

Research letters

HIV-1 in semen: an isolated virus reservoir

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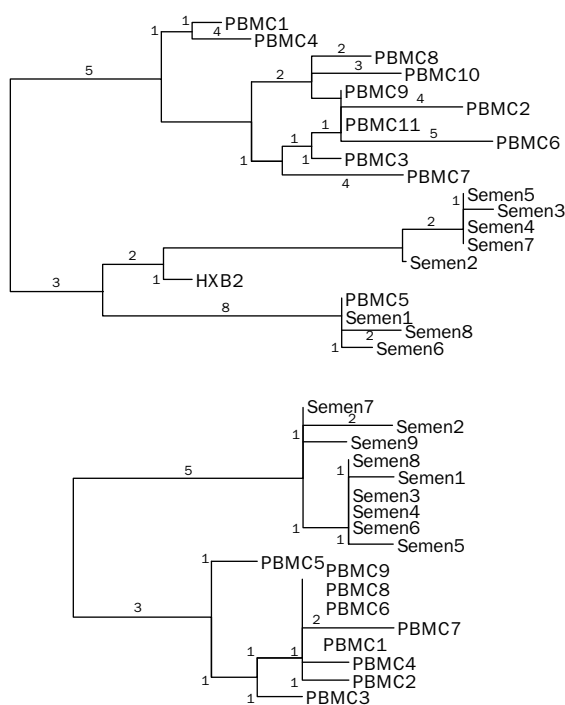
The reservoir of HIV-1 in semen is unknown. Semen is comprised of secretions and cells from seminal vesicles, prostate, testis, epididymis, and ejaculatory ducts; leucocytes are present in semen, although their source and their role in the semen viral burden is unclear.¹ Reports that semen viral RNA concentrations do not correlate with those in plasma,² that infectious virus in semen is independent of plasma viraemia and discordant with respect to syncytium-inducing properties³ or nucleoside resistance,⁴ and that the envelope sequences of sexually transmitted virus differ from those in the blood of the transmitter,⁵ suggest that semen HIV-1 does not arise from the same reservoir of infection as peripheral blood.

We determined HIV-1 protease-gene sequences of infectious virus recovered from the cells of paired

specimens of blood and semen from two men infected with HIV-1 for more than 8 years. Both men were healthy with CD4⁺ counts above 400×10⁶/L, no known infected, and normal genitourological examination at the time of specimen donation. Protease-gene sequences were determined for 11 blood and eight semen virus clones from patient A who had not received antiretroviral therapy, and from nine blood and nine semen virus clones from patient B who had been on antiretroviral therapy for several years, including a protease inhibitor for 4 months. The sequences were aligned for maximum homology and phylogenetic analysis were done (figure).

Protease-gene sequences of all clones contained several mutations relative to the reference virus, hxb2. The phylogenetic analyses of the sequences from each patient revealed two distinct families of viruses, one in the blood and one in the semen. The differences between the families ranged from four to seven or from four to eight aminoacid substitutions for patients A and B, respectively. Blood clones from patient B contained mutations at aminoacid residues 36(I), 54(V), 63(P), and 82(A), characteristic of emerging resistance to the protease inhibitor. By contrast, protease resistance conferring mutations were not found in the semen virus clones from patient B.

These findings support the concept that semen HIV-1 arises from a distinct reservoir of HIV-1 infection which may be isolated from antiretroviral therapy and may function independently in the pathobiology of HIV-1 disease. This suggests that consideration of the specialised features of the semen compartment needs to be included in disease monitoring and the design of treatment strategies.



Phylogenetic analysis of protease genes sequenced from HIV-1 strains isolated from peripheral blood mononuclear cells and semen leucocytes

Sequences (available from the authors on request) were aligned for maximum homology with the pattern-induced multisequence alignment algorithm (PIMA) then phylogenetic analysis performed with maximum linkage parsimony. Similar results were obtained by PAUP with sequential branching and the Doolittle method of the Eugene package. The numbers on the lines represent relative phylogenetic distance.

