Acta Orthop Scand 1989;60(1):40–44

Fluorescein angiography for predicting healing of foot ulcers

Lena Wallin[1], Hjalti Björnsson[2†] and Anders Stenström[2]

Fluorescein angiography (FA) was performed on 83 patients (68 diabetics) with foot ulcer or gangrene. Densitometric measurements were made on the FA images, and different FA parameters were defined. These parameters, as well as systolic ankle and toe blood pressures, were evaluated for predicting the future course, i.e., whether healing would occur or whether major amputation below or above the knee had to be performed. The toe slope (i.e., the rate of increase of fluorescence on the big toe during the first 10 seconds after its appearance on the toe) predicted healing correctly in 0.83 and major amputation in 0.88. The ankle and toe pressures had only slightly lower predictive value. The combination of ankle pressure and toe slope predicted healing correctly in 0.91 and major amputation in 0.88. When ankle pressure cannot be measured, FA is the method of choice. Further, FA provides information on regional blood flow unobtainable by any other method.

Systolic arterial pressures in the ankle and the big toe are the most commonly used parameters for predicting healing of ulcers or gangrene on the foot and for the selection of amputation level in an ischemic limb (Carter 1978, Holstein and Lassen 1980). However, the pressures can be unreliable because of rigid sclerotic arteries or localized digital ischemia. This may lead to an unnecessarily high level of amputation.

The arterial pressure is only an indirect measure of skin perfusion. The distribution of fluorescence in the skin after intravenous injection of fluorescein is related to the distribution of blood flow and is useful for predicting healing of ischemic lesions (Lange and Boyd 1943, MacFarland and Lawrence 1982, Tanzer and Horne 1982). Lund and Lund (1972) introduced a rapid sequence photography of skin fluorescence that also offers the opportunity to measure the skin fluorescence densitometrically (Lund 1979). This would provide quantitative dynamic information about skin blood perfusion and its distribution.

We have measured different skin fluorescence parameters by densitometry. Their use for predicting the future course of ulcers and gangrene on the foot was compared with that of ankle and big toe systolic pressures.

Departments of Clinical Physiology[1] and Orthopedics[2], Lund University Hospital, S-221 85 Lund, Sweden

Patients and methods

From March 1983 to April 1985, we performed fluorescein angiography (FA) of the foot soles and measured distal systolic blood pressures in 83 patients (37 women) with ulcers or gangrene on the foot. Sixty-eight were diabetics and 15 had arteriosclerosis. The mean age was 70 (36–91) years. Thirteen patients (5 nondiabetics) had ulcers or gangrene bilaterally. Totally, 96 legs were evaluated.

Fluorescein angiography (FA)

The patient was given 1 mg clemastine (Tavegyl®, Sandoz) by mouth 2–4 hours before FA to prevent nausea. To ensure cutaneous vasodilation, 9.5 g ethanol (30 ml solution) was given orally, and the patient stayed in a warm room (27–29 °C) upon an electric blanket for about 30 min. Sodium fluorescein (Fluoresceite® injection 10 percent, Alcon), 10 mg/kg body weight, was rapidly injected i.v. Starting 10 s after injection, one picture was taken every 2 s during the first minute, then every 10 s during the recorded minute, and then after 2.5, 3, 4, 5, 10, and 15 min. The method has been described by Lund (1981). The appearance time in the cheek was recorded as a measure of the patient's central circulation time.

The optical density of three circular areas in the foot soles – viz., the center of the heel, an area proximal to the little toe, and the pad of the big toe – was measured with a Macbeth densitometer. Diagrams of density against time were then plotted (Figure 1). The appearance time for the fluorescence, the initial slope (the rate of density increase during the first 10 s after appearance), and maximal fluorescence (the average of the densities at 4, 5, and 10 min) were recorded. Maximal fluorescence and slope values for the measured areas were expressed in units defined as a percent of the highest values in any of the six measured areas on the feet.

