Buerger’s disease is a segmental inflammatory obliterator non-atherosclerotic disease of small- and medium-sized distal arteries, veins, and nerves. The prevalence of Buerger’s disease is greater in Asia and Eastern Europe than in North America and Western Europe. Although it is postulated that alteration of autoimmune response contributes to the pathogenesis of Buerger’s disease, the cause of Buerger’s disease remains unclear. Buerger’s disease is closely related to exposure to heavy tobacco smoking in relatively young men. The mortality rate is not higher in Buerger’s disease patients than in age-matched populations. Patients with Buerger’s disease, however, have lower quality of life because of intermittent claudication, rest pain, ulcers, and several episodes of lower extremity superficial thrombophlebitis.

Angiographic findings in Buerger’s disease involve small–medium-sized vessels of extremities, segmental occlusive lesions, and collateralization around areas of occlusion (cork-screw collaterals). A cork-screw collateral appearance on angiography is one of the diagnostic criteria for Buerger’s disease. The prevalence of ischemic ulcers was significantly higher in patients with types III and IV cork-screw collaterals than in patients with types I and II cork-screw collaterals either below or above the knee. Multiple regression analysis indicated that types III and IV below the knee are independent predictors of risk of ischemic ulcers.

Conclusions: The prevalence of ischemic ulcers is significantly higher in patients who have small cork-screw patterns in distal segments of limb collaterals than in patients who have large cork-screw collaterals.

Key Words: Buerger’s disease; Corkscrew collateral; Ischemic ulcer
Corkscrew Collaterals in Buerger’s Disease

Methods

Subjects
From September 2006 to June 2008, 28 patients with Buerger’s disease (24 men and 4 women; age range, 26–50 years; mean age, 43±11 years) who had no history of hypertension, diabetes mellitus, hyperlipidemia, cardiovascular disease, or other disease were enrolled in this study. Buerger’s disease was diagnosed on the previous criteria, including results of physical examinations, clinical symptoms, and angiographic findings: smoking history, onset before the age of 50 years, infrapopliteal arterial occlusive disease, either upper limb involvement or phlebitis migrans, and absence of atherosclerotic risk factors other than smoking. To rule out other vasculitis and hypercoagulable states, rheumatoid factor, lupus anticoagulants, and serologic investigations were evaluated. One patient had undergone major amputation above knee level, one patient had undergone major amputation below knee level, and 2 patients had undergone minor amputation of toes. Patients who had received surgical interventions such as bypass grafting, skin grafting, and sympathectomy and exercise training were excluded. The study protocol was approved by the Ethics Committee of Hiroshima University Graduate School of Biomedical Sciences. Written informed consent for participation in the study was obtained from all subjects.

DSA
All of the 28 patients underwent intra-arterial DSA in the course of examination for diagnosis of Buerger’s disease. Conventional DSA was performed with a 4-F pigtail catheter (Terumo, Tokyo, Japan) using DSA units (Siemens-Asahi Medical, Tokyo, Japan). The catheter tip was positioned at common iliac arteries, and multiple images that encompassed the thighs, knees and crural were acquired. At each station, 20 ml of iopromidum was injected at a rate of 10 ml/s. The lower leg artery was divided into 2 segments: above the knee (femoral and popliteal) and below the knee (calf and lower crural). The existence of corkscrew collaterals was confirmed on angiographic findings in all patients. We classified collateral arteries by artery amplitude and corkscrew formation pattern into four categories: type I, artery diameter >2 mm, large helical sign (Figure A); type II, artery diameter >1.5 mm and ≤2 mm, medium helical sign (Figure B); type III, artery diameter ≥1 mm and ≤1.5 mm; small helical sign (Figure C); and type IV, artery diameter <1 mm, tiny helical sign (Figure D).

Statistical Analysis
Data are expressed as mean±SD. P<0.05 was considered significant. The distributions of positive corkscrew collaterals and negative corkscrew collaterals among groups with different risk of ischemic ulcers were compared using the chi-squared test. To account for within-patient clustering, generalized estimating equation (GEE) models were used to estimate odds ratios (OR). GEE simple logistic regression models were used to estimate unconditional OR for ischemic ulcer. Independent association between types of corkscrew collaterals and risk of ischemic ulcers was analyzed using...
**Table 2. Corkscrew Collateral vs Presence of Ischemic Ulcer**

<table>
<thead>
<tr>
<th>Ischemic ulcer</th>
<th>Corkscrew collateral</th>
<th>OR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>Positive</td>
<td>19</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Negative</td>
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<td>Positive</td>
<td>16</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td>18</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>κ²=10.575, P=0.0011</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>OR=10.687 95% CI, 2.147–53.207</strong></td>
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</table>

OR, odds ratio; CI, confidence interval.