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Bioengineered skin

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Advances in tissue bioengineering, such as the development of biologically useful cells, tissue, and organs, are expected to revolutionise the practice of medicine.¹ Living skin equivalent (LSE), a bioengineered skin, is composed of an epidermis and dermis made of type I bovine collagen and cultured allogeneic cells (keratinocytes and fibroblasts) isolated from human neonatal foreskin. In controlled studies, LSE improved healing in venous ulcers² and in open studies it seemed to improve healing in thermal burns and acute wounds created by excision of skin cancer.³ We report a prospective, randomised, paired comparison of SEL split-thickness autograft, and polyurethane film (PUF) occlusion dressing for the treatment of split-thickness skin graft donor sites.

Three 2.5 cm×4.0 cm donor sites were created on the anterior thigh of 11 patients who required split-thickness skin grafts. Each patient's donor sites were randomly treated with meshed LSE, meshed autograft, or PUF. Evaluations were on day 7, every 2–3 days thereafter until healing of all three donor sites, and at 1 and 2 months. Endpoints were time to healing, pain, and cosmetic outcome (pigmentation, vascularity, and height).

The mean time to healing was 7.4 days (SD 0.9) for LSE, 7.9 days (1.5) for autograft, and 10.4 days (1.7) for PUF ($p=0.0006$). In addition to rapid healing, LSE and autograft reduced the pain associated with healing donor sites. No patients experienced pain with LSE or with autograft compared with PUF which was associated with mild pain in six of ten patients. LSE and autograft afforded a more desirable cosmetic result. At 2 months all sites were hyperpigmented, but the vascularity was different. LSE was pink, autograft was normal, and PUF was purple. The PUF sites were evaluated in eight of 19 patients at 2 months. There was a 90% incidence of clinical take and no signs of toxicity or clinically detectable rejection to LSE in the patients enrolled in this study. Our observations are consistent with those reported using LSE for the treatment of acute wounds after Mohs surgery.⁴

The use of LSE avoids obtaining tissue from the patient and in the case of donor sites avoids reapplying a portion of the graft. At present, LSE and other bioengineered

tissues are costly. For this reason most studies are aimed at diabetic,⁴ venous,² and pressure ulcers for which the costs of treatment are high.

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Increase in primary liver cancer in the UK, 1979–94

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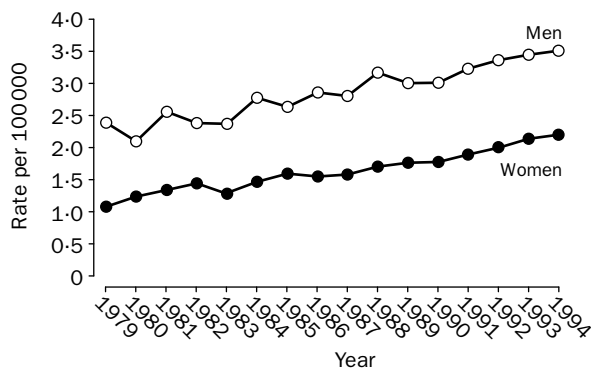
Hepatocellular carcinoma (HCC) is a recognised complication of chronic liver disease, with the development of cirrhosis being the most significant predisposing factor. Hepatitis B and hepatitis C infection are associated with a significantly higher risk of HCC than other causes of cirrhosis. This increased risk is reflected in the incidence of HCC, which has a marked geographical variation, being commoner in areas of the world where viral hepatitis is more prevalent.¹ Hepatitis C virus (HCV) infection usually causes a symptomless acute hepatitis; in about 80% of cases the infection becomes chronic.² The true prevalence of chronic infection with the HCV virus in the UK is unknown, but current estimates suggest up to 1% of the population is infected.² About 30% of individuals then develop cirrhosis over a period of up to 30 years after the initial infection; the subsequent incidence of HCC is then up to 5% per year.