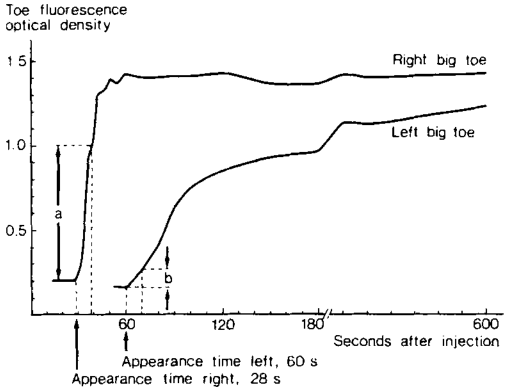

Figure 1. Toe fluorescence in diabetic male, group 1. Normal findings on the right side. Gangrene on the left foot with abnormally late and slow arrival of fluorescence. Initial density increase a and b were used to calculate right (65 units) and left (8 units) toe slope, respectively.

The systolic arm blood pressure was measured by conventional auscultatory technique. Systolic ankle and big toe pressures were measured by means of inflatable cuffs at the ankle and toe, respectively. For toe pressure, and usually for ankle pressure, the flow signal was measured from the distal portion of the big toe by a strain-gauge technique (Strandness and Bell 1965, Gundersen 1972). In some patients the flow signal for ankle pressure was detected by a Doppler ultrasound probe at the posterior tibial or dorsal pedal artery (Carter 1969).

FA values, pressures, and combinations of these parameters were compared for predicting the fate of the leg. The discriminating values of the different parameters were chosen so as to give the best separation in the sense of lowest number of false predictions. The number of false predictions was the number of legs that healed on the foot and had a parameter value predicting major amputation plus the number of legs that underwent major amputation and had a parameter value predicting healing.

Treatment and clinical course

Conservative treatment consisted of ulcer dressing and unloading by special shoes. Osteitis and infections were promptly treated with antibiotics. Arterial reconstructions were made in 4 patients.

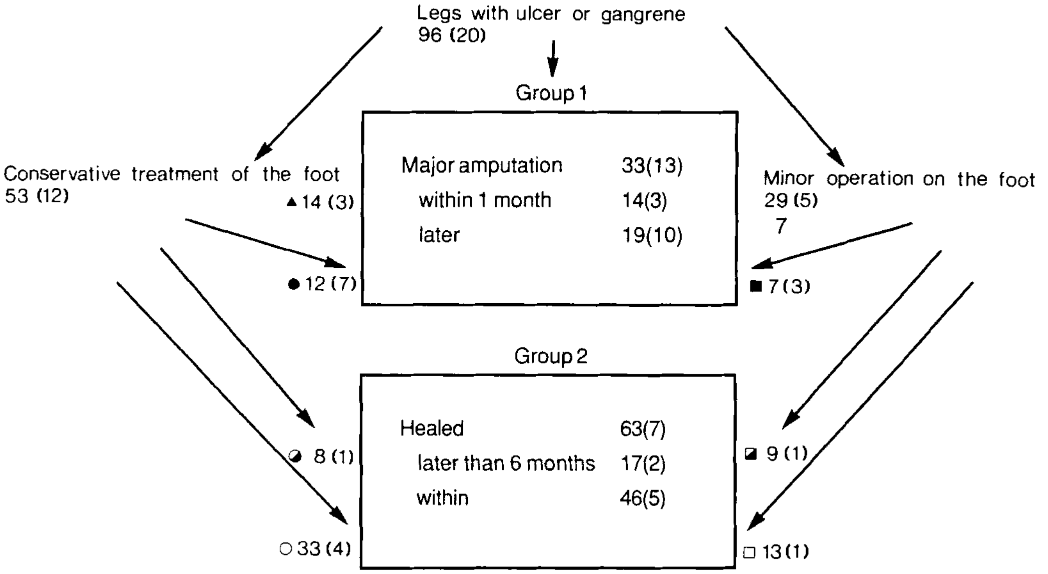

Figure 2. Survey of the fate of the legs examined with fluorescein angiography. Nondiabetics in brackets.
Explanation of symbols
Group 1: ▲ Major amputation within one month, ■ Minor operation on the foot. Later major amputation, ● Conservatively treated. Later major amputation.
Group 2: ◪ Minor operation on the foot. Healed later than 6 months, ◑ Conservatively treated. Healed later than 6 months, □ Minor operation on the foot. Healed within 6 months, ○ Conservatively treated. Healed within 6 months.