GEE multiple logistic analysis with existence of ischemic ulcers as the dependent variable and type III above the knee, type IV above the knee, type III below the knee, and type IV below the knee as covariates. The interobserver variability was calculated using κ statistics. All interpretations of detection of corkscrew collaterals using DSA were performed by 2 observers who did not know the study protocol. The data were processed using Stata version 9 (Stata, College Station, TX, USA) and Super analysis of variance (Abacus Concepts, Berkeley, CA, USA).

**Results**

**Clinical Characteristics**

The baseline clinical characteristics of the patients with Buerger’s disease are summarized in Table 1. In the present study, ischemic ulcers were found in 19 of the 28 patients (21 of the 55 limbs).

**Type of Corkscrew Collateral in Limb Segments**

Corkscrew collaterals were classified into 4 types (Figure). The corkscrew collaterals included 14 type I, 29 type II, 32 type III, and 13 type IV. Thirty-nine corkscrew collaterals were observed above the knee (14 in the femoral artery and 25 in the popliteal artery) and 49 corkscrew collaterals were observed below the knee (19 in the calf artery and 30 in the lower crural artery). The interobserver agreements for characterization of type of corkscrew collaterals on DSA were substantial to excellent (Type I, κ=0.95; type II, κ=0.94; Type III, κ=0.91; and Type IV, κ=0.89).

**Ischemic Ulcers and Type of Corkscrew Collateral in Limb Segments**

Corkscrew collaterals were found in 19 of the 21 limbs with ischemic ulcers and in 16 of the 34 limbs without ischemic ulcers. The prevalence of ischemic ulcers was significantly higher in limbs with corkscrew collaterals than in limbs without corkscrew collaterals (Table 2).

Univariate analysis showed that the prevalence of ischemic ulcers was significantly higher in limbs with types III and IV corkscrew collaterals below the knee than in limbs with types I and II corkscrew collaterals below the knee, and that the prevalence of ischemic ulcers was significantly higher in limbs with types III and IV corkscrew collaterals above the knee than in limbs with types I and II corkscrew collaterals above the knee (Table 3). On other analysis, the distribution of corkscrew collateral types among groups with different risk for ischemic ulcers was evaluated using logistic regression analysis. Types III and IV were independent predictors of risk of ischemic ulcer among the 4 groups (OR=9.598, 95% confidence interval (CI)=2.182–42.227, P=0.0028; OR=10.738, 95% CI=1.514–76.126, P=0.0175, respectively). The distribution of above-knee and below-knee among groups with different risk of ischemic ulcers was compared using chi-square test. The frequency of ischemic ulcers in the below-knee group was significantly higher than in the above-knee group (χ²=6.697, OR=7.78, P=0.0035).

Thus, we determined whether there was a significant difference between the presence of ischemic ulcers and existence of corkscrew collaterals in limb segments. Multivariate analysis was performed to explain variability of risk of ischemic ulcers (type III above the knee, type IV above the knee, type III below the knee, and type IV below the knee being asso-
associated with risk of ischemic ulcer). Types III and IV below the knee were independent predictors of risk of ischemic ulcer (Table 3).

**Ischemic Conditions and Types of Corkscrew Collateral in Limb Segments**

There was no significant difference in ankle–brachial pressure index between 21 limbs with ischemic ulcers and 34 limbs without ischemic ulcers (0.82±0.30 vs 0.93±0.21, P=0.101). There was no significant difference between ankle-brachial pressure index and existence or type of corkscrew collaterals in limb segments.

We measured skin perfusion pressure in 16 patients (28 limbs). Data could not be obtained for 7 limbs because of undetectable skin perfusion pressure or severe pain during measurement of skin perfusion pressure. Mean skin perfusion pressure was 35.3±24.9 mmHg in 21 limbs. Skin perfusion pressure was significantly lower in 8 limbs with ischemic ulcers than in 13 limbs without ischemic ulcers (20.4±16.8 mmHg vs 44.5±25.1 mmHg, P=0.026). There was no significant difference between skin perfusion pressure and existence or type of corkscrew collateral in limb segments.

**Discussion**

In the present study we classified the patterns of corkscrew collaterals into 4 types (type I, large helical sign; type II, medium helical sign; type III, small helical sign; and type IV, tiny helical sign) according to DSA observations and we demonstrated that prevalence of ischemic ulcer was significantly higher in limbs with small corkscrew collaterals, types III and IV, than in limbs with large corkscrew collaterals, types I and II, in distal segments of lower extremities. Univariate analysis showed that types III and IV below the knee were associated with risk of ischemic ulcer.