Studies from France and Italy have suggested that, in particular, HCV genotype 1b is associated with the highest risk of developing HCC.³ This may be responsible for an increased prevalence of this tumour in Europe. It is difficult to ascertain whether there has been an increased incidence of deaths from HCC in the UK because in some cases, primary liver cancer is recorded in the mortality statistics rather than a definitive diagnosis of HCC or cholangiocarcinoma. However, mortality from all causes of primary liver cancer has almost doubled in 15 years: from 919 in 1979 to 1764 in 1994.⁴ Between 1979 and 1994, the age-standardised mortality rates per 100 000 UK population have increased from 2.39 to 3.56 in men and from 1.08 to 2.22 in women (figure). Where a histological diagnosis is given, the mortality rates of cholangiocarcinoma have increased during the reported period, but the recorded rates of HCC have remained relatively static. Whether any contribution to the overall rise in primary liver cancer is due to an increasing incidence of HCV-induced cirrhosis in the UK or to other causes is unknown.

Mortality from primary liver cancer is comparable to rates of other cancers which have received much attention in terms of prevention, such as malignant melanoma (2.7 per 100 000 people) and carcinoma of the cervix (5.6 per 100 000 people).⁵ 5-year survival rates for primary liver cancers in the UK remain poor. Both cholangiocarcinomas and HCCs are frequently diagnosed at too late a stage for hepatic resection (or liver transplantation) to be a viable



Circular LSE being lifted out of its plastic carrying tray containing pink-colored gel support medium



Age standardised mortality rate per 100 000 of the population in the UK for primary liver cancer 1979-1994

(Data from the Office of National Statistics, London.)

option. Early diagnosis of cholangiocarcinoma is difficult and increased vigilance in the at-risk populations such as those with primary sclerosing cholangitis is required. Screening programmes for HCC in patients with cirrhosis of all aetiologies also need to be evaluated. A combination of regular 3-6 monthly hepatic ultrasound examinations and measurement of serum α fetoprotein to detect HCCs at an earlier stage is one possible option. This approach is particularly important in HCV-induced cirrhosis, because the natural history of HCV infection would suggest that many of those individuals who contracted the virus from intravenous drug use in the late 1960s and early 1970s are developing cirrhosis and are currently at risk of HCC. This is likely therefore to increase the incidence of HCC in the UK during the next few years.

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Safety of first-trimester exposure to topical tretinoin: prospective cohort study

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13-cis-retinoic (Accutane) causes a characteristic retinoid embryopathy. Its isomer, all-trans-retinoic acid (tretinoin) is teratogenic in animals when administered orally but information after topical use in pregnancy is limited. 291 pregnancy outcomes have been published which show no difference in the rates of malformation between exposed and unexposed fetuses.¹⁻⁵ This drug is contraindicated for use in pregnancy.

Motherisk is a service that provides information about gestational exposure to drugs, chemicals, radiation, and

	Tretinoin exposed (n=94)	Controls (n=133)	p
Pregnancy outcome			
Live births	86 (91%)	119 (89%)	0.99
Miscarriage	6	12	0.63
Elective termination	3	2	0.69
Major malformations in live births	2/86 (2%)	4/119 (3%)	0.30*
Gestational age (weeks)	39.6±1.5 (35-42)	39.6±1.5 (36-42)	0.99
Premature (<37 weeks)	4/86 (5%)	5/119 (4%)	0.25*
Birthweight (g)	3354.5±470.2 (2272-4487)	3501.9±553.5 (2074-5396)	0.05
Low birthweight (<2500 g)	4/86 (5%)	4/119 (3%)	0.25*
Method of delivery			
Caesarean section	19/86 (22%)	24/119 (20%)	0.81
Vaginal	67/86 (78%)	95/119 (80%)	

*Fisher's exact test.

Pregnancy outcome

infectious diseases. We conducted a prospective, observational, controlled study to compare the rate of malformations among fetuses exposed and unexposed to tretinoin. The exposed group consisted of women who voluntarily contacted Motherisk between 1988 and 1996 for information about gestational exposure to tretinoin. After the expected date of delivery, follow-up was conducted by telephone interview and verified by the infants' physician to obtain details of labour and delivery, neonatal complications, and postnatal growth and development. Controls were pregnant women who voluntarily contacted Motherisk to enquire about exposures not known or suspected to be teratogenic or fetotoxic. Data collection was identical to that in the tretinoin group.