Amputation of one or more toes or transmetatarsal amputation was performed in 29 feet. Major amputations consisted of below-the-knee amputations in 30 legs and above-the-knee amputations in three legs. Indications for major amputation were intractable pain or rapidly progressive gangrene. The rate of major amputation was two thirds in the nondiabetics and one fourth in the diabetics ($P < 0.005$).

The legs were divided into two groups according to their fate, e.g., major amputation or not. Further, both groups were subdivided into subgroups according to treatment and healing time (Figure 2). There was no difference in the rate of major amputations between legs with minor operations on the foot and legs with conservative treatment.

Analysis of data

Predictive values for major amputation and for healing were then determined using the following definitions:

Major amputation = the number of legs that underwent major amputation – and had a parameter value predicting major amputation – divided by the total number of legs with a parameter value predicting major amputation.

Healing = the number of legs that healed on the foot – and had a parameter value predicting healing – divided by the total number of legs with a parameter value predicting healing.

Analysis of differences in predictive value was performed with the chi-square test for two-by-two contingency tables using Yates' correction for continuity.

Results

There were only four legs out of 24 with an ankle pressure < 70 mmHg that healed on the foot. On the other hand, there were eight legs out of 58 with an ankle pressure ≥ 70 mmHg that underwent major amputation. There were seven legs out of 22 with a toe pressure < 20 mmHg that healed on the foot and eight legs out of 51 with a toe pressure ≥ 20 mmHg that underwent major amputation (Figure 3).

The discriminating value for the toe slope was 18 units; only three legs out of 24 with lower values healed on the foot, and 11 legs out of 65 with higher values underwent major amputation.

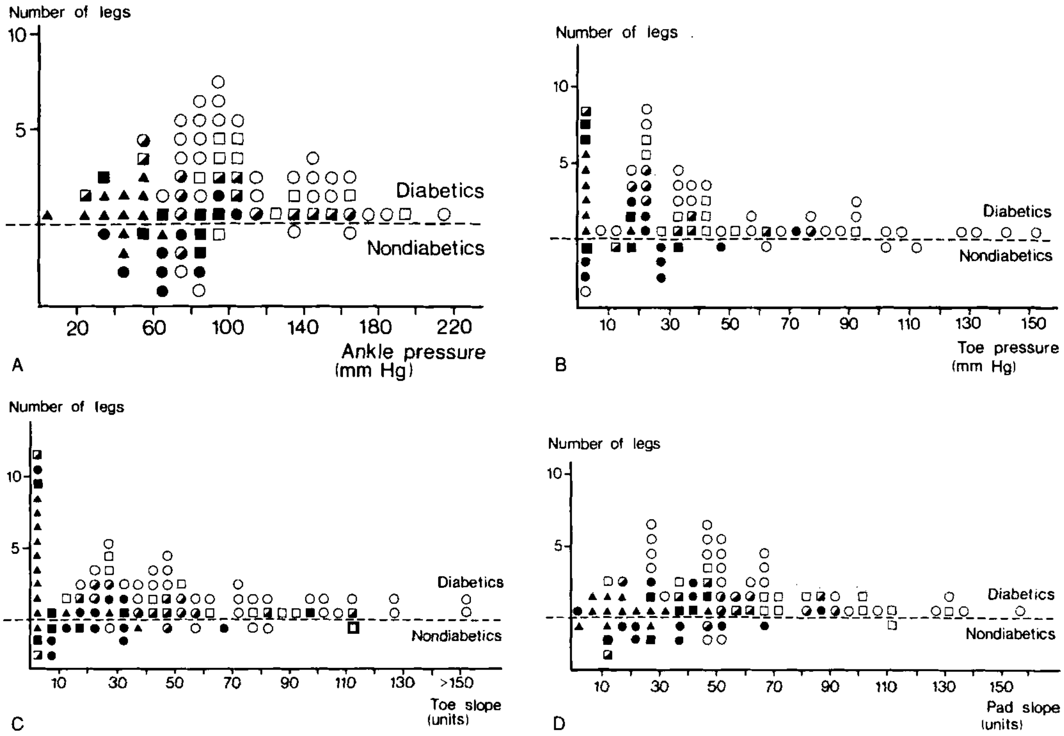

Figure 3. Type of treatment and fate of 82 legs in relation to ankle pressure (A), of 73 legs in relation to toe pressure (B), of 89 legs in relation to toe slope (C), and of 83 legs in relation to pad slope (D). Above the dashed line the symbols represent legs of diabetic patients and under it legs of nondiabetic patients. Explanation of symbols in Figure 2.

