The Effect of Cigarette Smoking on the Survival of Free Vascularized and Pedicled Epigastric Flaps in the Rat

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Microsurgeons suspect that cigarette smoking reduces the survival of free vascularized flaps and replantations, but this has never been proven. This experimental study investigates the effect of smoking on free-flap survival.

A fasciocutaneous epigastric flap was used in 30 rats as a free flap and in 30 rats as a pedicled flap. Of each group, 10 rats were smoked 6 weeks before and 2 weeks after surgery, 10 rats were smoked only 6 weeks before surgery, and 10 rats underwent the sham smoking procedure. Also, a distally based dorsal skin flap was cut in all rats, representing a random vascularized flap. Vitality and size of both flaps and patency of the vascular anastomoses were assessed 14 days after surgery. The epigastric flaps were monitored by laser Doppler flowmetry and thermometry during the experiment.

Survival of the free vascularized epigastric flaps was significantly lower in smoking rats. All pedicled flaps except one survived. The epigastric flaps only necrosed or survived completely, exactly correlating to the patency of the vascular anastomoses. The mean surviving area of the dorsal flaps was best for nonsmoking rats, worse for only preoperatively smoking rats, and worst for preoperatively and postoperatively smoking rats. The differences were statistically significant. Postoperative laser Doppler flow differed significantly between surviving and dying flaps, affirming the value of laser Doppler flow monitoring in microvascular surgery.

In conclusion, this study proves that smoking of cigarettes is detrimental to the survival of free vascularized flaps. (*Plast. Reconstr. Surg.* 97: 86, 1996.)

Microsurgeons suspect that cigarette smoking reduces the survival of both free vascularized tissue transfers and replantations. In macrovascular surgery, the patency rates of arterial reconstructions decreased when cigarettes were smoked.[1,2] Besides a case report concerning the damaging effect of smoking on digital revascularization,[3] little is known of the effect of smoking on the success rate of microvascular surgery. Experimental and clinical studies concerning the effect of cigarette smoking on random vascularized pedicled skin flaps showed an increase in partial flap necrosis in smokers.[4–9] This negative effect is explained by an increased platelet aggregation,[10–12] a decreased oxygen transport due to COHb formation, and an impaired microcirculation due to the combination of macroangiopathy and microangiopathy and vasoconstriction.[13,14] Several studies indicated impaired microvascular flow during smoking in healthy tissues[15–18] and replanted digits.[19]

The aim of this experimental study was to investigate the effects of cigarette smoking on the survival of free vascularized and pedicled tissue transfers.

Materials and Methods

Experimental Design

Experiments were carried out on 60 healthy male Wistar rats weighing 250 to 300 gm. Epigastric flaps including the lateral branch of the epigastric vessels, described by Petry and Wortham[20] as an axial flap, were used as a free vascularized flap model. In 30 rats a free flap and in 30 a pedicled flap were performed. A distally based dorsal skin flap of 3 cm width and about 10 cm length also was created in all rats, representing a random vascularized skin flap. Of each group, 10 rats were smoked 6 weeks preoperatively and 2 weeks postoperatively, 10 rats were smoked only 6 weeks preoperatively,

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and 10 rats underwent only the sham smoking procedure (Fig. 1). The sequence of entering the study was formally randomized. Three rats died preoperatively, 2 being smoked and 1 being sham smoked, so 63 rats entered the study and 60 rats were operated on by the same surgeon.

Laser Doppler flow and temperature were assessed before, during, and after operation to study the microcirculation of the epigastric flaps. Nicotine, cotinine, and carbon monoxide hemoglobin were measured to objectivize the smoking procedure preoperatively and postoperatively. Two weeks after operation, the epigastric and dorsal flaps were studied by clinical parameters, measurement of flap size, and fluorescein staining. Patency of the vessels was established by clinical parameters and histology (Fig. 2 and Table I).

Smoking Procedure

The rats were daily exposed to cigarette smoke in the Hamburg II smoking apparatus for laboratory animals (Heinr. Borgwaldt, Hamburg, Germany) during 3 periods of 20 minutes with a 4-hour interval.[21] The animals were placed in Plexiglas cylinders with their faces in a smoking room of 525 ml. Every 2 seconds, 35 ml cigarette smoke (1.5 mg nicotine and 18 mg tar per cigarette) diluted with 700 ml air (1:20) was blown into the smoking room, containing 20.8% oxygen, 0.3% carbon dioxide, and 200 ppm carbon monoxide.

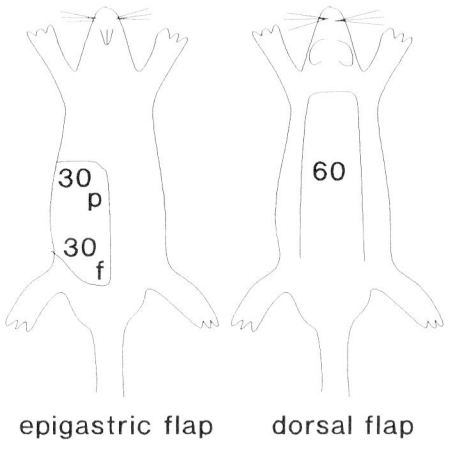
In the sham smoking procedure (i.e., the same procedure without cigarette smoke), the animals were placed during 20 minutes 3 times daily in the Plexiglas cylinders with their faces into normal air. On the day of operation, the rats were not smoked.