The 94 tretinoin-exposed cases and their 133 controls were similar with respect to maternal age, patterns of smoking, and alcohol use. Pregnancy outcome did not differ between cases and controls (table). There was no difference in the rates of live births, miscarriages, or elective terminations of pregnancy. Among live-born babies who were exposed to tretinoin during the first trimester, the incidence of major malformations did not differ from the controls. Major defects among tretinoin-exposed infants were seen in two babies, one with a bicuspid aortic valve and the other with dysplastic kidneys. Neither of the major defects in these infants were consistent with the retinoic-acid embryopathy. Defects among controls were two newborn babies with congenitally dislocated hips: one with aortic valvular stenosis and one with imperforate anus. There was a difference of 148 g in the mean birthweights between the two groups (3354.5 vs 3501.9 g, p=0.05); but after removal of one control infant with a birthweight of 5396 g, this difference was not statistically significant.

With the use of topical tretinoin for anti-ageing preparations, the population base of users will expand from teenagers who use it for acne to young and middle-aged adults, which will include women of childbearing age. Our study includes the largest sample size to date of women who used topical tretinoin in early pregnancy. The results failed to show an increased risk in congenital malformations for users of topical tretinoin.

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HHV-8 and multiple myeloma in France

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HHV-8 is associated with Kaposi's sarcoma, primary effusion lymphomas, and HIV-I-associated Castleman's disease.¹ A PCR-based study suggested an association between HHV-8 and multiple myeloma and monoclonal gammopathy of undetermined significance (MGUS).² We looked for antibodies to HHV-8 in patients with multiple myeloma and MGUS.

59 patients were enrolled: 23 with multiple myeloma, three with MGUS, 13 with non-Hodgkin lymphoma, ten with AIDS-associated Kaposi's sarcoma, and ten with classic Kaposi's sarcoma. Immunofluorescence assay was done on a PEL cell line latently infected with HHV-8 but not by Epstein-Barr virus (BCP-1, provided by P S Moore, NY City, USA).³ Sera were also tested for other herpesviruses antibodies by ELISA: herpes simplex virus (HSV), varicella-zoster virus (VZV), human cytomegalovirus (HCMV), and Epstein-Barr virus (EBV-EBNA). HHV-8 antibodies were found in all patients with classic Kaposi's sarcoma and in 70% of patients with AIDS-associated Kaposi's sarcoma. We did not detect HHV-8 antibodies in sera of patients with multiple myeloma and non-Hodgkin lymphoma. Only one patient with MGUS had antibodies to HHV-8. Most patients had antibodies to HSV, VZV, EBV, and HCMV (table).

Epidemiological studies have clearly identified a link between multiple myeloma and MGUS and a slight excess of multiple myeloma incidence in men.⁴ There is also a difference between races with higher rates among blacks in North America and South Africa, and low incidence among Chinese and Japanese. However, there is no epidemiological association between Kaposi's sarcoma and multiple myeloma. In our study, none of the patients with multiple myeloma had antibodies to HHV-8. The prevalence of antibodies to HHV-8 in patients with Kaposi's sarcoma were similar to those reported in both HIV-1 infected or uninfected patients.

Our results could not be explained by a defective humoral response to HHV-8 in patients with multiple myeloma because of the normal serological results for other human herpesviruses. It would be improbable that patients with multiple myeloma are infected with HHV-8 and seronegative for this virus. The absence of an epidemiological link between multiple myeloma and Kaposi's sarcoma, together with our findings, suggest that there is no association between HHV-8 and multiple myeloma. However, because we used a serological assay that detected antibodies against a latent nuclear antigen encoded by open reading frame 73,⁵ we could not exclude that patients with multiple myeloma are infected with a defective virus. This hypothesis could explain the discrepancy between our results and those previously reported.² Among patients with MGUS, one patient of Caribbean origin was found to be seropositive for HHV-8.

