

Thromboangiitis Obliterans: 110 Years Old and Little Progress Made

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Since the landmark article by Leo Buerger in 1908, there has been little progress in the understanding of the cause, pathophysiology, and optimum treatment of patients with thromboangiitis obliterans (TAO).¹ There are \approx 40 to 50 articles published on TAO every year, and for the most part, they comprise case reports, small series, and review articles. There has been only incremental new information published since the articles published from the 1960s to the present time.^{2–9}

TAO is a nonatherosclerotic, inflammatory vascular disease that affects the small- and medium-size arteries and veins in the upper and lower extremities. The pathological hallmark of this disease is the presence of a highly inflammatory thrombus in the affected arteries and veins.^{2,7} There is a strong association with the use of tobacco products as well as cannabis.^{8,10,11} There has never been a well-documented case of Buerger's disease published in a patient proven not to be using tobacco or cannabis in some form (ie, confirmation of smoking cessation by measuring urine nicotine or cotinine levels and toxicology screen). The prevalence of TAO is much higher in the Middle East and Asia as compared with North America and Western Europe. It appears that the prevalence of TAO is declining in North America and Western Europe because of a decline in the rate of smoking and the use of stricter criteria in the diagnosis of TAO.^{10,12,13} There has been no significant change in the way patients with Buerger's disease are medically treated over the past 20 years.^{3,14} The most effective way to "treat" these patients is to convince

them that complete abstinence of tobacco and cannabis use will substantially lessen the likelihood of amputation.^{8,13,14} However, there have been significant advances in endovascular therapy over the past decade. In 2 recent reports, it was shown that in addition to discontinuing smoking, endovascular therapy may be an effective way to preserve the limb and speed the healing of ischemic ulcers in selected patients with TAO.^{15,16} While the sample size in each of these studies was small (35 and 44 patients, respectively), the technical results and immediate and late clinical outcomes resulted in amputation-free survival rates similar to those of patients undergoing surgical bypass procedures, and the healing of ischemic ulcers occurs much sooner than with discontinuation of smoking alone.

Several studies have evaluated the long-term outcomes, including rates for major and minor amputations and survival in patients with TAO.^{4,8,17} Ohta and colleagues reported on 110 patients from 1978 to 2001. Using the Kaplan–Meier life table method, they reported a cumulative survival of 84% with a mean follow-up of 10.6 years. The total amputation rate was 43% with 12% of patients undergoing a major (above the ankle) amputation.¹⁷ We reported an amputation rate of 27% in 112 patients followed over a mean of 91.6 months.⁸ In a study from the Mayo Clinic, 111 patients with TAO were followed for a mean of 15.6 ± 10.1 years.⁴ The risk of major amputation was 11% at 5 years, 21% at 10 years, and 23% at 20 years. Minor amputations occurred with a higher frequency. As in virtually every other published study, tobacco abstinence was associated with a favorable prognosis. However, the study by Cooper and associates was the only study that demonstrated reduced life expectancy (average age of death was 52 years) in patients with TAO compared with the remainder of the population in the United States.⁴

In this issue of the *Journal of the American Heart Association (JAHA)*, Le Joncour and associates published the largest series to date on the long-term outcome of patients with TAO from a Western country.¹⁸ They retrospectively identified 224 patients from 1970 to 2016, from multiple institutions in France who met the criteria for the diagnosis of Buerger's disease as proposed by Papa, Rabi, and Adar.¹⁹ The vascular event-free survival was 41% at 5 years and 24% at 10 years. Total amputation-free survival at 5, 10, and 15 years was 85%, 74%,

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

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J Am Heart Assoc. 2018;7:e011214. DOI: 10.1161/JAHA.118.011214.

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and 66%, respectively. Major amputation-free survival occurred in 94%, 91%, and 91% over 5, 10, and 15 years. As shown in many other studies, patients who stopped using tobacco had a significantly lower risk of amputation as compared with those who continued smoking. This observational study, however, identified 2 additional predictors of a poor outcome in a multivariable model: nonwhites had a higher vascular event rate than whites (hazard ratio [95% confidence interval] of 2.35 [1.30–4.27], $P=0.005$) and those patients with a limb infection at diagnosis (hazard ratio 12.1 [3.5–42.1], $P<0.001$) had a significantly higher amputation rate.

