Capillary Abnormalities in Polyvinyl Chloride Production Workers

Examination by In Vivo Microscopy

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• **Examination by wide-field capillary microscopy of the hands of 152 workers in vinyl chloride (VC) polymerization plants demonstrated scattered, scleroderma-like microvascular abnormalities in 21 workers and isolated capillary abnormalities in 27, as compared with only three isolated abnormalities in 50 manual workers not exposed to vinyl chloride. Thirteen of 17 VC workers with objective evidence of VC-associated abnormalities (angiosarcoma or fibrosis of liver, acroosteolysis, or scleroderma-like skin lesions) were observed to have microvascular abnormalities.**

If prospective studies confirm the implications of this study, capillary microscopy may become a useful mass-screening procedure in the early detection and prevention of VC-associated disease.

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INITIAL reports of human disease in which vinyl chloride (VC) has been implicated as pathogenetic were limited to descriptions of such peripheral changes as distal phalangeal resorption, ie, acroosteolysis (AOL).[1-3] Recently, a systemic effect of VC has been suggested by an unusual pattern of hepatic portal, intralobular, and capsular fibrosis; angiosarcoma of the liver; and pulmonary functional abnormalities suggesting early pulmonary fibrosis, all of which occur more frequently among workers employed in polyvinyl chloride production plants than among the general population.[4-10] Furthermore, animal experiments have demonstrated that VC can produce a variety of tumors in rodents.[11,12]

There are several similarities between VC disease and scleroderma (systemic sclerosis): Raynaud phenomenon is prominent among the symptoms associated with AOL[3,5,6,9,13]; localized scleroderma-like lesions have been reported in some patients with AOL[5,14]; and, in both VC-associated disease and scleroderma, small-blood-vessel lesions and interstitial fibrosis are thought to be important in pathogenesis.[10,12,14]

In scleroderma, changes in small blood vessels of the skin have been observed in vivo by capillary microscopy.[15,16] Using the technique of wide-field capillary microscopy, distinctive abnormal capillary patterns in the fingers of patients with Raynaud syndrome and scleroderma have been demonstrated.[16] Furthermore, a positive correlation is noted between the severity of capillary pattern abnormalities and multisystem involvement in these connective-tissue disorders.[17] The possibility that VC-associated disease might be characterized by microvascular abnormalities similar to those observed in scleroderma led to the present study of VC workers, using techniques of wide-field capillary microscopy. The specific questions of this study were the following: (1) Do symptomatic VC workers have finger-skin-capillary abnormalities? (2) Are the abnormalities similar to or different from those seen in patients with idiopathic scleroderma and Raynaud syndrome? (3) Are microvascular abnormalities related to the type of VC-associated abnormality (peripheral vs systemic), especially liver abnormalities? (4) Are microvascular abnormalities related to the nature and duration of VC-exposure? (5) Are microvascular abnormalities found in a control group of manual workers not exposed to VC?

SUBJECTS

VC Workers Selected by Symptoms (n=44).—The 44 subjects in this group gave a history of symptoms and signs possibly related to VC exposure. They were 31- to 57-year-old men (mean age, 42 years) who had worked in the polyvinyl chloride industry for 5 to 28 years (mean, 15 years). A history of past reactor-cleaning experience (ranging from 0.2 to 8 years; mean, 2.5 years) was present in 35 of 44 workers. Table 1 shows the complaints and the pathologic findings in group 1.

VC Workers Selected by Question-

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naire (n = 108).—These subjects were selected on the basis of their answers to a questionnaire used in the polyvinyl chloride production plant to detect early AOL. All available subjects who had given one or more affirmative answers to the questionnaire (Q+) were examined, a total of 66 subjects. Seventy-one subjects were examined from a random selection of those who had given negative answers to all questions (Q−). Data on 29 of the 137 subjects examined were excluded because of unreliable observations caused by skin injuries or deep pigmentation, leaving 108 employees (50 Q+ and 58 Q−) in this group.

Control Manual Workers (n = 50).—The possibility that repeated minor injuries associated with manual labor might contribute to the abnormal findings seen in VC workers led to the examination of workers from companies making neither VC nor polyvinyl chloride and hospital employees working as carpenters, truck drivers, and maintenance men, a total of 50 workers. All were men and ranged in age from 19 to 62 years (mean age, 43 years).

METHODS

Wide-field Capillary Microscopy.—The technique of wide-field capillary microscopy as previously reported[9] consists of the observation of selected skin sites under immersion oil, using a stereo wide-field microscope at magnification ×12. Wide-field microscopy permits the detection of microvascular patterns, such as the presence and distribution of dilated or deformed microvessels and the absence of capillary loops, without attempting to measure absolute vessel dimensions. The technique is rapid and suitable for mass screening.

