardiac biopsy, of which 4 were positive. Among the AVB and VT patients, the diagnosis of CS was made based on modified JMHW with positive cardiac biopsy (n=4) or with positive systemic biopsy (n=10). There were 6 patients who had a clinical diagnosis of systemic sarcoidosis based on findings on chest CT who met modified JMHW criteria.

FDG PET Results
On visual analysis alone 27 of 28 patients showed evidence of focal or focal on diffuse uptake of FDG within the myocardium suggestive of active CS, whereas 1 AVB patient with a long-standing diagnosis of CS had equivocal FDG uptake with resting perfusion defects on visual analysis. Semi-quantitative segmental analysis showed a trend toward more abnormal segments in VT patients (mean 8.62±3.85 VT versus 5.58±2.5 AVB versus 4.7±1.8 clinically silent CS patients) that was not statistically significant (P=0.076). There were no significant differences between VT or AVB patients in the number of segments with either; normal perfusion/focal FDG, abnormal perfusion/focal FDG, or abnormal perfusion/no FDG (Table 1). However, there were no patients with segments showing abnormal perfusion in the clinically silent CS group. Furthermore there was a significant negative correlation between the number of abnormal segments and LVEF (Spearman’s coefficient –0.61, P=0.0005).

Analysis of the whole body scan showed extracardiac uptake in 58% of VT/AVB patients and 72% of controls, primarily in the lungs and hilar lymph nodes.

Left Ventricular SUV Data
On quantitative analysis both mean overall LV SUV and the maximum mean segmental SUV were significantly higher in patients in the VT cohort compared with those with AVB (mean SUV: VT median 5.33, range 4.7–9.35 versus AVB median 2.48, range 0.86–8.59, P=0.016; max SUV: VT median 11.07, range 9.24–14.4 versus AVB median 5.63, range 3.42–15.71, P=0.005; Figure 4). ROC analysis showed AUCs of 0.93 and 0.895 for a mean LV SUV of >3.42 and a max SUV >8.56, respectively for identification of patients with VT (P<0.001, Figure 5) with sensitivity of 100% and specificities of 90% and 79%, respectively.

Both mean overall SUV and max SUV were also significantly higher in the VT cohort when compared with clinically silent CS patients (P<0.016). However, there was no significant difference in either parameter between AVB patients and clinically silent CS patients (Figure 4).

Segmental Evaluation, Regional Heterogeneity, and RV Uptake
Evaluation of the distribution of FDG uptake showed that uptake was highest in the basal segments in all patient groups. Furthermore, the ratio of mean septal to mean lateral wall SUV was higher in AVB and VT patients when compared with controls (1.24±0.5 versus 1.42±0.64 versus 0.84±0.05 <0.001, Figure 5) with sensitivity of 100% and specificities of 90% and 79%, respectively.

Both mean overall SUV and max SUV were also significantly higher in the VT cohort when compared with clinically silent CS patients (P<0.016). However, there was no significant difference in either parameter between AVB patients and clinically silent CS patients (Figure 4).
for AVB, VT, and clinically silent CS patients, respectively; \( P=0.04 \). However, this difference was no longer significant on pairwise analysis when the Bonferroni corrected probability value cutoff of 0.0166 was applied.

Maximum SUV was found in the basal septum in 7 of 11 AVB patients with no clear pattern in VT patients. In the clinically silent control cohort, Maximum SUV was found in the lateral wall in 6 of 7 patients (Table 3). However, focal FDG uptake was seen in either the septum or anterior walls in all clinically silent patients but was of lesser intensity than the lateral wall in all but 1 patient.

The COV was significantly higher in AVB and VT patients than those with clinically silent CS patients (Figure 4). However, there was no significant difference in COV between AVB and VT patients (0.34±0.13 versus 0.35±0.16, \( P=0.9 \)), indicating a similar degree of heterogeneity of FDG uptake between these 2 cohorts (Figure 4).

There was a significant correlation between Mean Overall LV SUV and the number of abnormal segments on visual analysis (Spearman’s coefficient=0.506, \( P=0.006 \)) as well as a negative correlation with resting LVEF (Spearman’s coefficient=-0.42, \( P=0.024 \)).

On visual analysis RV uptake of FDG was present in 5 of 12 of AVB and 4 of 8 of VT patients. It was not observed in any of the clinically silent CS patients. There was no significant difference in mean or max mean segmental SUVs, LVEF, or number of abnormal segments between patients with or without RV uptake within the AVB or VT patient cohorts although the numbers for comparison were small.

Resting Perfusion
Abnormalities (SRS >2) were seen in 7 of 8 VT patients, 8 of 12 AVB patients, and none of the clinically silent CS patients. The majority of patients had undergone coronary angiography within 3 months of PET scanning, whereas others had normal cardiac enzymes and no symptoms of chest pain. Mean SRS was higher in VT patients than those with AVB but this difference was not statistically significant (VT median 7, range 0–15 versus AVB median 3.5, range 0–9; \( P=0.13 \)). There was a significantly greater SRS in CS patients with VT and AVB compared with the clinically silent CS patients (\( P=0.0037; \) Figure 4).