Three days before starting the smoking procedure, the rats were acclimatized to the cylinders.

Surgical Technique

Under ether anesthesia, the skin was dry-shaved, and the rat was operated on on a heating mattress. First, a caudally based 3-cm-wide dorsal skin flap with panniculus carnosus reaching from the hip joint to the inferior scapular angle (approximately 10 cm) was cut and resutured.[22] Second, a right-sided epigastric flap limited by the abdominal midline, sternal xyphoid process, and os pubis and laterally including the lateral branch of the epigastric vessels was raised from the abdominal-wall musculature and completely isolated on its epigastric vessels. These vessels are too small (diameter about 0.3 mm) to perform reliable microvascular anastomoses, so subsequently the flap was pedicled on the femoral artery and vein by ligating and transecting them distal to the epigastric vessels. In the case of a pedicled procedure, the flap was resutured (operating time 3 hours). When the free vascularized flap was performed, the femoral artery and vein were cut, and end-to-end anastomoses were made by

EPIGASTRIC AND DORSAL FLAPS IN 60 RATS



SMOKING	EPIGASTRIC FLAP	
	free vascularized	pedicled
none	n = 10	n = 10
6 weeks before operation	n = 10	n = 10
6 weeks & before 2 weeks after operation	n = 10	n = 10

FIG. 1. In 60 rats 60 dorsal flaps were created as well as 30 pedicled epigastric flaps (*p*) and 30 free vascularized epigastric flaps (*f*). Of each group, 10 rats were smoked 6 weeks before and 2 weeks after surgery, 10 rats were smoked only 6 weeks before surgery, and 10 rats underwent the sham smoking procedure.

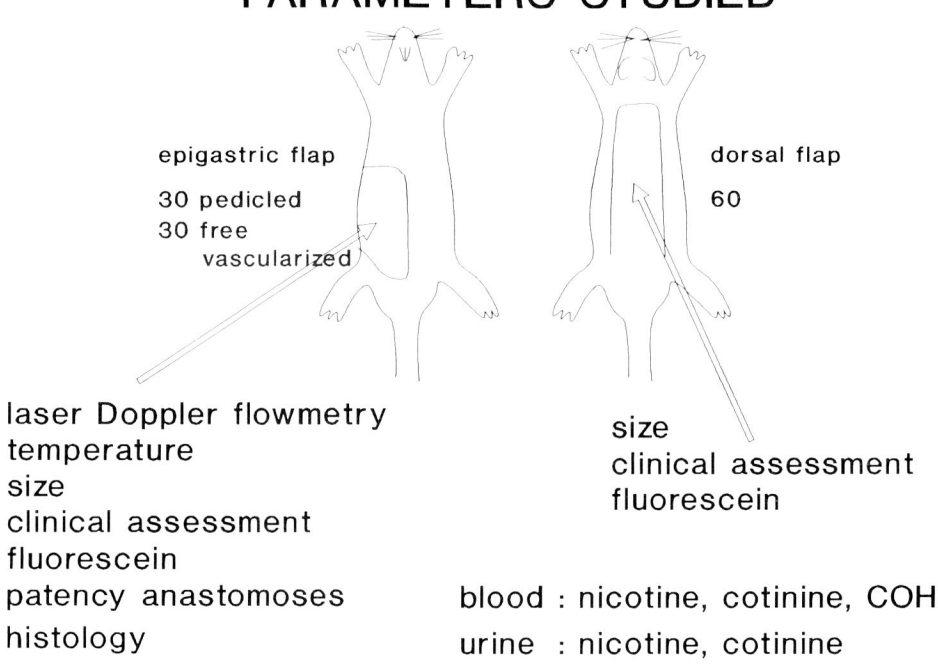


FIG. 2. Parameters determined from the epigastric flaps, dorsal flaps, blood, and 24-hour urine.