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Diseases	HHV-8	HSV	VZV	HCMV	EBV
Multiple myeloma (n=23)	0	21 (91%)	19 (83%)	14 (61%)	21 (91%)
MGUS (n=3)	1 (33%)	3 (100%)	3 (100%)	2 (66%)	3 (100%)
Non-Hodgkin lymphoma (n=13)	0	12 (92%)	13 (100%)	9 (69%)	13 (100%)
Total (n=39)	1 (3%)	36 (92%)	35 (90%)	25 (64%)	37 (95%)
Clinical Kaposi's sarcoma (n=10)	10 (100%)	ND	ND	ND	ND
AIDS-associated Kaposi's sarcoma (n=10)	7 (70%)	ND	ND	ND	ND

ND=not done.

Results of serological assays

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HHV-8 and multiple myeloma in the UK

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Rettig and colleagues¹ reported an association between HHV-8 and multiple myeloma. HHV-8 genomic sequences were detected by PCR in cultured bone-marrow stromal cells from 15 of 15 patients with multiple myeloma and from two of eight patients with monoclonal gammopathy of uncertain significance, but not from 26 controls. The association is biologically plausible since HHV-8 encodes an interleukin-6 (IL-6) homologue and IL-6 is known to be an important growth factor for myeloma cells; furthermore Rettig and colleagues¹ showed expression of viral IL-6 in three of three myeloma bone-marrow stromal cells. The investigators therefore proposed that HHV-8 has a causative, albeit indirect, role in the pathogenesis of multiple myeloma.

Unlike other human herpesviruses, with the exception of herpes simplex virus type 2, infection with HHV-8 is not widespread in the population. Serological assays seem to give the best indication of prevalence.^{2,3} On the basis of antibody reactivity to a latency associated nuclear antigen (LANA) and a recombinant capsid-related protein, encoded by open reading frame (orf) 65.2, HHV-8 seroprevalence in the UK is estimated at about 5%; in the USA it appears to be a little higher. In some Mediterranean countries HHV-8 seroprevalence is around 10-20%, and in Uganda around 50%.² By an immunofluorescence assay for lytic HHV-8 antigens, an upper estimate for the HHV-8 prevalence in the USA is around 25%.³ All three assays suggest a marked geographical variation in prevalence.

Multiple myeloma does not show a similar geographical variation, although incidence data relating to myeloma must be evaluated with care in view of diagnostic uncertainties.⁴ The risk of developing myeloma is slightly increased in individuals infected with HIV-1 and the increase is not as marked as that seen with Kaposi's sarcoma or non-Hodgkin lymphomas and has not been observed in several studies.⁵

To further evaluate the association between HHV-8 and myeloma, we investigated whether the prevalence of HHV-8 is greater in myeloma patients than in healthy controls. Serum samples from 78 cases and 37 healthy controls from the UK were assayed for antibodies to HHV-8 lytic and latent antigens with an ELISA detecting reactivity to the orf 65.2 protein and immunofluorescence on the BCP-1 cell line, respectively.² Confirmatory Western blotting, with the orf 65.2 protein, was done on all samples that were positive or borderline in either assay. All assays were done as described previously.² HHV-8 antibodies were detected in about 80% and 90% of cases of AIDS-associated and classic Kaposi's sarcoma, respectively. Samples from two patients with myeloma and two healthy controls were scored as positive. There was, therefore, no significant difference in HHV-8 seroprevalence between cases and controls.

In view of the low HHV-8 seroprevalence in myeloma, we examined whether myeloma serum could have an inhibitory effect in the ELISA assay. An HHV-8 antibody-positive sample was added to dilutions of the two myeloma samples with the highest concentrations of paraprotein; no inhibitory effects were observed. Because immunosuppression is a known feature of multiple myeloma, we then addressed the possibility that myeloma patients might have diminished or undetectable antibody responses to persistent viral infections. All samples were assayed for antibodies to the EBNA1 protein of Epstein-Barr virus with Western blotting. Serum samples from 73 of 78 cases of myeloma and 35 of 37 healthy controls reacted with the EBNA1 protein at a 1:10 dilution; there was no evidence for reduced antibody responses in the group of patients.