Twelve standard sites were examined in each subject: four nailfolds and two each of the following sites: dorsum of the distal phalanx other than the nailfold, dorsum of the middle phalanx, dorsum of the proximal interphalangeal joint, and the finger pad.

Photography of Microvessels.—The wide-field photographic technique as previously described[9] was used to photograph at least one finger of each subject. All photographs were coded for blind comparison of capillary findings in VC workers and control subjects.

Clinical and Occupational Data.—All subjects were interviewed as to length of employment, job assignment, general state of health, presence or absence of Raynaud phenomenon, and smoking and drinking habits. A limited physical examination was performed. All data were coded for later analysis and were unknown to the capillary observer and photographer.

Table 1.—Clinical Findings and Complaints of Group 1 Vinyl Chloride Workers*

	No. of Subjects Examined	No. of Subjects With Capillary Changes†
Severe AOL with Raynaud phenomenon	6	4
Scleroderma-like skin lesions with Raynaud phenomenon	5	4
Liver abnormalities‡	6	5
Subtotal	17	13
Healed AOL with Raynaud phenomenon	6	0
Healed AOL without Raynaud phenomenon	1	0
Raynaud phenomenon alone	9	3
Nonspecific skin rashes without Raynaud phenomenon	7	1
Miscellaneous complaints	4	0
Subtotal	27	4
Total	44	17

*AOL indicates acroosteolysis.

†Of 17 subjects with abnormal capillaries, ten had scattered changes (8/13 and 2/4 of the two groups above) and seven had isolated changes.

‡Two patients with angiosarcoma of the liver and one each with (1) portal fibrosis and enlarged spleen, (2) portal fibrosis with early cirrhosis and fatty metamorphosis, (3) thrombosis of the splenic vein, mild liver damage, and reticuloendothelial cell hyperplasia, (4) fatty metamorphosis with focal capsular and subcapsular fibrosis and splenomegaly with vascular congestion.

Table 2.—Comparison of Capillary Observations Between VC Workers and Controls*

	Employees of VC Industry	Manual Workers Not Exposed to VC
Scattered capillary abnormalities	11	0
Abnormal capillaries present, but few in number	27	3
No capillary abnormalities seen	70	47
Total	108	50

*VC indicates vinyl chloride. Difference in the prevalence of capillary abnormalities between VC workers and controls is statistically significant ($\chi^2 = 15.50$, $P<.001$).

RESULTS

Group 1 (VC Workers Selected by Symptoms).—Examination of group 1 subjects showed scattered capillary abnormalities similar to those found in scleroderma (Fig 1 and 2). Definitely dilated capillary loops were seen in the nailfold and in other finger sites, contrasting with the surrounding normal vasculature. Pale avascular areas were frequently observed. The capillary abnormalities were usually more discrete and less numerous than those seen in most patients with scleroderma. They were seen more frequently in subjects with severe AOL, liver abnormalities (as defined in Table 1) and scleroderma-like lesions (13/17) than in those with healed AOL, nonspecific skin rashes, or Raynaud phenomenon alone (4/27; $\chi^2 = 14.21$, $P < .001$). Moreover, 5 of 6 subjects with liver abnormalities verified by biopsy specimens had microvascular abnormalities (Table 1).

In a few subjects, lesions resembling mini versions of clinically visible papular skin lesions were observed microscopically (Fig 3, left). In two subjects with active AOL, capillary hemorrhages were observed under the proximal nail plate in addition to the common type of "splinter hemorrhages" under the distal nail plate (Fig 3, center).

Group 2 (VC Workers Selected by Questionnaire).—Dilated capillaries were observed in 38 of 108 group 2 workers; both the number and distribution of dilated capillaries differed from those observed in most scleroderma patients. Many group 2 workers had isolated, extremely dilated capillaries (Fig 3, right and Table 2). No correlation was found between the length of time employed as a reactor-cleaner (or the length of time with the company) and the capillary abnormalities. Office and supervisory personnel who had never been produc-