TABLE I
Parameters Studied

	Preoperative Day							Postoperative Day						
	42	39	36	14	7	4	1	0	1	3	7	10	13	14
Laser Doppler flow	◘	◘	◘		◘	◘	◘	◘	◘	◘	◘		◘	
Temperature	◘	◘	◘		◘	◘	◘	◘	◘	◘	◘		◘	
COHb (blood)				◆										◆
Nicotine and cotinine (blood)				◆										◆
Nicotine and cotinine (urine)				■										■
Clinical assessment								◙	◙	◙	◙	◙		◙
Flap size								◙	◙	◙	◙	◙		◙
Fluorescein														◙
Patency of vascular anastomoses														◘
Histology														◘

Note: Parameter determined from ◆, blood; ■, 24-h urine; ◘, epigastric flap; ◙, epigastric and dorsal flap.
This table shows at which day the parameters were measured in the preoperative or postoperative phase or during operation (day 0 = day of operation).

eight Ethilon 11-0 BV8 (Ethicon) sutures under the operating microscope. Subsequently, the flap was resutured (operating time 4.5 hours; flap ischemia 1 to 1.5 hours). To prevent autocannibalization of the flap, all animals were dressed in a vest made of an x-ray film strip, as described by Westin and Heden.[23]

Carbon Monoxide Hemoglobin (COHb), Nicotine, and Cotinine

On day 14 before and on day 14 after the operation, 24-hour urine was collected, and blood was taken from the retro-ocular venous plexus approximately 5 minutes after the third smoking session (see Table I). The COHb content was measured by spectrophotometry. The nicotine and cotinine contents of urine and plasma were assessed by high-performance liquid chromatography.

Laser Doppler Flowmetry

The laser Doppler flowmeter (Perimed KB, Sweden) has been extensively described previously.[24–27] Values are presented in perfusion units (P.U.). The laser Doppler probeholder was fixed by medical adhesive tape to the center of the epigastric flap. Measurements were obtained under ether anesthesia before, during, and after operation (see Table I). Every day, three values were obtained by three short-in-

terval (10 seconds) measurements approximately 5 minutes after stopping the third smoking or sham-smoking procedure.

Thermometry

The temperature was measured by a thermocouple connected to a Y.S.I. 44 TA thermograph (Yellow Springs, Ohio). Temperature is an indirect measurement of skin perfusion and is influenced by the temperature of the deeper tissues and surroundings. The thermocouple was fixed by medical adhesive tape to the center of the epigastric flap. Temperature and laser Doppler flow were measured simultaneously (see Table I).

Establishing Flap Viability and Patency of the Microvascular Anastomoses

Postoperatively, viability of epigastric and dorsal flaps was established clinically; viable skin shows a normal color and is pliable and soft with hair growth, whereas avital skin is contracted to a crust. By injection of 60 mg/kg fluorescein intravenously, viability of the flaps was assessed under ultraviolet light. The viable and necrotic parts of the flaps were drawn on tracing paper, and the sizes were calculated in square centimeters by a computerized system. Flap sizes also were assessed on the day of operation as reference (see Table I).

Patency of microvascular anastomoses was established on day 14 after operation. After dissecting the anastomoses, the filling of the artery distal to the anastomosis and of the vein proximal to the anastomosis was determined by Acland's filling test without touching the anastomoses. Next, the femoral vessels were cut distally to the anastomoses, and it was observed whether blood could pass the anastomoses. Finally, the microvascular anastomoses were examined histologically (see Table I).

Statistical Analysis

Mean values of laser Doppler flow and temperature in the sixth and first preoperative weeks, respectively, were calculated for every rat, serving as baseline values. The smoking rats were compared with nonsmoking rats (controls) by using the Mann-Whitney rank test (two-tailed). Since normality of distributions was not established in general, this test also was used for comparing COHb, nicotine, and cotinine measurements. Viability of the epigastric flap and patency of the vascular anastomoses were evaluated by the chi-squared test comparing three or more subgroups and, if significant, followed by the Fisher exact test (one-tailed) for comparing two specific subgroups without adjustment of p values for multiplicity. The ratios of flap sizes on the day of operation and on day 14 were analyzed by the Kruskal Wallis test to compare all subgroups followed by the Mann-Whitney rank test (two-tailed) to compare two specific subgroups.

Postoperatively, rats were divided into 12 subgroups depending on the smoking procedure (none, only preoperatively, preoperatively and postoperatively), the type of epigastric flap (free vascularized or pedicled), and the survival of the epigastric flap (survival or necrosis). For every rat, daily mean values of the laser Doppler

TABLE II

Carbon Monoxide Hemoglobin (COHb), Nicotine, and Cotinine

	Smoking Rats			Nonsmoking Rats		
	Mean	SD	n	Mean	SD	n
Day 14 before operation						
Plasma nicotine (ng/ml)	273	109	38	0.0	0.0	18*
Plasma cotinine (ng/ml)	567	304	38	0.0	0.0	18*
COHb (%)	17.9	5.9	40	3.3	2.7	18*
Urine nicotine (μg/24 h)	62	40	40	0.5	1.2	18*
Urine cotinine (μg/24 h)	55	30	40	0.0	0.0	18*
Day 14 after operation						
Plasma nicotine (ng/ml)	366	176	20	0.0	0.0	39*
Plasma cotinine (ng/ml)	733	314	20	0.0	0.0	39*
COHb (%)	22.4	6.4	19	1.4	3.1	35*
Urine nicotine (μg/24 h)	128	61	19	0.0	0.0	38*
Urine cotinine (μg/24 h)	94	45	19	0.0	0.0	38*

* Smoking versus nonsmoking: $p < 0.000005$ (two-tailed Mann-Whitney rank test).