We found no evidence for an association between HHV-8 and multiple myeloma. HHV-8 seroprevalence was similar in patients with myeloma and healthy controls and the results were consistent with previous estimates of HHV-8 seroprevalence in the UK. It is difficult to reconcile these findings with those of Rettig and colleagues because persistent herpesvirus infections are normally accompanied by a continued antibody response.

This work was supported by the LRF, MRC, and the R L Gardner Cancer Research Fund.

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Migraine and cerebral blood flow during centrifugation

Colleen Schmidt

I studied the incidence of migraine among freestyle figure skaters (with rotational spinning motion) and ice dancers (same conditions and venue, but without spinning). My hypothesis was that freestylers would experience centrifugation of blood away from the central axis of a spin, whereas ice dancers, even with similar exertion, would experience no such centrifugation. The common freestylers' experience of having fluid forced from the nose during a fast spin indicates that simple fluid dynamics govern the distribution of bodily fluids; more liquid than solid body parts are displaced from the central axis while spinning. If, as predicted by the primary vascular hypothesis of migraine,¹ blood drains from the central cerebral vasculature and pools in the outer vessels, then the migraine experience resembles a skater's spin, at least with regard to blood flow. The primary vascular hypothesis of migraine first proposed by Wolff¹ in 1963 has been bolstered by research such as Sakai's² measurement of regional cerebral blood flow with single photon-emission computed tomography, which showed that regional ischaemia exists during migraine aura and is attributable to cerebral vasospasm rather than primary neuronal factors. Panconesi and colleagues³ showed that migraineurs may be differentiated from non-migraineurs by the pain they feel during hyperaemia, even in other parts of the body.

We found that 11 (22%) freestylers compared with one (4%) ice dancer reported migraines. A change in migraines while skating was felt by ten (91%) of the freestyle-migraineurs, most of whom mentioned that spinning affected their migraines. However, only one (10%) of those with non-migraine headaches found that skating had an effect on their headaches.

This difference is partially due to the fact that strenuous exercise tends to either exacerbate (as reported by Davidoff⁴) or alleviate (as reported by Darling⁵) a migraine. However, such findings do not explain why so many respondents mentioned spinning in particular as affecting their migraines. Also, although both Darling and Davidoff agree that regular long-term exercise tends to prevent migraine, seven (64%) of our surveyed freestyle-migraineurs began to have migraines after taking up the sport of freestyle skating (one of whom had the first migraine while actually on the ice). Because a slight majority, six (55%), of freestyle-migraineurs felt worse from spinning than the four (36%) whose migraines improved, it is not clear and cannot be concluded decisively from this study alone whether freestyle skating exacerbates or alleviates migraine. However, the data support a difference between migraines and other headaches, which is consistent with blood redistribution toward extracranial arteries in the former and lack of this effect in the latter.

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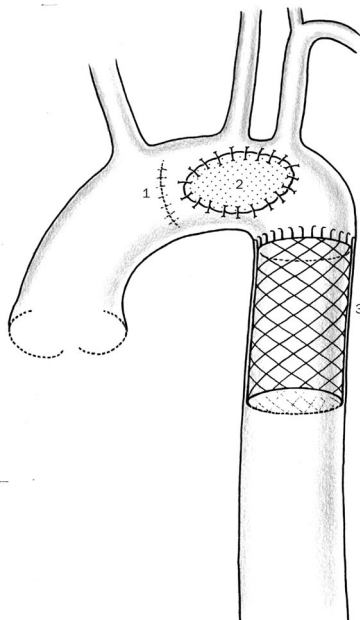
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Combined endovascular and surgical treatment of complex traumatic lesions of thoracic aorta