**LV Function**
Mean EF as measured on gated rest PET perfusion scanning was lower in the VT patients compared to those with AVB (VT median 33%, range 15–56 versus AVB median 51%, range 18–71, \( P=0.082 \)) and was significantly lower than clinically silent CS patients (\( P=0.0026 \)). Mean EF was lower in AVB...
patients when compared to clinically silent CS patients but the difference was not significant when corrected for multiple comparisons ($P=0.017$; Figure 4).

**Other Imaging Results**

There were 12 of 27 patient who underwent cardiac MR scanning, and of these 7 showed foci of late gadolinium enhancement suggestive of CS. MRI scanning was negative in 1 patient with AVB and 4 clinically silent CS patients (Table 2).

**Discussion**

In this study we performed quantitative analysis of the uptake of FDG within the LV in patients with cardiac sarcoidosis using a semiautomated method, and related the mean overall SUV and maximum mean segmental SUV values to the patient’s clinical presentation. Although preliminary in nature, the results show that patients with episodes of sustained VT had significantly higher FDG uptake when compared with...
patients presenting with AVB and to a cohort of patients with clinically silent CS.

Studies reporting correlations between abnormalities on imaging and clinical presentation in CS patients, particularly using FDG PET, are extremely limited, and quantitative analysis of SUV values has not previously been used for this purpose. Banba et al\textsuperscript{17} performed Gallium scanning in 15 CS patients presenting with either AVB or VT. Interestingly, abnormal Gallium uptake was documented in 80% of AVB patients, but only 14% of the VT cohort. Similar to our results EF was lower and there was a high prevalence of perfusion abnormalities in the VT cohort. The authors therefore concluded that active inflammation was not closely associated with the development of VT. This is in contrast to our results. In our study 2 patients presenting with VT had normal LV function and normal/mildly abnormal rest perfusion. Our data suggest that active inflammation does play a role in the development of VT and that FDG may be a sensitive means of quantifying disease activity.

In preliminary findings published in abstract form, Chung et al\textsuperscript{18} visually analyzed Rb-82/FDG PET scans of 55 patients meeting JMHW criteria for CS and found that 83% of patients who demonstrated scar or inflammation in ≥2 basal or mid segments had VT. In this study we found no significant difference in the number of segments showing inflammation or scar between the 3 patient groups, although there was a trend toward more abnormal segments in the VT patient that is not statistically significant when corrected for multiple comparisons. F. LV ejection fraction as measured on gated PET was significantly lower in VT patients compared with controls with a trend toward a lower EF than those with presenting with AVB. *Significant Bonferroni corrected P value of 0.0166 to correct for multiple comparisons.
Quantitative analysis of SUVs has been used in several studies involving patients with suspected CS, although not specifically to identify which patients may have AVB versus VT. As described above, Tahara et al. also measured SUVs in a 17-segment model of the LV and determined the COV. In this cohort we found that this parameter did not differ significantly between patients with AVB or VT but the COV for clinically silent CS patients was significantly lower than for patients with either AVB or VT. Therefore, the COV does not seem to correlate with clinical presentation among CS patients with either VT or AVB.

American College of Cardiology/American Heart Association/Heart Rhythm Society guidelines give a Class IIa recommendation for ICD insertion for primary prevention in CS patients (level of evidence C), but there is wide variation in clinical practice in this regard at present. Moreover, European guidelines for pacing recommend pacemaker insertion for patients with AVB secondary to CS. The decision regarding ICD insertion is hampered by limited tools for patient risk stratification and a lack of knowledge regarding the true prevalence of ventricular arrhythmia in this population. Programmed ventricular stimulation has been shown to have some use in this regard, but there are limited studies in this area and the long-term prognostic significance of a normal study remains unclear.

As the use of advanced imaging with FDG-PET and MRI in patients with sarcoidosis becomes more widespread, a significant increase in the numbers of patients diagnosed with cardiac involvement at an early stage is being seen. Although currently unproven, it is likely that CS patients with either VT, AVB, or patients with clinically silent disease do not have the same prognosis, and therefore treatment strategies will differ between groups. Therefore methods to noninvasively identify patients at higher risk of potential arrhythmia would be of significant value. The results of this study are preliminary in nature, and therefore the hypothesis that there is a relationship between the extent and severity of cardiac involvement by sarcoidosis, as assessed on FDG PET, and the risk of significant arrhythmia requires further evaluation.