In a preliminary study we observed various types of corkscrew collaterals in ischemic limbs. In the present study we examined type of corkscrew collateral in detail. We classified corkscrew collaterals into 4 types according to artery diameter and formation pattern as follows: type I, large helical sign with artery diameter ≥2 mm being similar to or larger than diameters of original conduit arteries (Figure A); type II, medium helical sign with artery diameter >1.5 mm and ≤2 mm (Figure B); type III, small helical sign with corkscrew collaterals with diameter ≥1 mm and ≤1.5 mm (Figure C); and type IV, tiny helical sign with most of the corkscrew collaterals having a diameter <1 mm (Figure D). Although there was a significant difference in arterial diameter among the types of corkscrew collaterals, length of corkscrew collaterals varied from short to long. There was no significant difference in length of corkscrew collateral among the types of corkscrew collaterals.

Interestingly, the prevalence of ischemic ulcers was significantly higher in limbs with corkscrew collaterals than in limbs without corkscrew collaterals. Although it is not clear whether the existence of corkscrew collaterals is a cause or consequence of ischemic ulcer, we postulate that collateral arteries grow in relation to the progression of severity of Buerger’s disease. The existence of corkscrew collateral arteries is a predictor of risk of ischemic ulcers.

It is well known that there is a strong association between use of tobacco and progression of Buerger’s disease. In the present study all of the patients were current or past heavy smokers. Thromboangiitis obliterans is believed to be relatively acute onset in arteries without arteriosclerosis, while in patients with arteriosclerotic obliteration, chronic arterial stenosis and/or occlusion in the extremities are due to the progression of arteriosclerosis. The grade of growth of collaterals is important for prevention of clinical symptoms such as rest pain and ischemic ulcers in Buerger’s disease. Several investigators have shown that most of the patients with Buerger’s disease have corkscrew-like collaterals. In the present study corkscrew collaterals were observed in 35 (64%) of the 55 limbs. After acute arterial occlusion, various factors, including increase in shear stress, inflammation, mobilization of vascular progenitor cells, and migration and proliferation of endothelial cells and vascular smooth muscle cells, may contribute to growth of collateral arteries with the existence of an arteriolar network. The precise mechanism by which collaterals in Buerger’s disease develop into a corkscrew-like pattern remains unclear. Larger collaterals have better potential for blood flow supplementation and structural recovery. These findings can be explained by Poiseuille’s law. Indeed, the risk of ischemic ulcers was significantly higher in limbs with small corkscrew collaterals than in limbs with large corkscrew collaterals in distal arteries of the lower extremities.

**Study Limitations**

In the present study we observed mixed small and large types of corkscrew collaterals. Univariate and multivariate analyses clearly showed that small types of corkscrew collaterals are associated with risk of ischemic ulcer. The relationship, however, between type of corkscrew collateral and prognosis of Buerger’s disease is unclear. Prospective study is needed to determine whether limbs with types III and IV but without ulcers will develop ulcers in the future. And whether, in limbs with types I and II and without ulcers, the type of collateral will change to the small type or complicate the small type of collaterals in the future. In addition, unfortunately, we do not know for how long the small types of corkscrew collaterals are present before ischemic ulceration and whether the small types of corkscrew collaterals persist throughout the natural history of what is known to be a progressive disease. Further studies are needed to confirm these issues.

To observe corkscrew collaterals we performed high-quality DSA in all patients, but we cannot rule out the possibility that corkscrew collaterals, especially type IV, were missed in the present study. Large types of corkscrew collaterals are easily found on DSA. Although e of the interobserver agreements for characterization of small types of corkscrew collaterals were relatively high, small types of corkscrew collaterals, especially type IV, should be carefully assessed. In addition, in the present study standards of reference, including post-imaging confirmation of vascular anatomy and surgical findings, were not used.

It is well known that various types of collateral arteries other than corkscrew collaterals, including tree root pattern collaterals, are observed in patients with Buerger’s disease. In the present study also, we found tree root patterns of collaterals in one leg. Unfortunately we cannot analyze the role of existence or grade of tree root pattern collaterals in ischemic ulcer, because the number of patients who had tree root pattern collaterals was small. These analyses would enable more specific conclusions concerning the role of collaterals in ischemic ulcer in Buerger’s disease to be drawn.

In conclusion, various types of corkscrew collaterals in ischemic extremities can be detected using DSA. Small types of corkscrew collaterals, type III (small helical sign) and type IV (tiny helical sign), and/or the existence of corkscrew col-
laterals in distal segments of the limb were independent predictors of risk of ischemic ulcers in patients with Buerger’s disease. Assessment of corkscrew collaterals may be useful for predicting the development of ischemic ulcers.

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