Carbon monoxide hemoglobin (COHb), nicotine, and cotinine were determined in blood and urine 14 days before and 14 days after operation for smoking and nonsmoking rats. The values of COHb, nicotine, and cotinine in the smoking rats are comparable with human heavy smoking, and the values of the nonsmoking rats are comparable with human nonsmokers. All the differences between smoking and nonsmoking rats are statistically significant ($p < 0.000005$, two-tailed Mann-Whitney rank test).

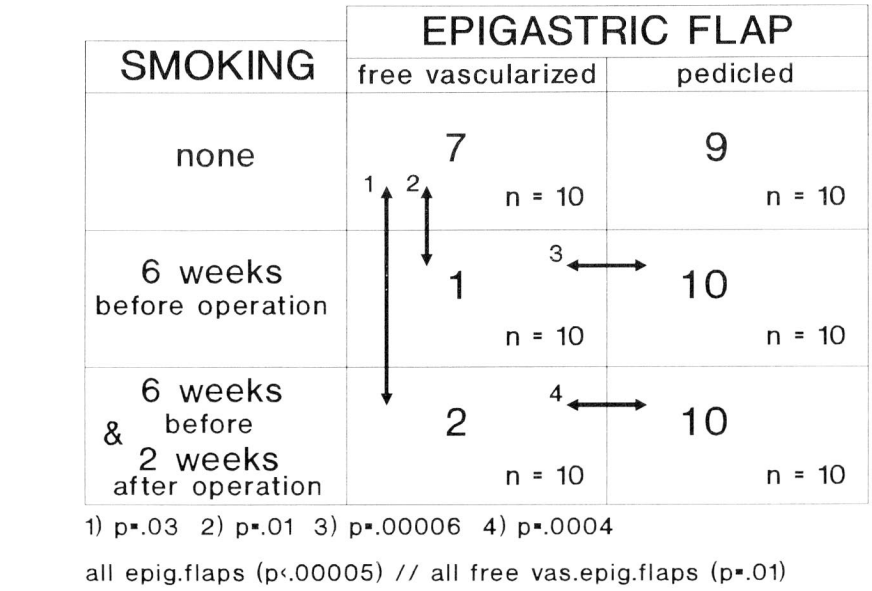


FIG. 3. Two weeks after surgery, survival of the epigastric flaps was judged clinically and by intravenous fluorescein injection. Also, the patency of the vascular anastomoses (free epigastric flaps) was established clinically and histologically as well as the passage through the epigastric vessels (pedicled epigastric flap). All epigastric flaps survived or necrosed completely, so partial necrosis was not seen. The arterial and venous microvascular anastomoses and the epigastric vessels were patent in all flaps that survived and occluded in all flaps that necrosed. All pedicled epigastric flaps survived except one in the nonsmoker group (probably as a result of vascular kinking), and no significant difference was seen for the three smoking groups ($p > 0.05$). Concerning the free flaps, survival was significantly better in the nonsmokers, but no significant difference was seen between the two smoking groups. Within the smoking groups, the pedicled flaps survived significantly better than the free flaps.

flow and temperature measurements were calculated. Assuming these mean values to be normally distributed, a repeated-measurements analysis was performed, taking into account the multivariate intercorrelation between measurements on consecutive days.

RESULTS

Carbon Monoxide Hemoglobin (COHb), Nicotine, and Cotinine

The values of COHb, nicotine, and cotinine in the smoking rats are comparable with those in human heavy smoking, and the values of the nonsmoking rats are comparable with those of human nonsmokers[28–33] (Table II). All the differences between smoking and nonsmoking rats are statistically significant ($p < 0.000005$, two-tailed Mann-Whitney rank test).

Survival of Epigastric Flaps and Patency of Vascular Anastomoses

Clinical judgment of flap survival and vascular patency, fluorescence, and histology correlated exactly, and the epigastric flaps only necrosed or survived completely (no partial necrosis). All pedicled epigastric flaps survived except one in the nonsmokers group. Concerning the free flaps, survival was significantly better in the nonsmokers, but no significant difference was seen between the two smoking groups. Within the smoking groups, the pedicled flaps survived significantly better than the free flaps (Fig. 3).

Laser Doppler Flowmetry

Before operation, the mean laser Doppler flow value was 34 P.U. (SD = 10) with no significant differences between (non-) smoking

groups. On the day of operation, just after finishing the flap procedure, a low mean laser Doppler flow value (11 P.U., SD = 5) was seen, with no significant differences among all groups. In the postoperative period, clearly significant differences in laser Doppler flow values were established between surviving and nonsurviving flaps, irrespective of the time of measurement, flap procedure, and smoking procedure. For surviving flaps, no significant differences were observed. On every postoperative day, all individual flaps that survived had a laser Doppler flow value of 20 P.U. or more, and all flaps that necrosed had a value below 20 P.U., except four flaps on the first postoperative day and one flap on the third postoperative day (Fig. 4).