LVEF was lower in the VT cohort and scar extent as quantified by SRS was also higher. These differences did not reach statistical significance when compared with AVB patients, most likely because of low patient numbers. However it is noteworthy that all clinically silent CS patient had normal resting perfusion and there was a significant correlation between mean LV SUV and LVEF and the number of abnormal segments, suggesting that scar formation may also play a significant role in the development of arrhythmia in addition to active inflammation. However larger studies with clinical and imaging follow-up to evaluate

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<th>FDG Uptake/Normal Perfusion</th>
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AVB indicates atrioventricular block; FDG, 18F-Fluorodeoxyglucose; LV, left ventricle; and SUV, standardized uptake value.
events and changes over time would be required to confirm this hypothesis. There was no significant difference in SUV values between patients presenting with AVB and clinically silent CS patients. However, the pattern of involvement seemed different in the 2 groups, with maximal uptake localizing to the basal septum in the majority of AVB patients, and although there was focal uptake of FDG in the septum or anterior segments in all clinically silent patients, the basal lateral wall was the site of maximal uptake in 72% of these patients. This observation suggests that acute inflammation within the basal septum may predispose to the development of AVB while lateral wall involvement may be more likely to be subclinical in nature.

There are several limitations to the current study. First, the number of patients is small but because of the low incidence of this condition this is a common limitation of studies involving CS patients. Going forward collaborative multi-center studies are required to prospectively evaluate the hypotheses generated by this study.

The JMHW criteria, although modified in this study to include FDG PET as a criterion, may be a relatively insensitive gold standard for CS, particularly in cases of asymptomatic patients with normal LV function, or in cases of isolated cardiac involvement, where a positive endomyocardial biopsy is required to confirm the diagnosis, which is difficult to achieve in patients with limited focal disease. Our control cohort included patients who did not fully meet the Japanese criteria but had biopsy proven extracardiac sarcoidosis with evidence of cardiac involvement on PET±MRI. Clinically it was thought that all of these patients had CS and several were commenced on steroid treatment on this basis.

Only a minority of patients underwent cardiac MRI scanning, and the majority of these were suggestive of CS. There are limited data comparing the FDG PET and MRI in CS but previous MRI studies have shown a high sensitivity and specificity of MRI when compared with JMHW criteria.26,27 In this study 4 clinically silent CS patients and 1 AVB patient had negative MRI scans, which is higher than that observed in other studies, and may be a reflection of the low specificity of the JMHW criteria, FDG PET, or both in asymptomatic patients.

From our registry there were 11 patients with a positive FDG PET who had insufficient evidence for a diagnosis of CS to be included in the analysis. Although several of these patients subsequently received alternative diagnoses, it is possible that some may have CS and thus there is a possible selection bias affecting these results.

We did not assess the reproducibility of SUV values within normal subjects, but this has been previously evaluated. Inglese et al28 evaluated a series of 49 oncology patients who underwent baseline and follow-up FDG PET scanning for cancer surveillance. They found no significant difference in maximum myocardial SUV between baseline and follow-up, although they did note regional heterogeneity in uptake between scans. Another series of 47 cancer patients undergoing serial PET scanning again showed little variation in myocardial FDG uptake, although this series used visual analysis of uptake.29

Sarcoidosis is a dynamic process and the interval between clinical presentation with AVB or VT and PET scanning was variable. This is a preliminary hypothesis-generating study and therefore potential changes in FDG uptake on serial scanning as well as the impact of immunosuppressive therapies were not evaluated. Ascertaining the true prognostic value of the degree and pattern of abnormalities on FDG PET scanning will require further prospective studies with long-term follow-up.

Conclusions
In this observational series, patients with CS presenting with VT showed significantly higher FDG SUV values when compared with those presenting with advanced AVB or to clinically silent CS patients. Furthermore, maximal FDG uptake localized to the basal septum in the majority of patients presenting with advanced AVB.

Both perfusion defect size (as measured by Summed Rest Score) and LVEF (as measured on gated PET) were lower in VT patients but did not reach statistical significance. These results suggest that there may be a relationship between the degree of FDG uptake and clinical presentation, particularly ventricular tachyarrhythmia.

However, larger prospective studies with longitudinal follow-up and repeat scanning are required to further investigate this finding and determine whether the degree of FDG uptake could potentially provide prognostic data on subsequent risk for arrhythmia.

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References
The role of F-18 fluorodeoxyglucose positron emission tomography (FDG PET) in the diagnosis of cardiac sarcoidosis (CS) has gained significant interest in the recent years. However, till date, there are no studies that evaluate the relationship between the degree and location of abnormalities on FDG PET and the clinical presentation in patients with CS, a condition with heterogeneous clinical presentations. We demonstrated more extensive and avid FDG uptake in patients presenting with ventricular tachycardia compared with patients with aortic valve bypass and patients with clinically silent CS. Appropriate management of patients with CS is currently a matter of debate, particularly in asymptomatic patients, and methods for risk stratification are limited. Although preliminary in nature, our results suggest a relationship between clinical presentation and abnormalities on FDG PET, which warrants further evaluation.
Is There an Association Between Clinical Presentation and the Location and Extent of Myocardial Involvement of Cardiac Sarcoidosis as Assessed by 18F- Fluorodeoxyglucose Positron Emission Tomography?

Brian A. Mc Ardle, David H. Birnie, Ran Klein, Rob A. de Kemp, Eugene Leung, Jennifer Renaud, Jean DaSilva, George A. Wells, Rob S. Beanlands and Pablo B. Nery

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