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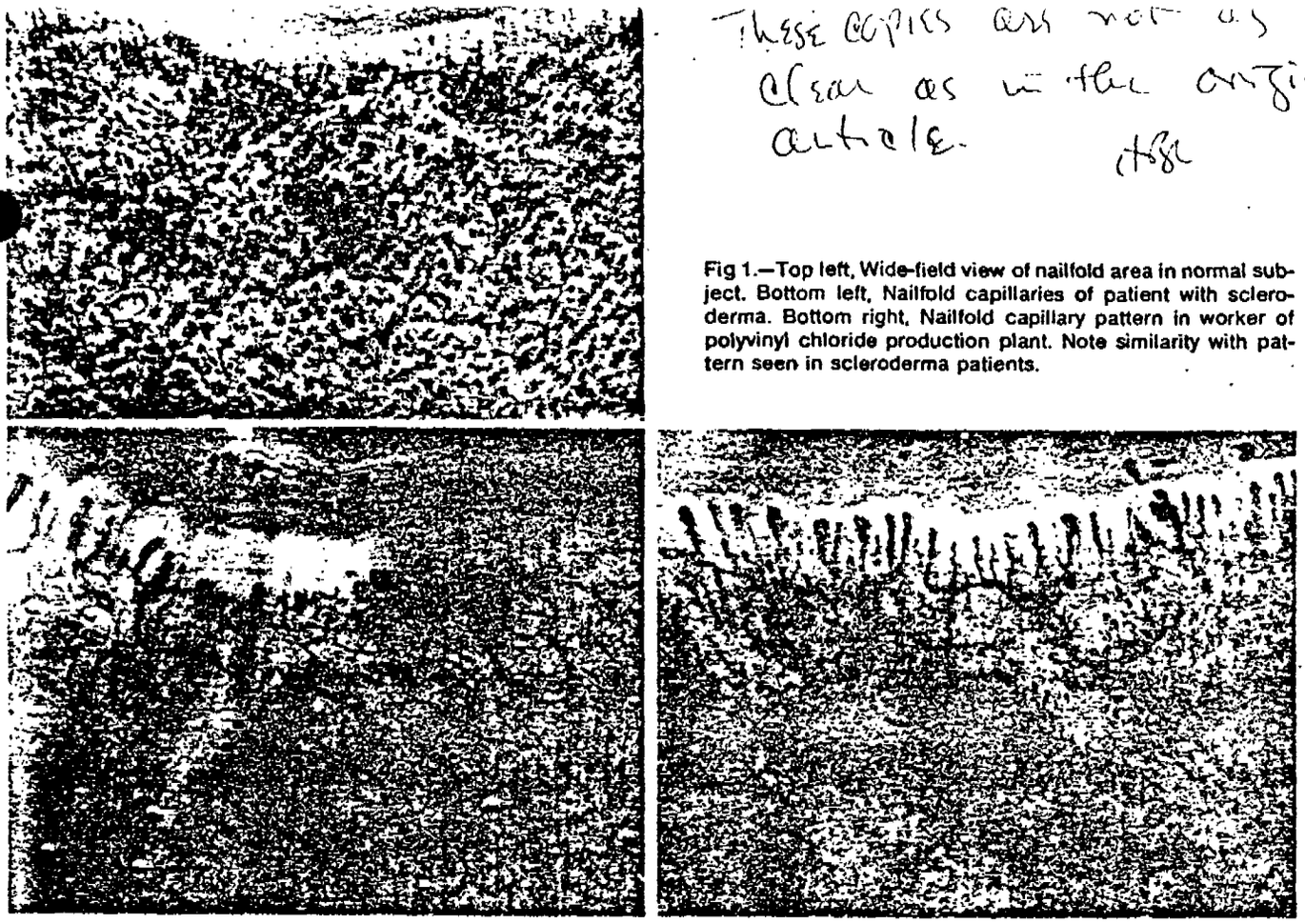

Fig 1.—Top left, Wide-field view of nailfold area in normal subject. Bottom left, Nailfold capillaries of patient with scleroderma. Bottom right, Nailfold capillary pattern in worker of polyvinyl chloride production plant. Note similarity with pattern seen in scleroderma patients.