Thermometry

Preoperatively, temperature was significantly lower in smokers (mean 31.2°C) than in nonsmokers (mean 32.8°C). On the day of operation, just after finishing the flap procedure, a low temperature (mean 30.8°C, SD = 0.8) was seen with no significant differences among all groups. On every postoperative day, mean temperature was lower for smoking rats, and on days 7 and 13, mean temperature was lower for necrosed flaps (Fig. 5).

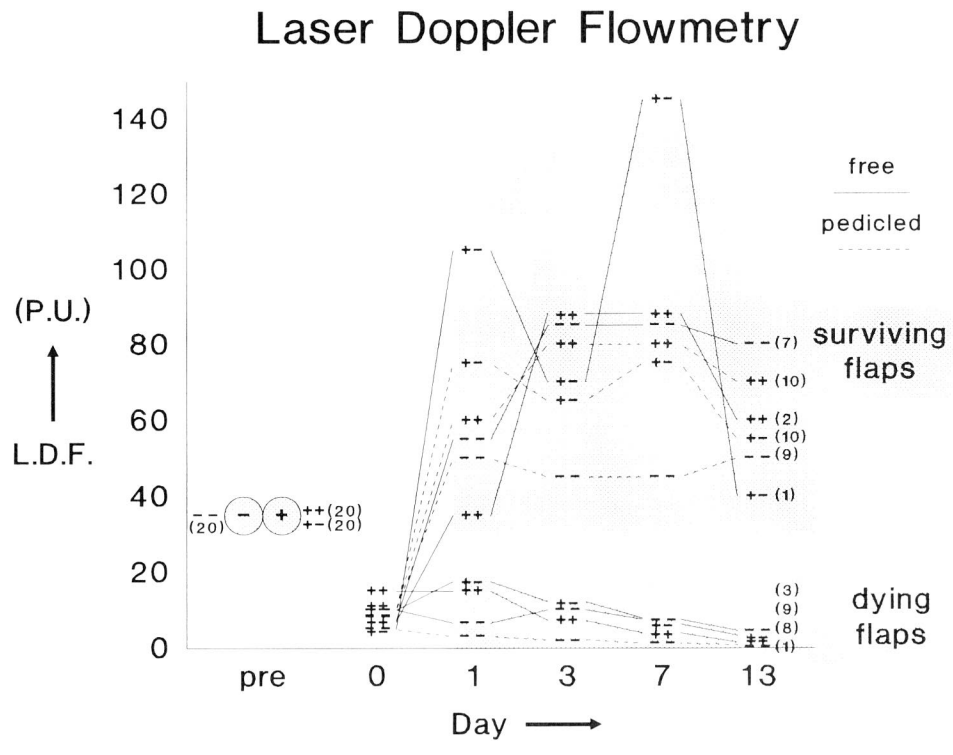


FIG. 4. Laser Doppler flow was measured in 30 free (——) and 30 pedicled (- - -) epigastric flaps in the preoperative phase (pre), on the day of operation just after finishing the flap procedure, and on days 1, 3, 7, and 13 after surgery. Of each group, 10 rats were smoked 6 weeks before and 2 weeks after surgery (++), 10 rats were smoked only 6 weeks before surgery (+−), and 10 rats underwent the sham smoking procedure (−−). A subdivision was made for surviving and dying epigastric flaps (*n*). The overall mean laser Doppler flow value before operation was 34 P.U. (SD = 10). Neither in the sixth week nor in the first week preoperatively did subgroups differ significantly ($p > 0.05$, Mann-Whitney two-tailed). On the day of operation, just after finishing the flap procedure, no significant differences were observed between subgroups ($p > 0.05$, Kruskal-Wallis); the mean laser Doppler flow value ($n = 60$) was 11 P.U. (SD = 5). No significant differences were observed among days 1, 3, 7, and 13 in any of the groups (repeated measurement analysis, $p > 0.05$). Clearly significant differences in laser Doppler flow values were established between surviving and nonsurviving flaps, irrespective of the time of measurement, flap procedure, and smoking procedure ($p < 0.00005$). For surviving flaps, no significant differences were observed either between free and pedicled flaps or between smoking categories ($p > 0.05$). On every postoperative day, all individual flaps that survived had a laser Doppler flow value of 20 P.U. or more, and all flaps that necrosed had a value below 20 P.U., except four flaps on the first postoperative day (values 29.3 P.U., ++f; 42.0 P.U., ++f; 45.3 P.U., +−f; 34.0 P.U., +−f) and one flap on the third postoperative day (25.3 P.U., ++f).