Table 1. Predictive values

	Predicitve value of healing	Predictive value of major amputation
Ankle pressure	0.86	0.83
Toe pressure	0.84	0.68
Toe slope	0.83	0.88
Pad slope	0.77	0.81
Ankle pressure + toe slope	0.91	0.88
Ankle pressure + pad slope	0.87	0.87
Ankle pressure + toe pressure	0.86	0.87

The discriminating value for the pad slope was 26 units; four legs out of 21 with lower values healed on the foot, and 14 legs out of 62 with higher values underwent major amputation.

There were no differences between the predictive values (Table 1).

The predictive values for amputation were 81–88 percent except for the toe pressure, which had a somewhat lower value, 68 percent (NS). The pad slope had a somewhat lower predictive value for healing, 77 percent (NS), than the other parameters, 83–91 percent.

The ankle pressure in combination with the toe slope (Figure 4) gave a slightly better (NS) result than all the other parameters separately or in various combinations. The ankle pressure alone, and in combination with pad slope or toe pressure, had nearly as high predictive values. The combination of the toe pressure with any FA parameter was not better than the FA parameter alone.

Combining ankle pressure with any of the other parameters clearly narrowed the intervals and reduced the number of patients for whom the prognosis was uncertain.

The maximal fluorescence values and the appearance times for the heel, the foot pad, or the big toe were not found useful as predictors for healing or amputation, neither was the heel slope.

The patients with slowly healing ulcers and wounds had, in general, lower ankle and toe pressures and lower FA-slope values than the patients who healed within 6 months.

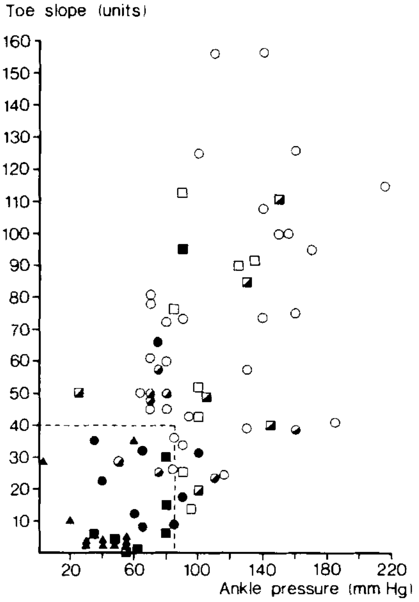

Figure 4. Relation between ankle pressure and toe slope in 78 legs. Discriminating values are marked by the dashed lines. Symbols on these lines and outside the square represent legs for which the combination ankle pressure-toe slope predicted healing. Five of these legs underwent major amputation. Symbols within the square represent the number of legs for which major amputation was predicted. Three of these legs healed on the foot. Explanation of symbols in Figure 2.

Discussion

It is reasonable to assume that the initial increase of fluorescence in the skin of the foot reflects the skin capillary blood flow (Perbeck et al. 1985). This would explain our finding that the FA slopes are useful predictors of wound and ulcer healing or amputation. Tanzer and Horne (1982) found that early skin fluorescence can be used to predict healing at the amputation site in 80 percent and amputation at a higher level in 43 percent of leg and foot amputations. This is a lower predictive power than that of FA slopes in the present study.

Contrary to our findings, MacFarland and Lawrence (1982) found that skin fluorescence 10 minutes after injection accurately predicted healing on the foot in 7 out of 9 cases. This late skin fluorescence can be enhanced by tissue damage and increased vascular permeability. It was not a reliable predictor of healing in our larger material.

Jogestrand and Berglund (1983) found that the appearance time of fluorescence in the big toe, uncorrected for central circulation time, was not better than toe pressure, pulse plethysmography, skin temperature, or capillary microscopy for evaluating patients with arterial disease of the leg. Appearance time corrected for central circulation time is a more reliable measure, and in our material this had only slightly lower predictive values than did the pad slope.

Two thirds of the foot ulcers healed in our patients. Holstein and Lassen (1980) reported the same healing rate, but they excluded legs amputated within 1 month. After similar exclusion (14 legs), our ulcer healing fraction was 0.8.