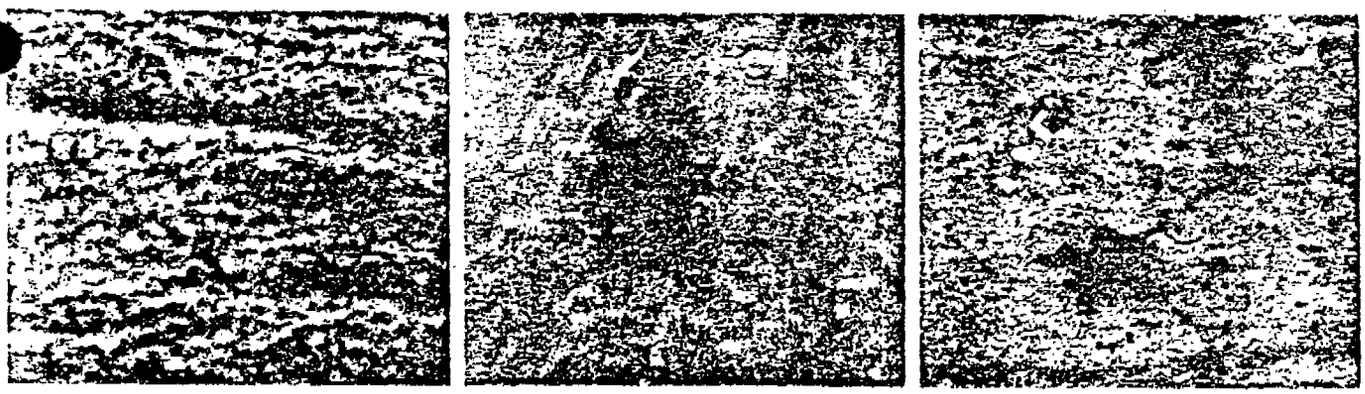

Fig 2.—Left, Dorsum of middle phalanx in normal subject. Center, Cluster of dilated capillaries in same anatomical site in patient with scleroderma. Right, Vinyl chloride worker with pattern similar to that seen in scleroderma.

Fig 3.—Left, Miniplaque on dorsum of distal phalanx in VC worker with acroosteolysis (AOL). Center, Capillary hemorrhages under both distal and proximal nail plate in a vinyl chloride (VC) worker with AOL. Right, Single extremely dilated capillary in nailfold of VC worker with liver abnormalities.

tion workers had fewer microvascular abnormalities (3/22) than production workers (35/86, $\chi^2 = 4.49$, $P < .05$); however, production workers showed no differences in capillary abnormalities according to job category. There was no significant difference ($\chi^2_{adj} = 1.32$, $P > .5$) between employees who had been classified as Q+ or Q− on the basis of the questionnaire. It was noted, however, that there was little or no correlation between the responses regarding Raynaud phenomenon obtained from the questionnaire and those obtained from the interview at the time of examination. Physical examination disclosed two workers with AOL (one "active" and one "healing" by roentgenographic examination) and papular skin lesions, and ten workers with hepatomegaly (4 cm or more below the right costal margin). The subject with active AOL showed scattered capillary changes, the subject with healing AOL had a "normal" capillary examination. There was no correlation between hepatomegaly and capillary findings.

Comparison of VC Workers With Control Subjects.—Capillary abnormalities in group 2 VC workers were significantly more frequent than in the control manual workers examined ($\chi^2 = 15.50$, $P < .001$) (Table 2).

Analysis of Photographic Data.—Three hundred seventeen unidentified photographs of VC workers were mixed with 136 photographs of control subjects and 130 photographs of patients with scleroderma and related diseases; all photographs were rated for the presence of capillary abnormalities. The results demonstrated that significantly more VC workers (39/152) than control subjects (3/50) had capillary abnormalities ($\chi^2 = 7.69$, $P < .01$). Although objective, for technical reasons, photographs are slightly less sensitive than direct observations in detecting capillary abnormalities.

COMMENT

The results of this study demonstrate that capillary abnormalities seen in the finger skin by in vivo microscopy are present in VC workers more frequently than in control subjects. These capillary abnormalities are not exclusively related to peripheral pathological conditions such as AOL, scleroderma-like lesions of hands, and Raynaud phenomenon, but are also found in subjects with liver abnormalities (as defined in Table 1) and in subjects who have papular lesions elsewhere on the body. Microscopic papular or fibrotic lesions can also be observed in VC workers. In 33% of the subjects who show any capillary changes, the pattern appears similar to the microvascular changes seen in scleroderma; in the remaining majority, changes consist of a few dilated capillaries only; very few control subjects show even these minimal capillary abnormalities. Since microvascular changes occur more frequently than overt VC-associated pathologic conditions in VC workers, they may represent an early manifestation of the VC effect.

More work is needed to determine the nature and evolution of such microvascular abnormalities, their relationship to VC-associated disease (as opposed to a transient reaction to VC exposure), and their relationship to the subject's susceptibility to VC disease. Further studies are also needed to compare the capillary changes reported here with those seen in small blood vessels and endothelia of animals exposed to VC.[11] Capillary microscopy might then be used as a reproducible, noninvasive technique to monitor VC workers and to identify VC-associated peripheral and visceral disease in susceptible individuals at an early and possibly preventable stage.

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