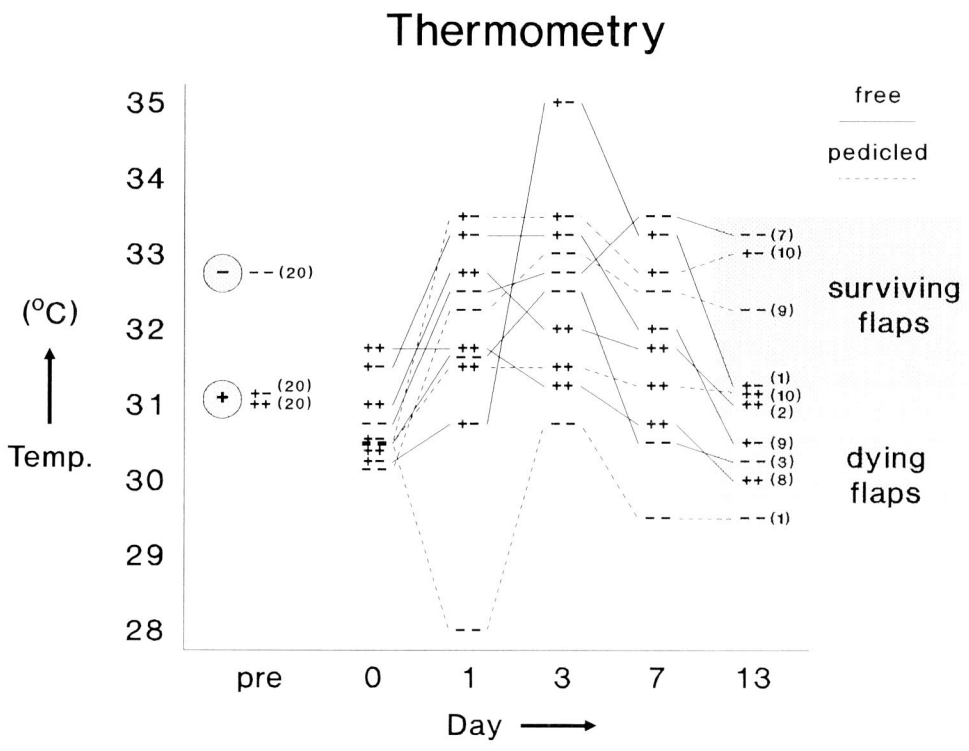


FIG. 5. Temperature was measured in 30 free (——) and 30 pedicled (- - -) epigastric flaps in the preoperative phase (pre), on the day of operation just after finishing the flap procedure, and on days 1, 3, 7, and 13 after surgery. Of each group, 10 rats were smoked 6 weeks before and 2 weeks after surgery (++), 10 rats were smoked only 6 weeks before surgery (+−), and 10 rats underwent the sham smoking procedure (−−). A subdivision was made for surviving and dying epigastric flaps (*n*). In the first and sixth preoperative weeks, temperature was significantly lower in smokers (mean 31.2°C) in comparison with nonsmokers (mean 32.8°C; $p < 0.000005$, Mann-Whitney two-tailed). On the day of operation, just after finishing the flap procedure, the mean temperature was 30.8°C (SD = 0.8), with no significant differences between subgroups ($p > 0.05$, Kruskal-Wallis). In the postoperative phase, all subgroups were significantly different on all days (day 1, $p = 0.02$; day 3, $p = 0.0002$; day 7, $p = 0.0001$; day 13, $p < 0.00005$; Kruskal-Wallis). Multivariate analysis confirmed these results, showing that they were caused by the difference in smoking procedure on every postoperative day (lower temperature for rats being smoked) and by the difference in flap survival on days 7 and 13 (lower temperature for necrosed flaps).

Vital Area of Dorsal Flaps

Survival of the dorsal flap was significantly worse in smoking rats than in nonsmoking rats. The difference between the smoking groups is not statistically significant (Fig. 6).

Area Measurement of Epigastric Flaps

The expected contraction of the necrotic epigastric flaps was at least to half the size of the surviving flaps. Concerning the contraction of the surviving pedicled flaps, highly significant differences were observed among the three smoking groups, showing a downward trend from nonsmoking, only preoperative smoking, to preoperative and postoperative smoking. A similar pattern of contraction was found in the surviving free epigastric flaps, but it was not statistically significant. Flap contraction in the nonsmoking group was more extensive for the surviving free flaps than for the pedicled flaps (Fig. 7).