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A 26-year-old man had a high-speed crash whilst snowboarding and fell into a crevasse about 10 m deep. During rescue, he was conscious and complained about severe chest pains and intermittent paraparesis. For transfer by helicopter, he was intubated in a regional hospital. On admission to our institution, a diagnosis was made of blunt thoraco-abdominal trauma and cerebral contusion with localised frontal haematoma. Cardiac contusion was suspected because of raised troponin-T, creatine kinase (CK), and CK-MB and right bundle branch block. Because the chest radiograph showed widening of the superior mediastinum, transoesophageal echocardiography was done, and showed a traumatic rupture of the descending aorta (approximately 3–4 cm below the origin of the left subclavian artery) and a localised hematoma around the aortic arch. Aspiration of the left pleural cavity showed a haemato-pneumothorax. He developed severe arterial hypertension in his arms which was treated with atenolol, captopril, and intravenous nifedipine and clonidine, but arterial pressure remained high (150/90 mm Hg); arterial pressure in his legs was lower (100/60 mm Hg). Since a pseudo-coarctation of the aorta was suspected, magnetic resonance imaging was done and confirmed a false aneurysm of the aortic arch as well as a contained rupture of the aortic isthmus with consecutive intussusception of the intimal cylinder into the distal aortic segment. The aortic arch as well as the origin of the left carotid artery were compressed and a tight stenosis was suspected at the level of the contained aortic rupture.

In light of these injuries, it was clear that neither median



Schematic representation of the repaired aorta

Showing direct suture of the aortic tear in the posterior wall of the aortic arch (1), patch enlargement of the aortic arch (2), and the endovascular prosthesis covering the traumatic rupture of the aortic isthmus (3).

sternotomy nor lateral thoractomy would allow full exposure of both lesions simultaneously. We decided to treat the contained rupture of the descending aorta with an endovascular stent implantation first and to postpone surgical repair of the aortic arch. A 18 F sheath was introduced through a cut-down in the left external iliac artery and advanced under fluoroscopic guidance. A headhunter catheter was placed in the left subclavian artery. The stent, 26 mm diameter and 8 cm long (Vanguard, Boston Scientific Corporation, Boston MA, USA), was introduced through the sheath and expanded at the site of the rupture. Surgical exploration was done 2 days later through a median sternotomy. Cardiopulmonary bypass was instituted and conducted in deep hypothermia. At a core temperature of 18°C, cardiopulmonary bypass was discontinued and the aortic arch was opened; inspection and palpation from inside the aorta revealed a proper placement of the endovascular prosthesis. A semi-circumferential intimal tear located between the innominate and the left carotid artery was closed from inside with interrupted polypropylene 4/0 sutures. The large pseudoaneurysm had compressed the origin of the left carotid artery and of the aortic arch. Closure of the arch was done with the insertion of a Vaskutek (Sulzer Medica, Winterthur, Switzerland) prosthetic patch to allow proper expansion. Postoperative recovery was uneventful, the arterial hypertension disappeared promptly after the surgical procedure and the patient was discharged one week after operation. Magnetic resonance imaging showed normal morphology of the aortic arch, complete exclusion of the pseudo-aneurysm and a normal configuration of the proximal descending aortic segment. The origin of the left carotid artery was patent.

Deceleration is one of the most common causes of injury of the thoracic aorta.¹ The timing of repair of traumatic injury of the aorta is still controversial: a secondary rupture of a pseudoaneurysm or intramural hematoma seems to be infrequent, providing that adequate anti-hypertensive treatment is given. Our own experience with traumatic aortic rupture has shown that patients who survived aortic rupture during the first 6–12 h seem to have a less catastrophic outcome than usually thought.² In this case, control of the arterial hypertension was not possible by drug therapy, most probably because of a significant obstruction of the aortic arch. For this reason and because of the rapid increase of the false aneurysm, a more aggressive treatment was selected. Both interventional and surgical procedures were successful and the patient recovered rapidly.

There are only a few reports dealing with intravascular stenting of a traumatic aortic injury.^{4,5} From this one experience, we believe that a combined stent-graft strategy represents an effective therapeutic option.

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