It is unfortunate that with rare diseases, virtually all studies are retrospective, observational cohorts. There are few randomized controlled trials in large part because of the inability to recruit enough patients over a short period of time. This is illustrated in the present study from the French TAO network; this study spanned 46 years (1970–2016) to achieve a sample size of 224 patients. The series from the Mayo Clinic and Cleveland Clinic spanned 17 to 22 years to achieve half of the sample size as in the current report.^{4,8} Since the study spanned a period of 46 years, Le Joncour and associates performed a sensitivity analysis stratified by year of diagnosis and found that it did not change the overall results of the study. This reinforces the concept that there has been very little progress in the early recognition and treatment of patients with TAO. The authors honestly and accurately acknowledge some of the limitations of this study.

There are several other points that need to be discussed regarding this study and many of the other publications on TAO^{2,4,6–9}: (1) Since this was a retrospective study, complete longitudinal data were not obtained in the majority of patients because the patients were only evaluated on an intermittent consultation basis. Thus, accurate natural history and outcomes data are still not known; (2) Cannabis use was not independently associated with a worse prognosis as has been reported elsewhere.¹¹ In France, patients often mix cannabis with tobacco and hand roll their cigarettes. If this is the case in patients using cannabis in this series, it would be very difficult to assess the role that cannabis played in vascular events and amputations; (3) One of the most important limitations of this study and virtually every other study of TAO is failure to objectively determine that the patient actually did stop using tobacco or cannabis. In this and other reports, smoking status was made by self-declaration. At first amputation, 5 (10.4%) of 48 patients stated they were not smoking and at the next amputation 8 (23.5%) of 34 patients were not smoking. These are very high amputation rates for patients who have stopped using tobacco or cannabis. In our series, there were 3 (5.5%) amputations among 55 patients who stated they stopped smoking. In all 3 cases, there was gangrene present at the time the patient discontinued smoking. As a general rule, if

the patient has stopped smoking or using tobacco in any form (as confirmed by urine testing) and there is no gangrene present, amputations do not occur.^{8,20} In order to be sure the patient is no longer using tobacco or cannabis, urine for nicotine, cotinine (the metabolic breakdown product of nicotine), and cannabis must be obtained at each office visit. In all likelihood, the number of patients who are not using tobacco or cannabis would be much smaller than relying on the self-declaration of not smoking. There are many questions that remain such as why do only 40% of patients who continue to smoke undergo an amputation? Other than continued tobacco use, what additional factors play a role in determining which patients are protected from amputation and which are more prone to amputation?; (4) It is not clear why nonwhites had a poorer prognosis than whites in this study. While the baseline differences between the 2 groups were not different, we have no information about the different socioeconomic factors between whites and nonwhites. There is the suggestion in some studies that the lower the socioeconomic status, the worse the prognosis in TAO.^{17,21} Thus, it may not be related to race but to other factors such as living conditions, income, and overall socioeconomic status; (5) While the amputation rate is lower in this study than in other studies, the authors acknowledge that this may be because of the difference in severity of disease at presentation as compared with other studies. Thirty percent of TAO patients had ischemic ulcers or necrosis at baseline, whereas it was observed in 45% to 80% of patients in other series. On the other hand, Fazeli and associates reported a similar amputation rate as in the current series and had similar rates of ischemic ulceration and gangrene.¹⁴ Thus, it appears that the milder the symptoms and signs at presentation, the lower the amputation rate.

Despite the difficulties in doing research on rare diseases, Le Joncour and colleagues have added to the knowledge base regarding outcomes in patients with Buerger's disease. As they noted, this is the largest study of patients with TAO from Western Europe and the United States. It is important to recognize that it took 46 years to accumulate a sample size of 224 patients and longitudinal follow-up is very difficult in patients with TAO. Thus, there are gaps in our understanding of the natural history in patients with Buerger's disease. The authors confirmed that cessation of tobacco use leads to a better prognosis. They also showed us that milder signs and symptoms at presentation leads to better outcomes and fewer amputations. Thus, it is important to recognize the signs and symptoms pointing to Buerger's disease so that it can be diagnosed earlier, with a goal of preventing major and minor amputations. Those who have advanced disease are more likely to have limb infection, which leads to a high likelihood of needing an amputation.

Disclosures

None.

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Key Words: Editorials • Buerger's disease • peripheral artery disease • peripheral vasculature • thromboangiitis obliterans