DISCUSSION

This study demonstrates that smoking of cigarettes is detrimental to survival of free vascularized epigastric flaps in rats, mainly because of preoperative smoking. Random vascularized dorsal flaps survived less as a result of preoperative smoking and increasingly less as a result of additional postoperative smoking. The survival of the pedicled epigastric flap was independent of smoking. Thus smoking is detrimental to survival of poorly vascularized parts of random vascularized flaps. According to Petry and Wortham,[20] the epigastric flap of the rat is mainly an axial-pattern vascularized flap with-

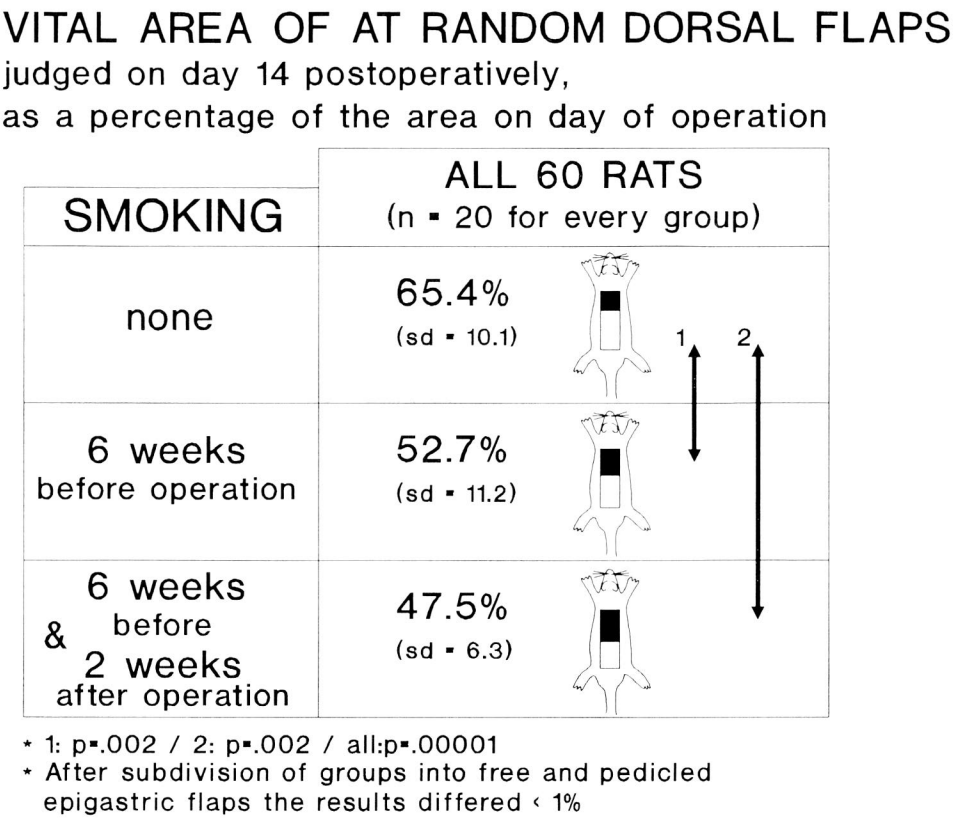


FIG. 6. The size of the vital part of the dorsal flaps on day 14 for each rat was expressed as a percentage of the size at the day of operation. As might be expected, no significant differences were observed between the two epigastric flap groups within each smoking category ($p > 0.05$, Mann-Whitney two-tailed), so the results were pooled by smoking category. The differences in survival of all groups were significant ($p = 0.00001$). Both smoking groups differed significantly from the nonsmoking group ($p = 0.002$, Mann-Whitney two-tailed) but not among themselves ($p > 0.05$, Mann-Whitney two-tailed).

out considerable random vascularized parts when the lateral branch of the epigastric vessels is included. This explains why partial necrosis of epigastric flaps did not occur. Complete necrosis of epigastric flaps has to be caused by cessation of the blood supply through the vascular pedicle. After performing the epigastric flap procedure, the flap is poorly or even not vascularized, as is shown by extremely low laser Doppler flow values, probably as a result of vasospasm of the vascular pedicle. If the vessels are not damaged surgically (i.e., the pedicled epigastric flap), the flap will be revascularized when vasospasm has faded away. When the vessels are injured by a microvascular anastomosis, the low-flow state may cause thrombosis. Thrombosis will occur more easily when rats are smoked, because smoking causes an increased platelet aggregation[10–12] and macroangiopathy and microangiopathy. Pitillo et al.[34] demonstrated endothelial changes following 6 weeks of smoking.

Some experimental studies on cigarette smoking and microvascular surgery, however, did not show damaging effects. Perioperative intraperitoneal nicotine injections[35] and 6 days of preoperative and 12 days of postoperative smoking[36] did not show a significant decrease in patency of femoral artery anastomoses in animals. Probably Rao et al.[35] did not see thrombosis because they only injected nicotine, whereas cigarettes contain numerous other harmful substances,[37] nor did Yaffe et al.,[36] since they only smoked the rats for a very brief period. Vasospasm also may be less vigorous when only an arterial anastomosis is made.