Holstein and Lassen (1980) claimed that toe pressure was more valuable than ankle pressure for judging the prognosis. Their claim was based on pressure measurements immediately after healing or immediately before major amputation. We calculated the predictive values for their toe and ankle pressures, measured when their patients entered the study. For toe pressure the predictive value for healing then became 0.8 and for major amputation 0.7, and the corresponding figures for ankle pressure were 0.8 and 0.8. These predictive values are quite similar to those in our material, and for toe pressure they were almost the same. A combination of toe and ankle pressures might be preferable. However, in one third of our legs only one pressure could be measured, and in 4 patients no pressures could be measured because of rigid arteries or ulcers. In these patients, FA is valuable. We found that the predictive values for the toe slope were as high as those for the combination of toe and ankle pressures. The pad slope might be useful when the big toe is amputated or necrotic.

In addition to the toe slope and other quantitative data, FA gives a photographic image that contains information probably representing the regional capillary blood flow of the foot sole. This might be of value in the choice of amputation level. However, this information was not analyzed in detail.

The FA toe slope in combination with ankle pressure will predict healing and major amputation more reliably than do ankle and toe pressures. The FA toe slope alone is the method of choice if the ankle pressure cannot be measured because of rigid arteries or ulcers. In patients where both ankle and toe pressures are available, the slight prognostic gain provided by FA may not justify this rather laborious investigation. Thus, the clinical value of FA appears to be the distribution image, which provides information about regional blood flow unobtainable by any other method, and the prognostic information in legs where either ankle or toe pressure is not available.

References

Carter S A. Role of pressure measurements in vascular disease. In: Noninvasive Diagnostic Techniques in Vascular Disease (Ed. Bernstein E F). Chapter 24. C.V. Mosby, St Louis 1978:261–84.

Carter S A. Clinical measurement of systolic pressures in limbs with arterial occlusive disease. JAMA 1969; 207(10):1869–74.

Gundersen J. Segmental measurements of systolic blood pressure in the extremities including the thumb and the great toe. Acta Chir Scand 1972;426(Suppl):1–90.

Holstein P, Lassen N A. Healing of ulcers on the feet correlated with distal blood pressure measurements in occlusive arterial disease. Acta Orthop Scand 1980;51(6):995–1006.

Jogestrand T, Berglund B. Estimation of digital circulation and its correlation to clinical signs of ischaemia a comparative methodological study. Clin Physiol 1983;3(4): 307–12.

Lange K, Boyd L J. Use of fluorescein method in establishment of diagnosis and prognosis of peripheral vascular diseases. Arch Intern Med 1943;74:175–84.

Lund F, Lund S. Dynamic fluorescein angiography. A new method for assessment of skin circulation of the limbs in peripheral arterial disease. In: Atherogenesis, Proceedings of the 2nd international symposium on atherogenesis, thrombogenesis, and pyridinolcarbamate treatment. (Ed. Shimamoto F, Numano F, Addison G M). Excerpta Medica International Congress Series 1972;269:333–46.

Lund F. Fluorescein angiography. An overview of technical improvements and recent experiences in previous and new clinical areas of application. Bibl Anat 1979;18: 322–7.

Lund F. An atlas of clinical fluorescein angiography in functional evaluation of nutritional blood perfusion and microvascular permeability of the skin, mucous membranes and visceral organs. In: Noninvasive Methods on Cardiovscular Haemodynamics (Ed. Jageneau A H M). Elsevier Excerpta Medica, Amsterdam 1981:357–92.

McFarland D C, Lawrence P F. Skin fluorescence, a method to predict amputation site healing. J Surg Res 1982;32(4): 410–5.

Perbeck L, Lund F, Svensson L, Thulin L. Fluorescein flowmetry: a method for measuring relative capillary blood flow in the intestine. Clin Physiol 1985;5(3):281–92.

Strandness D E Jr, Bell J W. Peripheral vascular disease: Diagnosis and objective evaluation using a mercury strain gauge. Ann Surg 1965;161(Suppl 4):3–35.

Tanzer T L, Horne J G. The assessment of skin viability using fluorescein angiography prior to amputation. J Bone Joint Surg (Am) 1982;64(6):880–2.

Acknowledgement

This study was supported by the Swedish Medical Research Council (grant no. 02872).