Cigarette smoking seems to be detrimental to wound healing, even when no necrosis occurs, because pedicled epigastric flaps show more contraction when rats are smoked. Furthermore, wound healing in the free flap may be impaired, because the free vascularized flap in the nonsmokers contracted to about 90 percent of the original size in contrast with the pedicled

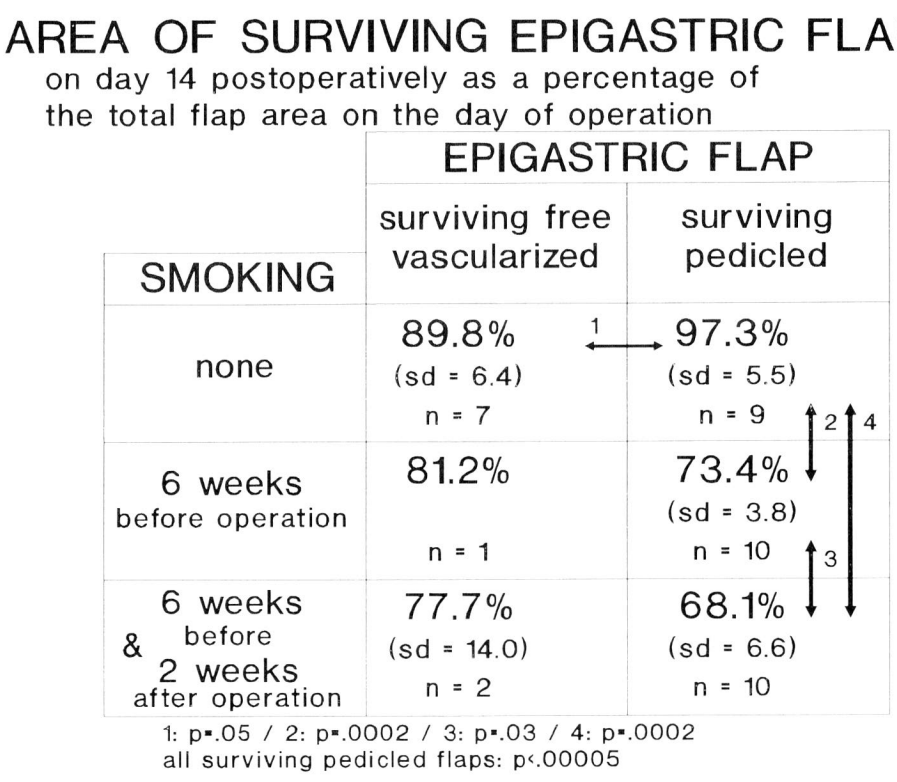


FIG. 7. On day 14, the size of the epigastric flaps for each rat was expressed as a percentage of the size at the day of operation. The results for the surviving flaps are shown for each treatment group. On the day of operation, the mean size of all 60 epigastric flaps was 34.7 cm^2 (SD = 2.6 cm^2), with no differences among the six treatment groups ($p > 0.05$). The expected contraction of the necrotic flaps was at least to half the size of the surviving flaps ($p < 0.05$). Concerning the contraction of the surviving pedicled flaps, highly significant differences were observed among the three groups ($p < 0.00005$), showing a downward trend from nonsmoking, only preoperative smoking, to preoperative and postoperative smoking. A similar pattern of mean contraction was found in the surviving free epigastric flaps, but the numbers are too small to attain statistical significance of differences. Flap contraction in the nonsmoking group was more extensive for the surviving free flaps than for the pedicled flaps ($p = 0.05$).

flaps. This may be caused by irreversible tissue damage due to ischemia or by emboli.[38]

The nicotine, cotinine, and COHb measurements demonstrate that the smoking procedure used is comparable with heavy cigarette smoking. However, 6 weeks of smoking cannot be compared with chronic cigarette smoking, which causes more macroangiopathy and microangiopathy. Unfortunately, it is very hard to smoke rats for at least 1 year. For practical reasons, we have chosen 6 weeks of preoperative smoking because at that time endothelial changes have been seen.[34]

Preoperative laser Doppler flow and temperature measurements about 5 minutes after stopping smoking gave different results. Laser Doppler flow of the normal skin was equal in smoking and nonsmoking rats, whereas the skin temperature was lower in the smokers. Microcirculation may be influenced by ether anesthesia, thereby hiding the vasoconstriction caused by cigarette smoking. The lower temperature may still be present at that moment. It is unlikely that vasoconstriction due to smoking has disappeared after 5 minutes. A second explanation is that a central temperature decrease is caused by smoking, giving an indirect temperature fall of the skin while no vasoconstriction is present. Postoperatively, the same discrepancy was found.

Laser Doppler flowmetry proved to be a good viability monitor in the postoperative period.[39] All surviving flaps had a laser Doppler flow value of 20 P.U. or more, whereas all dying flaps were below this level, except four flaps on the first postoperative day and one flap on the third postoperative day. These flaps may have been alive (with a relatively low flow) at that time and

necrosed later (as a result of complete thrombosis of the vascular anastomoses). Temperature of the dead flaps was lower on days 7 and 13 after operation, because at that time the flaps were transformed to crusts, which conduct heat poorly.

This study proves that cigarette smoking is detrimental to microvascular surgery. It is not known when smoking should be stopped before surgery to recover the damaging effects. It is unlikely that a full recovery will ever occur, because some changes (e.g., macroangiopathy) are hardly reversible.

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